Technische Universität München

Zentrum Mathematik

Mathematical Modelling of Tumour Radiotherapy

Master Thesis

Author:	Rachel Webersinke
Subject:	Mathematics M.Sc.
Thesis supervisor:	Prof. Dr. C. Kuttler
Thesis advisor:	Dr. J. Pérez-Velázquez
Submission date:	13 May 2013

Technische Universität München

Zentrum Mathematik

Mathematical Modelling of Tumour Radiotherapy

Master Thesis

Author:	Rachel Webersinke
Subject:	Mathematics M.Sc.
Thesis supervisor:	Prof. Dr. C. Kuttler
Thesis advisor:	Dr. J. Pérez-Velázquez
Submission date:	13 May 2013

Hiermit erkläre ich, dass ich die Masterarbeit selbstständig und nur mit den angegebenen Hilfsmitteln angefertigt habe.

München, den 13. Mai 2013

Kurzdarstellung

Nach der Entdeckung der Röntgenstrahlen 1895 wurde schnell festgestellt, dass diese Strahlen Zellen beschädigen. Schon bald darauf wurden Röntgen- oder Gammastrahlen zur Krebs-behandlung eingesetzt. Seitdem ist Radiotherapie ein wichtiges Instrument zur Krebsbekämpfung geworden. Heutzutage werden mehr als 50% der Tumorpatienten mit Radiotherapie behandelt.

Seit den Fünfzigerjahren hat die Radiotherapie auch in der mathematischen Modellierung eine wichtige Rolle erlangt. Dabei ist es möglich die Auswirkungen von Radiotherapie auf das Tumorwachstum zu simulieren.

In dieser Arbeit stelle ich zuerst sowohl die Grundprinzipien des Tumorwachstums, als auch der Radiotherapie dar. Des Weiteren erläutere ich die gängigen mathematischen Modelle, die zur Beschreibung von Tumorwachtum und den Gebrauch von Radiotherapie, um Krebszellen zu töten, verwendet werden. Auf dieser Basis habe ich die gegebenen Modelle erweitert, um mehrere Faktoren der Radiotherapie wie Reparatur, Repopulation und Radiosensitivität, zu integrieren. Dies wurde im Falle der kontinuierlichen als auch der periodischen Bestrahlung durchgeführt. In jedem Modell wurde analysiert welche Dosis an Radiotherapie benötigt wäre, um alle Tumorzellen zu töten. Zusätzlich wurden diese erweiterten Modelle anschließend mit Daten der T47D Zelllinie (Brustkrebszellen) verglichen.

Abstract

After Wilhelm Röntgen's discovery of X-rays in 1895, it was soon recognised that cells were damaged by radiation [AHN09]. Since then, radiotherapy has become a vital tool in fighting cancer. In fact, more than 50% of tumour patients are treated with radiotherapy [Wan00, AHN09].

Since the nineteen fifties, radiotherapy has also gained an important role in mathematical modelling, where it is possible to simulate the effects of radiotherapy on tumour growth.

This thesis begins with a biological introduction on tumour development and growth and how radiotherapy works as a treatment mechanism. Furthermore, I describe mathematical models for tumour growth which are currently in use and compare these to data collected in vitro. On this basis I propose new models to optimise the pre-existing ones and develop new approaches to modelling radiotherapy. This was done in two ways, one by assuming constant radiation and the other by assuming periodic radiation. Each model was then extended to either incorporate repair, repopulation or radiosensitivity. In each model the aim was to find the amount of radiation needed to kill all tumour cells. Finally, these models were compared to data collected in vitro of the T47D cell line (human breast cancer cells).

Contents

1. Introduction

The 'birth' of radiobiology can be traced back to Wilhelm Röntgen's discovery of X-rays in 1895. It was soon recognised that cells were damaged by radiation [AHN09]. Already in 1896 hair loss was observed in a radiation worker [Nia98]. Two years later Pierre and Marie Curie isolated the radioactive elements polonium and radium, which within a few years were used to treat cancer [HG12]. Since then, radiotherapy has become a vital tool in fighting cancer. In fact, more than 50% of tumour patients are treated with radiotherapy [Wan00, AHN09]. The goal of radiotherapy is to deliver high radiation doses to malignant tissue while at the same time radiating as little of the healthy tissue as possible.

Since the nineteen fifties, radiotherapy has also gained an important role in mathematical modelling, where it is possible to simulate the effects of radiotherapy on tumour growth. In this thesis I will describe mathematical models that are currently in use to describe tumour growth as well as models including the use of radiotherapy to kill tumour cells. On the basis of these models I will then develop further models that could improve the existing equations. In accordance to that goal, this thesis will be structured as follows.

Chaper 2 begins with a biological introduction on tumour development and growth and how radiotherapy works as a treatment mechanism. In chapter 3, I describe mathematical models for tumour growth which are currently in use and compare these to data collected in vitro from [Ana11]. Chapter 4 describes commonly used mathematical models that quantify the effect of radiotherapy on cells. In chapter 5, I aim to propose new models to optimise the pre-existing ones and to develop new approaches to modelling radiotherapy. These models are also compared to data collected in vitro of the T47D cell line (human breast cancer cells) by the Institute of Radiation Biology, Helmholtz-Zentrum München [AH12]. Finally, chapter 6 shows conclusions and results of this thesis as well as an outlook for possible further research.

2. Biological Background

2.1. Tumour Growth

A tumour is medically defined as:

> "A mass of tissue formed as a result of abnormal, excessive and inappropriate proliferation of cells, the growth of which continues indefinitely and regardless of the mechanisms which control normal cellular proliferation." ([And85])

Tumour cells have been found to have distinct features as mentioned in the above quote, for example, they can escape from the controls of normal birth and death processes and from the controls of maturation and differentiation processes, where normal cells begin to develop distinct phenotypes and form a certain type of tissue. Tumour cells have poor control over genetic processes, are insensitive to anti-growth signals and are able to produce their own nutrient supply. Finally, they are able to escape from the control of normal migration processes and apoptotic signals [Bri05, BCA08].

The words "cancer" and "tumour" are not interchangeable. In a clinical sense, cancer is when tumour cells have spread from the original site, the primary tumour, to numerous distant sites (metastasis).

The disorder seen in a tumour appears to be derived from the malfunction of the above mentioned controls, which are normally responsible for determining when and where cells will multiply or die [Wei07]. But why are these controls malfunctioning?

The reason for this can be a single alteration in a cell's genetic material, which can already result in the growth of a tumour. This alteration causes the cell to respond differently to normal growth regulators, which leads to uncontrolled proliferation of these cells [WK97]. Some tumours are caused by random acts of nature, however, some factors increase the total number of cancer cases, for example hereditary and environmental factors such as water, air and the lifestyle of a person [Wei07]. It is estimated that smoking 15 cigarettes is enough to cause one mutation [PSO+10]. [1]

Humans have 23 pairs of chromosomes, each comprising of two chromatids, joined together at the centromere. Each chromatid has alleles with different information. The combination of two alleles, one from the paternal gene and one from the maternal gene, encode one gene [ECAV07, BCA08]. If the information content of these genes is altered we call this a mutation. Mutant alleles of a gene can be passed from parent to offspring, through the germ cells (sperm and egg), if the specific mutation afflicted a gene carried in the genome of such a germ cell. Mutations affecting genomes of other cells (somatic mutations[2]) are not transferred to the offspring [Wei07]. Hereditary mutations only play a role in about 5% to 10% of all cancers; whereas most cancers are caused by somatic mutations [PV10].

As mentioned above, there are controls to prevent unrestrained growth of cells. This is ensured by specific genes. However, if these are mutated, cells become prone to developing a cancerous phenotype [WK05]. At least 200 genes that may promote or prevent

[1] This alone will not cause cancer. On average, lung cancer develops after 50 pack-years of smoking, meaning smoking a pack (20 cigarettes) per day for 50 years [PSO+10].

[2] Mutations of the DNA that occured after conception can occur in any cell except the germ cells

cancer have been identified in the human genome [GM03]. Two genes in particular that are involved in the development of tumours are oncogenes and tumour suppressor genes [Wei07]. In healthy cells, oncogenes are involved in the regulation of proliferation and differentiation [Bri05]. If one of its two alleles is mutated (meaning activated), orderly cell death (apoptosis) is suppressed and cells do not die [Wei07, BCA08]. They divide continuously irrespective of the presence or absence of growth signals [WK05]. Tumour suppressor genes (TSG) are anti-growth genes. They suppress cell proliferation if a cell is damaged or mutated. Since TSG are recessive genes, both alleles need to be mutated (meaning inactivated) to loose functionality [ECAV07, BCA08]. So if a TSG is mutated, the growth of a damaged cell is not prevented any more [WK05].

The protein p53 (a TSG) is contained in nearly all cells and makes sure that everything is in order. It arrests the advance of the cell through its cycle of growth and division, should genetic damage exist. If this functionality is lost, the cell can continue to proliferate inappropriately [Wei07]. p53 is inactivated in more than 50% of all cancers [WK05].

After one or more specific mutations have occured within a single cell, the uncontrolled division of that cell leads to the growth of an avascular tumour, meaning the tumour does not have its own blood supply [BK05]. Primary tumours like that are localised. They can reach up to 10^{10} or 10^{11} cells and are responsible for about 10% of deaths from cancer. As a reference, a cubic centimeter of tissue may contain up to 10^9 cells [Wei07].

A tumour needs oxygen and other nutrients to grow. In the early stages, a tumour does not have its own blood supply and relies on nutrients diffusing in from adjacent normal tissue. These are consumed by live, proliferating tumour cells. At first, the tumour cells receive enough nourishment from the existing vasculature, but as the tumour grows, not enough nutrients reach the cells in the centre of the tumour. The cells in the centre will stop proliferating and eventually die, creating a necrotic core, which continues to grow while the tumour increases. This decline in proliferation slows down the growth of the tumour. Figure 1 shows the structure of an avascular tumour, which consists of an outer rim of nutrient-rich, live and proliferating cells and a necrotic core. These regions can be separated by a layer of oxygen-deprived (hypoxic) cells that are quiescent - viable but not proliferating. They can recover if enough nourishment is restored [WK97, Bri05, BK05].

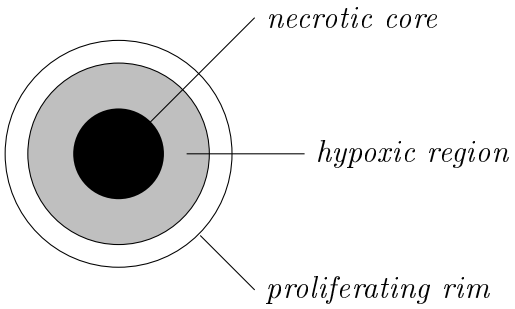


Figure 1: Tumour structure

However, an avascular tumour cannot grow indefinitely. At some point it reaches saturation, due to the limited nutrient level. Therefore, tumours enter into the vascular stage by stimulating blood vessel formation (angiogenesis) and thus being able to supply them-

selves with nutrients. These tumours can develop into malignant tumours and grow 16,000 times their original volume in a few weeks [Bri05].

When secondary tumours start to arise through metastasis, the disease becomes life threatening since they have access to nearly an endless supply of nutrients. Secondary tumours are responsible for about 90% of deaths from cancer [Bri05, Wei07, BK05].

Cancers can be grouped depending on the type of cells that are involved. Carcinomas are cancers of the epithelial cells, which form linings of the inner and outer body cavities. They account for 90% of all cancers and over 80% of cancer-related deaths in the western world. Sarcomas are cancers of the connective tissue (e.g. cancer of the bone or muscle) and only make up about 1% of all cancers. Then there are leukaemias, which are cancers of the blood cells and lymphomas, cancers of the lymphocytes (cells for the immune system) [Bri05, Wei07].

In the year 2008 cancer was one of the top ten leading causes of death, with 7.6 million people dying of the disease worldwide and 12.7 million new cases diagnosed. In Germany 45% of all deaths were related to cardiovascular diseases and 26% to cancer, making it the second most frequent cause of death [FSB+10].

Germany reported 480,000 new cancer cases in 2008, with the risk of developing cancer before the age of 75 being 23.6% in women and 32.5% in men. Of the 212,000 deaths due to cancer (Germany, 2008), 18% of the deaths in women were related to breast cancer, see figure 2. In men, lung cancer is the cause of 25% of all deaths due to cancer, see figure 3. As seen in figure 4, the three most frequent cancers in women are breast, colorectum and lung. Although breast cancer is by far the most common cancer in women, it has a low mortality, with roughly a quarter as many deaths as incidences in 2008, compared to lung or even pancreatic cancer with 98% as many deaths as incidences. In men the most frequent cancers are prostate, colorectum and lung. Together they make up nearly 50% of all cancer related deaths [FSB+10]. Data for figures 2 to 4 can be found in appendix A in tables 5 and 6.

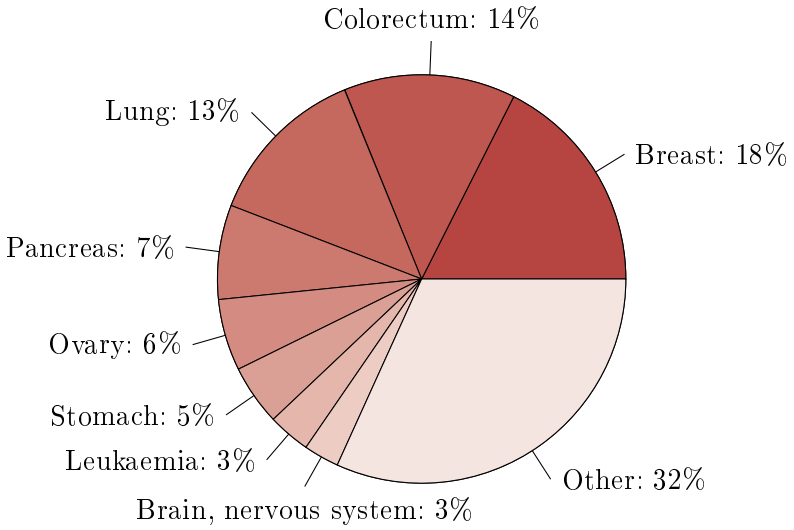


Figure 2: Percental distribution of deaths due to cancer in Germany, 2008 (female). Data from [FSB+10].

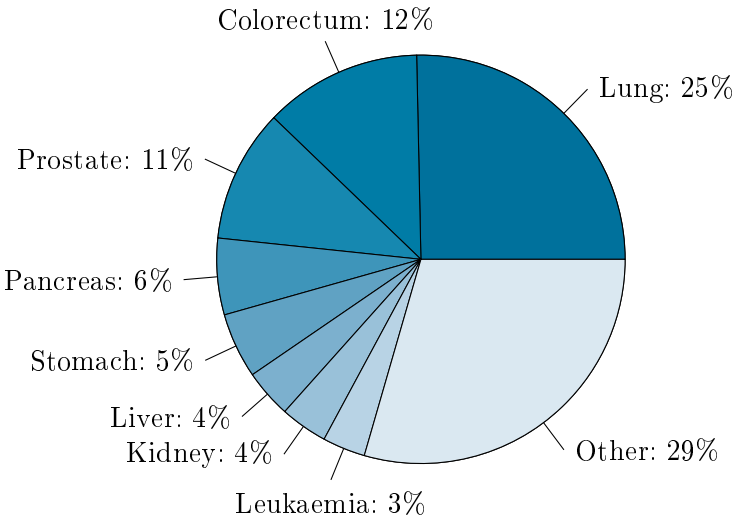


Figure 3: Percental distribution of deaths due to cancer in Germany, 2008 (male). Data from [FSB+10].

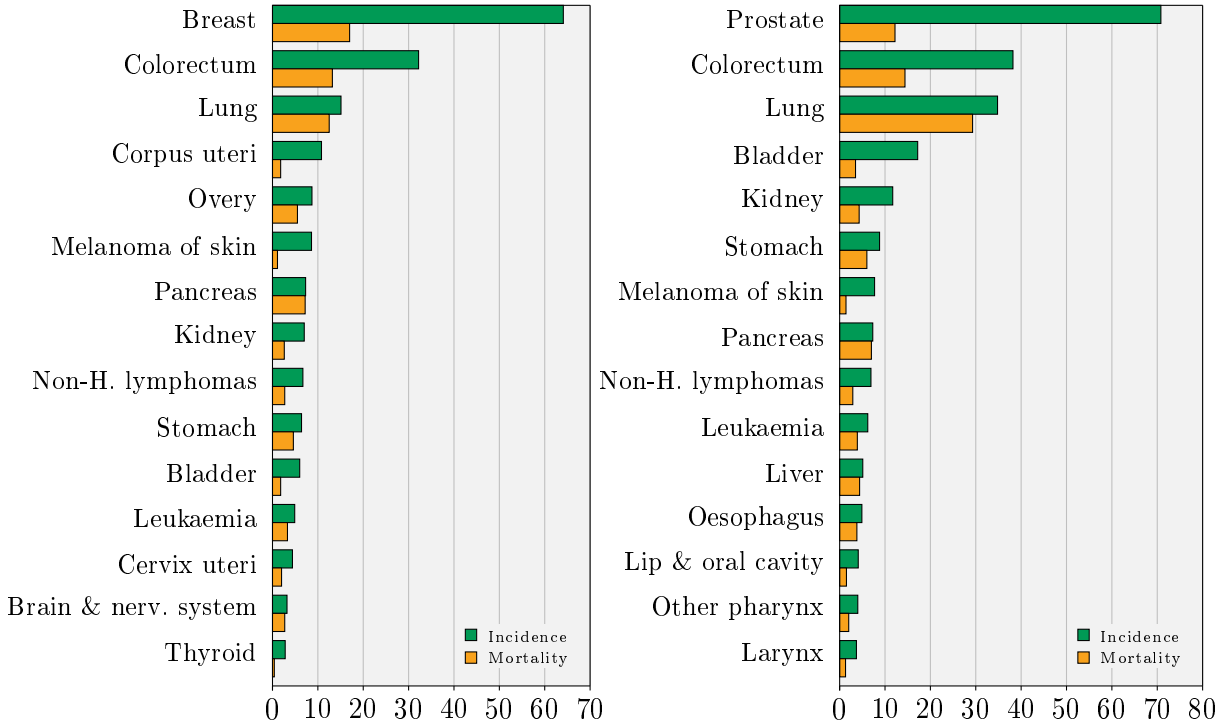


Figure 4: Incidence vs. mortality of cancer types in Germany, 2008, female (left) and male (right) (in thousands). Data from [FSB+10].

2.2. Radiation Therapy

From the above statistics one can see how vital research in the area of cancer is, especially in curing this disease.

There are three primary treatment modalities used to cure cancer, which are surgery, chemotherapy and radiation therapy. 50% to 60% of patients diagnosed with cancer will require radiation therapy, as a cure or palliation [Wan00].

Take early stage breast cancer, for example, the typical treatment being a lumpectomy (breast conserving surgery) followed by external beam radiotherapy. 30% of patients treated with lumpectomy alone develop a local recurrence within ten years of the primary treatment. Radiotherapy reduces this by about two thirds, leaving a recurrence rate of only 10%, 92% of those cases being at the site of the primary tumour [BCA08].

To understand how radiotherapy works, one needs to understand the cell cycle. Depending on the growth factors in a cell's surrounding, the cell receives signals and decides whether to enter into a quiescent state (phase $G0$) and not to multiply or to start the active cell cycle, seen in figure 5. If the cell is in the quiescent state it can enter the cell cycle at a later stage. In phase $G1$, the cell grows and goes over to phase S, where the DNA is replicated. This takes place about twelve to 15 hours after mitosis (phase M). DNA replication itself takes about six to eight hours. In phase $G2$ the cell prepares to divide, which takes about three to five hours. Finally, the cell returns to phase M (mitosis[3]) that is separated into prophase, metaphase, anaphase and telophase, altogether lasting about one hour. These time measurements depend greatly on the cell type and are only average values.

A healthy cell goes through various quality checks throughout the cycle. At checkpoint R the cell either goes into phase $G0$, remains in $G1$ or continues through the cycle. At the end of the growth phase ($G1$), the cell cannot enter phase S if the genome is damaged. A further check is in place in phase S: DNA replication is halted if the DNA is damaged. At the end of phase $G2$, the entrance into phase M is blocked if DNA replication is not complete. Cancer cells have inactivated one or more of these checks, making it possible to proliferate despite being mutated [Wei07].

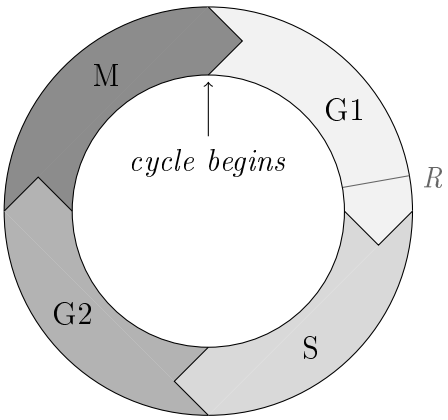


Figure 5: Cell cycle

[3]Where the mother cell is divided into two daughter cells

There are different forms of radiation used for treating cancer, one being external beam radiotherapy (EBT). Linear energy is transfered to stop the growth and death of tumour cells. This is done by emitting highly energized particles from a radioactive source that ionizes the atoms, which constitute the DNA. This in turn damages the DNA, resulting in single-strand breaks (SSB) or double-strand breaks (DSB). SSB are breaks where only one strand of the DNA double helix is broken. These breaks are repairable with time as the complementary base information on the opposite strand is still available. DSB are breaks of both strands of the DNA double helix, so the whole DNA chain is broken apart. They are the most difficult to repair. This is done by homologous recombination or non-homologous endjoining mechanisms. These are crucial DNA alterations and can lead to cell death. As mentioned above, normal healthy DNA has repair mechanisms at different checkpoints in the cell cycle, which can detect and fix most radiation damage induced by low dosages. Cancer cells, however, lack such mechanisms, thus the genetic damage is carried on or the cell dies. Hence it is common to receive treatment in fractioned doses, thereby allowing the healthy cells to repair themselves in-between radiation treatments. In 12% of all radiation-induced DSB, the mutations limit the cells' ability to survive. In this way a proportion of cells die with each small dose of radiation.

Another approach is targeted intraoperative radiotherapy (Targit). Hereby, the tumour bed is targeted with a single high dose delivered intraoperatively while the patient is anaesthetised. A geographical miss is neglected since the applicator is placed directly into the tumour bed [BCA08]. Misses in external beam radiotherapy, however, range between 24% to 88% [ECAV07].

Different factors affect the radiosensitivity of cells, meaning the sensitivity to radiation and how easily cells die from radiation. These can be the degree of oxygenation or hypoxia (low oxygenation), the phase of the cell cycle that the cell is in, the total dose and the dose per treatment, cell type and the ability to repair sublethal damage after radiation injury. Already in 1955 Thomlinson and Gray in [TG95] assumed that oxygenated cells are damaged more by irradiation than hypoxic cells, meaning they are more radiosensitive. In chapter 2.1 it was discussed that the necrotic core contains hypoxic cells. Therefore, radiation therapy will mostly only kill the outer rim of oxygenated cells, and less cells that are further in the centre of the tumour. However, once the outer rim has been eliminated, more nutrients can reach the quiescent cells and in the next few fractioned doses these cells will be more radiosensitive than before. According to Cappuccio et al. in [CHN09], oxygen is supplied via blood vessels and radioresistance depends on the underlying vasculature. Thomlinson and Gray, who are considered to have created the first mathematical model on tumour growth, were right. After the first dose, a proportion of the tumour cells are killed and therefore the oxygen consumption declines. In addition, radiation has been proven to increase blood perfusion. Thus due to less consumption and higher blood flow, oxygen levels increase. Consequently, quiescent cells can become active again and proliferate, subsequently changing the cell cycle distribution. In addition, proliferating cells in phase M have a greater sensitivity compared to cells in phase S of the cell cycle. For that reason, cells that survive the first dose of treatment will largely be cells that were in a radioresistant phase of the cell cycle during irradiation [Wan00, CHN09].

The total dose a patient receives depends on treatment time, number and dosage of daily fractions, cell type, tolerance of the tumour bed and the response of the tumour and

patient to the treatment [Wan00]. Radiation doses are nowadays measured in Gray (1 Gray = 1 Gy = 1 Joule/Kg) [CHN09]. As an example, using external beam radiotherapy, a radioresponsive tumour such as a germ cell (sperm or egg) tumour or a lymphoma would receive in total 30 to 40 Gy over the course of four to five weeks. A squamous cell carcinoma (type of skin cancer) would typically receive 65 to 70 Gy over seven to eight weeks. To cure a radioinsensitive (radioresistant) tumour, such as bone and soft tissue sarcomas, a dosage of more than 70 to 75 Gy over seven to eight weeks would be used [Wan00]. In 90% of all cases, 45 to 50 Gy in five weeks is enough to control a small accumulation of tumour cells. Larger tumours need 65 to 70 Gy in seven weeks and for advanced tumours with a large number of radioresistant hypoxic cells, a dose of 75 to 80 Gy is needed. However, it would be improbable to use radiotherapy in this case as it can go beyond the tolerance level of normal vascular connective tissue [Wan00]. Usually a combination of surgery and radiation therapy is used to cure a patient. Then radiotherapy can be used preoperatively or postoperatively, but usually the latter is used, for example to cure breast and chest tumours [CHN09]. The advantage of surgery compared to radiotherapy is that during surgery, the central core of the tumour containing radioresistant hypoxic cells can be removed. On the other hand, radiotherapy can destroy cells that are growing on the edge and surroundings of the tumour [Wan00].

Concluding, tumour cell survival is influenced by sublethal repair after radiation injury, oxygenation, total dose, dose per treatment and cell cycle phase. These factors will be analysed in the following chapters.

3. Modelling Tumour Growth

3.1. Homogeneous Tumour Growth

When modelling tumour growth, I will look at the population of cells making up the tumour. I start here by only considering one type of cells (a homogeneous population), thus assuming the tumour has no structure. In addition, I only consider tumours in their early stages, so those that have not developed their own blood supply (avascular tumours). There are many approaches to modelling the growth of a tumour. First of all, I need to decide if I am going to use a stochastic or a deterministic model. Since I am looking at a large population of cells, I choose to use a deterministic model, for example in form of ordinary or partial differential equations. Furthermore, I need to decide on a time setting. As I am not looking at single generations but at a continously growing population, I will only consider continuous time models (not discrete time models). A list of variables used in this thesis can be found in appendix B. In addition, all figures in this thesis were plotted using MATLAB (Mathworks), the codes can be found in appendix C.

3.1.1. Exponential Growth Equation

I start with a simple growth model, a first-order linear ordinary differential equation. Let $N(t)$ be the number of tumour cells at time t and r be the net proliferation rate, then the model reads

$$\begin{aligned} \frac{dN}{dt} &= rN, \\ N(0) &= N_0. \end{aligned} \tag{3.1}$$

The right-hand side of the equation describes how the number of tumour cells changes over time [Pre03]. N_0 represents the initial number of tumour cells, meaning from the start of the observation. The solution of equation (3.1) is

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

To analyse this model I introduce a definition.

Definition 3.1. *Let $f : \mathbb{R}^n \to \mathbb{R}^n$, $f \in C^0$, $(f, \mathbb{R}^n)$ is a time-continuous dynamical system via $x_0 \in \mathbb{R}^n$. $x(t)$ is the* solution *of*

$$x(0) = x_0, \ \frac{dx}{dt} = f(x).$$

$\overline{x}$ is called a stationary point *if $f(\overline{x}) = 0$. $\overline{x}$ is* stable *if $\forall \epsilon > 0$ there $\exists \delta > 0$ such that $\forall x_0$ with $|\overline{x} - x_0| < \delta$*

$$|x(t) - \overline{x}| < \epsilon$$

holds $\forall t$. $\overline{x}$ is locally asymptotically stable *if $\exists\ U \subseteq \mathbb{R}^n$, U open, $\overline{x} \in U$ $\forall x_0 \in U$ with*

$$\lim_{t \to \infty} x(t) = \overline{x}.$$

$\overline{x}$ is called unstable *otherwise. [Mül12]*

Stability guarantees that the solution will be near the stationary point $\overline{x}$, if it starts close enough to it. Asymptotic stability guarantees that the solution starting sufficiently close to $\overline{x}$ will really tend to it. The following theorem helps to analyse the stability of a stationary point.

Theorem 3.2. *Let $\frac{dx}{dt} = f(x)$, $x \in \mathbb{R}$, $f(\overline{x}) = 0$, $f \in C^2$, then $\overline{x}$ is locally asymptotically stable if $f'(x) < 0$ and unstable for $f'(x) > 0$. [Mül12]*

Proof. Refer to [Mül12]. □

In accordance with definition 3.1, equation (3.2) has one stationary point, namely

$$\overline{N} = 0.$$

Using theorem 3.2, the stability of the stationary point depends on the sign of the proliferation rate r, since $f'(\overline{N}) = r$. If $r > 0$ the stationary point is unstable and the population tends to infinity. On the other hand, if $r < 0$, $\overline{N} = 0$ is a stable stationary point and the population size will tend to zero. If $r = 0$ the population size does not change and stays constant. When considering tumour cells, one only looks at the case where $r > 0$ as this is the only realistic case when modelling tumour growth without therapy.

3.1.2. Logistic Growth Equation

The exponential equation assumes no constraints on cell growth so the population can grow without limitation. This is accurate in the beginning, but after some time has passed, the cells start to compete for space and nutrients. As these are not available endlessly, cell growth in fact slows down and eventually reaches a limit. Therefore we introduce a growth limited model, the logistic equation [Bri05].

$$\begin{aligned} \frac{dN}{dt} &= rN\left(1 - \frac{N}{K}\right) \text{ with } r, K > 0, \\ N(0) &= N_0 \end{aligned} \tag{3.3}$$

Again the right-hand side of equation (3.3) describes the rate of change of the population size over time. K is the carrying capacity of the tumour bed, meaning the maximum population size that can be reached due to spacial constraints and nutrient supply. Therefore the term in brackets, multiplied with the exponential growth model, limits cell growth. To solve the logistic equation, I introduce $v(t) := \frac{1}{N(t)}$ with $v(0) = v_0 = \frac{1}{N_0}$. Then

$$\begin{aligned} \frac{dv}{dt} &= -\frac{1}{N^2}N' \\ &= -\frac{1}{N^2}Nr\left(1 - \frac{N}{K}\right) \\ &= -\frac{1}{N}r + \frac{r}{K} \\ &= -rv + \frac{r}{K} \end{aligned}$$

Using variation of constants, it follows that

$$\begin{aligned} v(t) &= v_0 e^{-rt} + \frac{r}{K} \int_0^t e^{-rt+rs} \, \mathrm{d}s \\ &= v_0 e^{-rt} + \frac{r}{K} \left[\frac{1}{r} e^{-rt+rs} \right]_0^t \\ &= v_0 e^{-rt} + \frac{1}{K} \left(1 - e^{-rt}\right). \end{aligned}$$

Inserting $v(t) = \frac{1}{N(t)}$ yields the solution for equation (3.3)

$$\begin{aligned} N(t) &= \left(\frac{1}{N_0} e^{-rt} + \frac{1}{K} \left(1 - e^{-rt}\right) \right)^{-1} \\ &= \frac{N_0 K}{N_0 + e^{-rt}(K - N_0)}. \end{aligned} \tag{3.4}$$

The stationary points can be calculated as above. They are

$$\overline{N}_1 = 0 \text{ and } \overline{N}_2 = K.$$

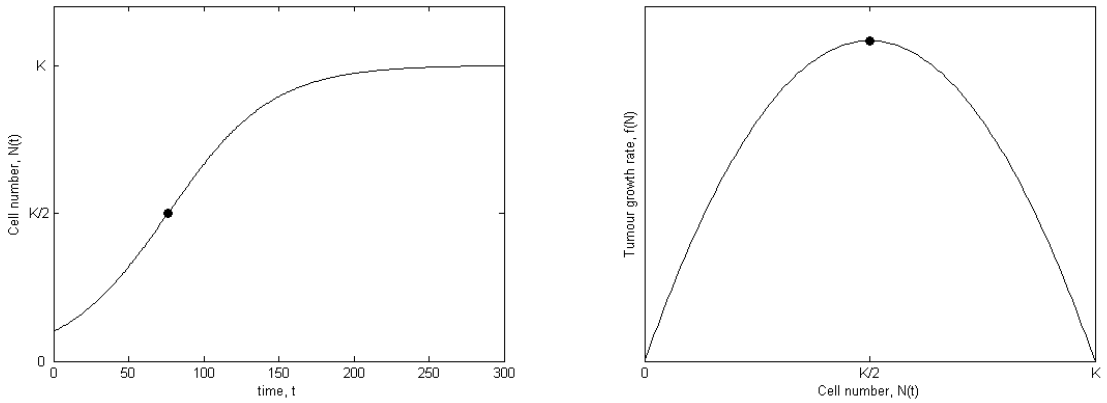
The derivative of equation (3.3) is

$$f'(\overline{N}) = r \left(1 - 2\frac{\overline{N}}{K} \right).$$

As $f'(\overline{N}_1) = r > 0$ (I am only interested in cases where $r > 0$), $\overline{N}_1 = 0$ is an unstable stationary point. In turn the stationary point $\overline{N}_2 = K$ is asymptotically stable because $f'(\overline{N}_2) = -r < 0$. Concluding, the population will tend to the carrying capacity over time.

At this point one can differentiate between the initial number of tumour cells N_0 being larger or smaller than K. If $N_0 > K$, $\frac{dN}{dt} < 0$ and the population decreases until it reaches the capacity. If the starting value lies between 0 and K, the population will grow and converge to K from below.

A problem with this model is that it is not very flexible when fitting data, since the steepest part of equation (3.4) is fixed at half the capacity $\left(\frac{K}{2}\right)$. This is the maximum of equation (3.3), in particular the maximum growth rate. In reality this is not always the case. Figure 6a shows the solution of the logistic equation (equation (3.4)) and figure 6b shows the right-hand side of the ODE function (equation (3.3)). From the figure on the left one can see that the population tends to the capacity when it starts in $(0, K]$. The dot indicates the maximum growth rate.



(a) Solution to the logistic growth equation, equation (3.4).

(b) Right hand side of the logistic ODE, equation (3.3).

Figure 6: Logistic growth equation, the dot marks the inflection point, the maximum growth rate.

3.1.3. Generalised Logistic Growth Equation

To avoid the above mentioned problem one can adjust the logistic growth equation to include a parameter that varies where the equation's maximum lies. This adjusted model is called the generalised logistic equation [Pre03]. Equation (3.5) is similar to the logistic equation but with an additional parameter α. Depending on the value of α the solution of this model can reach saturation faster ($\alpha < 1$) or slower ($\alpha > 1$). For $\alpha = 1$ the model is identical to the previous logistic equation (equation (3.3)).

$$\begin{aligned} \frac{dN}{dt} &= \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) \text{ with } \alpha > 0, \\ N(0) &= N_0 \end{aligned} \tag{3.5}$$

To solve equation (3.5) I use the same substitution as for the logistic equation, $v(t) := \frac{1}{N(t)}$ with $v(0) = v_0 = \frac{1}{N_0}$. Then

$$\begin{aligned} \frac{dv}{dt} &= -\frac{1}{N^2} N' \\ &= -\frac{1}{N^2} \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) \\ &= -\frac{1}{N} \frac{r}{\alpha} + \frac{r}{\alpha} \frac{N^{\alpha-1}}{K^{\alpha}} \\ &= -\frac{r}{\alpha} v + \frac{r}{\alpha K^{\alpha}} v^{1-\alpha} \end{aligned}$$

By using the substitution $z := v^\alpha$ with $z_0 = v_0^\alpha$ I can solve this Bernoulli differential equation.

$$\begin{aligned}\frac{dz}{dt} &= \alpha v^{\alpha-1} v' \\ &= \alpha v^{\alpha-1}\left(-\frac{r}{\alpha}v + \frac{r}{\alpha K^\alpha}v^{1-\alpha}\right) \\ &= -rv^\alpha + \frac{r}{K^\alpha} \\ &= -rz + \frac{r}{K^\alpha}\end{aligned}$$

This is just an inhomogeneous linear differential equation, which I have already solved for the logistic growth equation. The solution reads

$$z(t) = z_0 e^{-rt} + \frac{1}{K^\alpha}(1 - e^{-rt}).$$

Inserting the substitution for z results in

$$v(t) = \left(v_0^\alpha e^{-rt} + \frac{1}{K^\alpha}(1 - e^{-rt})\right)^{\frac{1}{\alpha}}.$$

Thereby using $N(t) = \frac{1}{v(t)}$, I get the solution for equation (3.5)

$$\begin{aligned}N(t) &= \frac{1}{\left(\frac{1}{N_0^\alpha}e^{-rt} + \frac{1}{K^\alpha}(1 - e^{-rt})\right)^{\frac{1}{\alpha}}} \\ &= \left(\frac{1}{\frac{1}{N_0^\alpha}e^{-rt} + \frac{1}{K^\alpha}(1 - e^{-rt})}\right)^{\frac{1}{\alpha}} \\ &= \left(\frac{N_0^\alpha K^\alpha}{K^\alpha e^{-rt} + N_0^\alpha(1 - e^{-rt})}\right)^{\frac{1}{\alpha}} \\ &= \frac{N_0 K}{(N_0^\alpha + e^{-rt}(K^\alpha - N_0^\alpha))^{\frac{1}{\alpha}}}.\end{aligned} \tag{3.6}$$

The stationary points are the same as for the logistic equation, $\overline{N}_1 = 0$ and $\overline{N}_2 = K$. In addition, the stability properties from the logistic equation are applicable to the two stationary points found here, since $f'(0) = \frac{r}{\alpha} > 0$ and $f'(K) = -r < 0$.

The inflection point of the solution, however, is not fixed at $\frac{K}{2}$ anymore, but varies depending on the value of α. This allows for much better data fitting and variability. By setting

$$\frac{df(N)}{dN} \stackrel{!}{=} 0$$

the inflection point can be calculated to

$$\Leftrightarrow N_{infl} = \frac{K}{(\alpha+1)^{\frac{1}{\alpha}}}.$$

Figure 7 shows three examples of the generalised logistic equation. The solid line is the simple logistic equation with $\alpha = 1$. Its maximum lies at $\frac{K}{2}$. The dashed line depicts the generalised logistic equation using $\alpha = 0.5$, its maximum lying at $\frac{4}{9}K$. Using $\alpha = 2$ results in the dotted line and a maximum larger than $\frac{K}{2}$.

Figure 8 compares all three models explained in this chapter. The green line uses the generalised logistic equation with $\alpha = 0.5$. As one can see, saturation is reached faster compared to the normal logistic equation using $\alpha = 1$ (blue line). On the other hand, using an $\alpha > 1$ (red line) results in saturation being reached at a later point in time. The exponential equation (black line) follows a similar growth pattern in the beginning, but then tends to infinity, whereas the other models converge to the carrying capacity.

3.1.4. Other Growth Models

There are many more approaches to modelling tumour growth. So far I have only looked at deterministic models, but stochastic models exist as well. In [WK05] for example, the probability of a mutation occuring during cell division is included in the modelling process.

Another deterministic approach could use partial differential equations as for example in works by Franks et al. [FBK+03, FBM+03], where the authors include the nutrient supply in their model. The tumour is described as a viscous fluid, using reaction-diffusion equations to model the fact that nutrients diffuse in from the surrounding material. This idea was based on the earlier work by Burton from 1966 [Bur66] and Greenspan from 1972 [Gre72].

Instead of just implementing ordinary differential equations, mathematicians have also come up with models using delay differential equations, as for example in [VR03]. The idea there is to incorporate the effect of the cell cycle on the tumour's growth.

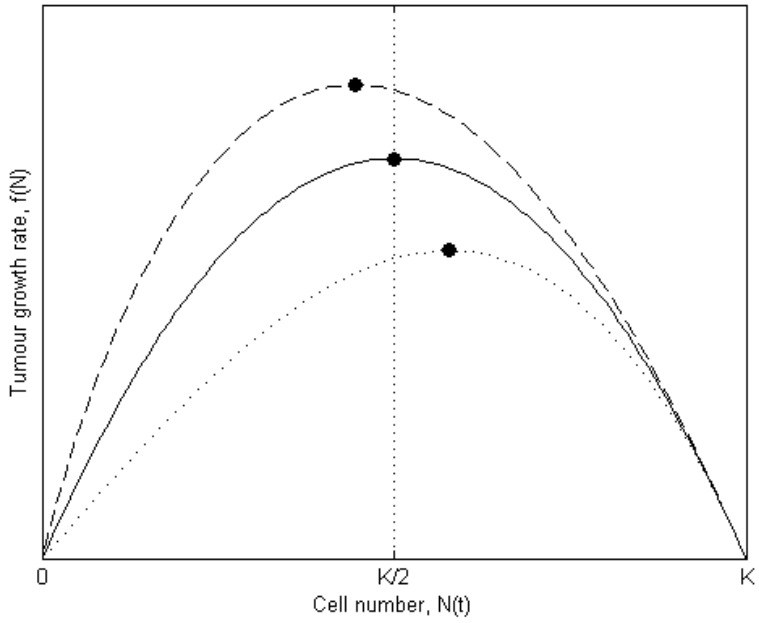


Figure 7: Comparison of different generalised logistic growth rates using equation (3.5), solid line for $\alpha = 1$, dashed line for $\alpha = 0.5$ and dotted line for $\alpha = 2$.

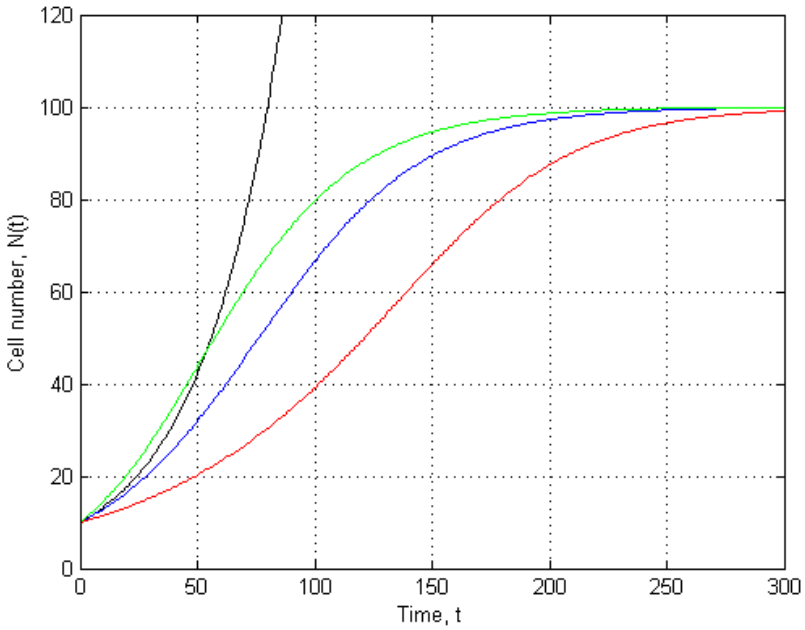


Figure 8: Comparison of different tumour growth models. Black line for the exponential equation (equation (3.2)), blue line for the logistic equation (equation (3.4)), green line for the generalised logistic equation with $\alpha = 0.5$ and red line for the generalised logistic equation with $\alpha = 2$ (equation (3.6)). Parameter values are $r = 0.0289$, $N_0 = 10$ and $K = 100$.

3.1.5. Model versus Data

Ehrlich Ascites Tumour Schuster and Schuster [SS94] experimented with the Ehrlich ascites tumour in a mouse. They measured the number of cells that grew over a time period of 17 days after having transplanted $4 \cdot 10^7$ cells into female mice on day 0. I used the generalised logistic growth equation (equation (3.6)) to model this experiment. The parameter values were taken from [KT85]. From figure 9 one can see that the equation manages to model the data well until about day eleven, when the model tends to the capacity and the data points decrease in value. This may have different reasons, for example the capacity in the model equation was set too high, the data could be incorrect or the cells started to die due to the experimental settings.

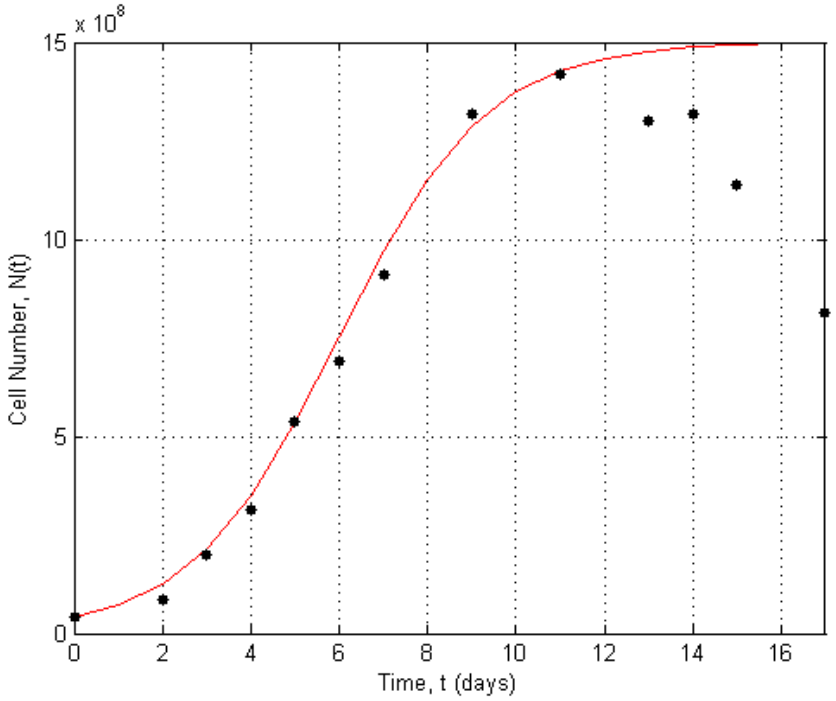


Figure 9: Modelling the growth of the Ehrlich ascites tumour in mice. Solid red line is the solution of the logistic equation with $\alpha = 1$ (equation (3.6)) and the black points are the data points. Further parameter values are $r = 0.6$, $N_0 = 4 \cdot 10^7$ and $K = 150 \cdot 10^7$. Data from [SS94].

As a result of the last data points not fitting the model, I calculated the weighted sum of squares for the parameters used in figure 9 according to equation (3.7).

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

Model_i represents the i-th point calculated in the model equation and Data_i is the i-th data point. The error calculated for the above mentioned parameters is 0.4201. Adjusting the carrying capacity to $K = 140 \cdot 10^7$, as seen in figure 10, results in a smaller error of

0.3414. This is mainly due to the fact that the last few data points stray so far away from the carrying capacity.

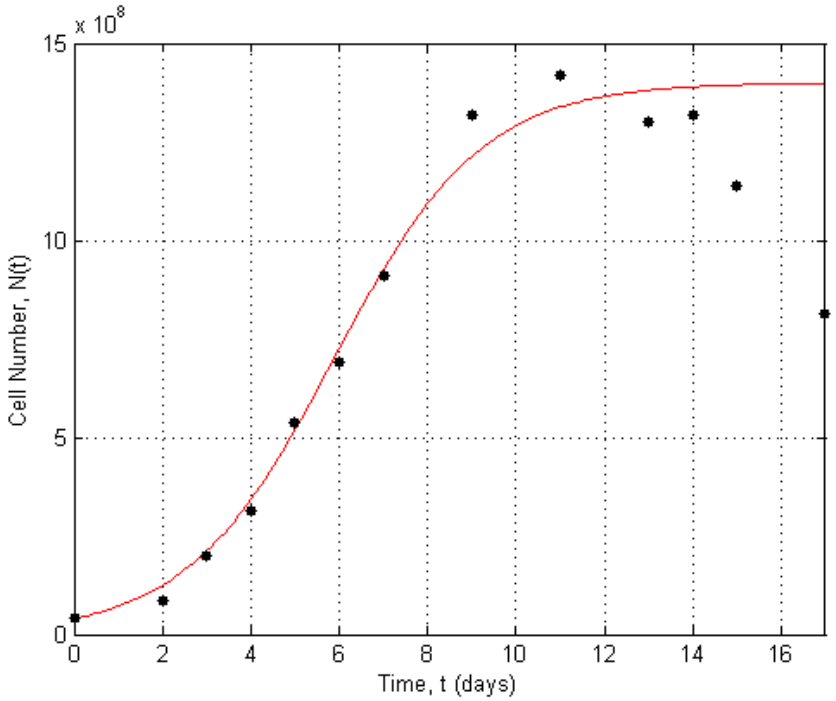


Figure 10: Modelling the growth of the Ehrlich ascites tumour in mice. Solid red line is the solution of the logistic equation with $\alpha = 1$ (equation (3.6)) and the black points are the data points. Further parameter values are $r = 0.6$, $N_0 = 4 \cdot 10^7$ and $K = 140 \cdot 10^7$. Data from [SS94].

Human Ductal Breast Epithelial Tumour Cells The growth of T47D cells (human breast cancer cells) was measured in vitro by the Institute of Radiation Biology, Helmholtz-Zentrum München [Ana11] using the xCELLigence System [MC09]. In this experiment, 10,000 cells were placed on a 96-well plate (at $t = 0$) and counted every 15 minutes for nearly 142 hours with a hemocytometer. The system counts the cells and returns a cell index value. This value is a measure for the amount of cells present. It is zero if no cells exist and grows or declines depending on if the cells multiply or die. Figure 11 shows how the data points (black line) are modelled by the generalised logistic growth equation (red line). The first 48 hours show a discrepancy between the data and the model, however this can be due to the way the experiment is carried out and how the cells are measured. I am interested in the growth of the tumour from day two onwards. Parameter values for the initial number of cells N_0 and the net proliferation rate r were chosen according to the given data. The parameter r can be calculated based on the doubling time of the tumour in the experiment. In accordance to [MC09] a doubling time of 19.8 hours was chosen, resulting in a proliferation rate of $r = \frac{\ln 2}{19.8} = 0.035$. Using algorithm 1 in appendix C, I calculated α and K that resulted in the smallest error. Figure 11 uses $\alpha = 0.017$ and $K = 4.978$. The value of α depends on the cell line and allows for better data fitting,

especially in this case as the carrying capacity is reached much faster than the normal logistic equation could model. The error was calculated using equation (3.7) and with the above mentioned parameters sums up to 294.5. However, since I am interested in tumour growth from day two onwards, I calculate the error from this point forth, resulting in an adjusted error of 0.0396. This is the smallest error I could find using algorithm 1, which calculated K and α to three decimal places.

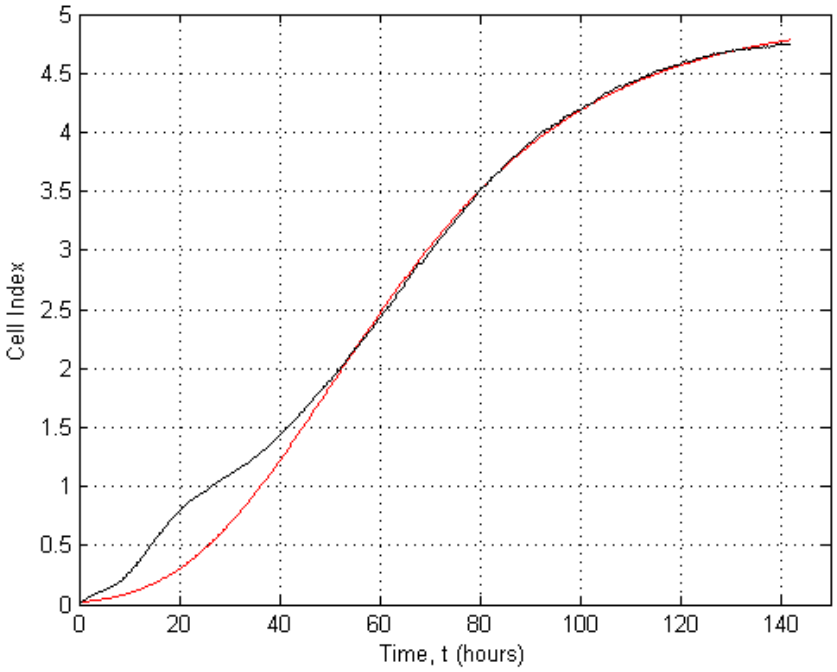


Figure 11: Modelling the growth of T47D breast cancer cells. Red line is the generalised logistic growth model (equation (3.6)) and the black curve are the data points. Parameter values are $r = 0.035$, $N_0 = 0.02$, $\alpha = 0.017$ and $K = 4.978$. Data from [Ana11].

Figures 12 and 13 show scatter plots of the errors calculated at the corresponding time points. From figure 12 one can see that the initial 40 hours show a much larger error compared to the later time points, as we have already seen in the comparison between the data and model in the previous figure. Figure 13 shows the same errors but zoomed in on the y-axis. Here one can see that after the initial 48 hours have passed, the model manages to depict the data very well, resulting in only a small error throughout.

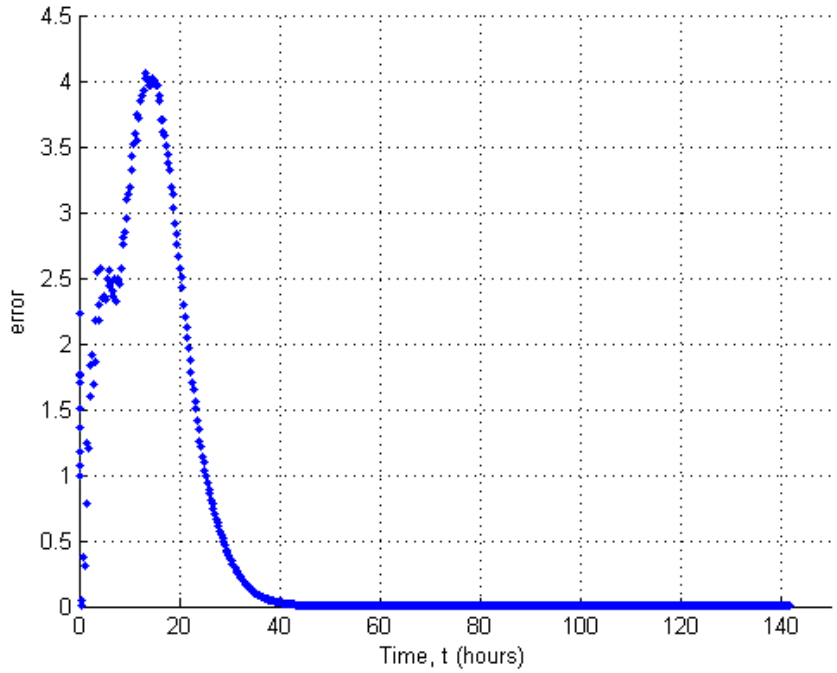


Figure 12: Error calculated using equation (3.7) and the values $r = 0.035$, $N_0 = 0.02$, $\alpha = 0.017$ and $K = 4.978$.

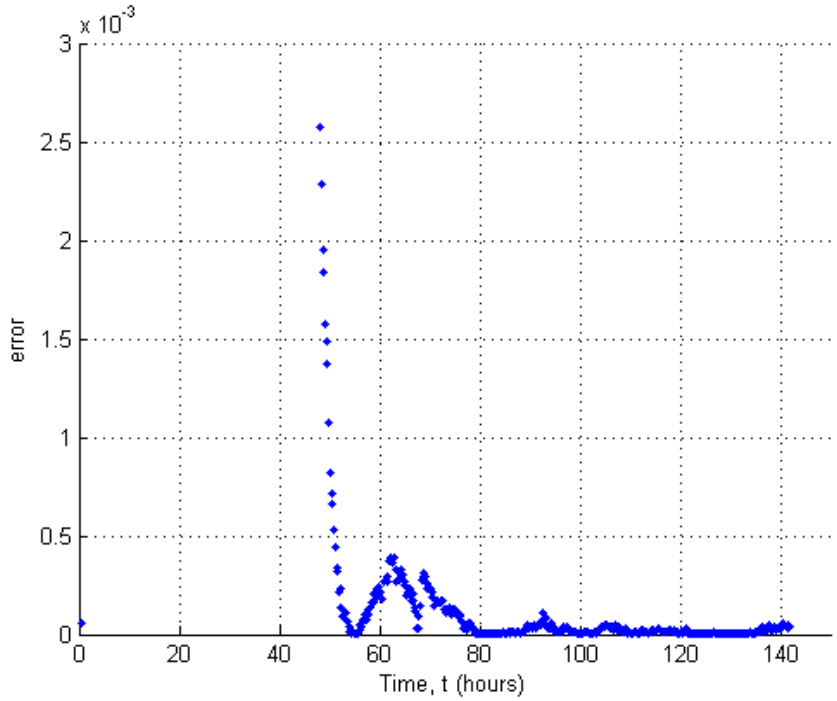


Figure 13: Error calculated using equation (3.7) and the values $r = 0.035$, $N_0 = 0.02$, $\alpha = 0.017$ and $K = 4.978$, y-axis from 0 to 0.003.

Human Breast Carcinoma Cells The second experiment done by the Institute of Radiation Biology, Helmholtz-Zentrum München [Ana11] used the same system and conditions as the previous experiment. This time a different cell line was chosen, the MDA361 cell line. Again the parameters N_0 and r were set according to the data given, with $N_0 = 0.01$ and $r = \frac{\ln 2}{7} = 0.099$. In addition K was set to 4.18 and α to 1.3. The results are shown in figure 14.

As one can see, the data is represented well by the model, however I used algorithm 2 in appendix C to try and find an even better fit. The programme found the best values (calculated to three decimal places) for α and K. These values were used in figure 15. Changing the parameter values results in an improved error of 3824.8 from the original error of 3841.5. If I look at the data points from $t = 48$ hours onwards, as with the previous experiment, I get an adjusted error of 0.2705 when using the better parameter values, compared to 0.3376 when using the values as in figure 14. This is an improvement of 20%.

Figures 16 and 17 show scatter plots of the errors calculated at the corresponding time points. From figure 16 one can see once more that the initial 40 hours show a much larger error compared to the later time points. Figure 17 shows the same errors but zoomed in on the y-axis. Here one can see that after the initial 48 hours have passed, the model manages to depict the data well, resulting in a small error.

Summarizing, I can say that the models introduced in this chapter succeed in modelling actual data. Using the generalised logistic growth equation allows me to shift the curve to the left or right depending on how fast the cells reach the capacity. This gives more flexibility and allows me to use the same equation with appropriate parameter values for different cell types.

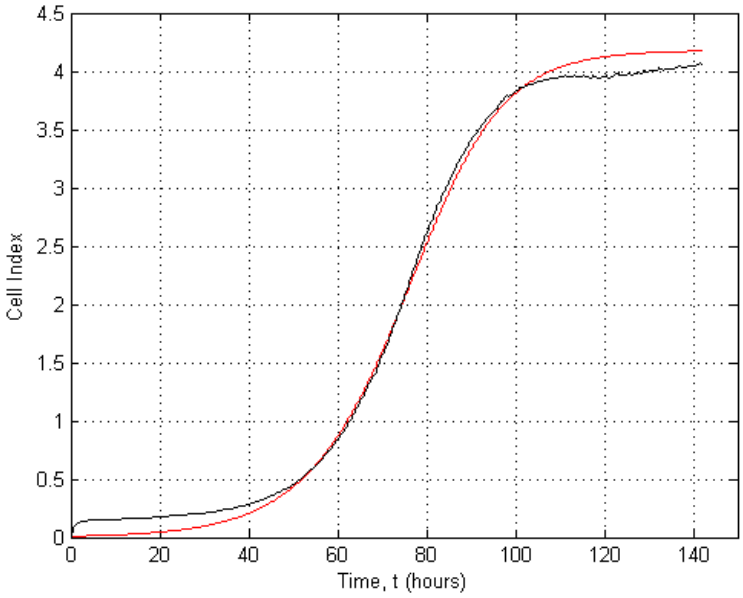


Figure 14: Modelling the growth of MDA361 cells. Red line is the generalised logistic growth model (equation (3.6)) and the black curve are the data points. Parameter values are $r = 0.099$, $N_0 = 0.01$, $\alpha = 1.3$ and $K = 4.18$. Data from [Ana11].

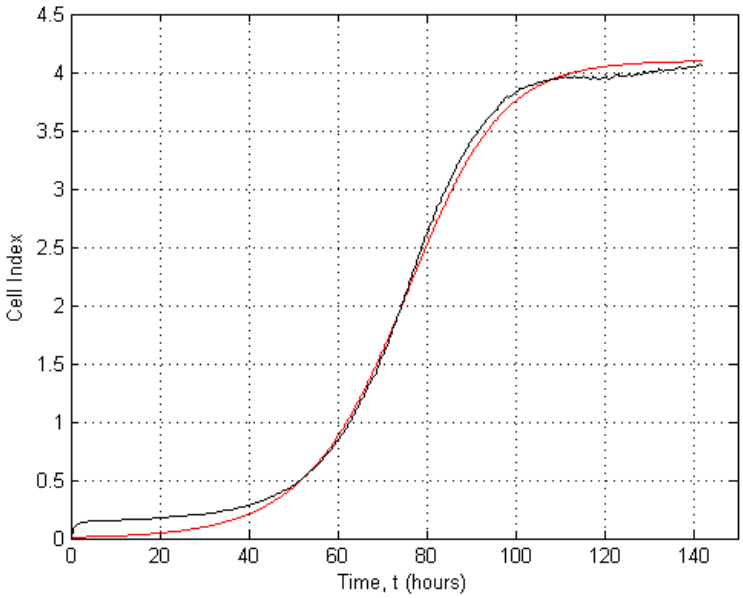


Figure 15: Modelling the growth of MDA361 cells. Red line is the generalised logistic growth model (equation (3.6)) and the black curve are the data points. Parameter values are $r = 0.099$, $N_0 = 0.01$, $\alpha = 1.296$ and $K = 4.101$. Data from [Ana11].

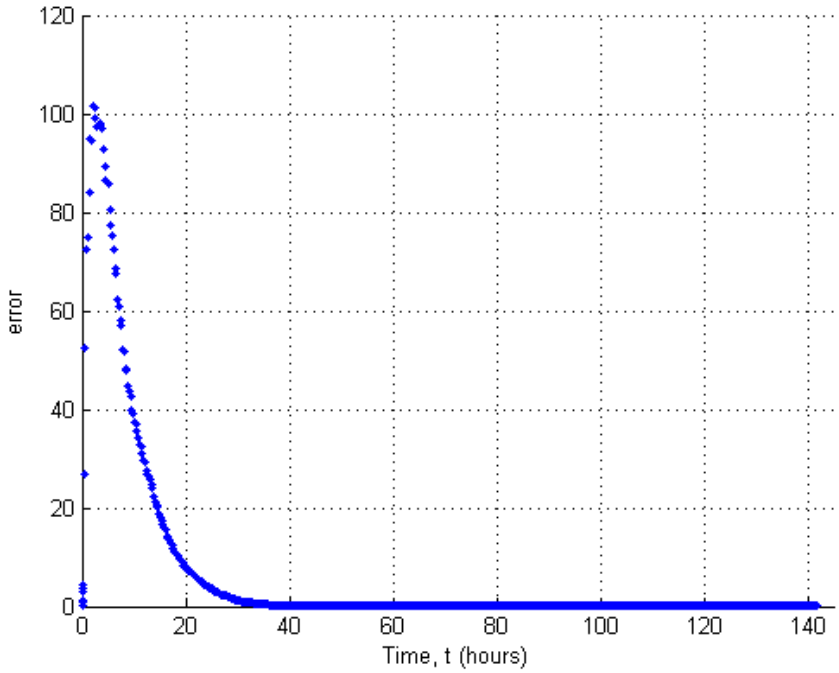


Figure 16: Error calculated using equation (3.7) and the values $r = 0.099$, $N_0 = 0.01$, $\alpha = 1.296$ and $K = 4.101$.

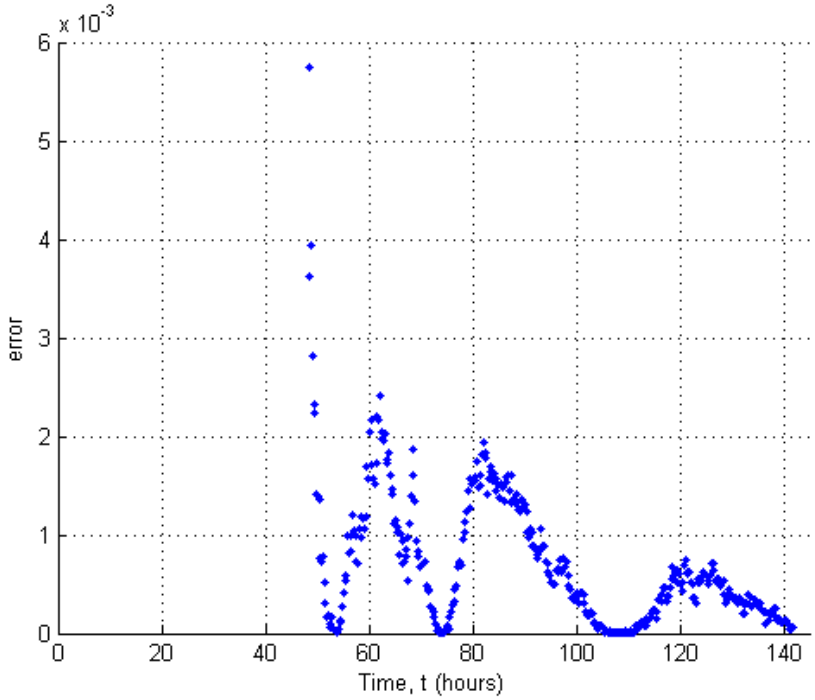


Figure 17: Error calculated using equation (3.7) and the values $r = 0.099$, $N_0 = 0.01$, $\alpha = 1.296$ and $K = 4.101$, y-axis from 0 to 0.006.

3.2. Heterogeneous Tumour Growth

In chapter 3.1 I introduced models for a homogeneous cell population but as described in chapter 2.1, tumours do not just consist of one type of cell. In the early stage, a tumour consists of proliferating cells but later on, as it becomes larger, fewer nutrients can reach the cells in the centre of the tumour and these cells stop proliferating. They become quiescent. While the tumour continues to grow, the cells in the centre are deprived of nutrients for too long so that they die, forming a necrotic core (see figure 1 on page 3). Therefore, a well-developed tumour consists of two or even three types of cells that behave differently. Necrotic tumour cells will not proliferate anymore and are degraded; quiescent cells are not dead and can proliferate again in the future should the nutrient level increase and finally, proliferating cells continue to multiply as they have enough nutrients to consume.

The following compartment model [Pre03] can be used to specify these three types of tumour cells with different rates describing how the cells switch from one compartment to the other.

Let $P(t)$ be the number of proliferating tumour cells at time t, $Q(t)$ the number of quiescent cells and $D(t)$ the number of dead tumour cells. Then the total number of tumour cells is

$$N(t) = P(t) + Q(t) + D(t).$$

The model equations read

$$\frac{dP}{dt} = (k_{PP} - k_{PQ} - k_{PD})P + k_{QP}Q, \tag{3.8}$$

$$\frac{dQ}{dt} = k_{PQ}P - (k_{QP} + k_{QD})Q, \tag{3.9}$$

$$\frac{dD}{dt} = k_{PD}P + k_{QD}Q - \lambda D \tag{3.10}$$

with initial values

$$P(0) = P_0,\ Q(0) = Q_0 \text{ and } D(0) = D_0.$$

The rates k_{ij} depend on the local nutrient level and describe the rate at which cells go from state i to state j.

Equations (3.8) to (3.10) respectively describe the change over time of the number of proliferating tumour cells, quiescent and dead cells. k_{PP} is the proliferation rate, k_{PQ} is the rate at which proliferating cells become quiescent and k_{PD} is the rate at which proliferating cells die due to natural causes. k_{QP} is the rate at which quiescent cells become viable again. k_{QD} used in equation (3.9) describes the rate at which quiescent cells become necrotic. λ is the degradation rate. Figure 18 illustrates the model equations.

This model can be extended to include more sophisticated proliferation rates as seen in chapter 3.1, for example

$$k_{PP} = r\left(1 - \frac{N}{K}\right)$$

or even

$$k_{PP} = \frac{r}{\alpha}\left(1 - \left(\frac{N}{K}\right)^{\alpha}\right).$$

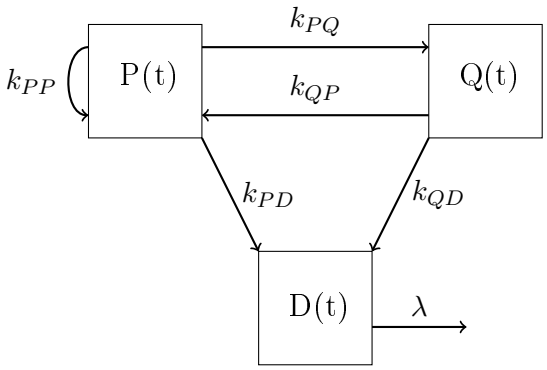


Figure 18: Model of equations (3.8) to (3.10).

I want to analyse the heterogeneous growth model and simplify it to two compartments: proliferating cells and quiescent cells. Then the model equations read

$$\frac{dP}{dt} = \frac{r}{\alpha}P\left(1-\left(\frac{P+Q}{K}\right)^{\alpha}\right) - k_{PQ}P + k_{QP}Q \qquad =: f(P,Q) \tag{3.11}$$

$$\frac{dQ}{dt} = k_{PQ}P - k_{QP}Q \qquad =: g(P,Q) \tag{3.12}$$

with initial values

$$P(0) = P_0 \text{ and } Q(0) = Q_0.$$

Thus the whole tumour is made up of proliferating and quiescent cells, meaning $N(t) = P(t) + Q(t)$. Both equations (3.11) and (3.12) are zero if $(\overline{P}_1, \overline{Q}_1) = (0,0)$. The second stationary point can be calculated by setting equation (3.12) to zero.

$$\Rightarrow \overline{Q}_2 = \frac{k_{PQ}}{k_{QP}}P$$

Inserting the result for Q into equation (3.11) results in

$$\overline{P}_2 = K\frac{k_{QP}}{k_{QP}+k_{PQ}}$$

$$\Rightarrow \overline{Q}_2 = K\frac{k_{PQ}}{k_{QP}+k_{PQ}}.$$

Adding both points together results in the same nontrivial stationary point as in the homogeneous generalised logistic growth model

$$\overline{P}_2 + \overline{Q}_2 = K = \overline{N}_2.$$

Of course this is also true for the trivial stationary point. To find the stability of the two stationary points I calculate the Jacobian matrix of the coupled system.

$$J(P,Q) = \begin{pmatrix} \frac{\partial f}{\partial P} & \frac{\partial f}{\partial Q} \\ \frac{\partial g}{\partial P} & \frac{\partial g}{\partial Q} \end{pmatrix}$$

$$= \begin{pmatrix} \frac{r}{\alpha}\left(1-\left(\frac{(P+Q)}{K}\right)^{\alpha}\right) - \frac{r}{K^{\alpha}}P(P+Q)^{\alpha-1} - k_{PQ} & k_{QP} - \frac{r}{K^{\alpha}}P(P+Q)^{\alpha-1} \\ k_{PQ} & -k_{QP} \end{pmatrix}$$

Inserting the trivial stationary point yields

$$J(0,0) = \begin{pmatrix} \frac{r}{\alpha} - k_{PQ} & k_{QP} \\ k_{PQ} & -k_{QP} \end{pmatrix} \tag{3.13}$$

The stationary point $(0,0)$ is stable if both eigenvalues of the Jacobian matrix in equation (3.13) are smaller than zero. The eigenvalues are calculated to

$$\lambda_{1/2} = -\frac{1}{2}(-\frac{r}{\alpha} + k_{PQ} + k_{QP}) \pm \sqrt{\frac{1}{4}(-\frac{r}{\alpha} + k_{PQ} + k_{QP})^2 + \frac{r}{\alpha}k_{QP}}$$

Both eigenvalues are larger than zero since $\frac{r}{\alpha}k_{QP} > 0$, thus the trivial stationary point $(0,0)$ is unstable. This corresponds to the results from chapter 3.1, where the tumour cells grew until they reached their capacity, the nontrivial stationary point. I insert the second stationary point into the Jacobion matrix to analyse its stability.

$$J(\overline{P}_2, \overline{Q}_2) = \begin{pmatrix} -k_{PQ} - r\frac{k_{QP}}{k_{QP}+k_{PQ}} & k_{QP} - r\frac{k_{QP}}{k_{QP}+k_{PQ}} \\ k_{PQ} & -k_{QP} \end{pmatrix} \tag{3.14}$$

The eigenvalues of the Jacobian matrix are

$$\lambda_{1/2} = -\frac{1}{2}\Gamma \pm \sqrt{\frac{1}{4}\Gamma^2 - r\frac{k_{QP}(k_{QP}+k_{PQ})}{k_{QP}+k_{PQ}}}$$

with

$$\Gamma = (k_{PQ} + k_{QP} + r\frac{k_{QP}}{k_{QP}+k_{PQ}}).$$

Both eigenvalues are smaller than zero, meaning the nontrivial stationary point is stable, if $0 < rk_{QP}$, which is always the case. Thus the tumour cells will tend to $(\overline{P}_2, \overline{Q}_2)$ over time.

Since they are not stiff differential equations, I used the explicit euler method to solve the coupled system of equations in Matlab to be able to plot simulations of the model. Starting with the initial value (P_0, Q_0) each next value can be calculated by setting

$$\begin{pmatrix} P_{i+1} \\ Q_{i+1} \end{pmatrix} = \begin{pmatrix} P_i \\ Q_i \end{pmatrix} + h \cdot \begin{pmatrix} \frac{r}{\alpha}P_i\left(1 - \left(\frac{P_i+Q_i}{K}\right)\right)^{\frac{1}{\alpha}} - k_{PQ}P_i + k_{QP}Q_i \\ k_{PQ}P_i - k_{QP}Q_i \end{pmatrix} \tag{3.15}$$

with h being the step size [QSS00].

Figure 19 shows the complete tumour growth in black, the proliferating cells in red and the quiescent cells in green. Since I chose a higher rate for k_{PQ} than for k_{QP} the tumour will be predominantly made up of quiescent cells after a certain period of time. This corresponds to findings by Thomlinson and Gray in [TG95]. Together both type of cells reach their capacity of 100 cells, since $(\overline{P}_2, \overline{Q}_2) = (17, 83)$. Changing the rates to make k_{QP} larger than k_{PQ} results in figure 20. Here the tumour (black line) is predominantly made up of proliferating tumour cells (red line). However, this is not a realistic case.

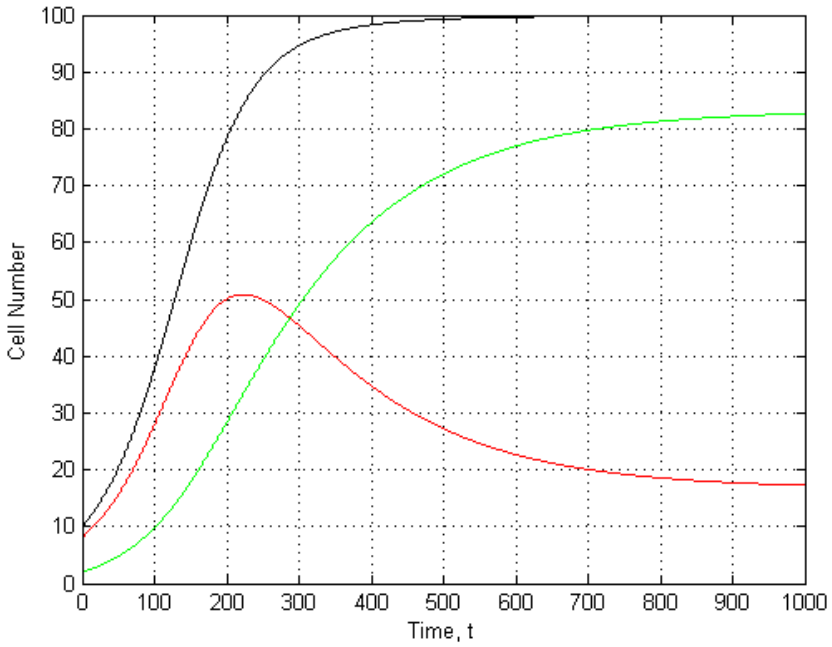


Figure 19: Total number of tumour cells in black, proliferating cells in red and quiescent cells in green using equation (3.15). Parameter values are $h = 0.1$, $r = \ln 2/24$, $P_0 = 8$, $Q_0 = 2$, $K = 100$, $\alpha = 1.5$, $k_{PQ} = 0.005$ and $k_{QP} = 0.001$

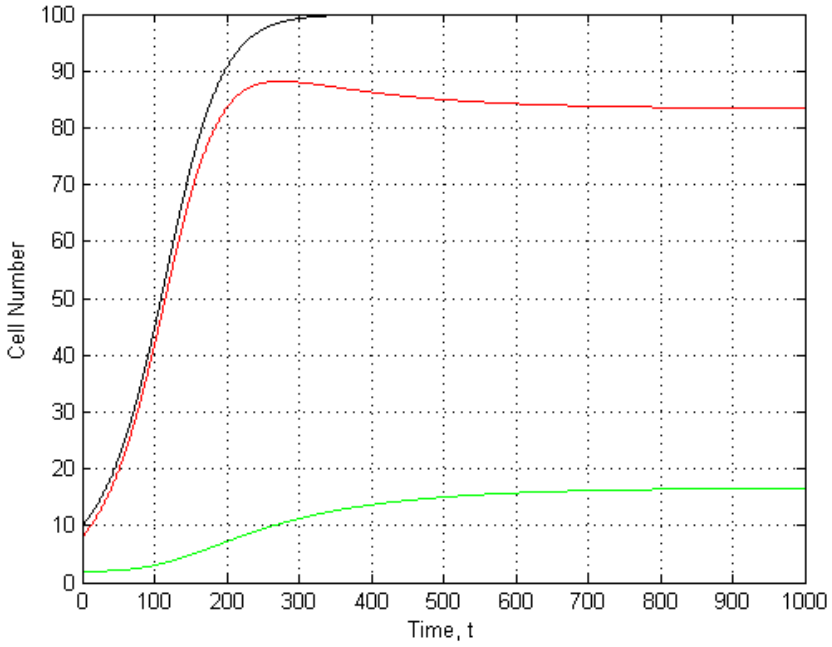


Figure 20: Total number of tumour cells in black, proliferating cells in red and quiescent cells in green using equation (3.15). Parameter values are $h = 0.1$, $r = \ln 2/24$, $P_0 = 8$, $Q_0 = 2$, $K = 100$, $\alpha = 1.5$, $k_{PQ} = 0.001$ and $k_{QP} = 0.005$

4. Modelling Radiotherapy

One model that has been predominantly used since the sixties to explain the relationship that radiotherapy has on tumour growth is the linear-quadratic model (LQ-model) [CHN09]. Over the years many publications have been made to improve this model, e.g. by adding terms to the equation to try and incorporate the complexity of the results that radiotherapy has on cells. In this chapter I will look at the basic LQ-model and its more complex variations.

4.1. Linear Quadratic Model

As explained in chapter 2.2, the most important radiation damage is to the DNA in a cell, especially double-strand breaks (DSBs) of the DNA double helix. A dose of one Gy results in thousands of ionizations in the cell's nucleus of which a small part (about 40 in humans) induce DSBs. Most of these DSBs are repaired and some are misrepaired. Many misrepairs involve a reaction between two different DSBs. At a typical dose of several Gy, at least one misrepair usually occurs, resulting in the cell's death [SHH01].

The LQ-model incorporates these aspects and renders a survival fraction depending on the dose administered. This model is used to develop treatment schedules based on the best outcome of the equation [OMH09].

The model describes cell killing by the following mechanisms: a single radiation track (e.g. γ-ray) produces various lethal lesions (DSBs) with a yield proportional to the dose, and misrepair of pairs of DSBs produced from different radiation tracks produce lethal lesions with a yield proportional to the square of the dose. This results in the following equation for the yield of lethal lesions

$$Y = \alpha D + \beta D^2 \text{ with } \alpha, \beta > 0. \tag{4.1}$$

D is the dose administered in Gy, αD are the lethal lesions produced per single radiation track and βD^2 are the lethal lesions produced from different radiation tracks [OMH09, ECAV07, BHH+98, CHN09]. If more than one unrepaired break exists in a cell at the same time, a misjoining can produce a lethal lesion. These lethal lesions follow a poisson distribution from cell to cell [CHN09]. Therefore, the LQ-model reads

$$S = \frac{S^*}{S_0} = \exp(-Y) = e^{-\alpha D - \beta D^2} \tag{4.2}$$

where S is the survival fraction, S^* are the number of cells left after radiation and S_0 are the initial number of cells.

Figure 21 shows three survival curves using equation (4.2), each with a different value for the ratio $\frac{\alpha}{\beta}$. The red curve depicts a survival curve for prostate cancer, the green curve for non-small cell cancers and the blue curve for advanced head and neck cancer. The ratios were taken from [OMH09]. From this plot one can see how different cancer types need different radiation doses to kill the same percentage of cells. Clearly, advanced head and neck cancer cells are more radioresistant and need a higher dose to die compared to prostate cancer cells.

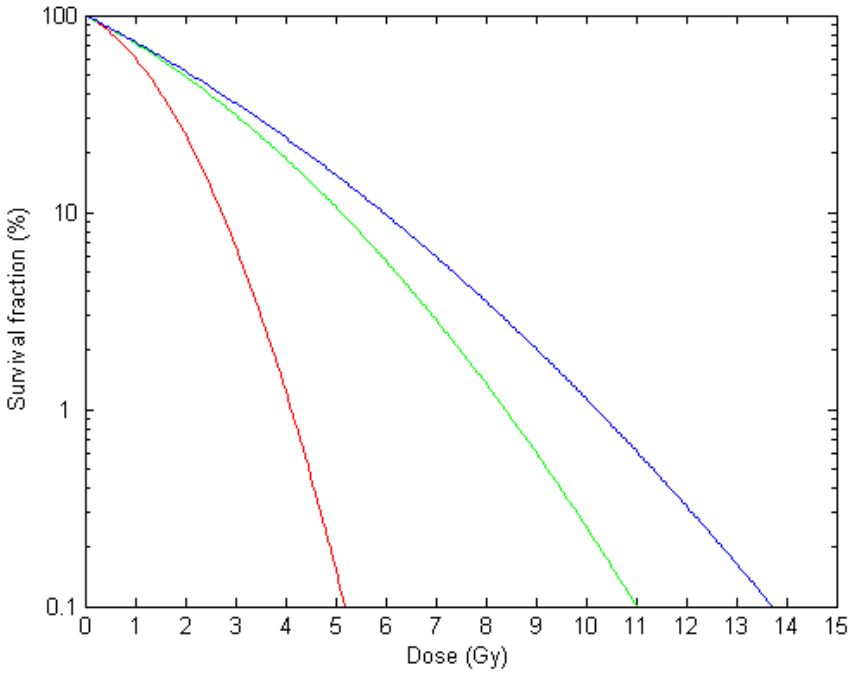


Figure 21: Cell survival curves after a single dose of radiation using equation (4.2), with red for $\alpha/\beta = 1.5$, green for $\alpha/\beta = 10$ and blue line for $\alpha/\beta = 20$. Ratios from [OMH09].

The ratio $\frac{\alpha}{\beta}$ is a measure of a tissue's sensitivity. Prostate cancer is slow proliferating and the tissue responds late, thus having a higher repair capacity (since the cells have time to repair the damage before replicating) compared to advanced head and neck cancer, which is an early responding tissue with an aggresive cell proliferation rate and low repair capacity [OMH09]. Low $\frac{\alpha}{\beta}$ ratios are equivalent to a higher capacity for self-repair (e.g. normal tissue) and high ratios mean that the capacity for self-repair is low (e.g. tumours). Most normal tissue ratios are about one to three Gy whereas most tumours have a ratio of about ten Gy [CHN09].

The LQ-model in equation (4.2) only allows for a single dose of radiation. However, if the dose is not administered in one single session but in n fractions, each of dose d, the equation reads

$$S = e^{-\alpha n d - \beta n d^2}. \tag{4.3}$$

So far this is a very simple model that describes cell killing depending on the dose of radiation. However, as mentioned in chapter 2.2 there are more factors that influence the capability of cells surviving radiation. These are known as the "5 Rs" of radiobiology: repair, repopulation, re-distribution over the cell cycle, re-oxygenation and radioresistance [OMH09, CHN09]. Some of these factors have been included in extended LQ-models and I will analyse them in the following.

Repair As mentioned previously, DSBs can be repaired, which is modelled by a constant repair rate λ. Therefore, a term is included in the model that reduces cell killing due to repair between dose fractions or during continued low dose-rate radiation, resulting in equation (4.4) [BHH+98].

$$S = e^{-\alpha D - \beta G D^2} \tag{4.4}$$

$G \in [0, 1]$ is the generalised Lea-Catcheside time factor. If $G = 1$ equation (4.4) goes back to being the standard LQ-model and if $G < 1$ cell killing is reduced. The function for the time factor reads

$$G = \frac{2}{D^2} \int_{-\infty}^{\infty} \dot{D}(t)\,\mathrm{d}t \int_{-\infty}^{t} e^{-\lambda(t-t')} \dot{D}(t')\,\mathrm{d}t'.$$

The term after the second integral depicts the first pair of DSBs required to produce a lethal lesion. The exponential term is the reduction in numbers of such DSBs through repair. DSBs produced at t' may interact (if not repaired) with a second lethal lesion. The term after the first integral is the second DSB interacting with DSBs produced earlier that have not been repaired yet [BHH+98]. If radiation is given at a constant dose-rate of D/T over a period of time T, G becomes

$$G = \frac{2}{(\lambda T)^2}(e^{-\lambda T} - 1 + \lambda T) \tag{4.5}$$

λ is the repair rate with $\lambda = \frac{\ln 2}{\tau}$, τ being the repair half-time. If radiation is given in n short fractions, separated by a time T, G results in

$$G = \frac{2e^{-\lambda T}}{1 - e^{-\lambda T}} \left(\frac{n - (1 - e^{-\lambda T})^n}{1 - e^{-\lambda T}} \right). \tag{4.6}$$

Figure 22 depicts equation (4.5) with $\tau = 1$ hour. Inserting this equation into the LQ-model results in figure 23, where one can see that the survival fraction slows down decreasing due to repair. The solid line shows the normal LQ-model using $\frac{\alpha}{\beta} = 1.5$ (prostate cancer) and two different repair half-times $\tau = 2$ hours (dashed line) and $\tau = 1$ hour (dotted line).

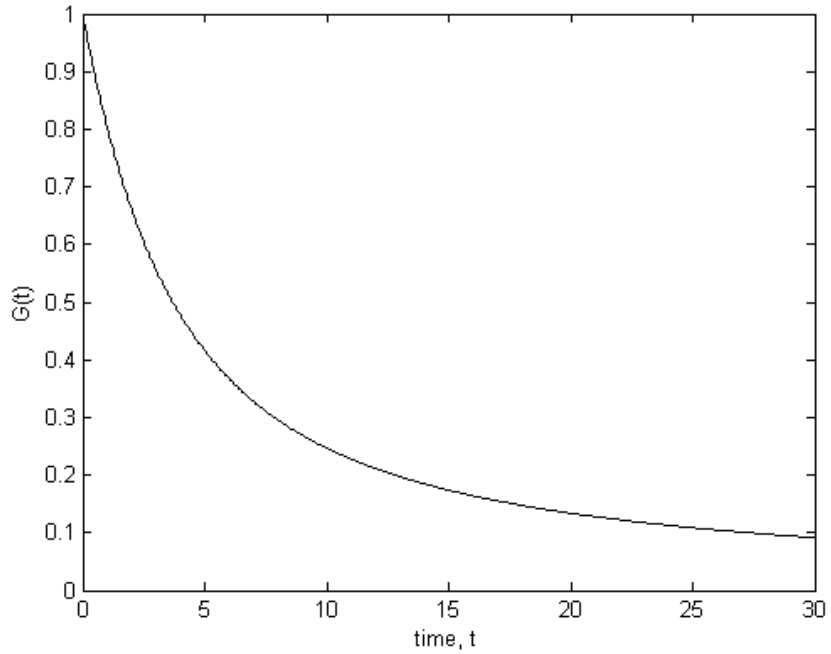


Figure 22: Lea-Catcheside time factor (using equation (4.5)) with a repair rate of $\lambda = \ln 2$.

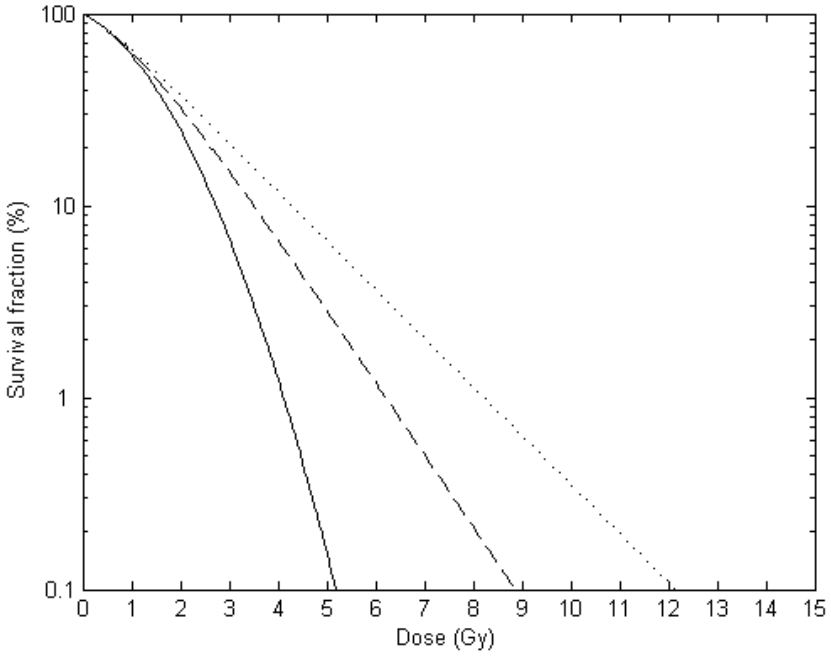


Figure 23: Solid line shows the standard LQ-model for prostate cancer ($\alpha/\beta = 1.5$). Dashed line shows equation (4.4) using equation (4.5) for the time factor ($\tau = 2$) and the dotted line uses $\tau = 1$.

Repopulation In between fractions of radiation, tumour cells do not only repair themselves but they can also continue to proliferate [OMH09, CHN09]. If I assume that the repopulation constant is

$$\mu = \frac{\ln 2}{T_p}$$

where T_p is the doubling time and T the overall exposure time (complete timescale of the treatment), then the equation for the adjusted LQ-model reads

$$S = e^{-\alpha n d - \beta n d^2 + \mu T}. \tag{4.7}$$

Usually repopulation does not begin straight away but after a certain delay, thus I add a time delay, T_k, to equation (4.7), resulting in

$$S = e^{-\alpha n d - \beta n d^2 + \mu (T - T_k)}. \tag{4.8}$$

For simplicity I have assumed a constant doubling time, however, in reality larger tumours have a longer doubling time than smaller tumours in some cancer types.

Hypersensitivity It has been shown that the normal LQ-model underestimates cell response in a low dose range of up to one Gy. In fact, cells may show an abnormally high radiosensitivity (hypersensitivity), which is not included in the LQ-model from equation (4.2). Therefore, the model was extended to include a hypersensitivity factor $h(D)$ in equation (4.9).

$$h(D) = 1 + \left(\frac{\alpha_s}{\alpha} - 1\right) e^{-D/d_c} \tag{4.9}$$

with d_c being the threshold dose to which the cells are hypersensitive. For small doses the survival fraction S is decreased more and for larger doses $h(D) \approx 1$ holds, meaning the hypersensitivity factor does does not change the survival fraction [CHN09]. Figure 24 models this equation using a threshold dose of 0.5 Gy. Integrating equation (4.9) into the LQ-model results in

$$S = e^{-h(D)\alpha D - \beta D^2}. \tag{4.10}$$

Figure 25 shows the effect that adding $h(D)$ into the model has on the survival fraction. The dashed line shows the normal LQ-model for prostate cancer ($\alpha/\beta = 1.5$) and the solid line shows the LQ-model including the hypersensitivity factor (equation (4.10)) with a threshold dose of 0.5 Gy. The adjusted model takes on the same values as the normal LQ-model from about four Gy onwards, but due to hypersensitivity the amount of cells surviving radiation is decreased significantly in the low dose range.

Summing up, one can see that these are very simple models. The two main parameters needed (α and β) are known for many tissues and cancer types. Unfortunately, a strong drawback of the LQ-model is the fact that the time course of the treatment is not included. I will try to improve this in the following chapters.

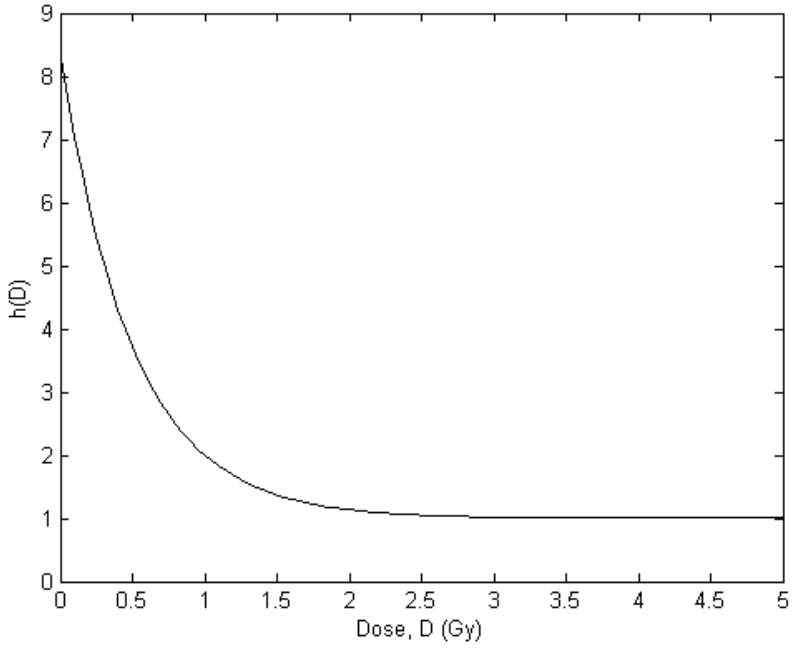


Figure 24: Using equation (4.9) to model hypersensitivity. Parameter values are $d_c = 0.5$ and $\alpha_s = 2.5$.

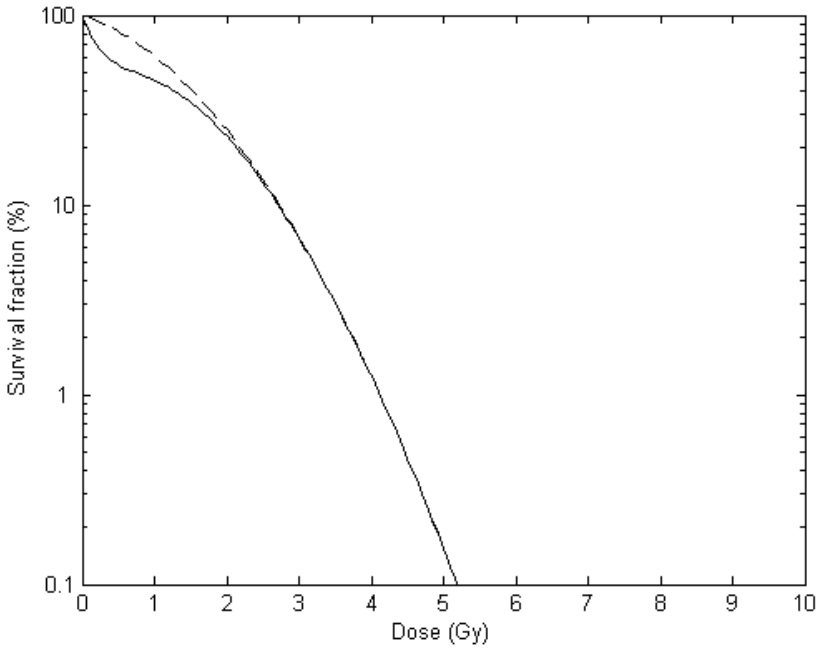


Figure 25: Dashed line depicts the normal LQ-model and the solid line the LQ-model including hypersensitivity (equation (4.10)). Parameter values are $d_c = 0.5$, $\alpha_s = 2.5$, $\alpha/\beta = 1.5$

4.1.1. Biological Effective Dose

One can calculate the total dose of a treatment schedule, which would have the same effect on a given tissue as another treatment schedule with different doses of radiation [OMH09]. The same physical dose is administered in both schedules but in different fractions. This results in different biological effects. Two schemes that deliver the same biological effective dose are called "iso-effective" [CHN09]. The biological effective dose (BED) is defined as

$$\begin{aligned} \text{BED} &:= \frac{-\ln S}{\alpha} \\ &= \frac{\alpha nd + \beta nd^2}{\alpha} \\ &= D + \frac{\beta}{\alpha} Dd \\ &= D\left(1 + \frac{\beta}{\alpha} d\right). \end{aligned} \tag{4.11}$$

The term in brackets is the relative effectiveness of a treatment. An increased BED, means an increased biological effect, which in turn means a reduced survival fraction S. Table 1 lists treatment examples where in each case the BED for normal tissue (BED_3, $\alpha/\beta = 3$) and cancer tissue (BED_{20}, $\alpha/\beta = 20$) has been calculated using equation (4.11).

D	d	n	BED_3	BED_{20}
66	2.2	30	114.4	73.26
66	2	33	110	72.6
59.4	1.8	33	95	64.7

Table 1: Biological effective dose

One can see that a total dose of 66 Gy in 30 fractions (row 1) results in an increased BED for normal and cancer tissue, compared to 66 Gy in 33 fractions (row 2). Therefore this treatment schedule results in a higher toxicity, and fewer tumour cells as well as healthy cells would survive. This is the same when we compare the second and third row of table 1, where we have the same amount of treatment fractions, but using a lower total dose. Of course the higher total dose results in more healthy and cancer cells dying than using a lower total dose.

The aim of a treatment schedule is to minimise BED_3 and to maximize BED_{20} since one wants as many healthy cells as possible to survive and as many cancer cells as possible to die. Therefore, the optimum treatment means I want to maximise

$$\begin{aligned} & BED_{20} - BED_3. \\ \Leftrightarrow \max(BED_{20} - BED_3) &= \max\left(D\left(1 + \frac{d}{20}\right) - \left(1 + \frac{d}{3}\right)\right) \\ &= \max\left(D\left(\frac{d}{20} - \frac{d}{3}\right)\right) = \max\left(-\frac{17}{60} Dd\right). \end{aligned} \tag{4.12}$$

For smaller fractioned doses d, the difference between healthy tissue and tumour tissue is increased, which is the aim of a successful treatment. Therefore, one would opt for more frequent smaller doses resulting in the same total dose [OMH09].

4.1.2. Tumour Control Probability

Furthermore, one can measure how much a tumour is controlled by radiation. In the ideal case, all tumour cells should die as a result of radiation, leaving a surviving fraction of zero. The tumour control probability (TCP) calculates the probability of no tumour cells surviving radiation [OMH09, CHN09]. As in the previous section, I start with an initial number of tumour cells S_0. After treatment S^* cells are left. I assume that S^* is random with distribution $P(S^*)$. Since TCP is the probability that no tumour cells are left, I define it as

$$TCP := P(0).$$

I differentiate between two cases, first S^* is poisson distributed and secondly S^* is binomially distributed [OMH09, CHN09].

If I assume a poisson distribution, I assume that S_0 is large, cell survival is a rare event and the probability that k cells survive is

$$P(S^* = k) = \lambda^k \cdot \frac{e^{-\lambda}}{k!} \tag{4.13}$$

with $\lambda = S_0 \cdot S$ being the expected value. Then the tumour control probability can be calculated as

$$TCP = P(0) = e^{-S_0 \cdot S}. \tag{4.14}$$

In the case that S^* is binomial distributed, I assume that p is the survival probability of a cell, cells are independent and identical and the probability that k cells survive is

$$P(S^* = k) = \binom{S_0}{k} p^k (1-p)^{S_0 - k}. \tag{4.15}$$

Then the tumour control probability can be calculated to

$$TCP = P(0) = (1-S)^{S_0}. \tag{4.16}$$

Figure 26 shows three tumour control probability curves using equation (4.14) and $S_0 = 100$. The red curve uses an $\frac{\alpha}{\beta}$ ratio of 1.5, the green line of 10 and the blue line of 20. As we saw earlier in figure 21, prostate cancer (red line) needs a much lower radiation dose than an advanced head and neck cancer (blue line) to die. Prostate cancer cells would only need just over six Gy to completely die compared to over 18 Gy for advanced head and neck cancer.

4.1.3. Normal Tissue Complication Probability

The equivalent model to the TCP for normal healthy tissue is the normal tissue complication probability (NTCP). NTCP is the probability that a given treatment induces severe side effects to normal tissue. These side effects can be damage to epithelial surfaces for

example, or other organs suffering from side effects depending on where the tumour is located. In addition, radiation itself is a potential cause of cancer (seen in a minority of patients) [CHN09].

Figure 27 compares TCP (dashed line) and NTCP (solid line) for $\frac{\alpha}{\beta} = 1.5$. The red dots mark a TCP of 90% and a NTCP of 23%. An increase of just five percent points to 95% of the TCP (blue dots) already results in a NTCP of 38%. The aim, of course, is to have the curves as far apart as possible, resulting in less normal tissue damage per percentage point increase in TCP.

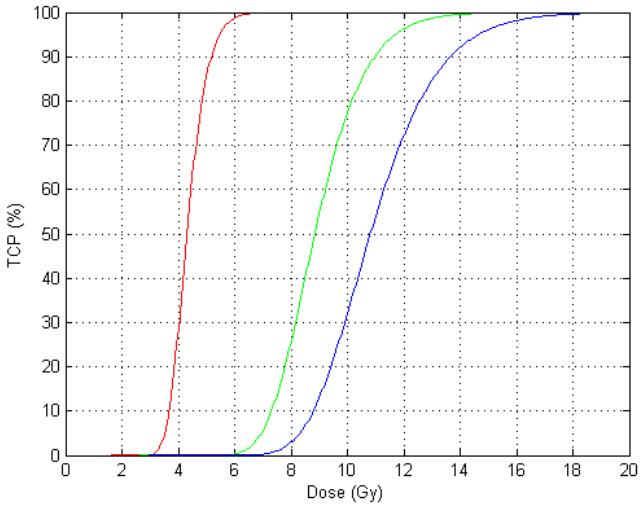


Figure 26: Modelling tumour control probability using equation (4.14). Parameter values are $S_0 = 100$, $\alpha/\beta = 1.5$ (red), $\alpha/\beta = 10$ (green) and $\alpha/\beta = 20$ (blue).

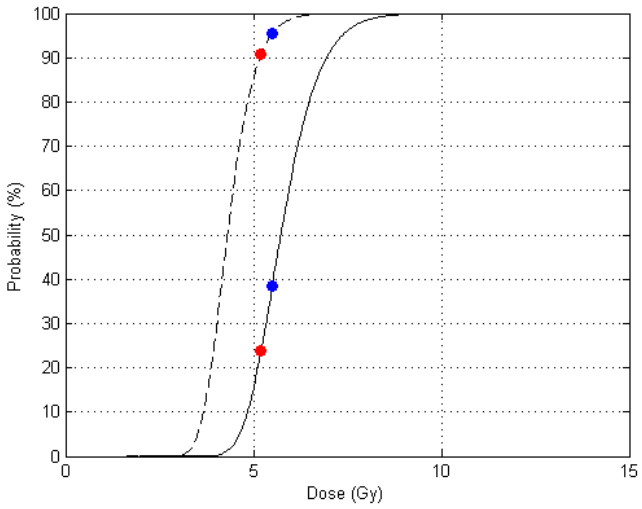


Figure 27: Dashed line models the tumour control probability and the solid line models the normal tissue complication probability. Red dots mark a TCP of 90% and a NTCP of 23%. Blue dots mark a TCP of 95% and a NTCP of 38%.

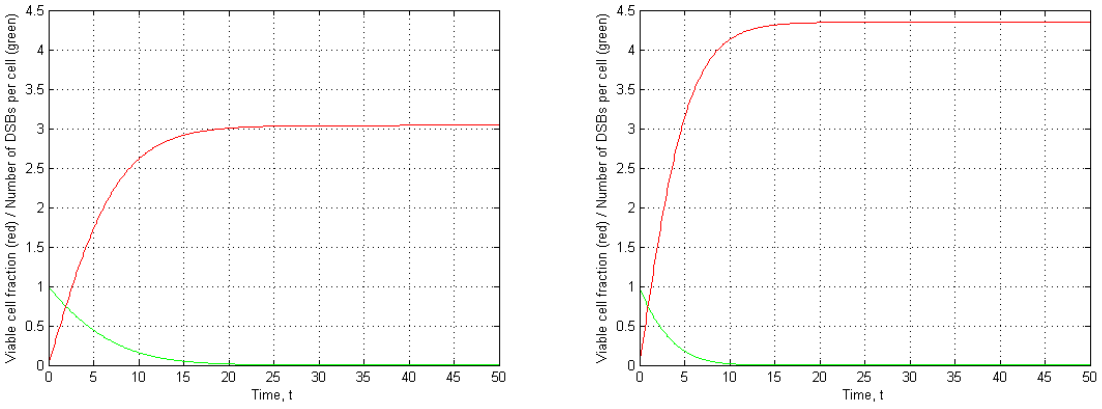
4.2. Other Radiation Models

As mentioned above, the LQ-model is the model predominantly used in modelling radiation and in calculating the optimal dosage. However, other models have been set up to simulate the effects radiation has on tumour growth. For example a two compartment ordinary differential equation model by Capuccio, Herrero and Nunez in [CHN09]. Here, the authors modelled the fraction of viable cells with C and the mean number of DSBs per cell that are caused by radiation by U. Then the model reads

$$\begin{aligned} \frac{dC}{dt} &= -\left(\alpha\dot{D} + \frac{1}{2}kU^2\right)C \\ \frac{dU}{dt} &= \delta\dot{D} - \omega U - 2kU^2 \end{aligned} \tag{4.17}$$

First, look at the equation for U, where $\delta\dot{D}$ is the production of non-repairable DSBs, which depend on the dose rate $\dot{D}$. ω is the DSB repair constant. Thus the repaired DSBs are subtracted from the equation. Furthermore, kU^2 is the DSB misrepair rate, whereby two DSBs are needed to create a misrepair. On average half of these misrepairs turn out to be lethal and result in cell death. This is modelled by subtracting the term off the fraction of viable cells ($\frac{1}{2}kU^2$). Finally, the lethal action of radiation due to non-repairable lesions is denoted by α.

Figure 28 shows solutions to the above mentioned model with different amounts of radiation. The red line shows the number of DSBs per cell, which starts at 0 and tends to about 3 with a dose of 0.5 Gy and about 4.4 when a dose of 1 Gy is administered. The green line shows the fraction of viable cells, which starts at 1, meaning that all cells are viable, and decreases until all cells are killed by radiation.



(a) $\dot{D} = 0.5$ (b) $\dot{D} = 1$

Figure 28: Solution to equations (4.17) with viable cells in red and number of DSBs per cell in green. Parameter values are $k = 0.05$, $\alpha = 0.3$, $\delta = 0.8$, $\omega = 0.01$ $C_0 = 1$ and $U_0 = 0$.

Another model in [CHN09] is used to simulate postoperative radiotheray and development of local recurrence. Hereby a set of partial differential equations were used. n

denotes the tumour cell concentration, f the extracellular matrix (ECM) and m the matrix-degrading enzymes. Then the equation for n reads

$$\frac{\partial n}{\partial t} = \lambda n(1 - f - n) + d_n \nabla^2 n - \gamma \nabla \cdot (n \nabla f).$$

Tumour cells, assumed here, proliferate (first term), diffuse with diffusion coefficient d_n (second term) and move along the ECM due to haptotaxis (third term). The equation for the ECM reads

$$\frac{\partial f}{\partial t} = -\nu m f.$$

The extracellular matrix is degraded by the enzymes m. The equation for these enzymes on the other hand reads

$$\frac{\partial m}{\partial t} = d_m \nabla^2 m + \alpha n(1 - m) - \beta m.$$

The enzymes diffuse with diffusion coefficient d_m (first term), are produced by the tumour cells n (second term) and decay with rate β (third term).

Since radiation was applied postoperatively, the equations were set to zero after surgery. Then the LQ-model was applied to the tumour and healthy cell population. The results demonstrated that radiotherapy kills tumour cells that may have been missed in the operation. However healthy cells with genetic mutations that were close to the primary tumour have an increased susceptibility to further mutations, which could result in a new tumour. Using targeted intraoperative radiotherapy (Targit) as explained in chapter 2.2 may eliminate these potentially malignant cells surrounding the site of the primary tumour. Targit is believed to have a bigger advantage compared to conventional fractional therapy [CHN09].

5. Improved Models for Radiotherapy

5.1. Cell Population Models

As we saw in chapter 4, the existing radiotherapy model (LQ-model) does not include the time course t of the treatment in its equation. This is a huge disadvantage as one cannot see the long term effect of radiation and should be included in future models. Therefore, I will revisit the previous growth models from chapter 3 that were able to replicate real data and incorporate radiotherapy in them.

5.1.1. Continuous Radiation

Basic Model Once again I look at a population of tumour cells and assume the avascular tumour has no structure. When I compared data to the mathematical models, I saw that the generalised logistic growth model from equation (3.5) in section 3.1.3 succeeded in replicating the data in the best possible way and gives me enough variability to fit the solution curve to the data.

To derive a model (based on a model in [Pre03]) that includes radiation, I add a term to the existing model that reduces the amount of cells if radiation is administered.

$$\begin{aligned} \frac{dN}{dt} &= \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N \text{ with } \mu > 0, \\ N(0) &= N_0 \end{aligned} \tag{5.1}$$

The right hand side of equation (5.1) is the same as the generalised logistic growth model (equation (3.5)) except for the term μAN being subtracted from the growth term. A is the amount of radiation administered (in Gy) and μ relates to how much the drug damages the cell per Gy. I assume continuous radiation and therefore set

$$A = a \ \forall t \geq 0.$$

a is a constant amount of radiation given. If $a = 0$, i.e. no radiation is administered, the model is reduced to the growth model of equation (3.5).
To solve equation (5.1) I introduce $v(t) := \frac{1}{N(t)}$ with $v(0) = v_0 = \frac{1}{N_0}$ as in chapter 3. Then

$$\begin{aligned} \frac{dv}{dt} &= -\frac{1}{N^2} N' \\ &= -\frac{1}{N^2} \left(\frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N\right) \\ &= v \left(\mu A - \frac{r}{\alpha}\right) + \frac{r}{\alpha K^{\alpha}} v^{1-\alpha} \end{aligned}$$

By using the substitution $z := v^{\alpha}$ with $z_0 = v_0^{\alpha}$ I can solve this Bernoulli differential equation.

$$\begin{aligned} \frac{dz}{dt} &= \alpha v^{\alpha-1} v' \\ &= z(\alpha \mu A - r) + \frac{r}{K^{\alpha}} \end{aligned}$$

This is similar to the inhomogeneous linear differential equation, which I have already solved in chapter 3. The solution reads

$$z(t) = z_0 e^{-rt+\alpha\mu At} + \frac{r}{K^\alpha(r-\alpha\mu A)}(1 - e^{-rt+\alpha\mu At}).$$

Inserting the substitution for z results in

$$v(t) = \left(v_0^\alpha e^{-rt+\alpha\mu At} + \frac{r}{K^\alpha(r-\alpha\mu A)}(1 - e^{-rt+\alpha\mu At}) \right)^{\frac{1}{\alpha}}.$$

Thereby using $N(t) = \frac{1}{v(t)}$, I get the solution for equation (5.1)

$$N(t) = \frac{N_0 K}{\left(\frac{N_0^\alpha r}{r-\alpha\mu A} + e^{-rt+\alpha\mu At}(K^\alpha - \frac{N_0^\alpha r}{r-\alpha\mu A}) \right)^{\frac{1}{\alpha}}}. \tag{5.2}$$

The stationary points of the model can be calculated by setting equation (5.1) to zero.

$$\begin{aligned} \frac{dN}{dt} &\stackrel{!}{=} 0 \\ \Rightarrow \overline{N}_1 &= 0 \end{aligned}$$

This trivial stationary point of no tumour existing, only exists if I start with no tumour cells ($N_0 = 0$) or if radiation damages all cells. As in the previous chapters I only look at the case where $N_0 > 0$. The non trivial stationary point is calculated to

$$\begin{aligned} &\frac{r}{\alpha}\left(1 - \left(\frac{N}{K}\right)^\alpha\right) - \mu A = 0 \\ \Leftrightarrow &-\frac{r}{\alpha}\frac{N^\alpha}{K^\alpha} = \mu A - \frac{r}{\alpha} \\ \Leftrightarrow &N^\alpha = K^\alpha\left(1 - \frac{\alpha\mu A}{r}\right) \\ \Rightarrow &\overline{N}_2 = K\left(1 - \frac{\alpha\mu A}{r}\right)^{\frac{1}{\alpha}}. \end{aligned}$$

In chapter 3 I saw that if $N_0 \in (0, K]$ the tumour tends to its carrying capacity K. However, if a certain amount of radiation is given ($A > 0$) the tumour cells can tend to $\overline{N}_2$, which is smaller than its carrying capacity K. Now I want to know how high the radiation dose has to be so that all tumour cells die, meaning the tumour does not tend to $\overline{N}_2$ but to zero ($\overline{N}_1$). To find the stability of the two stationary points I differentiate the function $\frac{dN}{dt} = f(N)$ with respect to N.

$$\frac{df(N)}{dN} = \frac{r}{\alpha} - \mu A - \frac{r}{\alpha}\frac{N^\alpha}{K^\alpha}(\alpha + 1)$$

Inserting the trivial stationary point leads to

$$\frac{df(\overline{N}_1)}{dN} = \frac{r}{\alpha} - \mu A.$$

$\overline{N}_1$ is asymptotically stable if

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

and unstable if $A < \frac{r}{\alpha\mu}$. Inserting the nontrivial stationary point results in

$$\frac{df(\overline{N}_2)}{dN} = \alpha\mu A - r.$$

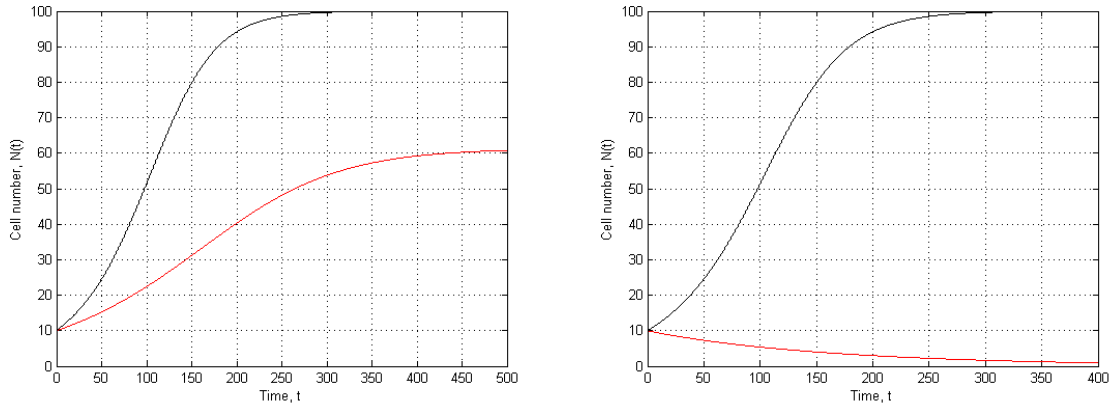
Clearly $\overline{N}_2$ is asymptotically stable if

$$A < \frac{r}{\alpha\mu}$$

and unstable if $A > \frac{r}{\alpha\mu}$. This means that if the radiation dose is high enough (larger than $\frac{r}{\alpha\mu}$) the trivial stationary point is stable and the nontrivial stationary point is unstable, eventually resulting in the death of all tumour cells. If the dose is too small (lower than $\frac{r}{\alpha\mu}$) not enough tumour cells die and the surviving cells continue to proliferate, eventually tending to $\overline{N}_2$. Therefore A is a bifurcation parameter. This means that the stability of a stationary point changes depending on the value of the bifurcation parameter.

Figure 29a shows the difference a dose of 0.1 Gy has on a tumour cell population. The black line is the solution to the generalised logistic growth equation. As one can see the tumour starts with an initial number of tumour cells larger than zero and tends to the capacity of 100 cells. Plotting the solution of my model for radiation (equation (5.2)) renders the red line. As I chose a too low dose ($A = 0.1 < 0.1925 = \frac{r}{\alpha\mu}$) not all tumour cells are killed by radiation and enough are left to proliferate, eventually tending to $\overline{N}_2 = K\left(1 - \frac{\alpha\mu A}{r}\right)^{1/\alpha} = 61.4$. The red line in figure 29b on the other hand uses a dose of 0.3 Gy, which is larger than $0.1925 = \frac{r}{\alpha\mu}$. One can see that the cell number tends to zero, all tumour cells will die.

Figure 30 shows the solution curve for different values of μ, the degree to which the cells are affected by radiation. Increasing the value of μ reduces the value of the stationary point $\overline{N}_2$, which the tumour tends to as long as $\mu < \frac{r}{\alpha A}$. The blue line uses a low "effectiveness" of the radiation on the cells whereas the green curve uses a higher value, resulting in more cells being killed.



(a) $A = 0.1$ (b) $A = 0.3$

Figure 29: Tumour growth without radiation in black and with continuous radiation in red, using equation (5.2). Parameter values are $N_0 = 10$, $K = 100$, $\alpha = 1.5$, $r = \ln 2/24$ and $\mu = 0.1$.

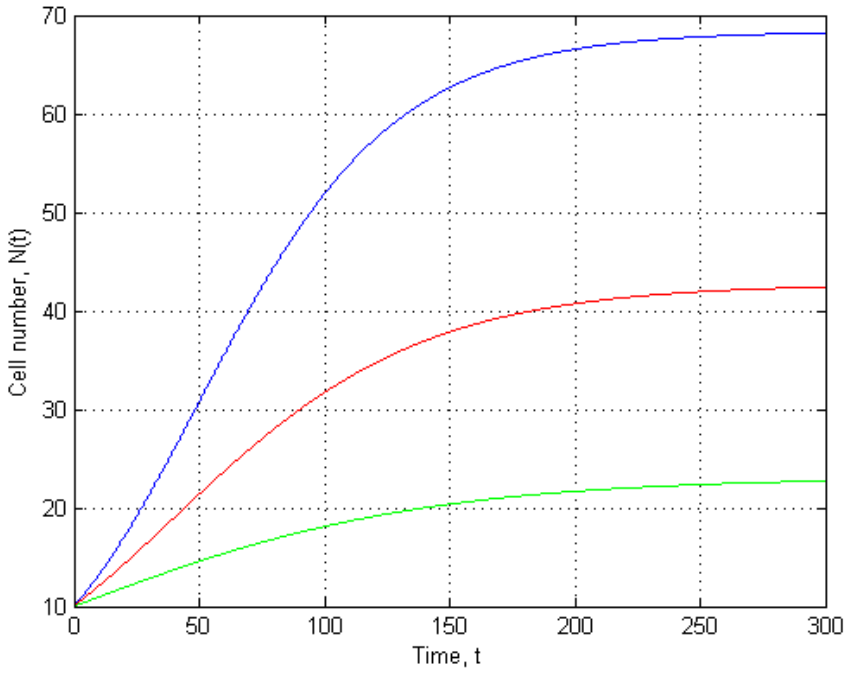
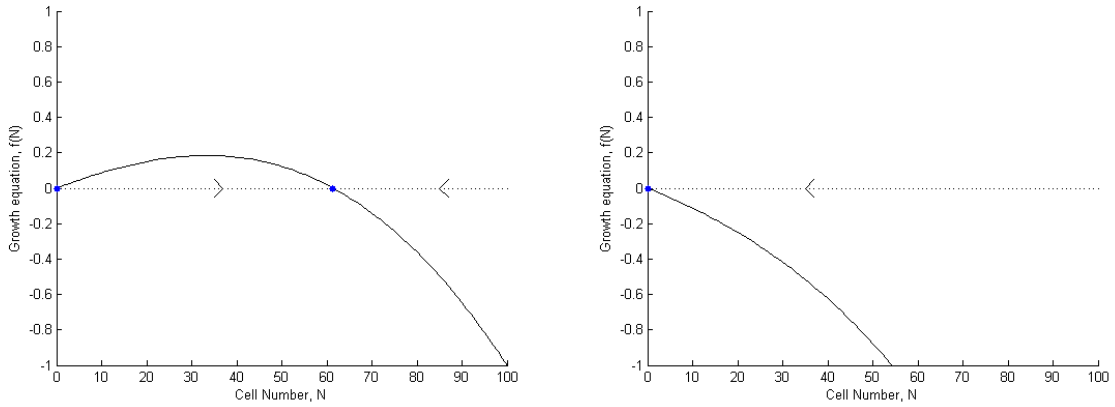


Figure 30: Comparison of how cells are affected by radiation using equation (5.2) with blue for $\mu = 0.1$, red for $\mu = 0.2$ and green line for $\mu = 0.3$. Parameter values are $N_0 = 10$, $K = 100$, $\alpha = 0.5$, $r = \ln 2/24$ and $A = 0.1$.

Figures 31 and 32 show how the stability of the model depends on the bifurcation parameter A. Figure 31 shows two graphs of the right-hand side of the model equation (5.1). The arrows on the x-axis indicate if the population grows or decreases. If $A < \frac{r}{\alpha\mu} = 0.1925$, the nontrivial stationary point $\overline{N}_2 = 61.4$ is stable. Once A is larger than 0.1925 the trivial stationary point becomes stable and the population will tend to zero.
Figure 32 is a bifurcation diagramm. $\overline{N}_1 = 0$ is unstable for $A < 0.1925$ (dotted line) and becomes stable once $A > 0.1925$ (blue line). $\overline{N}_2 = K(1 - \frac{\alpha\mu A}{r})^{1/\alpha}$ is stable for $A < 0.1925$ (blue curve). The two branches intersect at $A = 0.1925$ and exchange their stability.



(a) $A = 0.1$ (b) $A = 0.3$

Figure 31: Comparison of the change in the value of the bifurcation parameter A. Additional parameter values are $r = \ln 2/24$, $N_0 = 10$, $K = 100$, $\alpha = 1.5$ and $\mu = 0.1$.

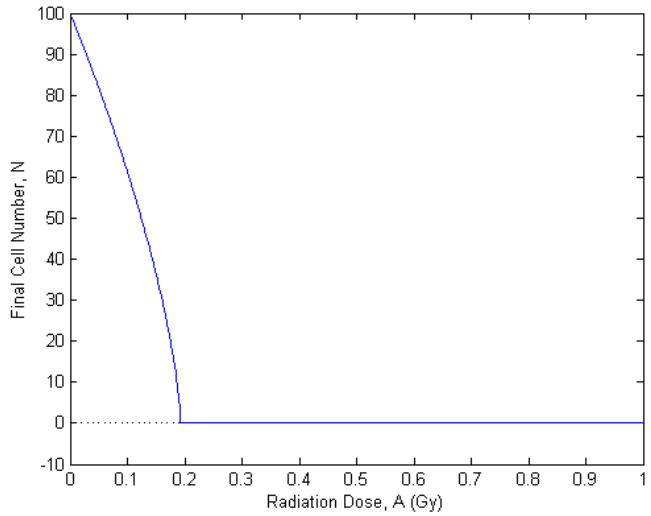


Figure 32: Stability depends on the value of the bifurcation parameter A. The blue line shows the stable node and the dotted line shows the unstable node. Parameter values are as in figure 31.

Now that I have a basic model for radiotherapy, I can include different factors that effect tumour growth, as discussed in chapter 2.2.

Repair Since I know that DSBs caused by radiation can be repaired (see chapter 2.2), I want to include this in my model by adding a term, which increases the number of cells. The equation reads

$$\begin{aligned} \frac{dN}{dt} &= \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N + \rho\lambda A N \text{ with } \rho > 0, \\ N(0) &= N_0 \end{aligned} \tag{5.3}$$

ρ represents the factor of cells that are able to repair themselves after radiation and λ is the repair rate as in chapter 4, with $\lambda = \frac{\ln 2}{T_r}$, T_r being the repair half-time. To find the solution of this model I use the same method as with equation (5.1). The solution reads

$$N(t) = \frac{N_0 K}{\left(\frac{N_0^{\alpha} r}{r - \alpha\mu A + \alpha\rho\lambda A} + e^{-rt + \alpha\mu A t - \alpha\rho\lambda A t}\left(K^{\alpha} - \frac{N_0^{\alpha} r}{r - \alpha\mu A + \alpha\rho\lambda A}\right)\right)^{\frac{1}{\alpha}}}. \tag{5.4}$$

The stationary points of the model can be calculated by setting equation (5.3) to zero.

$$\begin{aligned} \frac{dN}{dt} &\stackrel{!}{=} 0 \\ \Rightarrow \overline{N}_1 &= 0 \end{aligned}$$

The trivial stationary point is the same as with the previous model. The nontrivial stationary point, however, reads

$$\begin{aligned} 0 &= \frac{r}{\alpha}\left(1 - \frac{N^{\alpha}}{K^{\alpha}}\right) - \mu A + \rho\lambda A \\ \Rightarrow \overline{N}_2 &= K\left(1 - \frac{\alpha\mu A}{r} + \frac{\alpha\rho\lambda A}{r}\right)^{\frac{1}{\alpha}}. \end{aligned}$$

This stationary point is larger than the nontrivial stationary point in the previous model without repair, which is clear since more cells will survive radiation due to self-repair.

By analysing the stability of the two stationary points I can determine which radiation dose is required to kill all tumour cells, thus for the trivial stationary point $\overline{N}_1$ to be stable. To do this, I differentiate equation (5.3) with respect to N and insert the stationary points.

$$\begin{aligned} \frac{df(N)}{dN} &= \frac{r}{\alpha} - \mu A + \rho\lambda A - \frac{r}{\alpha}\frac{N^{\alpha}}{K^{\alpha}}(\alpha + 1) \\ \Rightarrow \frac{df(\overline{N}_1)}{dN} &= \frac{r}{\alpha} - A(\mu - \rho\lambda) \end{aligned}$$

$\overline{N}_1$ is asymptotically stable if

$$A > \frac{r}{\alpha(\mu - \rho\lambda)}$$

and unstable if $A < \frac{r}{\alpha(\mu-\rho\lambda)}$. Inserting the nontrivial stationary point results in

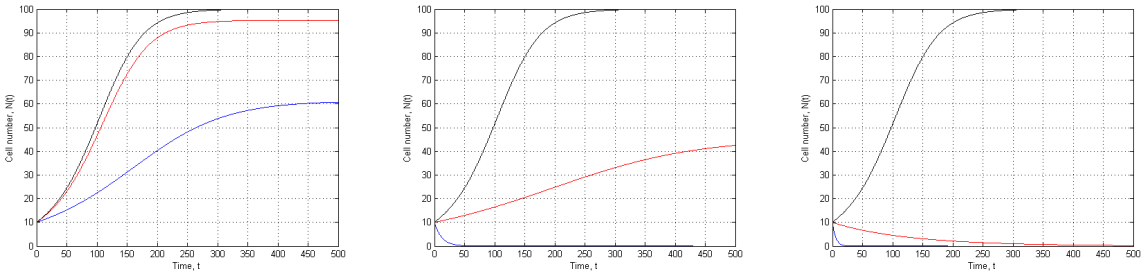
$$\frac{df(\overline{N}_2)}{dN} = A(\alpha\mu - \alpha\lambda\rho) - r.$$

Clearly $\overline{N}_2$ is asymptotically stable if

$$A < \frac{r}{\alpha(\mu - \rho\lambda)}$$

and unstable if $A > \frac{r}{\alpha(\mu-\rho\lambda)}$. This means that the radiation dose A now needs to be higher for all tumour cells to die and the trivial stationary point to be stable, compared to the basic model without repair.

Figure 33 shows three different plots using equation (5.4). I used the same parameters as in figure 29a and 29b, however varying the amount of radiation A. The black line shows the tumour growth without radiation and the blue line shows tumour growth including radiation. As one can see from the blue curve in plot 33a, the tumour cell population tends to $\overline{N}_2 = 61.4$ if the radiation dose is too low. This was shown in the previous model. Now that I have included repair, the tumour cell population tends to a higher level, $\overline{N}_2 = 95.3$ (red curve). Plot 33b shows the difference between the model without repair and the one with repair, which is that the amount of radiation A now needs to be higher than before, to result in the death of all cells. For $A > \frac{r}{\alpha(\mu-\rho\lambda)} = 1.4415$ the cell population tends to zero (plot 33c).



(a) $A = 0.1$ (b) $A = 1$ (c) $A = 2$

Figure 33: Tumour growth without radiation in black, with radiation in blue and including repair in red, using equation (5.4). Additional parameter values are $r = \ln 2/24$, $N_0 = 10$, $K = 100$, $\alpha = 1.5$, $\mu = 0.1$, $\rho = 0.5$ and $\lambda = \ln 2/4$.

Repopulation In addition to repair, cells can also continue to proliferate, either between fractions of radiation or during continued low dose radiation. If I assume β to be the amount of cells able to proliferate, then the model reads

$$\begin{aligned} \frac{dN}{dt} &= \frac{r}{\alpha}N\left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu AN + \beta A\frac{r}{\alpha}N\left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) \text{ with } \beta > 0, \\ N(0) &= N_0 \end{aligned} \tag{5.5}$$

The solution of equation (5.5) is

$$N(t) = \frac{N_0 K}{\left(\frac{N_0^\alpha(r+\beta A r)}{r-\alpha\mu A+\beta A r} + e^{-rt+\alpha\mu A t-\beta A r t}(K^\alpha - \frac{N_0^\alpha(r+\beta A r)}{r-\alpha\mu A+\beta A r})\right)^{\frac{1}{\alpha}}}. \tag{5.6}$$

The stationary points of the model can be calculated by setting equation (5.5) to zero.

$$\begin{aligned} \frac{dN}{dt} &\stackrel{!}{=} 0 \\ \Rightarrow \overline{N}_1 &= 0 \end{aligned}$$

The nontrivial stationary point reads

$$\begin{aligned} 0 &= \frac{r}{\alpha}\left(1-\frac{N^\alpha}{K^\alpha}\right) - \mu A + \beta A \frac{r}{\alpha}\left(1-\frac{N^\alpha}{K^\alpha}\right) \\ \Rightarrow \overline{N}_2 &= K\left(1-\frac{\alpha\mu A}{r(1+\beta A)}\right)^{\frac{1}{\alpha}}. \end{aligned}$$

This stationary point is larger than the nontrivial stationary point in the basic model without repopulation, which is clear since more cells will exist due to repopulation.

By analysing the stability of the two stationary points I can determine which radiation dose is required to kill all tumour cells, in order for the trivial stationary point $\overline{N}_1$ to be stable. To do this, I differentiate equation (5.5) with resect to N and insert the stationary points.

$$\begin{aligned} \frac{df(N)}{dN} &= \frac{r}{\alpha} - \mu A + \beta A \frac{r}{\alpha} - \frac{r}{\alpha}\frac{N^\alpha}{K^\alpha}(\alpha+1) - \beta A \frac{r}{\alpha}(\alpha+1)\frac{N^\alpha}{K^\alpha} \\ \Rightarrow \frac{df(\overline{N}_1)}{dN} &= \frac{r}{\alpha} - A(\mu - \beta\frac{r}{\alpha}) \end{aligned}$$

$\overline{N}_1$ is asymptotically stable if

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

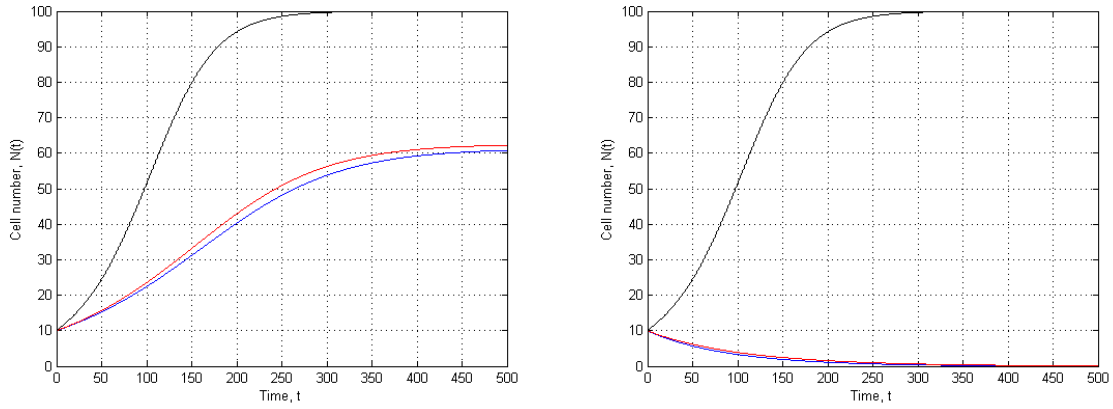
and unstable if $A < \frac{r}{\alpha\mu-\beta r}$. The nontrivial stationary point is asymptotically stable if

$$A < \frac{r}{\alpha\mu - \beta r}$$

and unstable if $A > \frac{r}{\alpha\mu-\beta r}$. This means that the radiation dose A needs to be higher compared to the basic model without repopulation, for all tumour cells to die and the trivial stationary point to be stable.

Figure 34 shows two different plots using equation (5.6). I used the same parameters as in figure 29a and 29b. The black line shows tumour growth without radiation, the blue line shows tumour growth including radiation, as in the basic model, and the red curve uses the model with repopulation. As one can see from the blue line in plot 34a, the tumour cell population tends to $\overline{N}_2 = 61.4$ if the radiation dose is too low. The red curve tends to $\overline{N}_2 = 62.6$. This is higher since more cells survive radiation. For $A > \frac{r}{\alpha\mu-\beta r} = 0.2403$ the tumour cell population including repopulation tends to zero (plot 34b). Of course the

model without repopulation (blue line) does so as well, since the A only had to be larger than 0.1925 in this model.



(a) $A = 0.1$ (b) $A = 0.3$

Figure 34: Tumour growth without radiation in black, with radiation in blue and including repopulation in red, using equation (5.6). Additional parameter values are $r = \ln 2/24$, $N_0 = 10$, $K = 100$, $\alpha = 1.5$, $\mu = 0.1$ and $\beta = 0.3$.

Radiosensitivity of proliferating and quiescent tumour cells In chapter 3.2 I introduced a model for heterogenous tumour growth. The idea is that a tumour does not consist of a uniform cell population that proliferates at the same rate, but of different cell types. I assume here that the tumour consists of proliferating and quiescent cells. Proliferating cells are radiosensitive and can be killed by radiation, quiescent cells cannot [Wan00, CHN09, TG95]. Let $P(t)$ be the number of prolilferating cells and $Q(t)$ be the number of quiescent cells. Then the model equations read

$$\begin{aligned} \frac{dP}{dt} &= \frac{r}{\alpha} P \left(1 - \left(\frac{P+Q}{K}\right)^{\alpha}\right) - \mu A P - k_{PQ} P + k_{QP} Q &=: f(P,Q) \\ \frac{dQ}{dt} &= k_{PQ} P - k_{QP} Q &=: g(P,Q) \end{aligned} \tag{5.7}$$

with initial values

$$P(0) = P_0 \text{ and } Q(0) = Q_0.$$

Then the total number of tumour cells is

$$N(t) = P(t) + Q(t).$$

The rate k_{PQ} in equations (5.7) is the rate at which proliferating cells become quiescent. This can be due to the lack of nutrients as the tumour increases in size. The rate at which quiescent cells become viable again is k_{QP}. Therefore the two populations differ in the way that only proliferating cells can multiply and are able to be killed by radiation whereas quiescent cells cannot multiply and are not affected by radiation.

Again I find the trivial stationary point to be zero

$$(\overline{P}_1, \overline{Q}_1) = (0, 0).$$

Setting $\frac{dQ}{dt} = 0$ I find that

$$Q = \frac{k_{PQ}}{k_{QP}} P. \tag{5.8}$$

Inserting Q from equation (5.8) into $\frac{dP}{dt} = 0$ results in

$$\begin{aligned} \overline{P}_2 &= K\left(1 - \frac{\alpha\mu A}{r}\right)^{\frac{1}{\alpha}} \cdot \frac{k_{QP}}{k_{PQ} + k_{QP}} \\ \Rightarrow \overline{Q}_2 &= K\left(1 - \frac{\alpha\mu A}{r}\right)^{\frac{1}{\alpha}} \cdot \frac{k_{PQ}}{k_{PQ} + k_{QP}} \end{aligned}$$

Both points together add up to the same nontrivial stationary point as in the basic model.

$$\overline{P}_2 + \overline{Q}_2 = K\left(1 - \frac{\alpha\mu A}{r}\right)^{\frac{1}{\alpha}} = \overline{N}_2$$

From equation (5.8) I know that either both types of cells do not exist $(\overline{P}_1, \overline{Q}_1)$ or they coexist $(\overline{P}_2, \overline{Q}_2)$. To find the stability of the two stationary points I calculate the Jacobian matrix of the coupled system.

$$\begin{aligned} J(P,Q) &= \begin{pmatrix} \frac{\partial f}{\partial P} & \frac{\partial f}{\partial Q} \\ \frac{\partial g}{\partial P} & \frac{\partial g}{\partial Q} \end{pmatrix} \\ &= \begin{pmatrix} \Gamma_1 & \Gamma_2 \\ k_{PQ} & -k_{QP} \end{pmatrix} \end{aligned} \tag{5.9}$$

with

$$\Gamma_1 := \frac{r}{\alpha}\left(1 - \frac{1}{K^\alpha}(P+Q)^\alpha - \frac{\alpha}{K^\alpha}P(P+Q)^{\alpha-1}\right) - \mu A - k_{PQ}$$

and

$$\Gamma_2 := k_{QP} - \frac{r}{K^\alpha}P(P+Q)^{\alpha-1}$$

Inserting the trivial stationary point yields

$$J(0,0) = \begin{pmatrix} \frac{r}{\alpha} - \mu A - k_{PQ} & k_{QP} \\ k_{PQ} & -k_{QP} \end{pmatrix} \tag{5.10}$$

The stationary point $(0,0)$ is stable if both eigenvalues of the Jacobian matrix in equation (5.10) are smaller than zero. The eigenvalues are calculated to

$$\lambda_{1/2} = -\frac{1}{2}(\mu A - \frac{r}{\alpha} + k_{PQ} + k_{QP}) \pm \sqrt{\frac{1}{4}(\mu A - \frac{r}{\alpha} + k_{PQ} + k_{QP})^2 - k_{QP}(\mu A - \frac{r}{\alpha})}$$

Therefore for λ_1 and λ_2 to be smaller than zero,

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

has to hold. If $A < \frac{r}{\alpha\mu}$ both eigenvalues are larger than zero and the trivial stationary point is unstable. This is the same criteria for stability as in the basic model for the trivial stationary point $\overline{N}_1 = 0$. Inserting the nontrivial stationary point $(\overline{P}_2, \overline{Q}_2)$ into equation (5.9) results in

$$J(\overline{P}_2, \overline{Q}_2) = \begin{pmatrix} -k_{PQ} - r\left(1 - \frac{\alpha\mu A}{r}\right)\frac{k_{QP}}{k_{QP}+k_{PQ}} & k_{QP} - r\left(1 - \frac{\alpha\mu A}{r}\right)\frac{k_{QP}}{k_{QP}+k_{PQ}} \\ k_{PQ} & -k_{QP} \end{pmatrix} \tag{5.11}$$

The eigenvalues of the Jacobian matrix are

$$\lambda_{1/2} = -\frac{1}{2}\Lambda \pm \sqrt{\frac{1}{4}\Lambda^2 - k_{QP}(r - \alpha\mu A)}$$

with

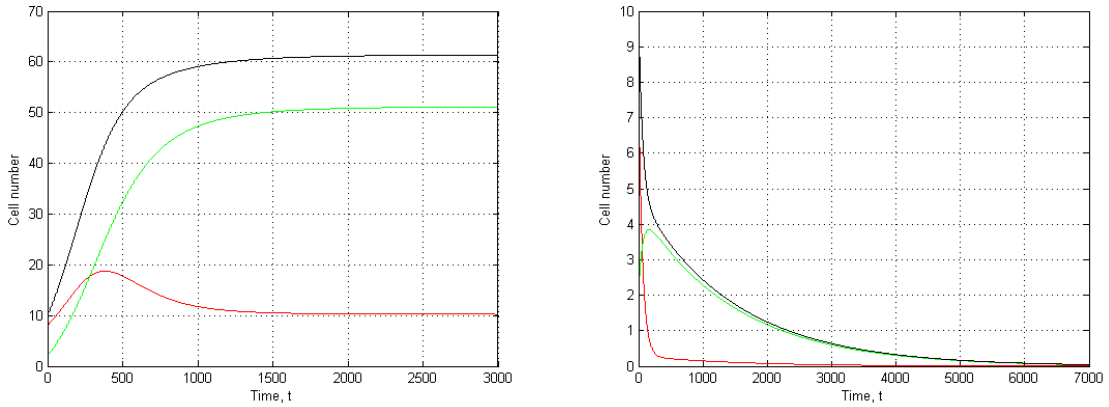
$$\Lambda := k_{PQ} + k_{QP} + \frac{k_{QP}}{k_{QP} + k_{PQ}}(r - \alpha\mu A)$$

Both eigenvalues are smaller than zero, meaning the nontrivial stationary point is stable, if

$$A < \frac{r}{\alpha\mu}$$

and unstable if $A > \frac{r}{\alpha\mu}$. Again, the stability property of the nontrivial stationary point $\overline{N}_2 = K\left(1 - \frac{\alpha\mu A}{r}\right)^{\frac{1}{\alpha}}$ of the basic model is applicable here.

I used the explicit euler method to solve the coupled system of equation (5.7) in Matlab. Figure 35 shows the model using different doses of radiation. Proliferating cells are marked in red, quiescent cells in green and the total number of tumour cells are shown in black. A is still below the threshold of $\frac{r}{\alpha\mu} = 0.1925$ in plot 35a and therefore the cells tend to the nontrivial stationary point $(\overline{P}_2, \overline{Q}_2) = (10.2, 51.2)$. In total the population tends to $\overline{N}_2 = 61.4$ as in the basic model. However, looking at the x-axis in figure 35a one can see that it takes much longer for the tumour to reach its capacity compared to figure 29a. This also holds true for the case where $A > 0.1925$ in plot 35b. Here the tumour cells tend to the trivial stationary point $(0, 0)$ since the radiation dosage is high enough. The reason for the more lengthy timespan is the fact that only the proliferating cells P are affected by the radiation. The quiescent cells Q can 'escape' from it, leaving a smaller population to be irradiated at a certain point in time. In figure 35 one can see that the quiescent cells make up the majority of the tumour. This is due to $k_{PQ} > k_{QP}$, so the rate at which proliferating cells become quiescent is higher than the rate at which quiescent cells become viable again. This makes sense since it has been shown that the oxygen deprived core of a larger tumour grows at the same rate as the whole tumour, leaving the rim of proliferating cells to stay constant over time [TG95].



(a) $A = 0.1$ (b) $A = 0.3$

Figure 35: Total number of tumour cells in black, proliferating cells in red and quiescent cells in green, using equation (5.7). Parameter values are $h = 0.1$, $r = \ln 2/24$, $P_0 = 8$, $Q_0 = 2$, $K = 100$, $\alpha = 1.5$, $\mu = 0.1$, $k_{PQ} = 0.005$ and $k_{QP} = 0.001$.

Figure 36 shows that no matter which starting point is used, the cell population will always tend to its nontrivial stationary point if A is small enough. It was produced using pplane in Matlab.

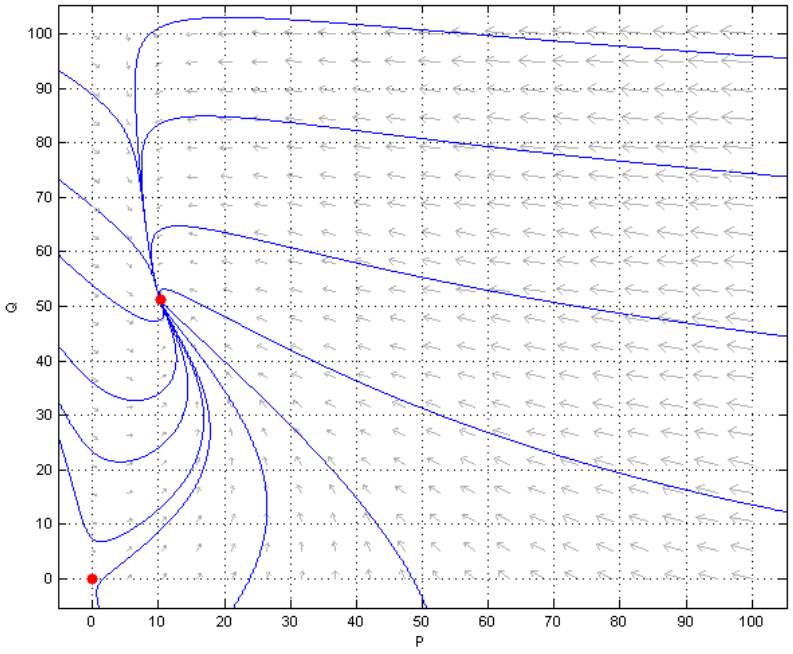


Figure 36: Global PQ diagram using equation (5.7). Red dots are the stationary points and the blue lines show possible trajectories. Parameter values are $A = 0.1$, $r = \ln 2/24$, $K = 100$, $\alpha = 1.5$, $\mu = 0.1$, $k_{PQ} = 0.005$ and $k_{QP} = 0.001$.

Radiosensitivity of sensitive and resistant tumour cells Another approach to modelling a heterogenous tumour population is to assume that some cells are more radiosensitive than others, but all being viable and not quiescent. As seen in chapter 4 cells that proliferate at a faster rate are more sensitive than those that grow at a slower rate [OMH09]. Let $S(t)$ be the number of radiosenstive tumour cells and $R(t)$ the number of radioresistant tumour cells. Then the model equations read

$$\begin{aligned} \frac{dS}{dt} &= \frac{r_1}{\alpha} S\left(1 - \left(\frac{S+R}{K}\right)^{\alpha}\right) - \mu_1 AS \quad =: f(S,R) \\ \frac{dR}{dt} &= \frac{r_2}{\alpha} R\left(1 - \left(\frac{S+R}{K}\right)^{\alpha}\right) - \mu_2 AR \quad =: g(S,R) \end{aligned} \tag{5.12}$$

with initial values

$$S(0) = S_0 \text{ and } R(0) = R_0.$$

The total number of tumour cells is

$$N(t) = S(t) + R(t).$$

Since the sensitive tumour cells grow faster and are more sensitive to radiation, I assume that $r_1 > r_2$ and $\mu_1 > \mu_2$. Therefore the two populations differ by their growth and death rates but are otherwise the same type of cell.

Again the trivial stationary point is zero

$$(\overline{S}_1, \overline{R}_1) = (0,0).$$

Setting $\frac{dS}{dt} = 0$ I find that

$$\overline{S} = K\left(1 - \frac{\alpha\mu_1 A}{r_1}\right)^{\frac{1}{\alpha}} - R.$$

Analogously setting $\frac{dR}{dt} = 0$ I find that

$$\overline{R} = K\left(1 - \frac{\alpha\mu_2 A}{r_2}\right)^{\frac{1}{\alpha}} - S.$$

By inserting $\overline{S}$ into $\frac{dR}{dt} = 0$ I find that R has to be zero and vice versa, meaning that both type of cells cannot coexist. The nontrivial stationary points are

$$(\overline{S}_2, \overline{R}_2) = (K\left(1 - \frac{\alpha\mu_1 A}{r_1}\right)^{\frac{1}{\alpha}}, 0)$$

and

$$(\overline{S}_3, \overline{R}_3) = (0, K\left(1 - \frac{\alpha\mu_2 A}{r_2}\right)^{\frac{1}{\alpha}}).$$

To find the stability of the three stationary points I calculate the Jacobian matrix of the coupled system.

$$J(S,R) = \begin{pmatrix} \frac{\partial f}{\partial S} & \frac{\partial f}{\partial R} \\ \frac{\partial g}{\partial S} & \frac{\partial g}{\partial R} \end{pmatrix} \tag{5.13}$$

with

$$\begin{aligned}
\frac{\partial f}{\partial S} &:= \frac{r_1}{\alpha}\left(1 - \frac{1}{K^\alpha}(S+R)^\alpha - \frac{\alpha}{K^\alpha}S(S+R)^{\alpha-1}\right) - \mu_1 A \\
\frac{\partial f}{\partial R} &:= \frac{r_1}{K^\alpha}S(S+R)^{\alpha-1} \\
\frac{\partial g}{\partial S} &:= \frac{r_2}{K^\alpha}R(S+R)^{\alpha-1} \\
\frac{\partial g}{\partial R} &:= \frac{r_2}{\alpha}\left(1 - \frac{1}{K^\alpha}(S+R)^\alpha - \frac{\alpha}{K^\alpha}R(S+R)^{\alpha-1}\right) - \mu_2 A
\end{aligned}$$

Inserting the trivial stationary point yields

$$J(0,0) = \begin{pmatrix} \frac{r_1}{\alpha} - \mu_1 A & 0 \\ 0 & \frac{r_2}{\alpha} - \mu_2 A \end{pmatrix} \tag{5.14}$$

The stationary point $(0,0)$ is stable if both eigenvalues of the Jacobian matrix in equation (5.14) are smaller than zero. The eigenvalues are

$$\begin{aligned}
\lambda_1 &= \frac{r_1}{\alpha} - \mu_1 A \\
\lambda_2 &= \frac{r_2}{\alpha} - \mu_2 A
\end{aligned}$$

Therefore if

$$A > \frac{r_1}{\alpha\mu_1} \text{ and } A > \frac{r_2}{\alpha\mu_2}$$

both eigenvalues are zero. If $A < \frac{r_1}{\alpha\mu_1}$ or $A < \frac{r_2}{\alpha\mu_2}$ at least one eigenvalue is positive and the trivial stationary point is unstable. Inserting the nontrivial stationary point $(\overline{S}_2, \overline{R}_2)$ into equation (5.13) yields

$$J(\overline{S}_2, \overline{R}_2) = \begin{pmatrix} -r_1 + \alpha\mu_1 A & r_1 - \alpha\mu_1 A \\ 0 & -\mu_2 A + \frac{r_2}{r_1}\mu_1 A \end{pmatrix} \tag{5.15}$$

The eigenvalues of the Jacobian matrix are

$$\lambda_{1/2} = -\frac{1}{2}\Lambda \pm \sqrt{\frac{1}{4}\Lambda^2 + A(r_1\mu_2 + \mu_1(-r_2 - \alpha\mu_2 A + \alpha\mu_1 A\frac{r_2}{r_1}))}$$

with

$$\Lambda := r_1 + A(-\alpha\mu_1 + \mu_2 - \frac{r_2}{r_1}\mu_1)$$

Both eigenvalues are negative, meaning the stationary point is stable if

$$A < \frac{r_1}{\alpha\mu_1}$$

and unstable else. Inserting the second nontrivial stationary point $(\overline{S}_3, \overline{R}_3)$ into equation (5.13) yields

$$J(\overline{S}_3, \overline{R}_3) = \begin{pmatrix} -\mu_1 A + \frac{r_1}{r_2}\mu_2 A & 0 \\ r_2 - \alpha\mu_2 A & -r_2 + \alpha\mu_2 A \end{pmatrix} \tag{5.16}$$

Both eigenvalues of this Jacobian matrix are negative, meaning the stationary point is stable if

$$A < \frac{r_2}{\alpha\mu_2}$$

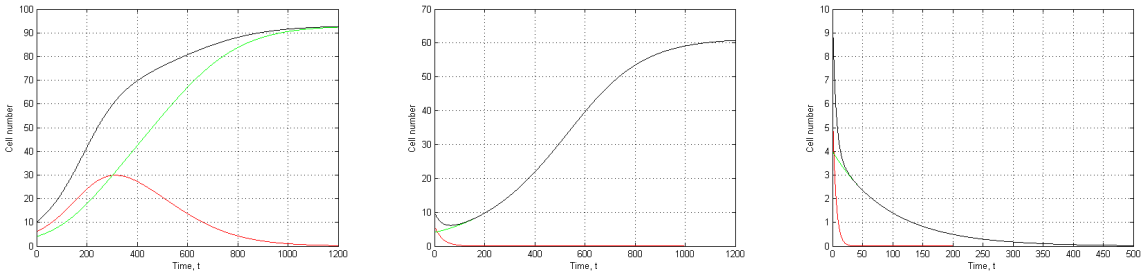
and unstable else.

Once again I used the explicit euler method to solve the coupled system of equations (5.12) in Matlab.

Figure 37 shows the model using different doses of radiation. Radiosensitive cells are marked in red, resistant cells in green and the total number of tumour cells are shown in black. I need to differentiate between two cases, one that the ratio $\frac{r_1}{\alpha\mu_1} < \frac{r_2}{\alpha\mu_2}$ and the other that the ratio $\frac{r_1}{\alpha\mu_1} > \frac{r_2}{\alpha\mu_2}$. Figure 37 shows the first case, with $\frac{r_1}{\alpha\mu_1} = 0.1925$ and $\frac{r_2}{\alpha\mu_2} = 0.9627$. Since the larger ratio is $\frac{r_2}{\alpha\mu_2}$, the cells will tend to the nontrivial stationary point $(\overline{S}_3, \overline{R}_3)$ if A is small enough, meaning that the resistant cells will survive and grow to their capacity and the sensitive cells will die. A is small enough in plot 37a and therefore the cells tend to the nontrivial stationary point $(0, 92.9)$. The green line is equal to the black line after a certain time period since the sensitive cells (red line) die out and only the resistant cells remain, making up the whole tumour. In figure 37b A is still smaller than $\frac{r_2}{\alpha\mu_2} = 0.9627$, therefore the resistant cells survive and the sensitive cells die out. The total population tends to 61.4 cells. Obviously fewer cells survive than in figure 37a since a higher radiation dose is administered. In figure 37c A is larger than $\frac{r_1}{\alpha\mu_1}$ and $\frac{r_2}{\alpha\mu_2}$ and therefore both cell types die out. The trivial stationary point $(0, 0)$ is stable.

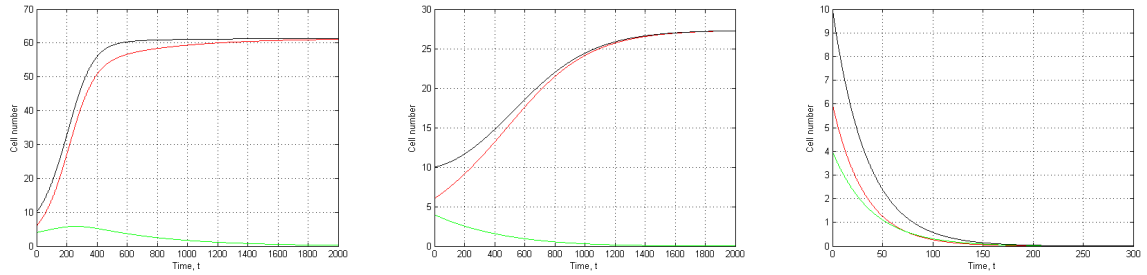
Figure 38 shows the second case, where $\frac{r_1}{\alpha\mu_1} = 0.1925 > 0.1373 = \frac{r_2}{\alpha\mu_2}$. In figures 38a and 38b $A < 0.1925$, therefore the tumour survives radiation. This time the stationary point $(\overline{S}_2, \overline{R}_2)$ is stable, thus the sensitive cells survive and the resistant cells die out.

Summing up, sensitive and resistant cells will die out if A is large enough, as seen in figures 37c and 38c. If A is too small, however, only one type of cell will survive. This depends on its ratio of $\frac{r_i}{\mu_i}$. The type of cell whose ratio is larger than that of the other type of cell, survives and the tumour ends up being made up solely of cells of that type. In addition, in both cases it does not take as long as in the previous model for all cells to die if A is large enough, thus for the trivial stationary point $(0, 0)$ to be reached. The time scale on the x-axis is similar to the basic model in figure 29b. This is due to the fact that both type of cells are 'attacked' by radiation and not just one as in the previous model.



(a) $A = 0.1$ (b) $A = 0.5$ (c) $A = 2$

Figure 37: Total number of tumour cells in black, proliferating cells in red and quiescent cells in green, using equation (5.12). Additional parameter values are $h = 0.1$, $r_1 = \ln 2/24$, $r_2 = \ln 2/48$, $S_0 = 6$, $R_0 = 4$, $K = 100$, $\alpha = 1.5$, $\mu_1 = 0.1$ and $\mu_2 = 0.01$.



(a) $A = 0.1$ (b) $A = 0.165$ (c) $A = 0.5$

Figure 38: Total number of tumour cells in black, proliferating cells in red and quiescent cells in green, using equation (5.12). Additional parameter values are $h = 0.1$, $r_1 = \ln 2/24$, $r_2 = \ln 2/48$, $S_0 = 6$, $R_0 = 4$, $K = 100$, $\alpha = 1.5$, $\mu_1 = 0.1$ and $\mu_2 = 0.07$.

5.1.2. Periodic Radiation

The idea behind the models in section 5.1.1 was to show the long term effect that radiation has on tumour cells compared to the LQ-model in chapter 4. However irradiating a patient with a constant amount of radiation over a certain period of time is not realistic and could be more harmful to healthy organs and tissue. In reality patients will receive periodic radiation treatments over a period of a few weeks, examples were listed in chapter 2.2. This gives the healthy cells time to repair in-between radiation sessions, unfortunately this is also the case for tumour cells.

Basic Model I use the basic model for continuous radiation (equation (5.1) on page 38) but change the variable A (based on a model in [Pre03]). Thus the model reads

$$\begin{aligned} \frac{dN}{dt} &= \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N \text{ with } \mu > 0, \\ N(0) &= N_0 \end{aligned} \tag{5.17}$$

Instead of administering a constant amount of radiation as before, I change A to be periodic.

$$A(t) = \begin{cases} a & \text{if } n < t \leq n + \tau, \\ 0 & \text{if } n + \tau < t \leq n + 1 \end{cases}$$

with $n = 0, 1, 2, ...$ being the radiation session and $\tau \in (0, 1)$ being the proportional duration of radiation. So inbetween each session there is a period of radiation, of amount a, and a period without radiation. τ decides how long the period of radiation is compared to the period without. If τ were 1, the model would be reduced to the continuous case.

The solution to equation (5.17) can be calculated as in the continuous case for $n < t \leq n + \tau$ and as in the generalised logistic growth equation for $n + \tau < t \leq n + 1$. The complete solution reads

$$N(t) = \begin{cases} \frac{N_n K}{\left(\frac{N_n^{\alpha} r}{r - \alpha\mu a} + e^{(-r + \alpha\mu a)(t-n)}(K^{\alpha} - \frac{N_n^{\alpha} r}{r - \alpha\mu a})\right)^{\frac{1}{\alpha}}} & \text{if } n < t \leq n + \tau, \\ \frac{N_{n+\tau} K}{\left(N_{n+\tau}^{\alpha} + e^{-r(t-n-\tau)}(K^{\alpha} - N_{n+\tau}^{\alpha})\right)^{\frac{1}{\alpha}}} & \text{if } n + \tau < t \leq n + 1. \end{cases} \tag{5.18}$$

The stationary points of the model can be calculated by setting equation (5.17) to zero.

$$\Rightarrow \overline{N}_1 = 0$$

The nontrivial stationary point switches between K as in the generalised logistic growth equation and $K\left(1 - \frac{\alpha\mu a}{r}\right)^{\frac{1}{\alpha}}$ as in the basic model with continuous radiation. By linearising equation (5.17) I can find the amount of radiation needed to kill off the tumour, resulting in the trivial stationary point $\overline{N}_1$ being stable.

$$\begin{aligned} \frac{\partial f(N)}{\partial N} &= \frac{r}{\alpha} - \mu A - \frac{r}{\alpha K^{\alpha}} N^{\alpha}(\alpha + 1) \\ \Rightarrow \frac{\partial f(\overline{N}_1)}{\partial N} &= \frac{r}{\alpha} - \mu A \\ \Rightarrow \frac{\partial f(\overline{N}_1)}{\partial N}(N(t) - \overline{N}_1) &= \left(\frac{r}{\alpha} - \mu A\right)(N(t) - \overline{N}_1) \end{aligned}$$

By setting $N^*(t) = N(t) - \overline{N}_1$ I can find the solution $N^*(t)$

$$\frac{dN^*}{dt} = \left(\frac{r}{\alpha} - \mu A\right) N^*(t)$$

$$\Rightarrow N^*(t) = \begin{cases} N_n^* e^{(r/\alpha - \mu a)(t-n)} & \text{if } n < t \leq n + \tau, \\ N_{n+\tau}^* e^{r/\alpha (t-n-\tau)} & \text{if } n + \tau < t \leq n + 1, \end{cases}$$

From the case with radiation I can calculate $N_{n+\tau}^*$

$$N_{n+\tau}^* = N^*(t = n + \tau) = N_n^* e^{(r/\alpha - \mu a)\tau}.$$

Then inserting this into the case without radiation I get

$$N_{n+1}^* = N^*(t = n + 1) = N_n^* e^{r/\alpha - \mu a \tau}.$$

For

$$a > \frac{r}{\alpha \mu \tau}$$

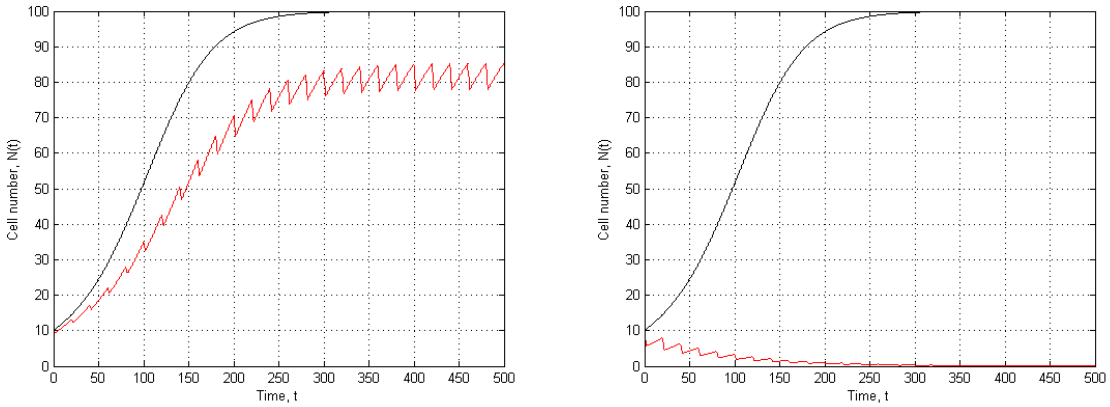
it holds that

$$N_{n+1}^* < N_n^* \ \forall n.$$

This means that when a is large enough the tumour shrinks each session, eventually dying out. This means that $\overline{N}_1 = 0$ is stable. a needs to be larger than in the case of continuous radiation ($\frac{r}{\alpha\mu\tau} > \frac{r}{\alpha\mu}$). This is not surprising since the cells are not radiated with the same total amount as in the continuous case.
For $a < \frac{r}{\alpha\mu\tau}$ $\overline{N}_1 = 0$ is unstable, since $N_{n+1}^* > N_n^* \ \forall n$ thus the tumour grows each session.

Figure 39a shows the difference a dose of 0.5 Gy has on a tumour cell population. The black line is the solution to the generalised logistic growth equation. As one can see the tumour starts with an initial number of tumour cells larger than zero and tends to the capacity of 100 cells. Plotting the solution of my model for periodic radiation (equation (5.18)) renders the red line. As I chose a too low dose ($a = 0.5 < 1.9254 = \frac{r}{\alpha\mu\tau}$) not all tumour cells are killed by radiation and enough are left to proliferate. The red line in figure 39b on the other hand uses a dose of 3 Gy, which is larger than $\frac{r}{\alpha\mu\tau}$. One can see that the cell number tends to zero, all tumour cells will die. For figure 39 I assumed the time between two sessions to be 20 hours and the duration of radiation in each session to be two hours, thus $\tau = 0.1$

Now I can implement different factors as in section 5.1.1 into this basic model for periodic radiation.



(a) $a = 0.5$ (b) $a = 3$

Figure 39: Tumour growth without radiation in black and with periodic radiation in red, using equation (5.18). Parameter values are $N_0 = 10$, $K = 100$, $\alpha = 1.5$, $r = \ln 2/24$, $\mu = 0.1$ and $\tau = 0.1$.

Repair As explained in section 5.1.1 tumour cells are able to repair themselves during low doses of radiation, so I want to include this in the model with periodic radiation as well. The equation reads

$$\begin{aligned} \frac{dN}{dt} &= \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N + \rho\lambda A N \text{ with } \rho > 0, \\ N(0) &= N_0 \end{aligned} \tag{5.19}$$

with

$$A(t) = \begin{cases} a & \text{if } n < t \leq n + \tau, \\ 0 & \text{if } n + \tau < t \leq n + 1. \end{cases}$$

The solution is

$$N(t) = \begin{cases} \dfrac{N_n K}{\left(\frac{N_n^{\alpha} r}{r - \alpha\mu a + \alpha\rho\mu a} + e^{(-r + \alpha\mu a - \alpha\rho\mu a)(t-n)}(K^{\alpha} - \frac{N_n^{\alpha} r}{r - \alpha\mu a + \alpha\rho\mu a})\right)^{\frac{1}{\alpha}}} & \text{if } n < t \leq n + \tau, \\ \dfrac{N_{n+\tau} K}{\left(N_{n+\tau}^{\alpha} + e^{-r(t-n-\tau)}(K^{\alpha} - N_{n+\tau}^{\alpha})\right)^{\frac{1}{\alpha}}} & \text{if } n + \tau < t \leq n + 1. \end{cases} \tag{5.20}$$

The stationary points of the model can be calculated by setting equation (5.19) to zero.

$$\Rightarrow \overline{N}_1 = 0$$

The nontrivial stationary point switches between K as in the generalised logistic growth equation and $K\left(1 - \frac{\alpha\mu a}{r} + \frac{\alpha\rho\lambda a}{r}\right)^{\frac{1}{\alpha}}$ as in the case with continuous radiation with repair. By linearising equation (5.19) I can find the amount of radiation needed to kill off the

tumour, thus for the trivial stationary point $\overline{N}_1$ to be stable.

$$\begin{aligned} \frac{\partial f(N)}{\partial N} &= \frac{r}{\alpha} - \mu A + \rho\lambda A - \frac{r}{\alpha K^\alpha} N^\alpha(\alpha+1) \\ \Rightarrow \frac{\partial f(\overline{N}_1)}{\partial N} &= \frac{r}{\alpha} - \mu A + \rho\lambda A \\ \Rightarrow \frac{\partial f(\overline{N}_1)}{\partial N}(N(t) - \overline{N}_1) &= \left(\frac{r}{\alpha} - \mu A + \rho\lambda A\right)(N(t) - \overline{N}_1) \end{aligned}$$

By setting $N^*(t) = N(t) - \overline{N}_1$ I can find the solution $N^*(t)$

$$\frac{dN^*}{dt} = \left(\frac{r}{\alpha} - \mu A + \rho\lambda A\right) N^*(t)$$

$$\Rightarrow N^*(t) = \begin{cases} N_n^* e^{(r/\alpha - \mu a + \rho\lambda a)(t-n)} & \text{if } n < t \leq n+\tau, \\ N_{n+\tau}^* e^{r/\alpha(t-n-\tau)} & \text{if } n+\tau < t \leq n+1, \end{cases}$$

From the case with radiation I can calculate $N_{n+\tau}^*$

$$N_{n+\tau}^* = N^*(t = n+\tau) = N_n^* e^{(r/\alpha - \mu a + \rho\lambda a)\tau}.$$

Then inserting this into the case without radiation I get

$$N_{n+1}^* = N^*(t = n+1) = N_n^* e^{r/\alpha - \mu a\tau + \rho\lambda a\tau}.$$

For

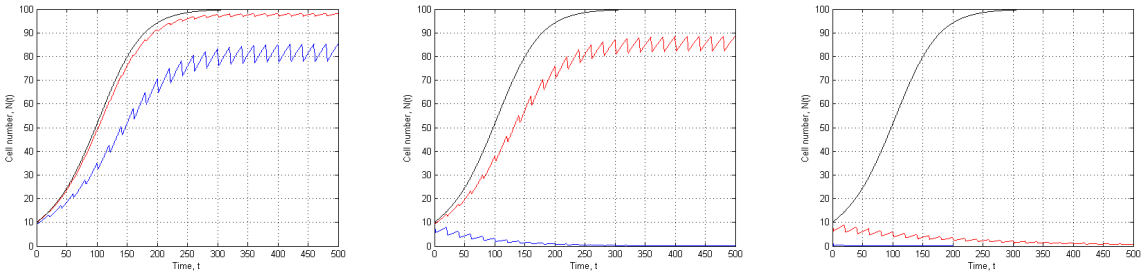
$$a > \frac{r}{\alpha(\mu - \rho\lambda)\tau}$$

it holds that

$$N_{n+1}^* < N_n^* \ \forall n.$$

This means that when a is large enough the tumour shrinks each session, eventually dying out. This means that $\overline{N}_1 = 0$ is stable. Again a needs to be larger than in the case of continuous radiation with repair ($\frac{r}{\alpha(\mu-\rho\lambda)\tau} > \frac{r}{\alpha(\mu-\rho\lambda)}$). For $a < \frac{r}{\alpha(\mu-\rho\lambda)\tau}$, $\overline{N}_1 = 0$ is unstable, since $N_{n+1}^* > N_n^* \ \forall n$ and the tumour would grow each session.

Figure 40 shows three different plots using equation (5.20). I used the same parameters as in figure 39, however, varying the amount of radiation A and setting $\rho = 0.5$ and $\lambda = \ln 2/4$. The black line shows the tumour growth without radiation and the blue line shows tumour growth including periodic radiation but without repair. As one can see from figure 40b A is large enough to kill all tumour cells in the case without repair (blue line) but not enough when I include repair in the model (red line). Here, A needs to be larger than $\frac{r}{\alpha(\mu-\rho\lambda)\tau} = 14.4$ to kill all tumour cells, as seen in figure 40c. In figure 40 I assumed a radiation session to take two hours, followed by a resting period of 18 hours, as in figure 39.



(a) $A = 0.5$ (b) $A = 3$ (c) $A = 18$

Figure 40: Tumour growth without radiation in black, with radiation in blue and including repair in red, using equation (5.20). Parameter values are $N_0 = 10$, $K = 100$, $\alpha = 1.5$, $r = \ln 2/24$, $\mu = 0.1$, $\rho = 0.5$, $\lambda = \ln 2/4$ and $\tau = 0.1$.

Repopulation In addition I want to include repopulation as in the case of continuous radiation, thus I assume β to be the amount of cells able to proliferate despite being radiated. Then the model reads

$$\begin{aligned} \frac{dN}{dt} &= \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) - \mu A N + \beta A \frac{r}{\alpha} N \left(1 - \left(\frac{N}{K}\right)^{\alpha}\right) \text{ with } \beta > 0, \\ N(0) &= N_0 \end{aligned} \tag{5.21}$$

The solution of equation (5.21) is

$$N(t) = \begin{cases} \frac{N_n K}{\left(\frac{N_n^{\alpha}(r+\beta a r)}{r-\alpha\mu a+\beta a r} + e^{(-r+\alpha\mu a-\beta a r)(t-n)}(K^{\alpha} - \frac{N_n^{\alpha}(r+\beta a r)}{r-\alpha\mu a+\beta a r})\right)^{\frac{1}{\alpha}}} & \text{if } n < t \leq n+\tau, \\ \frac{N_{n+\tau} K}{\left(N_{n+\tau}^{\alpha} + e^{-r(t-n-\tau)}(K^{\alpha} - N_{n+\tau}^{\alpha})\right)^{\frac{1}{\alpha}}} & \text{if } n+\tau < t \leq n+1. \end{cases} \tag{5.22}$$

The stationary points of the model can be calculated as usual

$$\Rightarrow \overline{N}_1 = 0.$$

The nontrivial stationary point switches between K as in the generalised logistic growth equation and $K\left(1 - \frac{\alpha\mu a}{r(1+\beta a)}\right)^{\frac{1}{\alpha}}$ as in the case with continuous radiation with repopulation. By linearising equation (5.21) I can find the amount of radiation needed to kill off the tumour, thus for the trivial stationary point $\overline{N}_1$ to be stable.

$$\begin{aligned} \frac{\partial f(N)}{\partial N} &= \frac{r}{\alpha} - \mu A + \beta A \frac{r}{\alpha} - \frac{r}{\alpha K^{\alpha}} N^{\alpha}(\alpha+1) - \beta A \frac{r}{\alpha}\left(\frac{N}{K}\right)^{\frac{1}{\alpha}}(\alpha+1) \\ \Rightarrow \frac{\partial f(\overline{N}_1)}{\partial N} &= \frac{r}{\alpha} - \mu A + \beta A \frac{r}{\alpha} \\ \Rightarrow \frac{\partial f(\overline{N}_1)}{\partial N}(N(t) - \overline{N}_1) &= \left(\frac{r}{\alpha} - \mu A + \beta A \frac{r}{\alpha}\right)(N(t) - \overline{N}_1) \end{aligned}$$

By setting $N^*(t) = N(t) - \overline{N}_1$ I can find the solution $N^*(t)$

$$\frac{dN^*}{dt} = \left(\frac{r}{\alpha} - \mu A + \beta A \frac{r}{\alpha}\right) N^*(t)$$

$$\Rightarrow N^*(t) = \begin{cases} N_n^* e^{(r/\alpha - \mu a + \beta a r/\alpha)(t-n)} & \text{if } n < t \leq n+\tau, \\ N_{n+\tau}^* e^{r/\alpha(t-n-\tau)} & \text{if } n+\tau < t \leq n+1, \end{cases}$$

From the case with radiation I can calculate $N_{n+\tau}^*$

$$N_{n+\tau}^* = N^*(t = n+\tau) = N_n^* e^{(r/\alpha - \mu a + \beta a r/\alpha)\tau}.$$

Then inserting this into the case without radiation I get

$$N_{n+1}^* = N^*(t = n+1) = N_n^* e^{r/\alpha - \mu a \tau + \beta a r/\alpha \tau}.$$

For

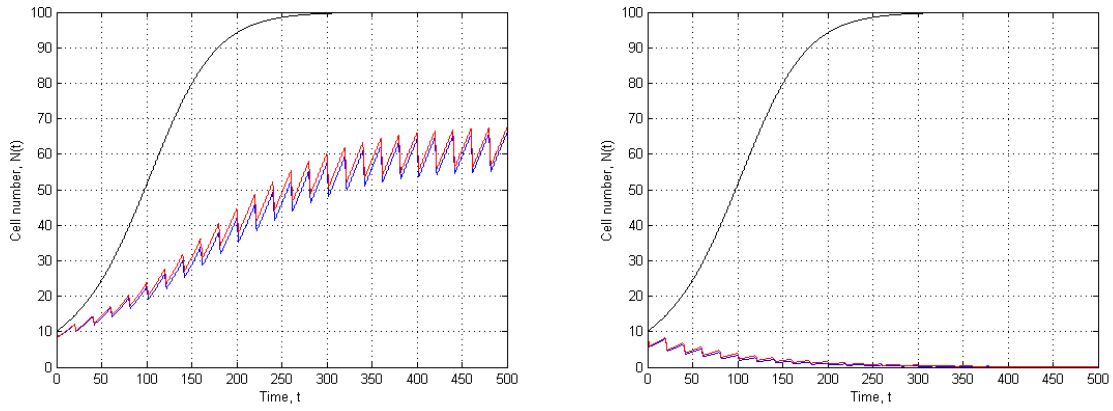
$$a > \frac{r}{(\alpha\mu - \beta r)\tau}$$

it holds that

$$N_{n+1}^* < N_n^* \ \forall n.$$

This means that when a is large enough the tumour shrinks each session, eventually dying out, meaning $\overline{N}_1 = 0$ is stable. Again a needs to be larger than in the case of continuous radiation with repopulation. For $a < \frac{r}{(\alpha\mu - \beta r)\tau}$, $\overline{N}_1 = 0$ is unstable, since $N_{n+1}^* > N_n^* \ \forall n$ thus the tumour grows each session.

Figure 41 shows two different plots using equation (5.22). I used the same parameters as in figure 39 as well as setting $\beta = 0.3$. The black line shows tumour growth without radiation, the blue line shows tumour growth including periodic radiation, as in the basic model, and the red curve uses the model with repopulation. As one can see, adding repopulation does not change the outcome as much as repair does, for example. This can be due to the parameter values chosen in figures 40 and 41. As one can see from the blue and the red line in plot 41a, the tumour cell population grows if the radiation dose is too low. For $a > \frac{r}{(\alpha\mu - \beta r)\tau} = 2.4$ the tumour cell population including repopulation tends to zero (plot 41b). Of course the model without repopulation (blue line) does so as well, since a only had to be larger than 1.925 in this model.



(a) $a = 1$ (b) $a = 3$

Figure 41: Tumour growth without radiation in black, with radiation in blue and including repopulation in red, using equation (5.22). Additional parameter values are $r = \ln 2/24$, $N_0 = 10$, $K = 100$, $\alpha = 1.5$, $\mu = 0.1$, $\tau = 0.1$ and $\beta = 0.3$.

5.1.3. Model versus Data

As I did in section 3.1.5 when I compared tumour growth data to my model, I now want to compare data of radiated tumour cells to the models in this chapter.

Human Ductal Breast Epithelial Tumour Cells The growth of T47D cells was measured in vitro by the Institute of Radiation Biology, Helmholtz-Zentrum München [AH12] using the GravityPLUS System from InSphero (www.insphero.com). This is the same cell line as one of the experiments in section 3.1.5 and is known to be radioresistant. In this experiment, 500 cells were placed on a 96-well plate and left to grow to a spheroid in a hanging drop for three days, after which it was dropped into a gravity plate and left for one more day. Time t was set to zero and the cells were radiated once with either 2, 4, 6 or 8 Gy of γ-rays. It is assumed that the γ-rays reach all cells equally. In addition, cells without radiation were measured to compare normal growth to growth with radiation. The area (in μm^2) of the spheroids were measured starting at $t = 0$ every three days until day 15. Each experiment was done twelve times and the mean of the collected data can be seen in table 2. To be comparable, the areas were normalised to the value at day zero and zero Gy.

Another experiment done by the same authors was a cell counting experiment (also with T47D cells). Various spheroids on four different days were measured and the cells were counted, resulting in a mean area of each measured day and a mean cell number per μm^2. I fitted these four data points to a function as seen in figure 42. This allowed me to approximate the number of cells for each measurement in table 2. The results of the function applied to the data in table 2 can be found in table 3. One can see from figure 42 that the larger the tumour becomes, the less space a single cell occupies. This means that in the early growth stages the cells are spaced further apart and take up more space than in the later stages. This is why I need to approximate the number of cells using a funtion as in figure 42 rather than using simple linear interpolation.

Area (μm^2)	*days*					
radiation	0	3	6	9	12	15
0 Gy	77,664	130,903	193,318	216,481	231,863	243,738
2 Gy	77,664	121,184	163,614	177,630	197,306	206,191
4 Gy	77,664	118,167	141,484	157,978	155,417	172,166
6 Gy	77,664	121,163	137,945	144,074	152,006	158,432
8 Gy	77,664	119,279	131,165	125,826	135,066	145,247

Table 2: Mean spheroid areas measured over a period of 15 days and different radiation doses; source: [AH12].

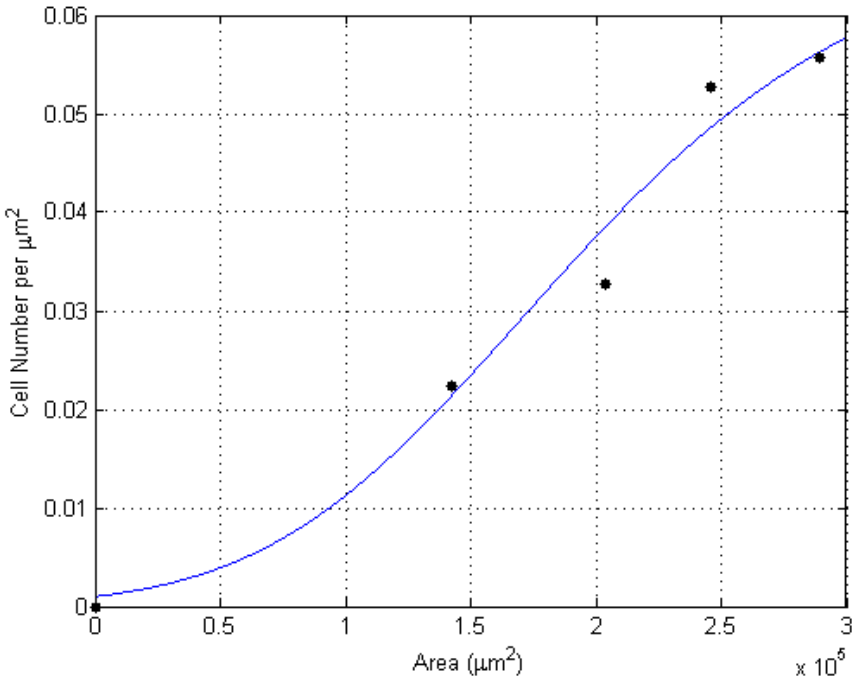


Figure 42: Function (blue line) to fit data (black dots) by [AH12].

No. of cells	*days*						
radiation	0	3	6	9	12	15	Survival
0 Gy	564.32	2,393.71	6,885.54	9,037.09	10,539.96	11,721.89	100%
2 Gy	564.32	1,922.83	4,455.84	5,545.76	7,243.12	8,060.54	69%
4 Gy	564.32	1,789.94	2,981.46	4,050.18	3,872.42	5,107.74	44%
6 Gy	564.32	1,921.87	2,776.20	3,137.19	3,642.32	4,082.09	35%
8 Gy	564.32	1,838.21	2,407.38	2,139.53	2,615.68	3,209.19	27%

Table 3: Corresponding number of cells based on data in table 2 approximated by the function in figure 42.

Before applying a model with radiation to the data, I need to find the basic model parameters for tumour growth. Thus I use the generalised logistic growth equation from section 3.1.3 to model the data with no radiation (0 Gy). The value for the initial number of tumour cells N_0 was set to 564.32 as in table 3 and the net proliferation rate r was set to $\frac{\ln 2}{60}$ as the cells have a doubling time of 60 hours. This means that the time between two successive mitoses is 60 hours. The values for the capacity K and α were chosen to minimise the error (calculated as in equation (3.7)). Therefore K was set to $12,690$ and α to 0.169. α is a lot smaller than one since this specific cell line reaches its capacity very quickly. In section 3.1.5 the growth of the T47D cell line was also analysed and α was equally fairly small. Figure 43 shows the results of the model (red line) compared to the data (black dots), resulting in an error of 0.0283. Since the model manages to capture the

data, I can now start applying radiation and compare this to the data for two to eight Gy.

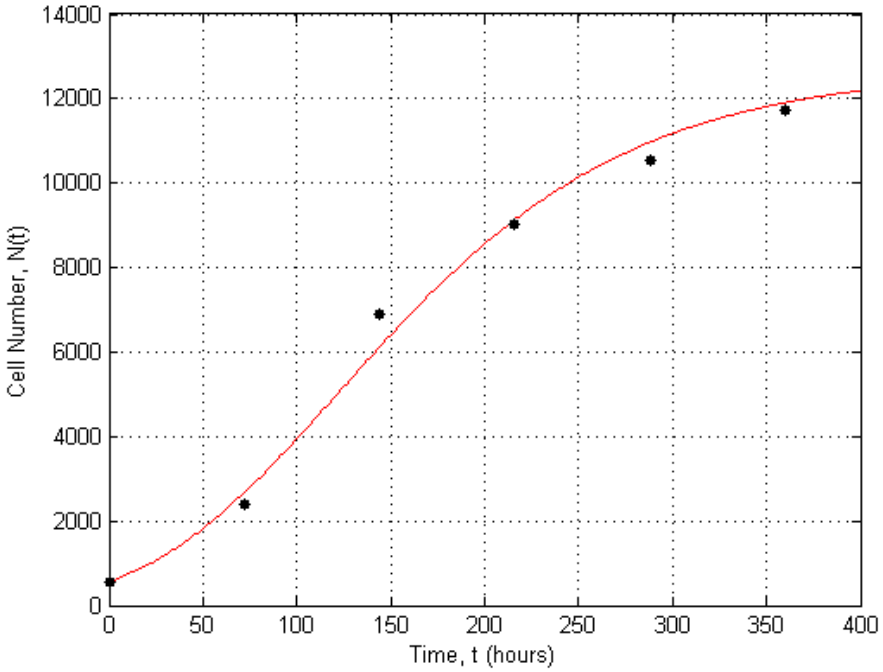
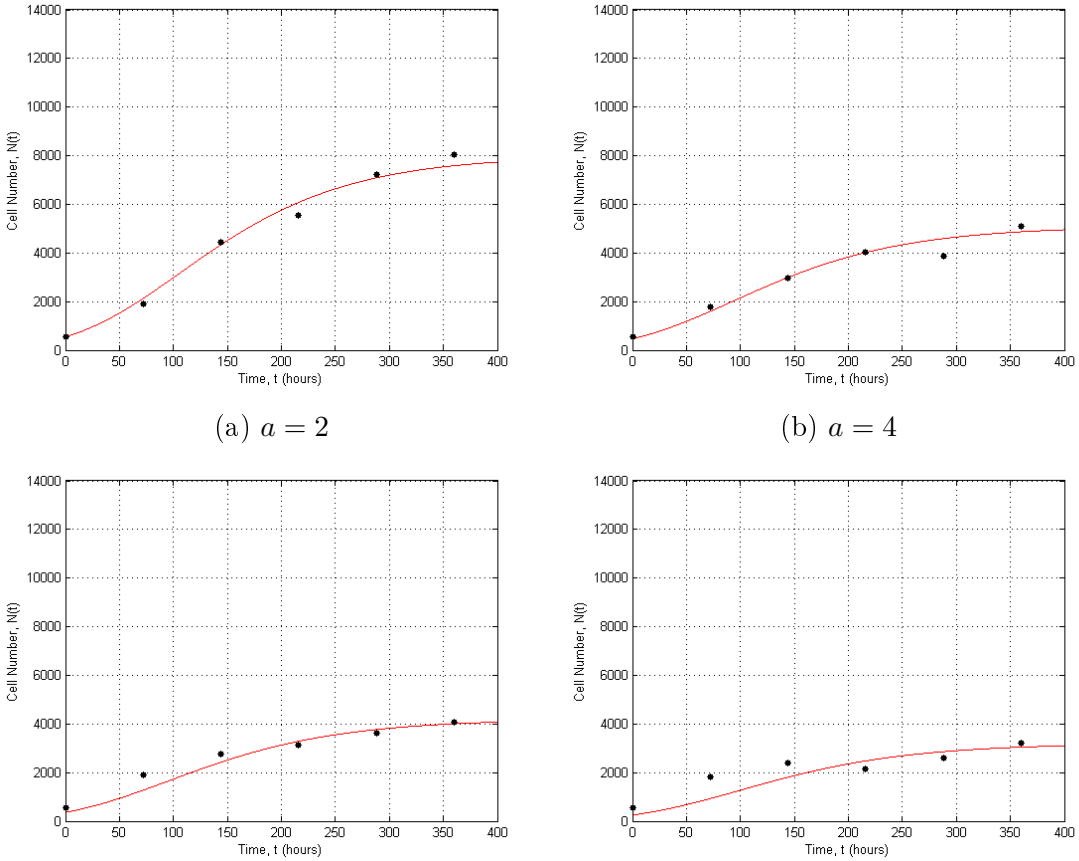


Figure 43: Modelling the growth of T47D breast cancer cells. Red line is the generalised logistic growth model (equation (3.6)) and the black dots are the data points. Parameter values are $r = \ln 2/60$, $N_0 = 564.32$, $\alpha = 0.169$ and $K = 12,690$. Data from [AH12].

To include radiation, I used a model with periodic radiation as in section 5.1.2 but with only one period, so $n = 0$, since the cells were only radiated once at $t = 0$ in this experiment. I began with comparing the data to the basic model from equation (5.17), setting $\mu = 0.4$ to get the best fit. This minimises the error (calculated as in equation (3.7)). After this, I compared the data to the extended model with repopulation. By setting β=0.9 I get the best fit to the data. This also further minimises the error, even if it is only a small improvement. As seen in figure 41 repopulation did not result in a huge change compared to the basic model. Figure 44 compares the model (red lines) with the above mentioned parameters to the data (black dots), whereby with each plot the amount of radiation increases. However, so do the errors, with the model for $a = 2$ having the best fit with an error of 0.0214 and the model for $a = 8$ the worst with an error of 1.1223. The error for $a = 4$ is 0.0429 and 0.2911 for $a = 6$. Figure 45 compares all five models for the different amounts of radiation.



(a) $a = 2$ (b) $a = 4$

(c) $a = 6$ (d) $a = 8$

Figure 44: Modelling the growth of T47D breast cancer cells. Red lines use the model for periodic radiation with repopulation (equation (5.22)). Black dots are the data points. Same parameters as in figure 43 with $\mu = 0.4$ and $\beta = 0.9$. Data from [AH12].

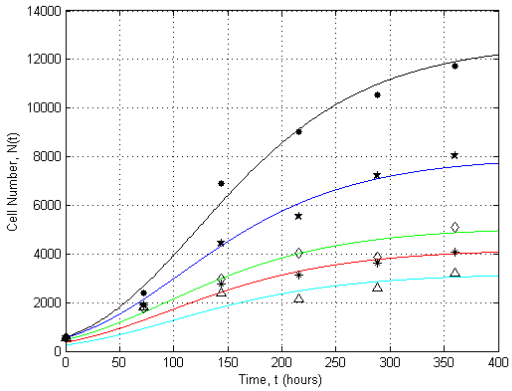


Figure 45: Comparison of the previous five figures with black/dots for 0 Gy, blue/stars for 2 Gy, green/diamonds for 4 Gy, red/crosses for 6 Gy and cyan/triangles for 8 Gy. Data from [AH12].

5.2. Spatial Model

The previous chapter showed that my mathematical models managed to capture the given data. However, since this data was only based on estimated number of cells, I now want to apply a model to the data that was actually measured. Table 2 in section 5.1.3 listed the means of the measured tumour areas over a period of 15 days and for different amounts of radiation. From this data I can easily calculate the corresponding mean radii. Consequently, I need to find an equation or a system of equations that can model the spatial growth of the tumour.

Burton [Bur66] and Greenspan [Gre72] created the earliest spatially-structured models of avascular tumour growth in the nineteen sixties and seventies. Thereby they were able to find the proportions of the tumour that were hypoxic and nectrotic. In this chapter I assume (as did Burton and Greenspan) that I am working with a radially-symmetric tumour in form of a spheroid [Pre03].

In chapter 2.1 I explained the structure of a tumour as seen again in figure 46. A tumour needs oxygen and other nutrients to grow. Nutrients diffusing in from adjacent normal tissue are consumed by proliferating tumour cells. As the tumour grows, not enough nutrients reach the cells in the centre of the tumour and they will stop multiplying and eventually die, creating a necrotic core, which continues to increase in size while the tumour grows. Figure 46 shows the structure of an avascular tumour, which consists of an outer rim of proliferating cells and a necrotic core. These regions are separated by a layer of hypoxic cells that are quiescent.

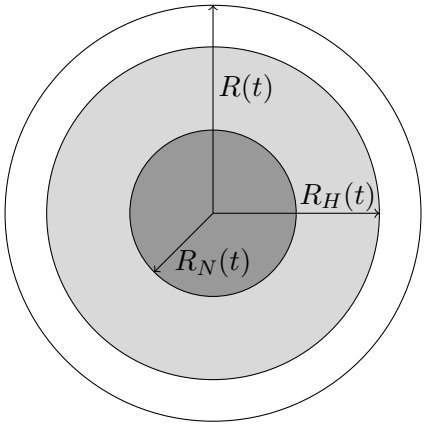


Figure 46: Tumour structure with outer radius $R(t)$, hypoxic radius $R_H(t)$ and necrotic radius $R_N(t)$.

$R(t)$ denotes the outer tumour radius, so the radius of the entire tumour, $R_H(t)$ the radius of the hypoxic part of the tumour, this includes the necrotic core if it exists and $R_N(t)$ denotes the radius of the necrotic core. All three radii change over time, thus this is a moving boundary problem. As explained in chapter 2.1 the growth of the tumour and the development of hypoxic and necrotic regions depends on the local nutrient concentration, hence this needs to be included in the following model.

5.2.1. Mathematical Model

The main source of motion and transport at a molecular level is diffusion. Cells move around in random motion and thereby spread out [Mur89]. Suppose $c(x,t)$ describes a population density at time $t \in [0,\infty)$ and spatial position $x \in \mathbb{R}$. Then a simple one-dimensional diffusion equation is

$$\begin{aligned} \frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} \\ \Leftrightarrow \frac{\partial c}{\partial t} &= D_c \nabla^2 c \end{aligned} \tag{5.23}$$

where D_c denotes the diffusion coefficient, which is constant and represents the degree of random motion [All07]. The left-hand side of the equation describes the rate of change of the population density.

From this diffusion equation I can obtain a simple reaction-diffusion equation of the form

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + f(c) \tag{5.24}$$

where $f(c)$ describes the population growth rate [Mur89].

For this spatial model I assume $c(r,t)$ to be the nutrient concentration at time t at distance r from the core of the tumour. Then the equation for c reads

$$\frac{\partial c}{\partial t} = D_c \nabla^2 c - \Gamma H(r - R_N) \tag{5.25}$$

where D_c denotes the constant diffusion equation of the nutrients [Pre03]. The reaction term in this equation is $f(c) = -\Gamma H(r - R_N)$ and it describes nutrient consumption by proliferating and quiescent cells at a constant rate Γ. The Heaviside step function $H(r - R_N)$ equals one if $r \geq R_N$ and zero otherwise. This means that the reaction term is $f(c) = -\Gamma$ if $r \geq R_N$ and zero otherwise, meaning only the cells in the hypoxic region and proliferating rim consume nutrients at rate Γ, necrotic cells do not.

Since I assume the tumour to be a radially-symmetric spheroid, the diffusion term of equation (5.25) reads

$$D_c \nabla^2 c = D_c \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial c}{\partial r} \right).$$

The equation for the nutrient concentration throughout the tumour is one part of the model. The other part is the growth of the tumour, which depends on the nutrient concentration. The rate of change of the tumour volume V is described by looking at the rate of change of the tumour radius R, since the volume of a spheroid is calculated based on its radius

$$V = \frac{4}{3}\pi R^3.$$

Therefore the equation for the rate of change of the tumour volume reads

$$\frac{1}{3}\frac{dR^3}{dt} = R^2 \frac{dR}{dt} = \int_{R_H}^{R} pc(r,t) r^2 \, \mathrm{d}r - \int_0^R p \left(\lambda_A + \lambda_N H(R_N - r) + \mu A \right) r^2 \, \mathrm{d}r \tag{5.26}$$

where the first integral describes the total rate of cell proliferation proportional to the nutrient concentration c and the second integral the total rate of cell death [Pre03]. Since cell proliferation only occurs in nutrient-rich regions, the first integral is larger than zero if $r \geq R_H$, meaning for radii in the proliferating rim. The total rate of cell death is the sum of the rate of apoptosis (orderly cell death) λ_A, which is constant throughout the tumour, the rate of necrosis $\lambda_N H(R_N - r)$ in nutrient-poor regions (in the necrotic core where $r \leq R_N$) and the rate of cell death due to radiation μA.

When considering other forms of treatment, for example, chemotherapy, the amount A could be substituted by $\int_0^R A(r,t)dr$ in the above equation since the curing chemical does not have the same concentration throughout the tumour. Then the equation for the rate of change of the chemical would read

$$\frac{\partial A}{\partial t} = D_A \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial A}{\partial r} \right).$$

However, as explained in section 5.1.3 all tumour cells received the same amount of radiation in the experiments done by the Institute of Radiation Biology, Helmholtz-Zentrum München [AH12], which I will later apply to the spatial model. Thus I set $\frac{\partial A}{\partial t} = 0 = \frac{\partial A}{\partial r}$ and $A(r,t) =: A$ constant throughout the tumour.

The boundaries of the inner radii are defined as

$$\begin{aligned}
&\bullet\ c(r,t) > c_H \ \forall r \in (0,R) \\
&\Rightarrow R_N = R_H = 0 \\
&\bullet\ \exists r \in (0,R(t)) \text{ s.t. } c_N < c(r,t) \leq c_H \\
&\Rightarrow R_N = 0 < R_H < R \text{ with } c(R_H,t) = c_H \\
&\bullet\ \exists r \in (0,R(t)) \text{ s.t. } c(r,t) \leq c_N < c_H \\
&\Rightarrow 0 < R_N < R_H < R \text{ with } c(R_N,t) = c_N \text{ and } c(R_H,t) = c_H
\end{aligned} \tag{5.27}$$

with c_H being the minimum nutrient concentration at which cells are able to proliferate and c_N the maximum nutrient concentration at which necrosis occurs [Pre03]. To complete the model, initial and boundary conditions need to be specified. They are given by

$$\begin{aligned}
&\bullet\ \frac{\partial c}{\partial r} = 0 \text{ at } r = 0 \\
&\bullet\ c = c_\infty \text{ on } r = R(t) \\
&\bullet\ c \text{ and } \frac{\partial c}{\partial r} \text{ continuous across } r = R_H(t) \text{ and } r = R_N(t) \\
&\bullet\ c(r,0) = c_0(r) \text{ and } R(t=0) = R_0.
\end{aligned} \tag{5.28}$$

On $r = 0$ the tumour is symmetric, so that there is no continuous movement in the core of the tumour. In addition, a constant nutrient concentration c_∞ governs outside of the tumour.

To be able to analyse the model, the system needs to be brought to a dimensionless form, meaning the variables need to be rescaled. In the following, dimensionless variables are denoted by carets. The variables are rescaled as followed

$$\hat{c} = \frac{c}{C}, \quad \hat{r} = \frac{r}{X}, \quad \hat{t} = \frac{t}{T}$$
$$\hat{R} = \frac{R}{X}, \quad \hat{R}_H = \frac{R_H}{X}, \quad \hat{R}_N = \frac{R_N}{X}$$

where C, X and T denote typical nutrient concentration, length and time scales. Substituting into the model gives the following dimensionless equations

$$\frac{\partial \hat{c}}{\partial \hat{t}} = \frac{TD_c}{X^2}\frac{1}{\hat{r}^2}\frac{\partial}{\partial \hat{r}}\left(\hat{r}^2\frac{\partial \hat{c}}{\partial \hat{r}}\right) - \frac{\Gamma T}{C}H(\hat{r} - \hat{R}_N) \tag{5.29}$$

$$\frac{d\hat{R}}{d\hat{t}}\hat{R}^2 = \int_0^{\hat{R}} p\left(\hat{c}CTH(\hat{r} - \hat{R}_N) - \lambda_A T - \lambda_N TH(\hat{R}_N - \hat{r}) - \mu AT\right)\hat{r}^2\,\mathrm{d}\hat{r} \tag{5.30}$$

I use the tumour doubling time $\frac{1}{pC}$ to set the timescale T. In addition, I know that $\mathcal{O}(\Gamma) = \mathcal{O}(D_c/X^2) \gg \mathcal{O}(1/T)$ from experiments and I multiply equation (5.29) with $\frac{X^2}{TD_c}$. This results in

$$\frac{\partial \hat{c}}{\partial \hat{t}}\frac{X^2}{TD_c} = 0 = \frac{1}{\hat{r}^2}\frac{\partial}{\partial \hat{r}}\left(\hat{r}^2\frac{\partial \hat{c}}{\partial \hat{r}}\right) - \hat{\Gamma}H(\hat{r} - \hat{R}_N) \tag{5.31}$$

$$\frac{d\hat{R}}{d\hat{t}}\hat{R}^2 = \int_0^{\hat{R}} \left(\hat{c}H(\hat{r} - \hat{R}_N) - \hat{\lambda}_A - \hat{\lambda}_N H(\hat{R}_N - \hat{r}) - \hat{\mu}A\right)\hat{r}^2\,\mathrm{d}\hat{r} \tag{5.32}$$

with $\hat{\Gamma} = \frac{\Gamma X^2}{D_c C}$, $\hat{\lambda}_A = \lambda_A C$, $\hat{\lambda}_N = \lambda_N C$ and $\hat{\mu} = \mu C$ [Pre03].
The initial and boundary conditions for the dimensionless system are given by

$$\begin{aligned}
&\bullet\ \frac{\partial \hat{c}}{\partial \hat{r}} = 0 \text{ at } \hat{r} = 0\\
&\bullet\ \hat{c} = \hat{c}_\infty = \frac{c_\infty}{C} \text{ on } \hat{r} = \hat{R}\\
&\bullet\ \hat{R}_H = 0 \text{ if } \hat{c} > \hat{c}_H = \frac{c_H}{C}\ \forall \hat{r} \text{ otherwise } \hat{c}(\hat{R}_H, \hat{t}) = \hat{c}_H\\
&\bullet\ \hat{R}_N = 0 \text{ if } \hat{c} > \hat{c}_N = \frac{c_N}{C}\ \forall \hat{r} \text{ otherwise } \hat{c}(\hat{R}_N, \hat{t}) = \hat{c}_N\\
&\bullet\ \hat{R}(0) = \hat{R}_0.
\end{aligned} \tag{5.33}$$

From now on I will drop the carets for brevity.

5.2.2. Model Analysis

Tumour growth can be split into three stages:

1 only proliferating cells exist,

2 due to a reduced nutrient concentration in the centre of the tumour, quiescent cells start to develop,

3 due to an even lower nutrient concentration in the tumour's core, cells start to die in the centre, giving rise to a fully developed avascular tumour with three different regions.

Stage 1 I solve equation (5.31) for the nutrient concentration

$$\begin{aligned} 0 &= \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right) - \Gamma \\ \Leftrightarrow c(r,t) &= \frac{\Gamma}{6}r^2 - \frac{z_1}{r} + z_2 \end{aligned}$$

with z_1 and $z_2 \in \mathbb{R}$. Applying the boundary conditions from equation (5.33) renders the exact solution for the nutrient concentration

$$c(r,t) = c_\infty - \frac{\Gamma}{6}(R^2 - r^2). \tag{5.34}$$

At this stage, the tumour only consists of proliferating cells, so $c > c_H \ \forall r \in (0, R)$ and $R_N = R_H = 0$. Therefore

$$\begin{aligned} c(r,t) > c_H &\Leftrightarrow c_\infty - \frac{\Gamma}{6}(R^2 - r^2) > c_H \\ &\Leftrightarrow \frac{6}{\Gamma}(c_\infty - c_H) > R^2 - r^2 \end{aligned}$$

Thus for this stage I only look at radii for which

$$0 < R^2(t) < \frac{6}{\Gamma}(c_\infty - c_H)$$

holds. Consequently, if $R^2 \to \frac{6}{\Gamma}(c_\infty - c_H)$ the nutrient concentration will tend to c_H for $r \to 0$. Meaning the nutrient concentration tends to c_H in the tumour's core if R^2 tends to its maximum for which only proliferating cells exist. This confirms that neither quiescent nor necrotic cells exist ($R_H = R_N = 0$).

Inserting the solution for the nutrient concentration into equation (5.32) for the tumour radius and setting $R_H = R_N = 0$ renders

$$\begin{aligned} \frac{dR}{dt}R^2 &= \int_0^R \left(c_\infty - \frac{\Gamma}{6}(R^2 - r^2) - \lambda_A - \mu A\right) r^2 \,\mathrm{d}r \\ \Rightarrow \frac{dR}{dt} &= \frac{R}{3}\left(c_\infty - \lambda_A - \frac{\Gamma}{15}R^2 - \mu A\right) \end{aligned} \tag{5.35}$$

Stage 2 The nutrient concentration for this stage is the same as in equation (5.34)

$$c(r,t) = c_\infty - \frac{\Gamma}{6}(R^2 - r^2)$$

since both proliferating and quiescent cells consume nutrients at the same rate. As proliferating and quiescent cells exist at this stage, $c(R_H, t) = c_H$ holds according to the boundary conditions and, therefore, the size of of quiescent radius can be calculated to

$$\begin{aligned} c_H &= c_\infty - \frac{\Gamma}{6}(R^2 - R_H^2) \\ \Leftrightarrow R_H^2 &= R^2 - \frac{6}{\Gamma}(c_\infty - c_H). \end{aligned} \tag{5.36}$$

Therefore, the outer tumour radius needs to be larger than $\frac{6}{\Gamma}(c_\infty - c_H)$ for both cell types to exist in this stage. In addition, no necrotic cells exist, so $c > c_N \; \forall r \in (0, R)$ and thereby $\frac{6}{\Gamma}(c_\infty - c_N) > R^2 - r^2$. Accordingly for this stage, I only look at radii for which

$$\frac{6}{\Gamma}(c_\infty - c_H) < R^2(t) < \frac{6}{\Gamma}(c_\infty - c_N)$$

holds. Hence if $R^2 \to \frac{6}{\Gamma}(c_\infty - c_N)$ the nutrient concentration will tend to c_N for $r \to 0$. Meaning the nutrient concentration tends to c_N in the tumour's core if R^2 tends to its maximum for which both proliferating and quiescent cells exist. This confirms that no necrotic cells exist ($0 = R_N < R_H$).

Inserting the solution for the nutrient concentration into equation (5.32) for the tumour radius and setting $R_N = 0$ renders

$$\frac{dR}{dt} = \frac{R}{3}\left(\left(c_\infty - \frac{\Gamma}{6}R^2 - \lambda_A - \mu A\right)\left(1 - \frac{R_H^3}{R^3}\right) + \frac{\Gamma}{10}R^2\left(1 - \frac{R_H^5}{R^5}\right)\right). \tag{5.37}$$

Stage 3 The final growth stage of an avascular tumour consists of necrotic, quiescent and proliferating cells. This time when solving equation (5.31) for the nutrient concentration, I need to differentiate between the case where r is smaller than R_N (no nutrients are consumed) and where r is larger than R_N (nutrients are consumed by quiescent and proliferating cells). The solution for the nutrient concentration is then

$$c(r,t) = \begin{cases} c_N & \text{if } 0 < r \leq R_N, \\ c_N + \frac{\Gamma}{6r}(r - R_N)^2(r + 2R_N) & \text{if } R_N < r < R. \end{cases} \tag{5.38}$$

The outer tumour radius needs to be larger than $\frac{6}{\Gamma}(c_\infty - c_N)$ for all three types of cells to exist. Thus for this stage I only look at radii for which

$$R^2(t) > \frac{6}{\Gamma}(c_\infty - c_N)$$

holds. The hypoxic radius can be calculated as in stage 2 and the necrotic radius as follows

$$R_N^2 = R^2 - \frac{6}{\Gamma}(c_\infty - c_N). \tag{5.39}$$

Inserting the solution for the nutrient concentration into equation (5.32) for the tumour radius renders

$$\begin{aligned}\frac{dR}{dt} =& \frac{R}{3}\left(c_N\left(1-\frac{R_H^3}{R^3}\right)-(\lambda_A+\mu A)\left(1+\frac{R_N^3}{R^3}-\frac{R_H^3}{R^3}\right)-\lambda_N\frac{R_N^3}{R^3}\right)\\ &+\frac{\Gamma}{6}R^3\left(\frac{1}{5}\left(1-\frac{R_H^5}{R^5}\right)-\frac{R_N^2}{R^3}\left(1-\frac{R_H^3}{R^3}\right)+\frac{R_N^3}{R^4}\left(1-\frac{R_H^2}{R^2}\right)\right)\end{aligned} \tag{5.40}$$

Now that I have a complete system for all three stages of growth I can apply the given data to this model.

5.2.3. Model versus Data

As explained in section 5.1.3 the growth of T47D cells was measured in vitro by the Institute of Radiation Biology, Helmholtz-Zentrum München [AH12] using the GravityPLUS System from InSphero (www.insphero.com). In this experiment, 500 cells were placed on a 96-well plate and left to grow to a spheroid in a hanging drop for three days, after which it was dropped into a gravity plate and left for one more day. Time t was set to zero and the cells were radiated once with either 2, 4, 6 or 8 Gy of γ-rays. It is assumed that the γ-rays reach all cells equally. In addition, cells without radiation were measured to compare normal growth to growth with radiation. The area (in μm^2) of the spheroids were measured starting at $t = 0$ every three days until day 15. Each experiment was done twelve times and the mean of the collected data can be seen in table 2. The areas were normalised to the value at day zero and zero Gy to be comparable. From the given tumour areas, I calculated the corresponding radii, which can be seen in table 4.

Radius (μm)	*days*					
radiation	0	3	6	9	12	15
0 Gy	157	204	248	263	272	279
2 Gy	157	196	228	238	251	256
4 Gy	157	194	212	224	222	234
6 Gy	157	196	210	214	220	225
8 Gy	157	195	204	200	207	215

Table 4: Mean spheroid radii corresponding to areas in table 2 measured over a period of 15 days and different radiation doses; source: [AH12].

As in the previous chapters, before applying the model with radiation to the data, I need to find the model parameters for tumour growth without radiation. To be able to implement the model I need to make the following assumptions: if the tumour radius is larger than $200\mu m$, a necrotic core exists [TG95, GMK96, DS81] and if the distance to the nutrients is larger than $100\mu m$, cells become quiescent [DS81]. In addition, the external nutrient concentration c_∞ is set to one, since this was an in vitro experiment. Based on

these assumptions I can calculate the concentrations c_H and c_N as follows

$$c_H = 1 - \frac{\Gamma}{6}100^2$$
$$c_N = 1 - \frac{\Gamma}{6}200^2.$$

To plot the model I used equation (5.35) (stage 1) if $R < 100\mu m$, equations (5.37) and (5.36) (stage 2) if $100\mu m \leq R < 200\mu m$ and equations (5.40), (5.36) and (5.39) if $R \geq 200\mu m$. I used algorithm 3 in appendix C to find smallest error based on equation (3.7). The algorithm finds the best values for λ_A, λ_N and Γ. Figure 47 uses $\lambda_A = 0.24$, $\lambda_N = 0.57$ and $\Gamma = 0.00014$ and the error is $4.85 \cdot 10^{-4}$. This is a much better fit than in section 5.1.3 where I looked at the estimated number of cells. Figure 47 compares the model to the data for no radiation, so $A = 0$.

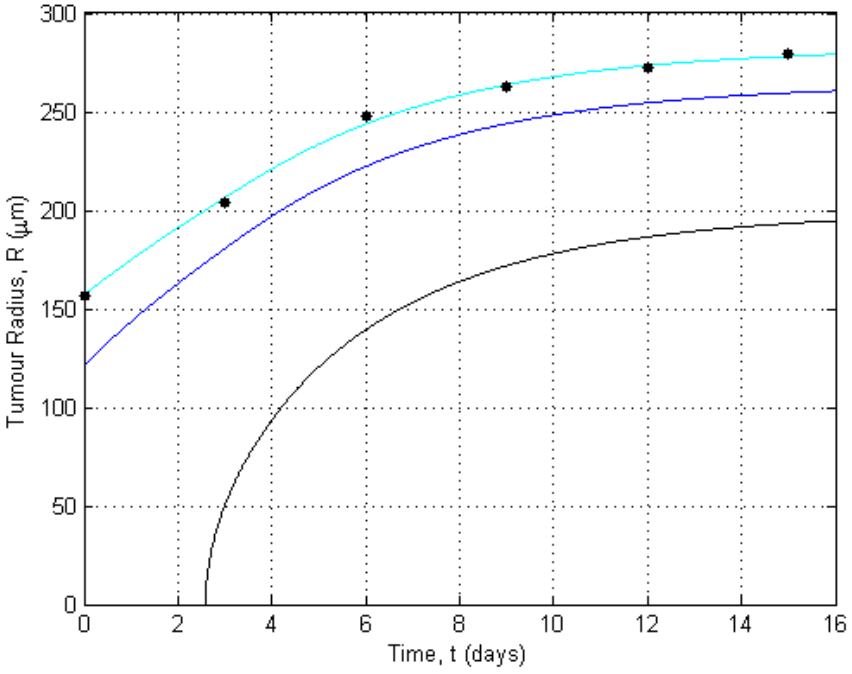
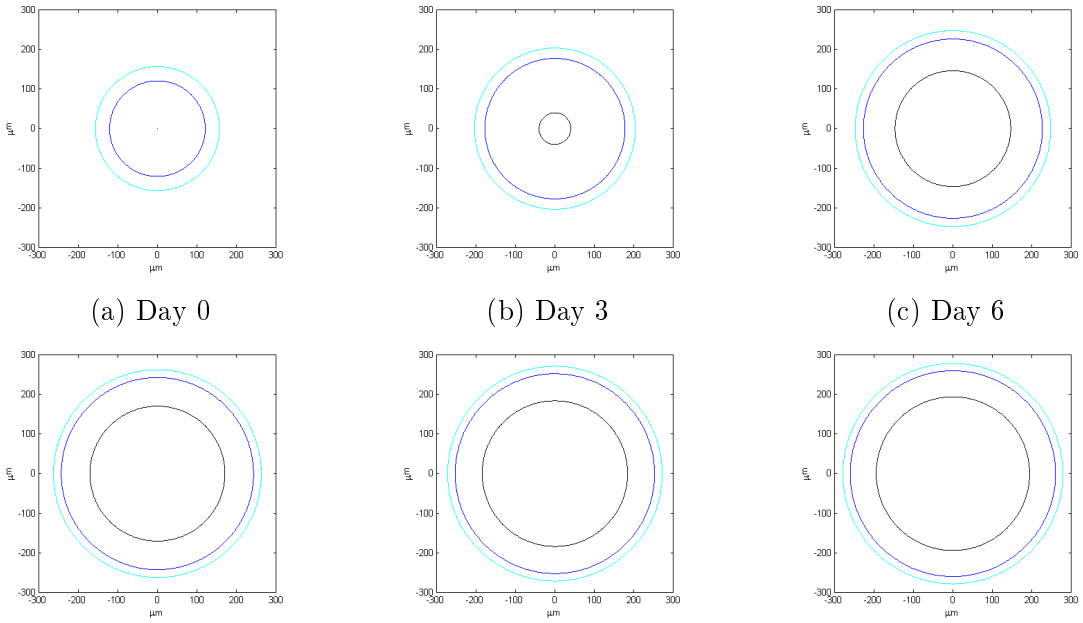


Figure 47: Modelling the growth of T47D breast cancer cells. Cyan line is the outer tumour radius, blue line the hypoxic radius and the black line the necrotic radius. Parameter values are $R_0 = 157$, $\lambda_A = 0.24$, $\lambda_N = 0.57$, $\Gamma = 0.00014$ and $A = 0$. Data from [AH12].

In figure 48 I plotted the outer tumour radius (cyan circles) using the data from table 4. The hypoxic (blue circles) and necrotic (black circles) radii were calculated by applying equations (5.36) and (5.39) to the data, which are the outer tumour radii. Here one can see that the thickness of the viable rim remains fairly constant once necrosis has started. In addition, one can see that the growth between day zero and day three is much larger than in the later stages, for example, between day twelve and day 15. This corresponds to the findings in chapter 3.1, where I analysed different tumour growth models. The result

being that the initial growth phase is exponential, which, however, slows down over time until the tumour eventually reaches its capacity.



(a) Day 0 (b) Day 3 (c) Day 6

(d) Day 9 (e) Day 12 (f) Day 15

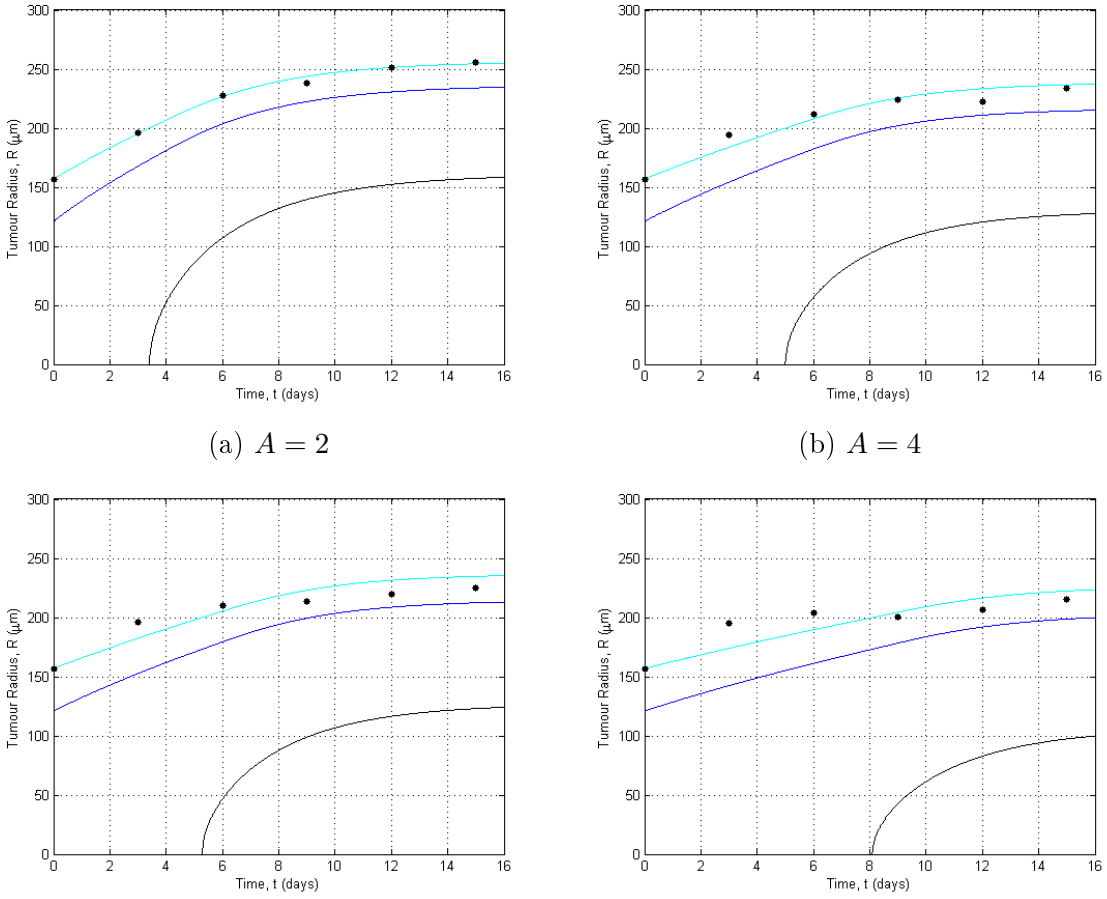
Figure 48: Modelling the growth of T47D breast cancer cells. Cyan lines are the outer tumour radii, blue lines the hypoxic radii and the black lines the necrotic radii. Parameter values are $R_0 = 157$, $\lambda_A = 0.24$, $\lambda_N = 0.57$, $\Gamma = 0.00014$ and $A = 0$. Data from [AH12].

To include radiation, I used the same models as for the plots above without radiation but set $A > 0$. Figure 49 compares the model (cyan lines) to the data (black dots), whereby the amount of radiation increases with each plot. The same parameter values were chosen as in the above plots for simple tumour growth. In addition, the parameter μ had to be set. As in the previous chapters I want to choose the paraemters so to minimise the error. However, plotting the model versus the data, I found that μ depends on the amount of radiation. Meaning here that lower doses of radiation have a higher impact than larger doses (per Gy). This suggests that cells show an abnormally high radiosensitivity (hypersensitivity) to lower doses of radiation, as discussed in chapter 4 [CHN09]. This can also be seen by looking at the data in table 4 from which one can calculate the mean volumes of the tumours. Whilst two Gy results in a decline of 22% of the tumour's volume after 15 days, eight Gy only results in a reduction of 54%, which is not four times as much as the result two Gy gives. For this reason I choose to differentiate between low radiation doses of up to five Gy and high radiation doses from five Gy onwards. Therefore the parameter μ takes on different values depending if $A \leq 5$ or $A > 5$. Setting

$$\mu = \begin{cases} 0.078 & \text{if } A \leq 5, \\ 0.055 & \text{if } A > 5 \end{cases}$$

results in the smallest error based on equation (3.7).

Figure 49 shows the results when using the above mentioned parameters and increasing radiation doses. The errors increase with the increase in radiation, however, they are still much smaller than in the previous section where I compared the estimated number of cells to my models. Using $A = 2$ results in an error of $6.9 \cdot 10^{-4}$, using $A = 4$ in an error of $6.1 \cdot 10^{-3}$, using $A = 6$ in an error of 0.0119 and, finally, using $A = 8$ results in an error of 0.0238. Looking at table 4 one can see that day three, does not show sinking radii values with increased radiation, as one would expect. In addition, looking at the values for eight Gy, one can see that the tumour radius seems to shrink at day nine and then grow again. Since these are only experimental values, some points can stray further away from the model solution curve. Figure 50 compares all five models for the different amounts of radiation.



(a) $A = 2$ (b) $A = 4$

(c) $A = 6$ (d) $A = 8$

Figure 49: Modelling the growth of T47D breast cancer cells using radiation. Cyan line is the outer tumour radius, blue line the hypoxic radius and the black line the necrotic radius. Black dots are the data points. Same parameters as in figure 43 with $\mu = 0.4$ and $\beta = 0.9$. Data from [AH12].

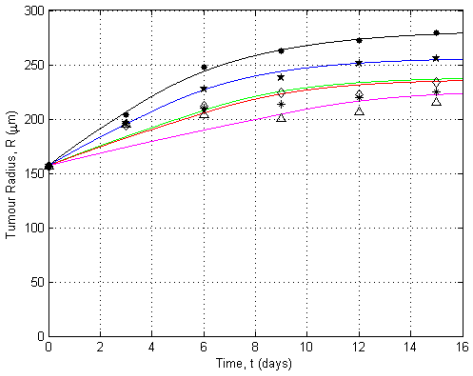
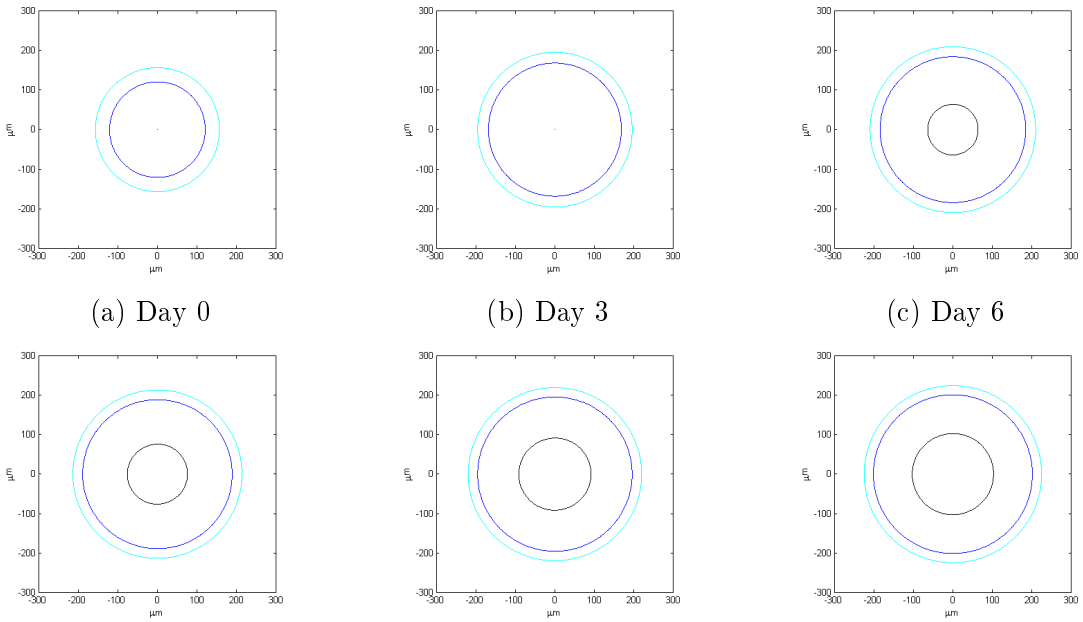


Figure 50: Comparison of the previous five figures with black/dots for 0 Gy, blue/stars for 2 Gy, green/diamonds for 4 Gy, red/crosses for 6 Gy and magenta/triangles for 8 Gy. Data from [AH12].

Figure 51 shows the development of the tumour as in figure 48 however using a radiation dose of six Gy this time. The outer tumour radii (cyan circles) are plotted using the data from table 4. The hypoxic (blue circles) and necrotic radii (black circles) were calculated by applying equations (5.36) and (5.39) to the data. Comparing these plots to the ones using no radiation in figure 48, one can see the effect radiation has on the growth of a tumour. Using radiation once at $t = 0$ clearly hinders the tumour from growing as fast and to the size it could without radiation.



(a) Day 0 (b) Day 3 (c) Day 6

(d) Day 9 (e) Day 12 (f) Day 15

Figure 51: Modelling the growth of T47D breast cancer cells using radiation. Cyan lines are the outer rumour radii, blue lines the hypoxic radii and the black lines the necrotic radii. Parameter values are $R_0 = 157$, $\lambda_A = 0.24$, $\lambda_N = 0.57$, $\Gamma = 0.00014$ and $A = 6$. Data from [AH12].

6. Conclusion

Discussion

In this thesis, I have presented two complementary modelling approaches that have been used to study the growth of avascular tumours. These range from cell population models, which can be formulated as coupled systems of ordinary differential equations, to moving boundary problems showing the spatial growth of a tumour. In each case, I applied radiation therapy to the growth models and compared these to data collected of the T47D cell line.

I refrained from using the LQ-model or any of its extensions, since its strong drawback is the fact that the time course of the treamtment is not included in the equations. In addition, the two main parameters α and β are known for many cell lines but not necessarily for all.

Having compared growth models for a tumour cell population to various data sets, I found that the generalised logistic equation allows for the best fit and flexibility and is well suited to represent data. Based on this model, I extended the growth equation to incorporate radiotherapy. This was done in two ways, one by assuming constant radiation and the other by assuming periodic radiation. Each model was then extended to either incorporate repair or repopulation. In addition, I looked at a heterogenous tumour cell population, whereby I differentiated between two cases. One was the case where I looked at proliferating and quiescent cells and their difference in radiosensitivity. This resulted in the possible coexistance of the two cell types. The second case looked at the difference in radiosensitivity of either more sensitive or more resistant cells. Hereby coexistance of the two cell types was not possible. In each model the aim was to find the amount of radiation needed to kill all tumour cells.

A complementary approach to modelling cell populations is to look at the spatial growth of the tumour. This was done in the final chapter. Again, radiotherapy was incorporated into the growth model and finally compared to the given data.

The spatial model was a much better fit to the given data. However, considering the fact that the cell population models with radiation were only compared to data of estimated number of cells, they also succeeded in modelling real data. Concluding, I can say that it is best to use a model that can be directly compared to given data as every estimation can further impair the quality and exactness of the data. On the other hand, it depends on what kind of information one is looking for and what the tolerated error is.

Outlook

The risk of developing cancer before the age of 75 is 23.6% in women 32.5% in men in Germany [FSB+10] and this motivates further research in this area.

The models in chapter 5.1 could be extended to include the nutrient concentration inside the tumour. For example, the rates for proliferating cells becoming quiescent and vice versa could depend on the local nutrient concentration c. Then the system of equations (5.7)

would become

$$\begin{aligned}\frac{dP}{dt} &= \frac{r}{\alpha}P\left(1-\left(\frac{P+Q}{K}\right)^{\alpha}\right) - \mu AP - k_{PQ}(c)P + k_{QP}(c)Q &=: f(P,Q)\\ \frac{dQ}{dt} &= k_{PQ}(c)P - k_{QP}(c)Q &=: g(P,Q)\end{aligned}$$

The equation for the nutrient concentration could be set as in the spatial model in chapter 5.2.

The spatial model could also be extended by only applying radiation to proliferating and quiescent cells, since necrotic cells are very radioresistant. Then the equation for the rate of change of the tumour volume would read

$$\frac{1}{3}\frac{dR^3}{dt} = R^2\frac{dR}{dt} = \int_{R_H}^{R} pc(r,t)r^2\,\mathrm{d}r - \int_0^R p\left(\lambda_A + \lambda_N H(R_N - r) + \mu AH(r-R_N)\right)r^2\,\mathrm{d}r$$

In addition to the factors repair, repopulation and radiosensitivity, the aspect of redistribution over the cell cycle could be analysed. This can be done with the help of delay differential equations.

However, analysing these models would go beyond the scope of this thesis.

Appendix A Data used for Figures in Chapter 2.2

Female			Male		
Deaths		Cancer type	Deaths		Cancer type
#	%		#	%	
16967	18%	Breast	29274	25%	Lung
13155	14%	Colorectum	14427	12%	Colorectum
12521	13%	Lung	12153	11%	Prostate
7216	7%	Pancreas	7016	6%	Pancreas
5486	6%	Ovary	5970	5%	Stomach
4606	5%	Stomach	4416	4%	Liver
3253	3%	Leukaemia	4328	4%	Kidney
2721	3%	Brain, nervous system	3917	3%	Leukaemia
2659	3%	Non-Hodgkin lymphoma	3818	3%	Oesophagus
2551	3%	Kidney	3487	3%	Bladder
2303	2%	Liver	3090	3%	Brain, nervous system
2210	2%	Gallbladder	2858	2%	Non-Hodgkin lymphoma
2018	2%	Cervix uteri	2026	2%	Other pharynx
1979	2%	Multiple myeloma	2021	2%	Multiple myeloma
1787	2%	Bladder	1488	1%	Lip, oral cavity
1760	2%	Corpus uteri	1403	1%	Melanoma of skin
1159	1%	Oesophagus	1371	1%	Gallbladder
1111	1%	Melanoma of skin	1270	1%	Larynx
621	1%	Lip, oral cavity	265	0%	Thyroid
433	0%	Thyroid	150	0%	Testis
398	0%	Other pharynx	127	0%	Hodgkin lymphoma
178	0%	Larynx	79	0%	Nasopharynx
111	0%	Hodgkin lymphoma	10617	9%	Other
40	0%	Nasopharynx			
9375	10%	Other			
96618	100%	Total	115571	100%	Total

Table 5: Data for Figures 2 and 3; Source: [FSB+10]

Incidence #	Mortality #	Cancer type	Incidence #	Mortality #	Cancer type
64,147	16,967	Breast	70,792	12,153	Prostate
32,165	13,155	Colorectum	38,239	14,427	Colorectum
15,070	12,521	Lung	34,799	29,274	Lung
10,776	1,760	Corpus uteri	17,183	3,487	Bladder
8,711	5,486	Ovary	11,673	4,328	Kidney
8,566	1,111	Melanoma of skin	8,840	5,970	Stomach
7,344	7,216	Pancreas	7,682	1,403	Melanoma of skin
6,996	2,551	Kidney	7,349	7,016	Pancreas
6,744	2,659	Non-Hodgkin lymphoma	6,879	2,858	Non-Hodgkin lymphoma
6,423	4,606	Stomach	6,162	3,917	Leukaemia
6,021	1,787	Bladder	5,131	4,416	Liver
4,917	3,253	Leukaemia	4,930	3,818	Oesophagus
4,440	2,018	Cervix uteri	4,145	1,488	Lip, oral cavity
3,233	2,721	Brain, nervous system	4,028	2,026	Other pharynx
2,823	433	Thyroid	3,676	1,270	Larynx
2,790	2,210	Gallbladder	3,630	150	Testis
2,718	1,979	Multiple myeloma	3,628	3,090	Brain, nervous system
2,543	2,303	Liver	2,932	2,021	Multiple myeloma
2,023	621	Lip, oral cavity	1,887	1,371	Gallbladder
1,409	1,159	Oesophagus	1,546	265	Thyroid
911	398	Other pharynx	861	127	Hodgkin lymphoma
674	111	Hodgkin lymphoma	208	79	Nasopharynx
479	178	Larynx	14,973	10,617	Other
113	40	Nasopharynx			
16,652	9,375	Other			
218,688	96,618	Total	261,173	115,571	Total

Table 6: Data for Figure 4 (left: female, right: male); Source: [FSB+10]

Appendix B List of Variables

Variables used in Chapter 3.1	
t	time
$N(t)$	number of tumour cells at time t
N_0	initial number of tumour cells
r	net proliferation rate, $r > 0$
K	carrying capacity
α	generalised logistic equation variable, $\alpha > 0$

Variables used in Chapter 3.2	
$N(t)$	total number of tumour cells at time t
$P(t)$	number of proliferating tumour cells
$Q(t)$	number of quiescent tumour cells
$D(t)$	number of dead tumour cells
λ	rate of degradation
k_{ij}	rate at which tumour cells leave state i for state j

Variables used in Chapter 4	
Y	yield of lethal lesions
S	survival fraction
S^*	number of cells left after irradiation
S_0	initial number of cells
D	radiation dose
α	cell kill per Gy of linear component
β	cell kill per Gy^2 of quadratic component
d	dose per fraction
n	number of fractions
λ	repair rate
τ	repair half-time
μ	repopulation constant
T_p	doubling time
T_k	time delay
d_c	threshold dose for hypersensitivity

Variables used in Chapter 5.1	
$A(t)$	amount of radiation administered at time t in Gy
μ	how much cells are damaged per Gy of radiation
ρ	how many cells are able to repair themselves in an hour per Gy
λ	repair rate
T_r	repair half-time (in hours)
β	how many cells are able to proliferate per Gy
$P(t)$	number of proliferating cells
$Q(t)$	number of quiescent cells

k_{PQ}	rate at which proliferating cells become quiescent
k_{QP}	rate at which quiescent cells become viable
$S(t)$	number of sensitive cells
$R(t)$	number of resistant cells
τ	proportional duration of radiation
n	radiation session

Variables used in Chapter 5.2	
$R(t)$	outer tumour radius
$R_H(t)$	hypoxic radius
$R_N(t)$	necrotic radius
$c(r,t)$	nutrient concentration
r	distance from tumour core
c_H	nutrient concentration at $r = R_H(t)$
c_N	nutrient concentration at $r = R_N(t)$
c_∞	external nutrient concentration
D_c	diffusion coefficient
Γ	nutrient consumption rate
λ_A	rate of apoptosis
λ_N	rate of necrosis
A	radiation dose administered in Gy
μ	how much cells are damaged per Gy of radiation

Table 7: Variables used in Chapters 3 to 5

Appendix C MatLab Codes

Chapter 3

Homogenous Tumour Growth

Used for figure 6a on page 12.

```
%log growth equation with inflection point
clear all
%parameter values
t=0:300;            %time
T=length(t);
N0=10;              %initial number of cells
r=log(2)/24;        %net proliferation rate
K=100;              %carrying capacity
N2=zeros(1,T);      %tumour cells
for j=1:T-1
    N2(1)=N0;
    N2(j+1)=K*N0/(N0+exp(-r*j)*(K-N0));
end
Ya=[' 0 ';'K/2';' K '];      %y-axis ticks
tinfl=log((K-N0)/N0)/r;      %inflection point
figure;
    plot (t,N2,'Color','k')
    hold on
    plot(tinfl,K/2,'ok','MarkerFaceColor','k')
    xlabel('time, t')
    ylabel('Cell number, N(t)')
    ylim([0 120])
    set(gca,'YTick',[0:50:100])
    set(gca,'YTickLabel',Ya)
```

Used for figure 6b on page 12.

```
%Tumour growth rate f(N) with inflection point
clear all
%parameter values
r=log(2)/24;        %net proliferation rate
K=100;              %carrying capacity
f=zeros(1,K);       %growth function
f(1)=0;
for N=1:K
    f(N+1)=r*N*(1-N/K);
end
Xa=[' 0 ';'K/2';' K '];      %x-axis ticks
figure;
    plot (0:100,f,'Color','k')
    hold on
    plot(K/2,r*K/4,'ok','MarkerFaceColor','k')
    ylabel('Tumour growth rate, f(N)')
    xlabel('Cell number, N(t)')
    ylim([0 0.8])
```

```
    set(gca,'YTick',[]);
    set(gca,'XTick',[0:50:100])
    set(gca,'XTickLabel',Xa)
```

Used for figure 7 on page 15.

```
%differnet values for alpha; inflection points
clear all
%parameter values
alpha1=1;           %general logistic equation parameter 1
alpha2=0.5;         %general logistic equation parameter 2
alpha3=2;           %general logistic equation parameter 3
r=log(2)/24;        %net proliferation rate
K=100;              %carrying capacity
f1=zeros(1,K);      %growth functions
f2=zeros(1,K);
f3=zeros(1,K);
for N=1:K
    f1(1)=0;
    f1(N+1)=r/alpha1*N*(1-(N/K)^alpha1);
end
for N=1:K
    f2(1)=0;
    f2(N+1)=r/alpha2*N*(1-(N/K)^alpha2);
end
for N=1:K
    f3(1)=0;
    f3(N+1)=r/alpha3*N*(1-(N/K)^alpha3);
end
Xa=[' 0 ';'K/2';' K '];          %x-axis ticks
figure;
    plot (0:100,f1,'Color','k')
    hold on
    plot (0:100,f2,'--k')
    hold on
    plot (0:100,f3,':k')
    hold on
    plot(K/2,r*K/4,'ok','MarkerFaceColor','k')
    hold on
    plot(K/(alpha2+1)^(1/alpha2),r/alpha2*K/(alpha2+1)^(1/alpha2)*(1-1/(...
        alpha2+1)),'ok','MarkerFaceColor','k')
    hold on
    plot(K/(alpha3+1)^(1/alpha3),r/alpha3*K/(alpha3+1)^(1/alpha3)*(1-1/(...
        alpha3+1)),'ok','MarkerFaceColor','k')
    ylabel('Tumour growth rate, f(N)')
    xlabel('Cell number, N(t)')
    ylim([0 1])
    grid on
    set(gca,'YTick',[]);
    set(gca,'XTick',[0:50:100])
    set(gca,'XTickLabel',Xa)
```

Used for figure 8 on page 15.

```
%comparison of models for tumour growth
clear all
%parameter values
t=0:300;        %time
T=length(t);
r=log(2)/24;    %net proliferation rate
N0=10;          %initial value
K=100;          %carrying capacity
alpha1=0.5;     %general logistic equation parameter 1
alpha2=2;       %general logistic equation parameter 2
N1=zeros(1,T);  %tumour cells, exp. equation
N2=zeros(1,T);  %tumour cells, log. equation
N3=zeros(1,T);  %tumour cells, log. equ., alpha1
N4=zeros(1,T);  %tumour cells, log. equ., alpha2
%exponential equation
for i=1:T-1
    N1(1)=N0;            %at t=0
    N1(i+1)=N0*exp(r*i); %from t=1 onwards
end
%log equation
for i=1:T-1
    N2(1)=N0;
    N2(i+1)=K*N0/(N0+exp(-r*i)*(K-N0));
end
%general log equation, alpha1
for i=1:T-1
    N3(1)=N0;
    N3(i+1)=K*(N0^alpha1/(N0^alpha1+(K^alpha1-N0^alpha1)*exp(-r*i)))^(1/...
        alpha1);
end
%general log equation,alpha2
for i=1:T-1
    N4(1)=N0;
    N4(i+1)=K*(N0^alpha2/(N0^alpha2+(K^alpha2-N0^alpha2)*exp(-r*i)))^(1/...
        alpha2);
end
figure
    plot(t,N1,'Color','k')
    hold on
    plot (t,N2,'Color','b')
    hold on
    plot (t,N3,'Color','g')
    hold on
    plot (t,N4,'Color','r')
    xlabel('Time, t')
    ylabel('Cell number, N(t)')
    grid on
    ylim([0 120])
```

Used for figures 9 and 10 on pages 16 and 17.

```
%EAT - Ehrlich Ascites Tumour Growth
clear all
%data
t=[0,2,3,4,5,6,7,9,11,13,14,15,17];                                    %days
EAT=[4,8.46,19.9,31.4,53.6,69.2,91.2,132,142,130,132,114,81.5]; %cell ...
    no.
EAT=EAT*10000000;
%parameter values
N0=EAT(1);
T=0:0.1:17;
TT=length(T);
K=150*10000000; r=0.6; alpha=1;      %error=0.4201; erroradj=0.1291
%K=140*10000000; r=0.6; alpha=1;     %error=0.3414; erroradj=0.1282
%K=160*10000000; r=0.6; alpha=1.1;   %error=0.4697; erroradj=0.0935

%general logistic equation
N=K*N0./(N0^alpha+(K^alpha-N0^alpha)*exp(-r.*T)).^(1/alpha);

figure
    plot(T,N,'Color','r')
    hold on
    plot(t,EAT,'.k','markersize',15)
    xlabel('Time, t (days)')
    ylabel('Cell Number, N(t)')
    grid on
    xlim([0 17])

%error
x(1)=((N(1)-EAT(1))/N(1))^2;
x(2)=((N(21)-EAT(2))/N(21))^2;
x(3)=((N(31)-EAT(3))/N(31))^2;
x(4)=((N(41)-EAT(4))/N(41))^2;
x(5)=((N(51)-EAT(5))/N(51))^2;
x(6)=((N(61)-EAT(6))/N(61))^2;
x(7)=((N(71)-EAT(7))/N(71))^2;
x(8)=((N(91)-EAT(8))/N(91))^2;
x(9)=((N(111)-EAT(9))/N(111))^2;
x(10)=((N(131)-EAT(10))/N(131))^2;
x(11)=((N(141)-EAT(11))/N(141))^2;
x(12)=((N(151)-EAT(12))/N(151))^2;
x(13)=((N(171)-EAT(13))/N(171))^2;
fehlerEAT=sum(x)
%adjusted error
y(1)=((N(1)-EAT(1))/N(1))^2;
y(2)=((N(21)-EAT(2))/N(21))^2;
y(3)=((N(31)-EAT(3))/N(31))^2;
y(4)=((N(41)-EAT(4))/N(41))^2;
y(5)=((N(51)-EAT(5))/N(51))^2;
y(6)=((N(61)-EAT(6))/N(61))^2;
y(7)=((N(71)-EAT(7))/N(71))^2;
y(8)=((N(91)-EAT(8))/N(91))^2;
```

```
y(9)=((N(111)-EAT(9))/N(111))^2;
fehleradjEAT=sum(y)
```

Parts of code used for figures 11,12 and 13 on pages 18 and 19.

```
%clear all
%function[N0,t,alpha,r,T,A34]=datagrowth()
t=[0,0.0008,0.0042,0.0292,0.0542,0.0792,0.1042,0.1292,0.1372,linspace(0...
    .3875,67.1375,268),67.1375+0.0008,67.1375+0.0028,linspace(67.1375+0...
    .2528,67.1375+72.5028,290),67.1375+72.7525,67.1375+73.0025,67.1375+73...
    .2525,67.1375+73.5025,67.1375+73.7525,67.1375+74.0025,67.1375+74.2525...
    ,67.1375+74.5025,67.1375+74.7522];

A34a=[0
-0.0045
-0.0033
```

...

```
%parameter values
N0=0.02;
T=length(t);
K=4.978; r=log(2)/19.8; alpha=0.017;    %cell multiplies every 19.8 ...
    hours

%general log equation for tumour growth, N3: cell index
N3=zeros(T,1);
for j=2:T
    N3(1)=N0;
    N3(j)=K*N0/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(j)))^(1/alpha);
end

%error
x=zeros(1,T);
errorA34=0;
for jj=1:T
    x(jj)=((N3(jj)-A34(jj))/N3(jj))^2;
    errorA34=errorA34+x(jj);
end
errorA34

%adjusted error
y=zeros(1,T-200);
erroradj=0;
for jj=201:T
    y(jj-200)=((N3(jj)-A34(jj))/N3(jj))^2;
    erroradj=erroradj+y(jj-200);
end
erroradj

figure
    plot(t,N3,'Color','r')
    hold on
```

```
    plot(t,A34,'k')
    xlabel('Time, t (hours)')
    ylabel('Cell Index')
    grid on
    ylim([0 5])
    set(gca,'XTick',[0:20:200])

figure
    scatter(t,x,'.b')
    xlabel('Time, t (hours)')
    ylabel('error')
    grid on
    %ylim([0 0.003])
    set(gca,'XTick',[0:20:200])

%end
```

Algorithm 1: Used to find best fitting K and α for the T47D cell line.

```
%to get best K and best alpha, given N0 and r
clear all
[N0,t,empty,r,T,A34]=datagrowth();

stepk=0.001;
stepa=0.001;
model=zeros(T-200,1);
capacity=4.5:stepk:5.1;
alphas=0.0001:stepa:0.2;
KK=length(capacity);
aa=length(alphas);
y=0;
errormat=zeros(aa,KK);

ii=1;
for alpha=0.0001:stepa:0.2
    i=1;
    for K=4.5:stepk:5.1
        for j=201:T
            model(j-200)=K*N0/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(j)))...
                ^(1/alpha);
            y=((model(j-200)-A34(j))/model(j-200))^2;
            errormat(ii,i)=errormat(ii,i)+y;
        end
    i=i+1;
    end
ii=ii+1;
end

[smallesterroralpha,indexalpha]=min(errormat);
[smallesterrorK,indexK]=min(smallesterroralpha);

Kbest=capacity(indexK)
alphabest=alphas(indexalpha(indexK))
```

```
erroradjusted=smallesterrorK
```

Parts of code used for figures 14, 15, 16 and 17 on pages 21 and 22.

```
%function[N0,t,alpha,r,T,E34]=datagrowth2()
clear all
t=[0,0.0008,0.0042,0.0292,0.0542,0.0792,0.1042,0.1292,0.1372,linspace(0...
    .3875,67.1375,268),67.1375+0.0008,67.1375+0.0028,linspace(67.1375+0...
    .2528,67.1375+72.5028,290),67.1375+72.7525,67.1375+73.0025,67.1375+73...
    .2525,67.1375+73.5025,67.1375+73.7525,67.1375+74.0025,67.1375+74.2525...
    ,67.1375+74.5025,67.1375+74.7522];

E34a=[0
0.0004
0.001
```

...

```
%model
N0=0.01;
T=length(t);
K=4.101; r=log(2)/7; alpha=1.296;   %cell doubles every 7 hours
%K=4.18; r=log(2)/7; alpha=1.3;     %error  3841.5; 0.3376

%general log equation
N3=zeros(T,1);
for j=2:T
    N3(1)=N0;
    N3(j)=K*(N0^alpha/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(j))))^(1/...
        alpha);
end

%error
x=zeros(1,T);
errorE34=0;
for jj=1:T
    x(jj)=((N3(jj)-E34(jj))/N3(jj))^2;
    errorE34=errorE34+x(jj);
end
errorE34

%adjusted error
y=zeros(1,T-200);
erroradjE34=0;
for jj=201:T
    y(jj-200)=((N3(jj)-E34(jj))/N3(jj))^2;
    erroradjE34=erroradjE34+y(jj-200);
end
erroradjE34

figure
    plot(t,N3,'Color','r')
    hold on
```

```
    plot(t,E34,'Color','k')
    xlabel('Time, t (hours)')
    ylabel('Cell Index')
    grid on
    set(gca,'XTick',[0:20:200])
    ylim([0 4.5])

figure
    scatter(t,x,'.b')
    xlabel('Time, t (hours)')
    ylabel('error')
    grid on
    %ylim([0 0.006])
    xlim([0 145])
    set(gca,'XTick',[0:20:200])
%end
```

Algorithm 2: Used to find best fitting K and α for the MDA cell line.

```
%to get best K and alpha, given N0 and r; cell line MDA
clear all
[N0,t,empty,r,T,E34]=datagrowth2();

stepk=0.001;
stepa=0.001;
model=zeros(T-200,1);
capacity=3.8:stepk:4.5;
alphas=0.8:stepa:1.2;
KK=length(capacity);
aa=length(alphas);
y=0;
errormat=zeros(aa,KK);

ii=1;
for alpha=0.8:stepa:1.2
    i=1;
    for K=3.8:stepk:4.5
        for j=201:T
            model(j-200)=K*N0/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(j)))...
                ^(1/alpha);
            y=((model(j-200)-E34(j))/model(j-200))^2;
            errormat(ii,i)=errormat(ii,i)+y;
        end
    i=i+1;
    end
ii=ii+1;
end

[smallesterroralpha,indexalpha]=min(errormat);
[smallesterrorK,indexK]=min(smallesterroralpha);

Kbest=capacity(indexK)
alphabest=alphas(indexalpha(indexK))
```

```
erroradj=smallesterrorK

N3=zeros(T,1);
for j=2:T
    N3(1)=N0;
    N3(j)=Kbest*N0/(N0^alphabest+(Kbest^alphabest-N0^alphabest)*exp(-r*t...
        (j)))^(1/alphabest);
end

figure
    plot(t,N3,'Color','r')
    hold on
    plot(t,E34,'k')
    xlabel('Time, t')
    ylabel('Cell Index')
    grid on
    ylim([0 4.5])
    set(gca,'XTick',[0:20:200])
```

Heterogenous Tumour Growth

Used for figures 19 and 20 on page 26.

```
%forward (explicit) Euler method to solve equations for P and Q
clear all
%parameter values
t0=0;           %start time
T=1000;         %end time
h=0.1;          %delta t - step size
t=t0:h:T;       %time
F0=[8,2];       %Starting points [P0,Q0]
tumour(:,1)=F0; %tumour cells
r=log(2)/24;    %net proliferation rate
K=100;          %carrying capacity
alpha=1.5;      %general logistic equation parameter
kPQ=0.005;      %rate from P to Q
kQP=0.001;      %rate from Q to P
%Euler method to solve equations
for i =1:length(t)-1
    tumour(:,i+1)=tumour(:,i)+h*[r/alpha*tumour(1,i)*(1-((tumour(1,i)+...
        tumour(2,i))/K)^alpha)-kPQ*tumour(1,i)+kQP*tumour(2,i),kPQ*tumour...
        (1,i)-kQP*tumour(2,i)]';
end
%end
tumour(:,end)
tumour(1,end)+tumour(2,end)
figure
    plot (t,tumour(1,:),'Color','r')                %P
    hold on
    plot (t,tumour(2,:),'Color','g')                %Q
    hold on
    plot (t,tumour(1,:)+tumour(2,:),'Color','k')    %N
```

```
28      xlabel('Time, t')
29      ylabel('Cell Number')
30      grid on
```

Chapter 4

LQ model

Used for figure 21 on page 28.

```
1  %LQ model; cell survival curves after single dose of radiation
2  clear all
3  %parameter values
4  alpha=1/3.35;        %ratios
5  beta1=alpha/1.5;
6  beta2=alpha/10;
7  beta3=alpha/20;
8  D=0:0.05:15;         %radiation dose
9  %survival fractions
10 S1=100*exp(-alpha.*D-beta1.*D.^2);
11 S2=100*exp(-alpha.*D-beta2.*D.^2);
12 S3=100*exp(-alpha.*D-beta3.*D.^2);
13
14 Ya=['0.1';' 1 ';' 10';'100'];           %y-axis ticks
15 figure
16     semilogy(D,S1,'Color','r')
17     hold on
18     semilogy(D,S2,'Color','g')
19     hold on
20     semilogy(D,S3,'Color','b')
21     xlabel('Dose (Gy)')
22     ylabel('Survival fraction (%)')
23     xlim([0 15])
24     ylim([0.1 100])
25     set(gca,'YTick',[0.1,1,10,100])
26     set(gca,'YTickLabel',Ya)
27     set(gca,'XTick',[0:1:15])
```

Used for figure 22 on page 30.

```
1  %LQ model; Lea-Catcheside time factor
2  clear all
3  %parameter values
4  lambda=log(2)/2;     %repair rate
5  T=0:0.05:30;         %time
6  %L-C function
7  G=(2./(lambda.*T).^2).*(exp(-lambda.*T)-1+lambda.*T);
8
9  figure
10     plot(T,G,'k')
11     xlabel('time, t')
12     ylabel('G(t)')
```

```
    xlim([0 30])
    ylim([0 1])
```

Used for figure 23 on page 30.

```
%LQ model including Lea-Catcheside time factor
clear all
%parameter values
alpha=1/3.35;
beta1=alpha/1.5;    %ratios
D=0:0.05:15;        %dose
lambda1=log(2)/2;   %repair rate 1
lambda2=log(2)/1;   %repair rate 2
T=0:0.1:30;         %time (hours)

G1=(2./(lambda1.*T).^2).*(exp(-lambda1.*T)-1+lambda1.*T); %lea-...
    catcheside 1
G2=(2./(lambda2.*T).^2).*(exp(-lambda2.*T)-1+lambda2.*T); %lea-...
    catcheside 2

S1=100*exp(-alpha.*D-beta1.*D.^2);          %normal LQ-model
S1G1=100*exp(-alpha.*D-beta1.*G1.*D.^2);    %with rate 1
S1G2=100*exp(-alpha.*D-beta1.*G2.*D.^2);    %with rate 2

Ya=['0.1';' 1 ';' 10';'100'];       %y-axis ticks

figure
    semilogy(D,S1,'Color','k')
    hold on
    semilogy(D,S1G1,'--k')
    hold on
    semilogy(D,S1G2,':k')
    xlabel('Dose (Gy)')
    ylabel('Survival fraction (%)')
    xlim([0 15])
    ylim([0.1 100])
    set(gca,'YTick',[0.1,1,10,100])
    set(gca,'YTickLabel',Ya)
    set(gca,'XTick',[0:1:15])
```

Used for figure 24 on page 32.

```
%LQ model; h(D)
clear all
%parameter values
D=0:0.05:5;         %dose
alpha=1/3.35;       %from LQ-model
dc=0.5;             %threshold dose
%hypersensitivity function
h=1+(2.5/alpha-1).*exp(-D./dc);

figure
    plot(D,h,'k')
```

```
    xlabel('Dose, D (Gy)')
    ylabel('h(D)')
    xlim([0 5])
    ylim([0 9])
```

Used for figure 25 on page 32.

```
%LQ model including hypersensitivity h(D)
clear all
%parameter values
alpha=1/3.35;       %ratios
beta1=alpha/1.5;
beta2=alpha/10;
beta3=alpha/20;
D=0:0.05:15;        %dose
dc=0.5;             %threshold dose
%hypersensitivity function
h=1+(2.5/alpha-1).*exp(-D./dc);

S1=100*exp(-alpha.*D-beta1.*D.^2);
S1h=100*exp(-alpha.*D.*h-beta1.*D.^2);
S2=100*exp(-alpha.*D-beta2.*D.^2);
S2h=100*exp(-alpha.*D.*h-beta2.*D.^2);
S3=100*exp(-alpha.*D-beta3.*D.^2);
S3h=100*exp(-alpha.*D.*h-beta3.*D.^2);

Ya=['0.1';' 1 ';' 10';'100'];
figure
    semilogy(D,S1,'--k')
    hold on
    semilogy(D,S1h,'k')
    xlabel('Dose (Gy)')
    ylabel('Survival fraction (%)')
    xlim([0 10])
    ylim([0.1 100])
    set(gca,'YTick',[0.1,1,10,100])
    set(gca,'YTickLabel',Ya)
    set(gca,'XTick',[0:1:15])
```

Used for figure 26 on page 35.

```
%TCP
clear all
%parameter values
alpha=1/3.35;
beta1=alpha/1.5;    %ratios
beta2=alpha/10;
beta3=alpha/20;
D=0:0.05:20;        %dose
S0=100;             %initial number of cells

TCP1=exp(-S0*exp(-alpha.*D-beta1.*D.^2))*100;    %in percent
TCP2=exp(-S0*exp(-alpha.*D-beta2.*D.^2))*100;
```

```
TCP3=exp(-S0*exp(-alpha.*D-beta3.*D.^2))*100;

figure
    plot(D,TCP1,'Color','r')
    hold on
    plot(D,TCP2,'Color','g')
    hold on
    plot(D,TCP3,'Color','b')
    grid on
    xlabel('Dose (Gy)')
    ylabel('TCP (%)')
```

Used for figure 27 on page 35.

```
%NTCP model
clear all
%parameter values
alpha=1/3.35;
beta1=alpha/1.5;    %ratio
D=0:0.05:15;        %dose
S0=100;             %initial number of cells

TCP1=exp(-S0*exp(-alpha.*D-beta1.*D.^2))*100;       %TCP
NTCP1=exp(-S0*exp(-alpha.*D-beta1/2.*D.^2))*100;    %NTCP

figure
    plot(D,TCP1,'--k')
    hold on
    plot(D,NTCP1,'k')
    hold on
    plot(D(105),TCP1(105),'or','MarkerFaceColor','r')
    hold on
    plot(D(105),NTCP1(105),'or','MarkerFaceColor','r')
    hold on
    plot(D(111),TCP1(111),'ob','MarkerFaceColor','b')
    hold on
    plot(D(111),NTCP1(111),'ob','MarkerFaceColor','b')
    grid on
    xlabel('Dose (Gy)')
    ylabel('Probability (%)')
```

Other Radiation Models

Used for figure 28 on page 36.

```
%forward (explicit) Euler method to solve equations
clear all
%parameter values
t0=0;           %start time
T=50;           %end time
h=0.1;          %delta t - step size
t=t0:h:T;       %time
```

```
F0=[1,0];        %Starting points [C0,U0]
model(:,1)=F0;   %model
alpha=0.3;       %lethal lesions
D=0.5;           %radiation dose rate
k=0.02;          %DSB misrepair rate
delta=0.8;       %production of non-rep. DSBs
omega=0.01;      %DSB repair constant
%Euler method to solve equations
for i =1:length(t)-1
    model(:,i+1)=model(:,i)+h*[-(alpha*D+0.5*k*(model(2,i))^2)*model(1,i...
        ),delta*D-omega*model(2,i)-2*k*(model(2,i))^2]';
end
figure
    plot (t,model(1,:),'Color','g')                    %C
    hold on
    plot (t,model(2,:),'Color','r')                    %U
    xlabel('Time, t')
    ylabel('Viable cell fraction (red) / Number of DSBs per cell (green)...
        ')
    grid on
    ylim([0 4.5])
```

Chapter 5

Cell Population Models

Used for figures 29 on page 41.

```
%model tumour growth with continuous radiation
clear all
%parameter values
t=[0:0.1:500];  %time
T=length(t);
r=log(2)/24;    %net proliferation rate
N0=10;          %initial value
K=100;          %carrying capacity
alpha=1.5;      %general logistic equation parameter
N=zeros(1,T);   %tumour cells
mu=0.1;         %how much drug damages cell
a=2;            %amount of radiation (Gy)
A=a;            %radiation

%model with radiation
for i=2:T
    N(1)=N0;
    N(i)=(K*N0)/((r*N0^alpha)/(r-alpha*mu*A)+(K^alpha-(r*N0^alpha)/(r-...
        alpha*mu*A))*exp((-r+alpha*mu*A)*t(i)))^(1/alpha);
end

%model without radiation
M=zeros(1,T);
for i=2:T
```

```
    M(1)=N0;
    M(i)=(K*N0)/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(i)))^(1/alpha);
end

%bifurcation parameter value:
bif= r/(alpha*mu)
%capacity tumour tends to with radiation
if A<bif
    cap=K*nthroot(1-alpha*mu*A/r,alpha)
else cap=0
end

figure
    plot (t,N,'Color','r')      %radiation
    hold on
    plot (t,M,'Color','k')      %no radiation
    xlabel('Time, t')
    ylabel('Cell number, N(t)')
    grid on
    ylim([0 K])
```

Used for figures 30 on page 41.

```
%model tumour growth with continuous radiation, different values for mu
clear all
%parameter values
t=[0:0.1:300];  %time
T=length(t);
r=log(2)/24;    %net proliferation rate
N0=10;          %initial value
K=100;          %carrying capacity
alpha=0.5;      %general logistic equation parameter
N=zeros(1,T);   %tumour cells
mu1=0.1;        %how much drug damages cell
mu2=0.2;        %how much drug damages cell
mu3=0.3;        %how much drug damages cell
a=0.1;          %amount of radiation (Gy)
A=a;            %radiation

%model with low mu
for i=2:T
    N(1)=N0;
    N(i)=(K*N0)/((r*N0^alpha)/(r-alpha*mu1*A)+(K^alpha-(r*N0^alpha)/(r-...
        alpha*mu1*A))*exp((-r+alpha*mu1*A)*t(i)))^(1/alpha);
end

%model with medium mu
M=zeros(1,T);
for i=2:T
    M(1)=N0;
    M(i)=(K*N0)/((r*N0^alpha)/(r-alpha*mu2*A)+(K^alpha-(r*N0^alpha)/(r-...
        alpha*mu2*A))*exp((-r+alpha*mu2*A)*t(i)))^(1/alpha);
end

```

```
%model with higher mu
L=zeros(1,T);
for i=2:T
    L(1)=N0;
    L(i)=(K*N0)/((r*N0^alpha)/(r-alpha*mu3*A)+(K^alpha-(r*N0^alpha)/(r-...
        alpha*mu3*A))*exp((-r+alpha*mu3*A)*t(i)))^(1/alpha);
end

%capacity tumour tends to with radiation
cap1=K*nthroot(1-alpha*mu1*A/r,alpha)
cap2=K*nthroot(1-alpha*mu2*A/r,alpha)
cap3=K*nthroot(1-alpha*mu3*A/r,alpha)

figure
    plot (t,N,'Color','b')
    hold on
    plot (t,M,'Color','r')
    hold on
    plot (t,L,'Color','g')
    xlabel('Time, t')
    ylabel('Cell number, N(t)')
    grid on
```

Used for figure 31 on page 42.

```
%model tumour growth with radiation
clear all
%parameter values
r=log(2)/24;     %net proliferation rate
N0=10;           %initial value
K=100;           %carrying capacity
alpha=1.5;       %general logistic equation parameter
mu=0.1;          %how much drug damages cell

%bifurcation parameter value
bif=r/(alpha*mu)
A=0.3;

if A<bif
    cap=K*nthroot(1-alpha*mu*A/r,alpha)
else cap=0
end

N=0:K;
f=r/alpha.*N.*(1-(N/K).^alpha)-mu*A*N;

figure
    %line([35,37],[0.05,0],'Color','k')  %arrows for bif1
    %hold on
    %line([35,37],[-0.05,0],'Color','k')
    %hold on
    %line([87,85],[0.05,0],'Color','k')
    %hold on
    %line([87,85],[-0.05,0],'Color','k')
```

```
    %hold on
    %line([37,35],[0.05,0],'Color','k')  %arrows for bif2
    %hold on
    %line([37,35],[-0.05,0],'Color','k')
    %hold on
    plot(0:1:100,0,'--k')
    hold on
    plot(N,f,'k')
    hold on
    plot(0,0,'.b','MarkerSize',15)
    hold on
    plot(cap,0,'.b','MarkerSize',15)
    xlabel('Cell Number, N')
    ylabel('Growth equation, f(N)')
    ylim([-1,1])
```

Used for figure 32 on page 42.

```
%model tumour growth with radiation
clear all
%parameter values
r=log(2)/24;     %net proliferation rate
N0=10;           %initial value
K=100;           %carrying capacity
alpha=1.5;       %general logistic equation parameter
mu=0.1;          %how much drug damages cell

%bifurcation parameter value:
bif= r/(alpha*mu)

A=0:0.001:1;
AA=length(A);
for i=1:AA
    if A(i)<bif
        N(i)=K*nthroot(1-alpha*mu*A(i)/r,alpha);
    else N(i)=0;
    end
end

figure
    plot(0:0.01:1,0,'--k')
    hold on
    plot(A,N,'b')
    xlabel('Radiation Dose, A (Gy)')
    ylabel('Final Cell Number, N')
    ylim([-10,K])
```

Used for figure 33 on page 44.

```
%model tumour growth with continuous radiation and repair
clear all
%parameter values
t=[0:0.1:500];      %time
```

```
T=length(t);
r=log(2)/24;          %net proliferation rate
N0=10;                %initial value
K=100;                %carrying capacity
alpha=1.5;            %general logistic equation parameter
N=zeros(1,T);         %tumour cells with radiation and no repair
L=zeros(1,T);         %tumour cells with radiation and repair
mu=0.1;               %how much drug damages cell
a=0.1;                %amount of radiation (Gy)
A=a;                  %radiation
rho=0.5;              %factor for the amount of cells able to repair
lambda=log(2)/4;      %repair rate

%model with radiation
for i=2:T
    N(1)=N0;
    L(1)=N0;
    N(i)=(K*N0)/((r*N0^alpha)/(r-alpha*mu*A)+(K^alpha-(r*N0^alpha)/(r-...
        alpha*mu*A))*exp((-r+alpha*mu*A)*t(i)))^(1/alpha);
    L(i)=(K*N0)/((r*N0^alpha)/(r-alpha*mu*A+alpha*rho*lambda*A)+(K^alpha...
        -(r*N0^alpha)/(r-alpha*mu*A+alpha*rho*lambda*A))*exp((-r+alpha*mu...
        *A-alpha*rho*lambda*A)*t(i)))^(1/alpha);
end

%model without radiation
M=zeros(1,T);
for i=2:T
    M(1)=N0;
    M(i)=(K*N0)/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(i)))^(1/alpha);
end

%bifurcation parameter value
bif= r/(alpha*(mu-rho*lambda))
%capacity tumour tends to with radiation
if A<bif
    cap=K*nthroot(1-alpha*mu*A/r+alpha*rho*lambda*A/r,alpha)
else cap=0
end

figure
    plot (t,N,'Color','b')      %radiation, no repair
    hold on
    plot (t,L,'Color','r')      %radiation, with repair
    hold on
    plot (t,M,'Color','k')      %no radiation
    xlabel('Time, t')
    ylabel('Cell number, N(t)')
    grid on
    ylim([0 K])

figure
    plot (t,A,'Color','b')
    xlabel('Time, t')
    ylabel('Radiation dose (Gy)')
```

```
56      grid on
```

Used for figure 34 on page 46.

```
1  %model tumour growth with continuous radiation and repopulation
2  clear all
3  %parameter values
4  t=[0:0.1:500];  %time
5  T=length(t);
6  r=log(2)/24;    %net proliferation rate
7  N0=10;          %initial value
8  K=100;          %carrying capacity
9  alpha=1.5;      %general logistic equation parameter
10 N=zeros(1,T);   %tumour cells with radiation and no repopulation
11 NN=zeros(1,T);  %tumour cells with radiation and repopulation
12 mu=0.1;         %how much drug damages cell
13 a=0.3;          %amount of radiation (Gy)
14 A=a;            %radiation
15 beta=0.3;       %factor of cells that are able to proliferate after ...
       radiation
16
17 %model with radiation
18 for i=2:T
19     N(1)=N0;
20     L(1)=N0;
21     N(i)=(K*N0)/((r*N0^alpha)/(r-alpha*mu*A)+(K^alpha-(r*N0^alpha)/(r-...
           alpha*mu*A))*exp((-r+alpha*mu*A)*t(i)))^(1/alpha);
22     L(i)=(K*N0)/(((r+beta*A*r)*N0^alpha)/(r-alpha*mu*A+beta*A*r)+(K^...
           alpha-((r+beta*A*r)*N0^alpha)/(r-alpha*mu*A+beta*A*r))*exp((-r+...
           alpha*mu*A-beta*A*r)*t(i)))^(1/alpha);
23 end
24
25 %model without radiation
26 M=zeros(1,T);
27 for i=2:T
28     M(1)=N0;
29     M(i)=(K*N0)/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(i)))^(1/alpha);
30 end
31
32 %bifurcation parameter value
33 bif= r/(alpha*mu-beta*r)
34 %capacity tumour tends to with radiation
35 if A<bif
36     cap=K*nthroot(1-alpha*mu*A/(r*(1+beta*A)),alpha)
37 else cap=0
38 end
39
40 figure
41     plot (t,N,'Color','b')      %radiation, no repair
42     hold on
43     plot (t,L,'Color','r')      %radiation, with repair
44     hold on
45     plot (t,M,'Color','k')      %no radiation
46     xlabel('Time, t')
```

```
47      ylabel('Cell number, N(t)')
48      grid on
49      ylim([0 K])
```

Used for figure 35 on page 49.

```
1  %forward (explicit) Euler method to solve equations for continuous
2  %radiation and heterogenous tumour growth
3  clear all
4  t0=0;             %start time
5  T=7000;           %end time
6  h=0.1;            %delta t - step size
7  t=t0:h:T;         %time
8  F0=[8,2];         %Starting points [P0,Q0] => N0=10
9  tumour(:,1)=F0;
10
11 %parameter values
12 r=log(2)/24;      %net proliferation rate
13 K=100;            %carrying capacity
14 alpha=1.5;        %general logistic equation parameter
15 mu=0.1;           %how much drug damages cell
16 a=0.1;            %amount of radiation (Gy)
17 A=a;              %radiation in total
18 kQP=0.001;        %rate at which quiescent cells become proliferating ...
       cells
19 kPQ=0.005;        %rate at which prolif. cells become quiescent
20
21 %Euler method
22 for i =1:length(t)-1
23      tumour(:,i+1)=tumour(:,i)+h*[r/alpha*tumour(1,i)*(1-((tumour(1,i)+...
            tumour(2,i))/K)^alpha)-mu*A*tumour(1,i)-kPQ*tumour(1,i)+kQP*...
            tumour(2,i),kPQ*tumour(1,i)-kQP*tumour(2,i)]';
24 end
25
26 %end
27 tumour(:,end)
28 tumour(1,end)+tumour(2,end)
29
30 figure
31      plot (t,tumour(1,:),'Color','r')       %P
32      hold on
33      plot (t,tumour(2,:),'Color','g')       %Q
34      hold on
35      plot (t,tumour(1,:)+tumour(2,:),'Color','k')       %N
36      xlabel('Time, t')
37      ylabel('Cell number')
38      grid on
```

Used for figures 37 and 38 on page 53.

```
1  %forward (explicit) Euler method to solve equations for sensitive and
2  %resistant tumour cells
3  clear all
```

```
t0=0;           %start time
T=1200;         %end time
h=0.1;          %delta t - step size
t=t0:h:T;       %time
F0=[6,4];       %Starting points [S0,R0] => N0=10
tumour(:,1)=F0;

%parameter values
r1=log(2)/24;   %net proliferation rate of the radiosensitive tumour ...
    cells
r2=log(2)/48;   %net proliferation rate of the radioresistant tumour ...
    cells
K=100;          %carrying capacity
alpha=1.5;      %general logistic equation parameter
mu1=0.1;        %how much drug damages radiosensitive cells
mu2=0.01;       %how much drug damages radioresistant cells
a=0.1;          %amount of radiation (Gy)
A=a;            %radiation in total

%Euler method to solve equations
for i=1:length(t)-1
    tumour(:,i+1)=tumour(:,i)+h*[r1/alpha*tumour(1,i)*(1-((tumour(1,i)+...
        tumour(2,i))/K)^alpha)-mu1*A*tumour(1,i),r2/alpha*tumour(2,i)...
        *(1-((tumour(1,i)+tumour(2,i))/K)^alpha)-mu2*A*tumour(2,i)]';
end

%end
tumour(:,end)
tumour(1,end)+tumour(2,end)

figure
    plot (t,tumour(1,:),'Color','r')                %S - sensitive
    hold on
    plot (t,tumour(2,:),'Color','g')                %R - resistant
    hold on
    plot (t,tumour(1,:)+tumour(2,:),'Color','k')    %N in total
    xlabel('Time, t')
    ylabel('Cell number')
    grid on
```

Used for figure 39 on page 56.

```
%model tumour growth with periodic radiation
clear all
%parameter values
t=0:0.1:500;    %time
T=length(t);
r=log(2)/24;    %net proliferation rate
N0=10;          %initial value
K=100;          %carrying capacity
alpha=1.5;      %general logistic equation parameter
N=zeros(1,T);   %tumour cells
A=zeros(1,T);   %total radiation
tau=0.1;        %interval of radiation
```

```
mu=0.1;          %how much drug damages cell
a=0.5;           %amount of radiation per session(Gy)

lenhour=20;               %length in hours
len=lenhour/(t(2)-t(1)); %length of a session (watch out for time spaces... in t)
maxn=(T-1)/len-1;         %number of sessions
tauindex=find(t==tau*len*(t(2)-t(1)));

N(1)=N0;
Nn=N0;                   %start at n=0
A(1)=a;
for n=0:maxn             %for each session do:
    for i=n*len+2:n*len+tauindex
        N(i)=(K*Nn)/((r*Nn^alpha)/(r-alpha*mu*a)+(K^alpha-(r*Nn^alpha)/(... r-alpha*mu*a))*exp((-r+alpha*mu*a)*(t(i)-n*len*(t(2)-t(1))))) ... ^(1/alpha);
        Ntau=N(n*len+tauindex);
        A(i)=a;
    end
    for i=n*len+tauindex+1:find(t==(n+1)*len*(t(2)-t(1)))
        N(i)=(K*Ntau)/(Ntau^alpha+(K^alpha-Ntau^alpha)*exp(-r*(t(i)-(n+... tau)*len*(t(2)-t(1)))))^(1/alpha);
        Nn=N(find(t==(n+1)*len*(t(2)-t(1))));
        A(i)=0;
    end
end

%model without radiation
M=zeros(1,T);
for i=1:T
   M(i)=(K*N0)/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(i)))^(1/alpha);
end

%bifurcation parameter value:
bifold= r/(alpha*mu)
bif=bifold/tau

figure
    plot(t,N,'Color','r')
    hold on
    plot (t,M,'Color','k')
    xlabel('Time, t')
    ylabel('Cell number, N(t)')
    grid on
```

Used for figure 40 on page 58.

```
%model tumour growth with periodic radiation and repair
clear all
%parameter values
t=0:0.1:500;        %time
T=length(t);
r=log(2)/24;        %net proliferation rate
```

```
N0=10;                %initial value
K=100;                %carrying capacity
alpha=1.5;            %general logistic equation parameter
N=zeros(1,T);         %tumour cells with repair
L=zeros(1,T);         %tumour cells with no repair
A=zeros(1,T);         %total radiation
tau=0.1;              %interval of radiation
mu=0.1;               %how much drug damages cell
a=18;                 %amount of radiation per session(Gy)
rho=0.5;              %amount of cells able to repair
lambda=log(2)/4;      %repair rate

lenhour=20;               %length in hours
len=lenhour/(t(2)-t(1)); %length of a session (watch out for time spaces... in t)
maxn=(T-1)/len-1;         %number of sessions
tauindex=find(t==tau*len*(t(2)-t(1)));

N(1)=N0;
Nn=N0;                   %start at n=0
L(1)=N0;
Ln=N0;
A(1)=a;
for n=0:maxn             %for each session do:
    for i=n*len+2:n*len+tauindex
        N(i)=(K*Nn)/((r*Nn^alpha)/(r-alpha*mu*a+alpha*rho*lambda*a)+(K^...
            alpha-(r*Nn^alpha)/(r-alpha*mu*a+alpha*rho*lambda*a))*exp((-r...
            +alpha*mu*a-alpha*rho*lambda*a)*(t(i)-n*len*(t(2)-t(1)))))...
            ^(1/alpha);
        Ntau=N(n*len+tauindex);
        L(i)=(K*Ln)/((r*Ln^alpha)/(r-alpha*mu*a)+(K^alpha-(r*Ln^alpha)/(...
            r-alpha*mu*a))*exp((-r+alpha*mu*a)*(t(i)-n*len*(t(2)-t(1)))))...
            ^(1/alpha);
        Ltau=L(n*len+tauindex);
        A(i)=a;
    end
    for i=n*len+tauindex+1:find(t==(n+1)*len*(t(2)-t(1)))
        N(i)=(K*Ntau)/(Ntau^alpha+(K^alpha-Ntau^alpha)*exp(-r*(t(i)-(n+...
            tau)*len*(t(2)-t(1)))))^(1/alpha);
        Nn=N(find(t==(n+1)*len*(t(2)-t(1))));
        L(i)=(K*Ltau)/((r*Ltau^alpha)/(r)+(K^alpha-(r*Ltau^alpha)/(r))*...
            exp((-r)*(t(i)-(n+tau)*len*(t(2)-t(1)))))^(1/alpha);
        Ln=L(find(t==(n+1)*len*(t(2)-t(1))));
        A(i)=0;
    end
end

%model without radiation
M=zeros(1,T);
for i=1:T
   M(i)=(K*N0)/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(i)))^(1/alpha);
end

%bifurcation parameter value:
```

```
bifold= r/(alpha*(mu-rho*lambda))
bif=r/(alpha*(mu-rho*lambda)*tau)

figure
    plot(t,N,'Color','r')   %radiation, repair
    hold on
    plot (t,M,'Color','k')  %no radiation
    hold on
    plot (t,L,'Color','b')  %radiation, no repair
    xlabel('Time, t')
    ylabel('Cell number, N(t)')
    grid on
```

Used for figure 41 on page 59.

```
%model tumour growth with periodic radiation and repopulation
clear all
%parameter values
t=[0:0.1:500];  %time
T=length(t);
r=log(2)/24;    %net proliferation rate
N0=10;          %initial value
K=100;          %carrying capacity
alpha=1.5;      %general logistic equation parameter
N=zeros(1,T);   %tumour cells with radiation and no repopulation
L=zeros(1,T);   %tumour cells with radiation and repopulation
A=zeros(1,T);   %total radiation
tau=0.1;        %interval of radiation
mu=0.1;         %how much drug damages cell
a=3;            %amount of radiation per session(Gy)
beta=0.3;       %factor of cells that are able to proliferate despite of...
    radiation

lenhour=20;               %length in hours
len=lenhour/(t(2)-t(1)); %length of a session (watch out for time spaces...
    in t)
maxn=(T-1)/len-1;         %number of sessions
tauindex=find(t==tau*len*(t(2)-t(1)));

N(1)=N0;
L(1)=N0;
Nn=N0;                   %start at n=0
Ln=N0;
A(1)=a;
for n=0:maxn             %for each session do:
    for i=n*len+2:n*len+tauindex
        N(i)=(K*Nn)/((r*Nn^alpha)/(r-alpha*mu*a)+(K^alpha-(r*Nn^alpha)/(...
            r-alpha*mu*a))*exp((-r+alpha*mu*a)*(t(i)-n*len*(t(2)-t(1)))))...
            ^(1/alpha);
        L(i)=(K*Ln)/(((r+beta*a*r)*Ln^alpha)/(r-alpha*mu*a+beta*a*r)+(K^...
            alpha-((r+beta*a*r)*Ln^alpha)/(r-alpha*mu*a+beta*a*r))*exp((-...
            r+alpha*mu*a-beta*a*r)*(t(i)-n*len*(t(2)-t(1)))))^(1/alpha);
        Ntau=N(n*len+tauindex);
        Ltau=L(n*len+tauindex);
```

```
34          A(i)=a;
35      end
36      for i=n*len+tauindex+1:find(t==(n+1)*len*(t(2)-t(1)))
37          N(i)=(K*Ntau)/(Ntau^alpha+(K^alpha-Ntau^alpha)*exp(-r*(t(i)-(n+...
                tau)*len*(t(2)-t(1)))))^(1/alpha);
38          L(i)=(K*Ltau)/(Ltau^alpha+(K^alpha-Ltau^alpha)*exp(-r*(t(i)-(n+...
                tau)*len*(t(2)-t(1)))))^(1/alpha);
39          Nn=N(find(t==(n+1)*len*(t(2)-t(1))));
40          Ln=L(find(t==(n+1)*len*(t(2)-t(1))));
41          A(i)=0;
42      end
43  end
44
45  %model without radiation
46  M=zeros(1,T);
47  for i=1:T
48     M(i)=(K*N0)/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(i)))^(1/alpha);
49  end
50
51  %bifurcation parameter value:
52  bif=r/((alpha*mu-beta*r)*tau)
53
54  figure
55      plot(t,N,'Color','b')       %basic radiation
56      hold on
57      plot (t,M,'Color','k')      %no radiation
58      hold on
59      plot (t,L,'Color','r')      %radiation with repopulation
60      xlabel('Time, t')
61      ylabel('Cell number, N(t)')
62      grid on
```

Used for figure 42 on page 61.

```
1  %function to find number of cells in tumour area
2  clear all
3  %area data
4  area=[0
5  142661
6  203765
7  246000
8  289332];
9  %no. of cells data
10 cells=[0
11  0.02234
12  0.03269
13  0.05269
14  0.05569];
15
16 x=0:1:300000; % Area (micrometer^2)
17
18 %parameters
19 A=0.069;
20 B=0.001;
```

```
C=0.000013;
D=0.325;

cellscalc=zeros(length(x),1);
for j=2:length(x)
    cellscalc(1)=B;
    cellscalc(j)=A*B/(B^D+(A^D-B^D)*exp(-C*x(j)))^(1/D);
end

errorcells=((cellscalc(142662)-cells(2))/cellscalc(142662))^2+((...
   cellscalc(203766)-cells(3))/cellscalc(203766))^2+((cellscalc(246001)-...
   cells(4))/cellscalc(246001))^2+((cellscalc(289333)-cells(5))/...
   cellscalc(289333))^2

figure
    plot(x,cellscalc)
    hold on
    plot(area,cells,'.k','markersize',15)
    xlabel('Area (\mum^2)')
    ylabel('Cell Number per \mum^2')
    grid on
    %ylim([0 0.06])
```

Used for figures 43, 44 and 45 on pages 62 and 63.

```
%T47D growth with radiation - repopulation model applied
clear all

%time
t=0:400;                %in hours
tmin=0:1/60:400;        %minute fractions

%data from H-Zentrum
time=[0,72,144,216,288,360];                                    %every 3 ...
   days
cells=[564.32,2393.71,6885.54,9037.09,10539.96,11721.89];     %0 Gy
cells_2=[564.32,1922.83,4455.84,5545.76,7243.12,8060.54];     %2 Gy
cells_4=[564.32,1789.94,2981.46,4050.18,3872.42,5107.74];     %4 Gy
cells_6=[564.32,1921.87,2776.20,3137.19,3642.32,4082.09];     %6 Gy
cells_8=[564.32,1838.21,2407.38,2139.53,2615.68,3209.19];     %8 Gy

%gen. log. growth model parameters
N0=cells(1);                        %initial value
T=length(t);
Tmin=length(tmin);
K=12690;                            %carrying capacity
r=log(2)/60;                        %cell multiplies every 60 hours
alpha=0.169;                        %equation parameter

%tumour cells, just growth
N=zeros(T,1);
for j=2:T
    N(1)=N0;
    N(j)=K*N0/(N0^alpha+(K^alpha-N0^alpha)*exp(-r*t(j)))^(1/alpha);
```

```
29 end
30
31 mu=0.4;                                %how much drug damages cell
32 rate=0.5;                               %rate at which cells are radiated ...
       per min in Gy
33 beta=0.9;                           %amount of cells able to proliferate ...
       despite being radiated
34
35 %data was received by radiating cells once at day 0 - 2 gy
36 a2=2;                                   %amount of radiation in Gy
37 tau2=(1/rate)*a2/(tmin(end)*60);        %interval of radiation
38 tauindex2=find(tmin==(1/rate)*a2/60);
39 M2=zeros(1,Tmin);
40 M2(1)=N0;
41 K2=8000;
42 for i=2:tauindex2
43     M2(i)=(K2*N0)/(((r+beta*a2*r)*N0^alpha)/(r-alpha*mu*a2+beta*a2*r)+(...
           K2^alpha-((r+beta*a2*r)*N0^alpha)/(r-alpha*mu*a2+beta*a2*r))*exp...
           ((-r+alpha*mu*a2-beta*a2*r)*(tmin(i))))^(1/alpha);
44     M2tau=M2(tauindex2);
45 end
46 for i=tauindex2+1:Tmin
47     M2(i)=(K2*M2tau)/(M2tau^alpha+(K2^alpha-M2tau^alpha)*exp(-r*(tmin(i)...
           -tau2)))^(1/alpha);
48 end
49
50 %data was received by radiating cells once at day 0 - 4 gy
51 a4=4;
52 tau4=(1/rate)*a4/(tmin(end)*60);
53 tauindex4=find(tmin==(1/rate)*a4/60);
54
55 %tumour cells with radiation- basic model
56 M4=zeros(1,Tmin);
57 M4(1)=N0;
58 K4=5100;
59 for i=2:tauindex4
60     M4(i)=(K4*N0)/(((r+beta*a4*r)*N0^alpha)/(r-alpha*mu*a4+beta*a4*r)+(...
           K4^alpha-((r+beta*a4*r)*N0^alpha)/(r-alpha*mu*a4+beta*a4*r))*exp...
           ((-r+alpha*mu*a4-beta*a4*r)*(tmin(i))))^(1/alpha);
61     M4tau=M4(tauindex4);
62 end
63 for i=tauindex4+1:Tmin
64     M4(i)=(K4*M4tau)/(M4tau^alpha+(K4^alpha-M4tau^alpha)*exp(-r*(tmin(i)...
           -tau4)))^(1/alpha);
65 end
66
67 %data was received by radiating cells once at day 0 - 6 gy
68 a6=6;
69 tau6=(1/rate)*a6/(tmin(end)*60);
70 tauindex6=find(tmin==(1/rate)*a6/60);
71
72 %tumour cells with radiation - basic model
73 M6=zeros(1,Tmin);
74 M6(1)=N0;
```

```
K6=4200;
for i=2:tauindex6
    M6(i)=(K6*N0)/(((r+beta*a6*r)*N0^alpha)/(r-alpha*mu*a6+beta*a6*r)+(...
        K6^alpha-((r+beta*a6*r)*N0^alpha)/(r-alpha*mu*a6+beta*a6*r))*exp...
        ((-r+alpha*mu*a6-beta*a6*r)*(tmin(i))))^(1/alpha);
    M6tau=M6(tauindex6);
end
for i=tauindex6+1:Tmin
    M6(i)=(K6*M6tau)/(M6tau^alpha+(K6^alpha-M6tau^alpha)*exp(-r*(tmin(i)...
        -tau6)))^(1/alpha);
end

%data was received by radiating cells once at day 0 - 8 gy
a8=8;
tau8=(1/rate)*a8/(tmin(end)*60);
tauindex8=find(tmin==(1/rate)*a8/60);

%tumour cells with radiation- basic model
M8=zeros(1,Tmin);
M8(1)=N0;
K8=3200;
for i=2:tauindex8
    M8(i)=(K8*N0)/(((r+beta*a8*r)*N0^alpha)/(r-alpha*mu*a8+beta*a8*r)+(...
        K8^alpha-((r+beta*a8*r)*N0^alpha)/(r-alpha*mu*a8+beta*a8*r))*exp...
        ((-r+alpha*mu*a8-beta*a8*r)*(tmin(i))))^(1/alpha);
    M8tau=M8(tauindex8);
end
for i=tauindex8+1:Tmin
    M8(i)=(K8*M8tau)/(M8tau^alpha+(K8^alpha-M8tau^alpha)*exp(-r*(tmin(i)...
        -tau8)))^(1/alpha);
end

bif2=r/((alpha*mu-beta*r)*tau2);
bif4=r/((alpha*mu-beta*r)*tau4);
bif6=r/((alpha*mu-beta*r)*tau6);
bif8=r/((alpha*mu-beta*r)*tau8);

figure
    plot(t,N,'Color','r')
    hold on
    plot(time,cells,'.k','markersize',15)
    xlabel('Time, t (hours)')
     ylabel('Cell Number, N(t)')
    grid on
    ylim([0 14000])

figure
    plot(tmin,M2,'Color','r')
    hold on
    plot(time, cells_2,'.k','markersize',15)
    xlabel('Time, t (hours)')
    ylabel('Cell Number, N(t)')
    grid on
    ylim([0 14000])
```

```
123
124      figure
125     plot(tmin,M4,'Color','r')
126     hold on
127     plot(time, cells_4,'.k','markersize',15)
128     xlabel('Time, t (hours)')
129     ylabel('Cell Number, N(t)')
130     grid on
131     ylim([0 14000])
132
133 figure
134     plot(tmin,M6,'Color','r')
135     hold on
136     plot(time, cells_6,'.k','markersize',15)
137     xlabel('Time, t (hours)')
138     ylabel('Cell Number, N(t)')
139     grid on
140     ylim([0 14000])
141
142 figure
143     plot(tmin,M8,'Color','r')
144     hold on
145     plot(time, cells_8,'.k','markersize',15)
146     xlabel('Time, t (hours)')
147     ylabel('Cell Number, N(t)')
148     grid on
149     ylim([0 14000])
150
151 figure
152     plot(t,N,'k')
153     hold on
154     plot(tmin,M2,'b')
155     hold on
156     plot(tmin,M4,'g')
157     hold on
158     plot(tmin,M6,'r')
159     hold on
160     plot(tmin,M8,'c')
161     hold on
162     plot(time, cells,'.k','markersize',15)
163     hold on
164     plot(time, cells_2,'pk','MarkerFaceColor','k')
165     hold on
166     plot(time, cells_4,'dk')
167     hold on
168     plot(time, cells_6,'*k')
169     hold on
170     plot(time, cells_8,'^k')
171     xlabel('Time, t (hours)')
172     ylabel('Cell Number, N(t)')
173     grid on
174     ylim([0 14000])
175
176
```

```
177 error2=((M2(4321)-cells_2(2))/M2(4321))^2+((M2(8641)-cells_2(3))/M2...
        (8641))^2+((M2(12961)-cells_2(4))/M2(12961))^2+((M2(17281)-cells_2(5)...
        )/M2(17281))^2+((M2(21601)-cells_2(6))/M2(21601))^2
178 error4=((M4(4321)-cells_4(2))/M4(4321))^2+((M4(8641)-cells_4(3))/M4...
        (8641))^2+((M4(12961)-cells_4(4))/M4(12961))^2+((M4(17281)-cells_4(5)...
        )/M4(17281))^2+((M4(21601)-cells_4(6))/M4(21601))^2
179 error6=((M6(4321)-cells_6(2))/M6(4321))^2+((M6(8641)-cells_6(3))/M6...
        (8641))^2+((M6(12961)-cells_6(4))/M6(12961))^2+((M6(17281)-cells_6(5)...
        )/M6(17281))^2+((M6(21601)-cells_6(6))/M6(21601))^2
180 error8=((M8(4321)-cells_8(2))/M8(4321))^2+((M8(8641)-cells_8(3))/M8...
        (8641))^2+((M8(12961)-cells_8(4))/M8(12961))^2+((M8(17281)-cells_8(5)...
        )/M8(17281))^2+((M8(21601)-cells_8(6))/M8(21601))^2
```

Spatial Model

Used for figures 47 on page 71.

```
1  %Radius and nutrient concentration
2  clear all
3  %data
4  time=[0,3,6,9,12,15];
5  R_0=[157,204,248,263,272,279];
6  R_2=[157,196,228,238,251,256];
7  R_4=[157,194,212,224,222,234];
8  R_6=[157,196,210,214,220,225];
9  R_8=[157,195,204,200,207,215];
10 %parameter values
11 t0=0;                        %start time
12 T=16;                        %end time (in days)
13 h=0.01;                      %delta t - step size
14 t=t0:h:T;                    %time
15 R0=[157,0,0];                %initial value from data
16 tradius=zeros(3,length(t));
17 tradius(:,1)=R0;
18 A=0;                         %radiation amount
19 mu=0;
20 lambdaA=0.24;                %rate of apoptosis
21 lambdaN=0.57;                %rate of necrosis
22 gamma=0.00014;               %rate of nutrient consumption
23 cinf=1;                      %nutrient concentration outside
24 cH=cinf-100^2*gamma/6;       %at r=R_H
25 cN=cinf-200^2*gamma/6;       %at r=R_N
26
27 %Euler method to solve equation for tumour radius
28 for i=1:length(t)-1
29     if tradius(1,i)<sqrt(6/gamma*(cinf-cH))
30         tradius(1,i+1)=tradius(1,i)+h*tradius(1,i)/3*(cinf-gamma/15*(...
               tradius(1,i))^2-lambdaA-mu*1*A);
31         tradius(2,i+1)=0;
32         tradius(3,i+1)=0;
33     elseif tradius(1,i)<sqrt(6/gamma*(cinf-cN))
34         tradius(3,i)=0;
```

```
35          tradius(2,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cH));
36          tradius(1,i+1)=tradius(1,i)+h*(tradius(1,i)/3*((cinf-gamma/6*(...
                tradius(1,i))^2-lambdaA-mu*1*A)*(1-(tradius(2,i))^3/(tradius...
                (1,i))^3)+gamma/10*(tradius(1,i))^2*(1-(tradius(2,i))^5/(...
                tradius(1,i))^5)));
37      else
38          tradius(2,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cH));
39          tradius(3,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cN));
40          tradius(1,i+1)=tradius(1,i)+h*(tradius(1,i)/3*(cN*(1-(tradius(2,...
                i))^3/(tradius(1,i))^3)-(lambdaA+mu*A)*(1+(tradius(3,i))^3/(...
                tradius(1,i))^3-(tradius(2,i))^3/(tradius(1,i))^3)-lambdaN*(...
                tradius(3,i))^3/(tradius(1,i))^3)+gamma/6*(tradius(1,i))...
                ^3*(1/5*(1-(tradius(2,i))^5/(tradius(1,i))^5)-(tradius(3,i))...
                ^2/(tradius(1,i))^3*(1-(tradius(2,i))^3/(tradius(1,i))^3)+(...
                tradius(3,i))^3/(tradius(1,i))^4*(1-(tradius(2,i))^2/(tradius...
                (1,i))^2)));
41      end
42  end
43  tradius(2,end)=sqrt((tradius(1,end))^2-6/gamma*(cinf-cH));
44  tradius(3,end)=sqrt((tradius(1,end))^2-6/gamma*(cinf-cN));
45
46  %plot time vs radius
47  figure
48      plot(t,tradius(1,:),'c')
49      hold on
50      plot(t,tradius(2,:),'b')
51      hold on
52      plot(t,tradius(3,:),'k')
53      hold on
54      plot(time,R_0,'.k','markersize',15)
55      xlabel('Time, t (days)')
56      ylabel('Tumour Radius, R (\mum)')
57      grid on
58      xlim([0 T])
59
60  %error
61  y=zeros(1,6);
62  for j=2:6
63      y(j)=((tradius(1,time(j)*100+1)-R_0(j))/tradius(1,time(j)*100+1))^2;
64  end
65  error=sum(y)
```

Algorithm 3: Used to find best fitting parameters.

```
1  %find smallest error
2  clear all
3  %data
4  time=[0,3,6,9,12,15];
5  R_0=[157,204,248,263,272,279];
6  %parameter values
7  t0=0;                        %start time
8  T=16;                        %end time (in days)
9  h=0.01;                      %delta t - step size
```

```
10 t=t0:h:T;                    %time
11 R0=[157,0,0];                %initial value from data
12 tradius=zeros(3,length(t));
13 tradius(:,1)=R0;
14 A=0;
15 mu=0.1;
16 cinf=1;
17
18 steplambdaA=0.01;
19 steplambdaN=0.01;
20 stepgamma=0.00001;
21 model=zeros(T-200,1);
22 LA=0:steplambdaA:1;
23 LN=0:steplambdaN:1;
24 G=0.00001:stepgamma:0.00014;
25 LLAA=length(LA);
26 LLNN=length(LN);
27 GG=length(G);
28 y=0;
29 fehlertens=zeros(GG,LLNN,LLAA);
30
31 jjj=1;
32 for gamma=0.00001:stepgamma:0.00014
33     jj=1;
34     cH=cinf-100^2*gamma/6;
35     cN=cinf-200^2*gamma/6;
36     for lambdaN=0:steplambdaN:1
37         j=1;
38         for lambdaA=0:steplambdaA:1
39             for i=1:length(t)-1
40                 if tradius(1,i)<sqrt(6/gamma*(cinf-cH))
41                     tradius(1,i+1)=tradius(1,i)+h*tradius(1,i)/3*(cinf-...
                           gamma/15*(tradius(1,i))^2-lambdaA-mu*A);
42                     tradius(2,i+1)=0;
43                     tradius(3,i+1)=0;
44                 elseif tradius(1,i)<sqrt(6/gamma*(cinf-cN))
45                     tradius(3,i)=0;
46                     tradius(2,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cH)...
                           );
47                     tradius(1,i+1)=tradius(1,i)+h*(tradius(1,i)/3*((cinf...
                           -gamma/6*(tradius(1,i))^2-lambdaA-mu*A)*(1-(...
                           tradius(2,i))^3/(tradius(1,i))^3)+gamma/10*(...
                           tradius(1,i))^2*(1-(tradius(2,i))^5/(tradius(1,i)...
                           )^5)));
48                 else
49                     tradius(2,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cH)...
                           );
50                     tradius(3,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cN)...
                           );
51                     tradius(1,i+1)=tradius(1,i)+h*(tradius(1,i)/3*(cN...
                           *(1-(tradius(2,i))^3/(tradius(1,i))^3)-(lambdaA+...
                           mu*A)*(1+(tradius(3,i))^3/(tradius(1,i))^3-(...
                           tradius(2,i))^3/(tradius(1,i))^3)-lambdaN*(...
                           tradius(3,i))^3/(tradius(1,i))^3)+gamma/6*(...
```

```
                        tradius(1,i))^3*(1/5*(1-(tradius(2,i))^5/(tradius...
                        (1,i))^5)-(tradius(3,i))^2/(tradius(1,i))^3*(1-(...
                        tradius(2,i))^3/(tradius(1,i))^3)+(tradius(3,i))...
                        ^3/(tradius(1,i))^4*(1-(tradius(2,i))^2/(tradius...
                        (1,i))^2)));
                end
                if i==301
                    y=((tradius(1,i)-R_0(2))/tradius(1,i))^2;
                elseif i==601
                    y=((tradius(1,i)-R_0(3))/tradius(1,i))^2;
                elseif i==901
                    y=((tradius(1,i)-R_0(4))/tradius(1,i))^2;
                elseif i==1201
                    y=((tradius(1,i)-R_0(5))/tradius(1,i))^2;
                elseif i==1501
                    y=((tradius(1,i)-R_0(6))/tradius(1,i))^2;
                else
                    y=0;
                end
                fehlertens(jjj,jj,j)=fehlertens(jjj,jj,j)+y;
            end
        j=j+1;
        end
    jj=jj+1;
    end
jjj=jjj+1;
end


[mini idx]=min(fehlertens(:));
[gidx lNidx lAidx]=ind2sub(size(fehlertens),idx);
mini

lambdaAbest=LA(lAidx)
lambdaNbest=LN(lNidx)
gammabest=G(gidx)
```

Used for figure 48 on page 72.

```
%tumour growth - area plots every 3 days
clear all
%data
R_0=[157,204,248,263,272,279];
R_2=[157,196,228,238,251,256];
R_4=[157,194,212,224,222,234];
R_6=[157,196,210,214,220,225];
R_8=[157,195,204,200,207,215];
%model parameter
lambdaA=0.24;           %rate of apoptosis
lambdaN=0.57;           %rate of necrosis
gamma=0.00014;          %rate of nutrient consumption
cinf=1;                 %nutrient concentration outside
cH=cinf-100^2*gamma/6; %min nutrient concentration needed for cell ...
    proliferation
```

```
cN=cinf-200^2*gamma/6; %max nutrient concentration at which necrosis ...
    occurs

%plot tumour area
for j=1:6
    r=R_0(j);
    rH=sqrt(r^2-6/gamma*(cinf-cH));
    if r>200
        rN=sqrt(r^2-6/gamma*(cinf-cN));
    else
        rN=0;
    end
    x=0;
    y=0;
    ang=0:0.01:2*pi;
    xp=r*cos(ang);
    yp=r*sin(ang);
    xpH=rH*cos(ang);
    ypH=rH*sin(ang);
    xpN=rN*cos(ang);
    ypN=rN*sin(ang);

    figure
        plot(x+xp,y+yp,'c');
        hold on
        plot(x+xpH,y+ypH,'b');
        hold on
        plot(x+xpN,y+ypN,'k');
        xlim([-300 300])
        ylim([-300 300])
        axis square
        xlabel('\mum')
        ylabel('\mum')
end
```

Used for figures 49 and 50 on pages 73 and 74.

```
%Radius and nutrient concentration
clear all
%data
time=[0,3,6,9,12,15];
R_0=[157,204,248,263,272,279];
R_2=[157,196,228,238,251,256];
R_4=[157,194,212,224,222,234];
R_6=[157,196,210,214,220,225];
R_8=[157,195,204,200,207,215];
%parameter values
t0=0;                       %start time
T=16;                       %end time (in days)
h=0.01;                     %delta t - step size
t=t0:h:T;                   %time
R0=[157,0,0];               %initial value from data
tradius=zeros(3,length(t));
tradius(:,1)=R0;
```

```
tradius_2=zeros(3,length(t));
tradius_2(:,1)=R0;
tradius_4=zeros(3,length(t));
tradius_4(:,1)=R0;
tradius_6=zeros(3,length(t));
tradius_6(:,1)=R0;
tradius_8=zeros(3,length(t));
tradius_8(:,1)=R0;
A_2=2;                          %radiation amount
A_4=4;
A_6=6;
A_8=8;
mu_2=0.078;
mu_4=0.078;
mu_6=0.055;
mu_8=0.055;
lambdaA=0.24;               %rate of apoptosis
lambdaN=0.57;               %rate of necrosis
gamma=0.00014;              %rate of nutrient consumption
cinf=1;                     %nutrient concentration outside
cH=cinf-100^2*gamma/6;
cN=cinf-200^2*gamma/6;

%Euler method to solve equation for tumour radius
for i=1:length(t)-1
    if tradius(1,i)<sqrt(6/gamma*(cinf-cH))
        tradius(1,i+1)=tradius(1,i)+h*tradius(1,i)/3*(cinf-gamma/15*(...
            tradius(1,i))^2-lambdaA);
        tradius(2,i+1)=0;
        tradius(3,i+1)=0;
    elseif tradius(1,i)<sqrt(6/gamma*(cinf-cN))
        tradius(3,i)=0;
        tradius(2,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cH));
        tradius(1,i+1)=tradius(1,i)+h*(tradius(1,i)/3*((cinf-gamma/6*(...
            tradius(1,i))^2-lambdaA)*(1-(tradius(2,i))^3/(tradius(1,i))...
            ^3)+gamma/10*(tradius(1,i))^2*(1-(tradius(2,i))^5/(tradius(1,...
            i))^5)));
    else
        tradius(2,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cH));
        tradius(3,i)=sqrt((tradius(1,i))^2-6/gamma*(cinf-cN));
        tradius(1,i+1)=tradius(1,i)+h*(tradius(1,i)/3*(cN*(1-(tradius(2,...
            i))^3/(tradius(1,i))^3)-(lambdaA+0)*(1+(tradius(3,i))^3/(...
            tradius(1,i))^3-(tradius(2,i))^3/(tradius(1,i))^3)-lambdaN*(...
            tradius(3,i))^3/(tradius(1,i))^3)+gamma/6*(tradius(1,i))...
            ^3*(1/5*(1-(tradius(2,i))^5/(tradius(1,i))^5)-(tradius(3,i))...
            ^2/(tradius(1,i))^3*(1-(tradius(2,i))^3/(tradius(1,i))^3)+(...
            tradius(3,i))^3/(tradius(1,i))^4*(1-(tradius(2,i))^2/(tradius...
            (1,i))^2)));
    end
end
tradius(2,end)=sqrt((tradius(1,end))^2-6/gamma*(cinf-cH));
tradius(3,end)=sqrt((tradius(1,end))^2-6/gamma*(cinf-cN));

%Euler method to solve equation for tumour radius, A=2 gy
```

```
for i=1:length(t)-1
    if tradius_2(1,i)<sqrt(6/gamma*(cinf-cH))
        tradius_2(1,i+1)=tradius_2(1,i)+h*tradius_2(1,i)/3*(cinf-gamma...
            /15*(tradius_2(1,i))^2-lambdaA-mu_2*1*A_2);
        tradius_2(2,i+1)=0;
        tradius_2(3,i+1)=0;
    elseif tradius_2(1,i)<sqrt(6/gamma*(cinf-cN))
        tradius_2(3,i)=0;
        tradius_2(2,i)=sqrt((tradius_2(1,i))^2-6/gamma*(cinf-cH));
        tradius_2(1,i+1)=tradius_2(1,i)+h*(tradius_2(1,i)/3*((cinf-gamma...
            /6*(tradius_2(1,i))^2-lambdaA-mu_2*1*A_2)*(1-(tradius_2(2,i))...
            ^3/(tradius_2(1,i))^3)+gamma/10*(tradius_2(1,i))^2*(1-(...
            tradius_2(2,i))^5/(tradius_2(1,i))^5)));
    else
        tradius_2(2,i)=sqrt((tradius_2(1,i))^2-6/gamma*(cinf-cH));
        tradius_2(3,i)=sqrt((tradius_2(1,i))^2-6/gamma*(cinf-cN));
        tradius_2(1,i+1)=tradius_2(1,i)+h*(tradius_2(1,i)/3*(cN*(1-(...
            tradius_2(2,i))^3/(tradius_2(1,i))^3)-(lambdaA+mu_2*A_2)*(1+(...
            tradius_2(3,i))^3/(tradius_2(1,i))^3-(tradius_2(2,i))^3/(...
            tradius_2(1,i))^3)-lambdaN*(tradius_2(3,i))^3/(tradius_2(1,i)...
            )^3)+gamma/6*(tradius_2(1,i))^3*(1/5*(1-(tradius_2(2,i))^5/(...
            tradius_2(1,i))^5)-(tradius_2(3,i))^2/(tradius_2(1,i))^3*(1-(...
            tradius_2(2,i))^3/(tradius_2(1,i))^3)+(tradius_2(3,i))^3/(...
            tradius_2(1,i))^4*(1-(tradius_2(2,i))^2/(tradius_2(1,i))^2)))...
            ;
    end
end
tradius_2(2,end)=sqrt((tradius_2(1,end))^2-6/gamma*(cinf-cH));
tradius_2(3,end)=sqrt((tradius_2(1,end))^2-6/gamma*(cinf-cN));

%Euler method to solve equation for tumour radius, A=4 gy
for i=1:length(t)-1
    if tradius_4(1,i)<sqrt(6/gamma*(cinf-cH))
        tradius_4(1,i+1)=tradius_4(1,i)+h*tradius_4(1,i)/3*(cinf-gamma...
            /15*(tradius_4(1,i))^2-lambdaA-mu_4*1*A_4);
        tradius_4(2,i+1)=0;
        tradius_4(3,i+1)=0;
    elseif tradius_4(1,i)<sqrt(6/gamma*(cinf-cN))
        tradius_4(3,i)=0;
        tradius_4(2,i)=sqrt((tradius_4(1,i))^2-6/gamma*(cinf-cH));
        tradius_4(1,i+1)=tradius_4(1,i)+h*(tradius_4(1,i)/3*((cinf-gamma...
            /6*(tradius_4(1,i))^2-lambdaA-mu_4*1*A_4)*(1-(tradius_4(2,i))...
            ^3/(tradius_4(1,i))^3)+gamma/10*(tradius_4(1,i))^2*(1-(...
            tradius_4(2,i))^5/(tradius_4(1,i))^5)));
    else
        tradius_4(2,i)=sqrt((tradius_4(1,i))^2-6/gamma*(cinf-cH));
        tradius_4(3,i)=sqrt((tradius_4(1,i))^2-6/gamma*(cinf-cN));
        tradius_4(1,i+1)=tradius_4(1,i)+h*(tradius_4(1,i)/3*(cN*(1-(...
            tradius_4(2,i))^3/(tradius_4(1,i))^3)-(lambdaA+mu_4*A_4)*(1+(...
            tradius_4(3,i))^3/(tradius_4(1,i))^3-(tradius_4(2,i))^3/(...
            tradius_4(1,i))^3)-lambdaN*(tradius_4(3,i))^3/(tradius_4(1,i)...
            )^3)+gamma/6*(tradius_4(1,i))^3*(1/5*(1-(tradius_4(2,i))^5/(...
            tradius_4(1,i))^5)-(tradius_4(3,i))^2/(tradius_4(1,i))^3*(1-(...
            tradius_4(2,i))^3/(tradius_4(1,i))^3)+(tradius_4(3,i))^3/(...
```

```
            tradius_4(1,i))^4*(1-(tradius_4(2,i))^2/(tradius_4(1,i))^2)))...
            ;
93      end
94  end
95  tradius_4(2,end)=sqrt((tradius_4(1,end))^2-6/gamma*(cinf-cH));
96  tradius_4(3,end)=sqrt((tradius_4(1,end))^2-6/gamma*(cinf-cN));
97
98  %Euler method to solve equation for tumour radius, A=4 gy
99  for i=1:length(t)-1
100     if tradius_6(1,i)<sqrt(6/gamma*(cinf-cH))
101         tradius_6(1,i+1)=tradius_6(1,i)+h*tradius_6(1,i)/3*(cinf-gamma...
            /15*(tradius_6(1,i))^2-lambdaA-mu_6*1*A_6);
102         tradius_6(2,i+1)=0;
103         tradius_6(3,i+1)=0;
104     elseif tradius_6(1,i)<sqrt(6/gamma*(cinf-cN))
105         tradius_6(3,i)=0;
106         tradius_6(2,i)=sqrt((tradius_6(1,i))^2-6/gamma*(cinf-cH));
107         tradius_6(1,i+1)=tradius_6(1,i)+h*(tradius_6(1,i)/3*((cinf-gamma...
            /6*(tradius_6(1,i))^2-lambdaA-mu_6*1*A_6)*(1-(tradius_6(2,i))...
            ^3/(tradius_6(1,i))^3)+gamma/10*(tradius_6(1,i))^2*(1-(...
            tradius_6(2,i))^5/(tradius_6(1,i))^5)));
108     else
109         tradius_6(2,i)=sqrt((tradius_6(1,i))^2-6/gamma*(cinf-cH));
110         tradius_6(3,i)=sqrt((tradius_6(1,i))^2-6/gamma*(cinf-cN));
111         tradius_6(1,i+1)=tradius_6(1,i)+h*(tradius_6(1,i)/3*(cN*(1-(...
            tradius_6(2,i))^3/(tradius_6(1,i))^3)-(lambdaA+mu_6*A_6)*(1+(...
            tradius_6(3,i))^3/(tradius_6(1,i))^3-(tradius_6(2,i))^3/(...
            tradius_6(1,i))^3)-lambdaN*(tradius_6(3,i))^3/(tradius_6(1,i)...
            )^3)+gamma/6*(tradius_6(1,i))^3*(1/5*(1-(tradius_6(2,i))^5/(...
            tradius_6(1,i))^5)-(tradius_6(3,i))^2/(tradius_6(1,i))^3*(1-(...
            tradius_6(2,i))^3/(tradius_6(1,i))^3)+(tradius_6(3,i))^3/(...
            tradius_6(1,i))^4*(1-(tradius_6(2,i))^2/(tradius_6(1,i))^2)))...
            ;
112     end
113 end
114 tradius_6(2,end)=sqrt((tradius_6(1,end))^2-6/gamma*(cinf-cH));
115 tradius_6(3,end)=sqrt((tradius_6(1,end))^2-6/gamma*(cinf-cN));
116
117 %Euler method to solve equation for tumour radius, A=4 gy
118 for i=1:length(t)-1
119     if tradius_8(1,i)<sqrt(6/gamma*(cinf-cH))
120         tradius_8(1,i+1)=tradius_8(1,i)+h*tradius_8(1,i)/3*(cinf-gamma...
            /15*(tradius_8(1,i))^2-lambdaA-mu_8*1*A_8);
121         tradius_8(2,i+1)=0;
122         tradius_8(3,i+1)=0;
123     elseif tradius_8(1,i)<sqrt(6/gamma*(cinf-cN))
124         tradius_8(3,i)=0;
125         tradius_8(2,i)=sqrt((tradius_8(1,i))^2-6/gamma*(cinf-cH));
126         tradius_8(1,i+1)=tradius_8(1,i)+h*(tradius_8(1,i)/3*((cinf-gamma...
            /6*(tradius_8(1,i))^2-lambdaA-mu_8*1*A_8)*(1-(tradius_8(2,i))...
            ^3/(tradius_8(1,i))^3)+gamma/10*(tradius_8(1,i))^2*(1-(...
            tradius_8(2,i))^5/(tradius_8(1,i))^5)));
127     else
128         tradius_8(2,i)=sqrt((tradius_8(1,i))^2-6/gamma*(cinf-cH));
```

```
129         tradius_8(3,i)=sqrt((tradius_8(1,i))^2-6/gamma*(cinf-cN));
130         tradius_8(1,i+1)=tradius_8(1,i)+h*(tradius_8(1,i)/3*(cN*(1-(...
                tradius_8(2,i))^3/(tradius_8(1,i))^3)-(lambdaA+mu_8*A_8)*(1+(...
                tradius_8(3,i))^3/(tradius_8(1,i))^3-(tradius_8(2,i))^3/(...
                tradius_8(1,i))^3)-lambdaN*(tradius_8(3,i))^3/(tradius_8(1,i)...
                )^3)+gamma/6*(tradius_8(1,i))^3*(1/5*(1-(tradius_8(2,i))^5/(...
                tradius_8(1,i))^5)-(tradius_8(3,i))^2/(tradius_8(1,i))^3*(1-(...
                tradius_8(2,i))^3/(tradius_8(1,i))^3)+(tradius_8(3,i))^3/(...
                tradius_8(1,i))^4*(1-(tradius_8(2,i))^2/(tradius_8(1,i))^2)))...
                ;
131     end
132 end
133 tradius_8(2,end)=sqrt((tradius_8(1,end))^2-6/gamma*(cinf-cH));
134 tradius_8(3,end)=sqrt((tradius_8(1,end))^2-6/gamma*(cinf-cN));
135
136 %plot time vs radius
137 figure
138     plot(t,tradius_2(1,:),'c')
139     hold on
140     plot(t,tradius_2(2,:),'b')
141     hold on
142     plot(t,tradius_2(3,:),'k')
143     hold on
144     plot(time,R_2,'.k','markersize',15)
145     xlabel('Time, t (days)')
146     ylabel('Tumour Radius, R (\mum)')
147     grid on
148     xlim([0 T])
149     ylim([0 300])
150
151 figure
152     plot(t,tradius_4(1,:),'c')
153     hold on
154     plot(t,tradius_4(2,:),'b')
155     hold on
156     plot(t,tradius_4(3,:),'k')
157     hold on
158     plot(time,R_4,'.k','markersize',15)
159     xlabel('Time, t (days)')
160     ylabel('Tumour Radius, R (\mum)')
161     grid on
162     xlim([0 T])
163     ylim([0 300])
164
165 figure
166     plot(t,tradius_6(1,:),'c')
167     hold on
168     plot(t,tradius_6(2,:),'b')
169     hold on
170     plot(t,tradius_6(3,:),'k')
171     hold on
172     plot(time,R_6,'.k','markersize',15)
173     xlabel('Time, t (days)')
174     ylabel('Tumour Radius, R (\mum)')
```

```
175     grid on
176     xlim([0 T])
177     ylim([0 300])
178
179 figure
180     plot(t,tradius_8(1,:),'c')
181     hold on
182     plot(t,tradius_8(2,:),'b')
183     hold on
184     plot(t,tradius_8(3,:),'k')
185     hold on
186     plot(time,R_8,'.k','markersize',15)
187     xlabel('Time, t (days)')
188     ylabel('Tumour Radius, R (\mum)')
189     grid on
190     xlim([0 T])
191     ylim([0 300])
192
193
194 figure
195     plot(t,tradius(1,:),'k')
196     hold on
197     plot(t,tradius_2(1,:),'b')
198     hold on
199     plot(t,tradius_4(1,:),'g')
200     hold on
201     plot(t,tradius_6(1,:),'r')
202     hold on
203     plot(t,tradius_8(1,:),'m')
204     hold on
205     plot(time, R_0,'.k','markersize',15)
206     hold on
207     plot(time, R_2,'pk','MarkerFaceColor','k')
208     hold on
209     plot(time, R_4,'dk')
210     hold on
211     plot(time, R_6,'*k')
212     hold on
213     plot(time, R_8,'^k')
214     xlabel('Time, t (days)')
215     ylabel('Tumour Radius, R (\mum)')
216     grid on
217     xlim([0 T])
218     ylim([0 300])
219
220 %errors
221 y_2=zeros(1,6);
222 for j=2:6
223     y_2(j)=((tradius_2(1,time(j)*100+1)-R_2(j))/tradius_2(1,time(j)...
            *100+1))^2;
224 end
225 error_2=sum(y_2)
226
227 y_4=zeros(1,6);
```

```
for j=2:6
    y_4(j)=((tradius_4(1,time(j)*100+1)-R_4(j))/tradius_4(1,time(j)...
        *100+1))^2;
end
error_4=sum(y_4)

y_6=zeros(1,6);
for j=2:6
    y_6(j)=((tradius_6(1,time(j)*100+1)-R_6(j))/tradius_6(1,time(j)...
        *100+1))^2;
end
error_6=sum(y_6)

y_8=zeros(1,6);
for j=2:6
    y_8(j)=((tradius_8(1,time(j)*100+1)-R_8(j))/tradius_8(1,time(j)...
        *100+1))^2;
end
error_8=sum(y_8)
```

Used for figure 51 on page 74.

```
%tumour growth - area plots every 3 days
clear all
%data
R_0=[157,204,248,263,272,279];
R_2=[157,196,228,238,251,256];
R_4=[157,194,212,224,222,234];
R_6=[157,196,210,214,220,225];
R_8=[157,195,204,200,207,215];
%model parameter
lambdaA=0.24;           %rate of apoptosis
lambdaN=0.57;           %rate of necrosis
gamma=0.00014;          %rate of nutrient consumption
cinf=1;                 %nutrient concentration outside
cH=cinf-100^2*gamma/6; %min nutrient concentration needed for cell ...
    proliferation
cN=cinf-200^2*gamma/6; %max nutrient concentration at which necrosis ...
    occurs

%plot tumour area
for j=1:6
    r=R_6(j);
    rH=sqrt(r^2-6/gamma*(cinf-cH));
    if r>200
        rN=sqrt(r^2-6/gamma*(cinf-cN));
    else
        rN=0;
    end
    x=0;
    y=0;
    ang=0:0.01:2*pi;
    xp=r*cos(ang);
    yp=r*sin(ang);
```

```
31      xpH=rH*cos(ang);
32      ypH=rH*sin(ang);
33      xpN=rN*cos(ang);
34      ypN=rN*sin(ang);
35
36      figure
37          plot(x+xp,y+yp,'c');
38          hold on
39          plot(x+xpH,y+ypH,'b');
40          hold on
41          plot(x+xpN,y+ypN,'k');
42          xlim([-300 300])
43          ylim([-300 300])
44          axis square
45          xlabel('\mum')
46          ylabel('\mum')
47  end
```

References

[AH12] N. Anastasov and I. Höfig. Experiment t47d growth with radiation. Helmholtz Center Munich, Institute of Radiation Biology, 2012.

[AHN09] J. C. L. Alfonso, M. A. Herrero, and L. Nunez. Modelling and optimization in radiotherapy. Lecture notes, 2009.

[All07] L. J. S. Allen, editor. *An Introduction to Mathematical Biology.* Pearson Education Inc., 2007.

[Ana11] N. Anastasov. Personalized radiation therapy group. experiment 'wachstumskurve t47d-mda361'. Helmholtz Center Munich, Institute of Radiation Biology, 2011.

[And85] J. R. Anderson, editor. *Muir's Textbook of Pathology.* Hodder Arnold, 1985.

[BCA08] N. Bellomo, M. Chaplain, and E. De Angelis, editors. *Selected Topics in Cancer Modeling.* Birkhäuser Boston, 2008.

[BHH+98] D. J. Brenner, L. R. Hlatky, P. J. Hahnfeldt, Y. Huang, and R. K. Sachs. The linear-quadratic model and most other common radiobiological models result in similar predictions of time-dose relationship. *Radiation Research*, 150:83–91, 1998.

[BK05] H. M. Byrne and J. R. King. Tumor modeling. In *Encyclopedia of Biostatistics.* John Wiley & Sons, 2005.

[Bri05] N. F. Britton. *Essential Mathematical Biology.* Springer-Verlag, 2005.

[Bur66] A. C. Burton. Rate of growth of solid tumours as a problem of diffusion. *Growth*, 30:157–176, 1966.

[CHN09] A. Cappuccio, M. A. Herrero, and L. Nunez. Tumour radiotherapy and its mathematical modelling. *Contemporary Mathematics*, 492:77–102, 2009.

[DS81] W. Düchting and Th. Vogel Saenger. Three-dimensional pattern generation applied to spheroidal tumor growth in a nutrient medium, 1981.

[ECAV07] H. Enderling, M. A. J. Chaplain, A. R. A. Anderson, and J. S. Vaidya. A mathematical model of breast cancer development, local treatment and recurrence. *Journal of Theoretical Biology*, 246:245–259, 2007.

[FBK+03] S. J. Franks, H. M. Byrne, J. R. King, J. C. E. Underwood, and C. E. Lewis. Modelling the early growth of ductal carcinoma in situ of the breast. *Journal of Mathematical Biology*, 47:424–452, 2003.

[FBM+03] S. J. Franks, H. M. Byrne, H. S. Mudhar, J. C. E. Underwood, and C. E. Lewis. Mathematical modelling of comedo ductal carcinoma in situ of the breast. *Mathematical Medicine and Biology*, 20:277–308, 2003.

[FSB+10] J. Ferlay, H. R. Shin, F. Bray, D. Forman, C. Mathers, and D. M. Parkin. Globocan 2008 v2.0, cancer incidence and mortality worldwide: Iarc cancerbase no. 10. Technical report, International Agency for Research on Cancer, http://globocan.iarc.fr, 2010.

[GM03] R. A. Gatenby and P. K. Maini. Cancer summed up. *Nature*, 421:321, 2003.

[GMK96] K. Groebe and W. Mueller-Klieser. On the relation between size of necrosis and diameter of tumor spheroids. *International Journal of Radiation Oncology, Biology, Physics*, 34:395–401, 1996.

[Gre72] H. P. Greenspan. Models for the growth of a solid tumor by diffusion. *Studies in Applied Mathematics*, 4:317–340, 1972.

[HG12] E. J. Hall and A. J. Giaccia. *Radiobiology for the Radiologist.* Lippincott Williams & Wilkins, 2012.

[KT85] H. Krug and G. Taubert. Zur praxis der anpassung der logistischen funktion an das wachstum experimenteller tumoren. *Archiv für Geschwulstforschung*, 55:235–244, 1985.

[MC09] P. Mandal and M. Conrad. Irradiation-induced cytotoxicity, monitoring of irradiation-induced cell damage using the xcelligence system. Technical report, Institute for Clinical Molecular Biology and Tumour Genetics, Helmholtz Center for Environmental Health, Munich, Roche Diagnostics GmbH 2009.

[Mül12] J. Müller. Mathematical biology 2. Lecture notes, 2012.

[Mur89] J. D. Murray, editor. *Mathematical Biology.* Springer-Verlag, 1989.

[Nia98] A. H. W. Nias. *An Introduction to Radiobiology.* John Wiley & Sons, 1998.

[OMH09] S. F. C. O'Rourke, H. McAneney, and T. Hillen. Linear quadratic and tumour control probability modelling in external beam radiotherapy. *Journal of Mathematical Biology*, 58:799–817, 2009.

[Pre03] L. Preziosi, editor. *Cancer Modelling and Simulation.* Chapman and Hall, 2003.

[PSO+10] E. D. Pleasance, P. J. Stephens, S. OMeara, D. J. McBride, A. Meynert, D. Jones, Meng-Lay L., D. Beare, King Wai Lau, C. Greenman, I. Varela, S. Nik-Zainal, H. R. Davies, G. R. Ordonez, L. J. Mudie, C. Latimer, S. Edkins, L. Stebbings, L. Chen, Mingming Jia, C. Leroy, J. Marshall, A. Menzies, A. Butler, J. W. Teague, J. Mangion, Yongming A. Sun, S. F. McLaughlin, H. E. Peckham, E. F. Tsung, G. L. Costa, C. C. Lee, J. D. Minna, A. Gazdar, E. Birney, M. D. Rhodes, K. J. McKernan, M. R. Stratton, P. A. Futreal, and P. J. Campbell. A small-cell lung cancer genome with complex signatures of tobacco exposure. *Nature*, 463:184–90, 2010.

[PV10] J. Pérez-Velázquez. Mathematical modelling of cancer and tumour growth. Lecture notes, 2010.

[QSS00] A. Quarteroni, R. Sacco, and F. Saleri. *Numerische Mathematik 2*. Springer, 2000.

[SHH01] R. K. Sachs, L. R. Hlatky, and P. Hahnfeldt. Simple ode models of tumor growth and anti-angiogenic or radiation treatment. *Mathematical and Computer Modelling*, 33:1297–1305, 2001.

[SS94] R. Schuster and H. Schuster. Reconstruction models for the ehrlich ascites tumor of the mouse. *Mathematical Population Dynamics: Analysis of Heterogenity*, 2:335–348, 1994.

[TG95] R. H. Thomlinson and L. H. Gray. The histological structure of some human lung cancers and the possible implications for radiotherapy. *British Journal of Cancer*, 9:539–549, 1995.

[VR03] M. Villasana and A. Radunskaya. A delay differential equation model for tumor growth. *Journal of Mathematical Biology*, 47:270–294, 2003.

[Wan00] C. C. Wang, editor. *Clinical Radiation Oncology*. Wiley-Liss, 2000.

[Wei07] R. A. Weinberg. *The Biology of Cancer*. Garland Science, 2007.

[WK97] J. P. Ward and J. R. King. Mathematical modelling of avascular-tumour growth. *IMA Journal of Mathematics Applied in Medicine & Biology*, 14:39–69, 1997.

[WK05] D. Wodarz and N. L. Komarova. *Computational Biology of Cancer - Lecture Notes and Mathematical Modeling*. World Scientific, 2005.

List of Figures

List of Tables