Robust Optimization for Uncertain Radiobiological Parameters in Inverse Dose Planning

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Abstract

Cancer is a common cause of death worldwide with radiotherapy as one of the most used treatments. Radiation treatment plans are normally optimized using constraints on the maximum dose to tumours and minimum dose to surrounding healthy structures. It has been suggested that utilizing biological models in the radiation plan optimization process could improve outcome significantly. Such treatment plans depend not only on the accuracy of the biological models, describing the dose response relations of different tumours and other structures, but also on the accuracy of tissue specific parameters in these models. Different sets of biological model parameters lead to different treatment plans and thus, uncertainties in these parameters may compromise the quality of the treatments.

In this thesis, several radiobiological optimization models have been developed, including either the concepts of Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP), or Equivalent Uniform Dose (EUD). The uncertainties of model parameters are expressed by probability density functions included in the dose optimization process. Robust optimization methods that account for the uncertainties have been developed and implemented in a MATLAB GUI created for Gamma Knife surgery. The robust optimized dose plans have been compared to non-robust plans using fixed parameter values. The results suggest that the final dose distribution strongly depend on the distribution functions and that the robust treatment plans are less dependent on variations in the model parameters.
Referat

Robust Optimering för Osäkerheter i Radiobiologiska Parametrar i Invers Dosplanering

Cancer är en av de strörsta dödsorsakerna i världen idag, och strålningsterapi är en vanligt förekommande behandlingsform. Vanligtvis optimeras behandlingsplaner för strålningsterapi genom att sätta villkor på en minimal dos till tumörer och en maximal dos till omkringliggande vävnad. Biologiska modeller har utvecklats som ett alternativ till dessa villkor, för att användas i optimeringen av behandlingsplaner. Resultatet av sådan radiobiologisk dosoptimering beror inte endast av kvaliteten på de biologiska modellerna, utan även på noggrannheten i de vävnadspezifika parametrar som finns i modellerna. Olika val av parametervärden leder till olika resultat och därför kommer osäkerheter i dessa parametrar att äventyra kvaliteten på strålningsterapi.

Radiobiologiska optimeringsmodeller som inkluderar koncepten Tumour Control Probability (TCP) och Normal Tissue Complication Probability (NTCP), eller Equivalent Uniform Dose (EUD) har utvecklats i detta examensarbete. De osäkra modellparametrar har uttryckts med sannolikhetsfördelningar och inkluderats i optimeringsmodellen. Robusta optimeringsmetoder som tar hänsyn till osäkerheter har utvecklats och implementerats i ett grafiskt användargränssnitt i MATLAB, med syftet att kunna användas i Gammaknivsvirurgi. De optimerade robusta dosplaner har jämförts med icke-robusta optimerade dosplaner där värden på de osäkra parametrarna är konstanta. Resultaten pekar på att dosplanerna starkt beror på de olika fördelningar av parametrar som använts och att robusta optimeringsmetoder ger behandlingsplaner som är mindre känsliga för variationer i de biologiska parametrarna.
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Preface

This master’s thesis project has been performed at Elekta Instrument AB, a company providing medical equipment for treatment of cancer and other brain disorders. I would like to thank my supervisors at the company, Håkan Nordström and Jonas Adler, for introducing me to the subject and generously sharing their valuable time and guidance. Furthermore, many thanks to my supervisor at the division of Optimization and Systems Theory at KTH, Johan Karlsson, for your highly appreciated input and encouragement.
1  |  Introduction

Cancer is one of the most common causes of death worldwide and it is estimated that every third person will get cancer during their lifetime. Treatment forms involve surgery, chemotherapy and radiation therapy, which in some cases involve the Gamma Knife.

Elekta Instrument AB is a medical technology company who sells and manufactures the Leksell Gamma Knife, which is a radiosurgical instrument used for treatment of various brain disorders, primarily cancer. This thesis concerns robust optimization approaches in the presence of parameter uncertainties in the treatment planning for the Gamma Knife.

Radiation treatment uses high-energy radiation which is aimed at the target from many angles, with the goal of damaging the DNA and eventually killing the cancer cells. Commonly, the treatment is divided into several fractions where radiation is given in small doses per treatment occasion. This method uses the fact that the tumour and the surrounding healthy tissues have different radiation sensitivities and hence let the normal tissue get a chance to heal. However, in the Gamma Knife the treatment in general consists of a single fraction with a high dose of radiation, a concept known as radiosurgery. This method uses the sharp gradients of the Gamma Knife to spare the normal tissue while killing the tumour with a high dose. The radiosurgical model is based on selectivity, coverage and gradient index to achieve high target coverage without covering the surrounding tissue and to get a sharp drop of dose outside the target.

In radiation therapy treatment planning, an optimization model is used to optimize the radiation dose distribution in the patient. The most used and available optimization techniques are based on physical dose methods where minimum and maximum doses are specified for targets and organs at risk. However, much research is being done to improve the treatment planning models by the use of radiobiology, which is the study of how living matter respond to radiation. These biological models are usually based on the probability of cell survival after radiation. Some biological optimization models uses the concepts of Tumour Control Probability (TCP), Normal Tissue Complication Probability (NTCP) and Equivalent Uniform Dose (EUD), see e.g., [27] [37] [31].

The treatment planning takes a wide range of input parameters for different models and many of these are very uncertain. The focus of this study is on radiobiological models and the biological parameters used in them. Uncertainties in
these parameters stem from the variation in radiosensitivity between different cells and functional subunits within an organ, as well as between different individuals. Robust optimization will be used in the plan construction and with the aim to improve the treatments and make them more robust. Here follows an introduction to the Leksell Gamma Knife which this work is done in consideration of.

1.1 The Leksell Gamma Knife

The Leksell Gamma Knife® is a radiosurgical instrument invented by Lars Leksell and Börje Larsson at the Karolinska Institute in Stockholm, 1969 [24]. It is used for treatment of tumours and other abnormalities in the brain. The latest model is the Leksell Gamma Knife Perfexion® which was introduced in 2006 and is shown in figure 1.1. The Gamma Knife is a gamma radiation based instrument which uses 192 beams of radiation from Cobalt-60 sources that are focused on the target. Although each beam has very little effect on the brain tissue it passes through, a strong dose of radiation is delivered in the focus point, called an isocenter. The precision of Gamma Knife radiosurgery results in minimal damage to healthy tissue surrounding the target.

The Gamma Knife consists of a stationary part, containing the collimator body and a platform on which the patients head is fixed and which can move in three dimensions. Due to the high doses delivered, high accuracy of the patient’s position is critical. Therefore the head is held still by attaching a stereotactic frame to it.
1.2 THE GAMMA KNIFE TREATMENT PLAN

using screws fastened to the skull. This frame is then attached to the Gamma Knife and becomes a reference for the coordinate system used in the treatment planning. The collimator body delivers radiation in cone shaped beams through eight different, individually controlled sectors and each sector can deliver beams of three different sizes, see figure 1.2. The collimator body is made of tungsten, which has good radiation shielding properties and is used to shape the beams. The treatment is specified with so called beam-on times, which is the time each beam is active in each state. The patient is moved during the treatment, although not during beam-on, for the isocenters to be shifted to different positions in the target.

1.2 The Gamma Knife Treatment Plan

Before the radiation treatment begins, a treatment plan must be generated. Treatment plans for the Gamma Knife are created in the Elekta-developed software called the Leksell Gamma Plan® 10 [13]. Information from diagnostic images is used in the treatment planning. These are commonly obtained using Magnetic Resonance Imaging (MRI) and sometimes with Computed Tomography (CT) scans. The planner manually delineates the tumour and organs at risk from these images and then set constraints on the dose distribution and parameters specific to the case. The plan is then made considering a trade off between the tumour, organs at risk and other healthy tissue. Treatment plans may be found by so called inverse planning, where the desired dose distribution is set beforehand and the optimization aims at finding the parameters to achieve this distribution [13]. The inverse planning has two main steps:

- A fill algorithm, for placing isocenters
- An optimization algorithm, for determining the beam-on times
The main purpose of the fill algorithm is to place isocenters in the delineated target volume. Shots are placed in the target to make sure each part of it get a desired dose and these shots are represented by isodose volumes. These volumes can be defined as all points with a higher dose than some specific dose level, given by the set \( \{ x \in \mathbb{R}^3 : d(x, p) \geq d^* \} \), where \( d(x, p) \) is the dose in the point \( x \) due to the shot with isocenter position \( p \) and \( d^* \) is the dose level. To find an initial start to the later optimization template shots are placed in the target volume. These templates are a fixed set of collimator settings of different shapes and sizes. The algorithm starts by placing as large shots as possible in the periphery of the target, without overlapping other shots too much. Eventually no more such shot positions exists even for the smallest shot size. The process is then repeated with the already covered volume treated as non-target. The target is thus filled from the surface and inwards, always with as large shots as possible. After the filling, the optimization can start. The optimization algorithm optimizes the beam-on time, position and collimator settings for each shot. The objective function to be optimized is based on selectivity, conformity, gradient index and time. It is possible to weigh different terms in the objective function and also to penalize the length of the treatment time. The four functions used in the optimization problem are:

- **Coverage**
  \[ C = \frac{V(PIV \cap TV)}{V(TV)} \]

- **Selectivity**
  \[ S = \frac{V(PIV \cap TV)}{V(PIV)} \]

- **Gradient Index**
  \[ GI = \frac{V(PIV_{ISO}/2)}{V(PIV_{ISO})} \]

- **Beam-on time**
  \[ T_{beam-on} = \sum_{i=1}^{N_{iso}} T_{beam-on, i} \]

\( PIV \) and \( TV \) stands for Planning Isodose Volume and Target Volume. The \( PIV \) is the volume covered by the planned dose distribution and the \( TV \) is the volume of the target. ISO stands for the isodose level in percentage. Here \( V(A) \) is the volume of the set \( A \), \( N_{iso} \) is the number of isocenters and \( T_{beam-on, i} \) is the beam-on time for isocenter \( i \). The optimization maximizes the following objective function:

\[ F = \frac{C^{min(2\alpha,1)} \cdot S^{min(2(1-\alpha),1)} + \beta \text{Grad} + \gamma \text{Time}}{1 + \beta + \gamma} \]

where \( \alpha, \beta, \gamma \in [0, 1] \) are weights defined by the user, \( \text{Grad} \) is a function of the gradient index and \( \text{Time} \) is a function of the beam-on times. The organs at risk are not considered in the objective function. However, penalizing poor selectivity will spare all tissue outside the target volume and penalizing a poor gradient index can create a steeper fall off of lower isodoses. During each step of the optimization a dose calculation is performed by a simplified algorithm [14]. The algorithm is able to compute the total dose received at any point within the three-dimensional
1.2 THE GAMMA KNIFE TREATMENT PLAN

stereotactic space defined by the frame coordinates. In general it is hard to decide what parameters to use in the optimization to create a good plan. Hence, the plan is developed through an iterative work-flow where inverse planning parameters can be adjusted and with continued optimization. For this to be possible some approximations in the algorithm for the dose calculations are used.

The planner is able to investigate the plan by a displaying of isodoses and Dose Volume Histograms (DVH). When the plan is approved it is sent to the Gamma Knife.
2 | Background

In this thesis work, optimization models for improving radiobiological therapy treatment plans are constructed and implemented in a test frame for the radiosurgical instrument the Gamma Knife. Here follows the theory of which the rest of the thesis is based on. It includes the concepts of radiotherapy, radiosurgery and radiobiology along with a description of uncertainties in treatment planning and robust optimization methods to handle them.

2.1 Radiation Therapy

Radiation therapy, or radiotherapy, is therapy using ionizing radiation as a part of primarily cancer treatment. It all started with the discovery of x-rays in 1895 by Wilhelm Röntgen and within a year the first attempts to use x-rays to treat cancer was reported [16]. The goal of the radiation treatment is to damage the DNA of tumour cells, which eventually lead to cellular death and prevent the cells from spreading. Radiotherapy is used both as stand-alone treatment and in combination with other cancer treatments such as chemotherapy and surgery.

The most common treatment is external radiation therapy, which means that the patient is irradiated by an external radiation source that directs the radiation to the target through a collimator body. The radiation is commonly delivered in the form of high-energy photon beams (gamma radiation) which ionizes the target tissue through gamma-electron interaction. For radiotherapy to be curative, all clonogenic cancer cells must be killed so that the result is permanent tumour control. The absorbed dose is what determines to which extent these effects occur. It is the energy imparted to matter per unit mass by ionizing radiation, commonly measured in Gray (1 Gy = 1 J/kg).

In the beginning, two-dimensional x-ray images were used in the radiation therapy planning and the beam set-ups where simple, using only a few beams. With the invention of computed tomography in the 1970’s a shift from 2-D to 3-D treatments was made since it was now possible to use better images of the patients anatomy and more accurately determine the dose distribution. It became practical to use beams from multiple angles, all shaped as their corresponding target projection. In this 3D Conventional Radiation Therapy (3D CRT) the beams have a uniform intensity field which makes it hard to shape the field to avoid organs at risk (OARs). It is manually optimized which means that the treatment planner chooses
all parameters, such as the number of beams, beam directions, shapes, beam times etc., and the computer calculates the resulting dose distribution. Major progress was made with intensity-modulated radiation therapy (IMRT) which is an advanced technique of high-precision radiotherapy where the radiation intensity across the beams can be modulated. The beams are shaped by means of multi-leaf collimators (MLCs), to conform the radiation to some intersection spots in the tumour [7]. The superposition of radiation of several beams from different angles provides high doses of radiation to the target volume (the tumour), while the doses to surrounding healthy tissues can be limited to some degree. Radiation can, apart from killing cancer cells in the short run, itself cause cancer in the longer run [33].

The process of radiotherapy starts with scanning of the patients, delineating areas of interest, creating the treatment plans and sending the data to the instrument used for radiation. An important part of this chain is the plan which is created in the treatment planning system. The radiation is then commonly delivered by IMRT in fractions, often small radiation doses every day during a certain period of time. Another way to treat patients with radiation is by radiosurgery which is presented next.

2.2 Radiosurgery

Lars Leksell defined the concept of stereotactic radiosurgery (SRS) in 1949, as “a single high dose fraction of radiation, stereotactically directed to an intracranial region of interest” [23] [32]. It is a technique for destruction of intra-cranial tissues or lesions, that may be inaccessible or unsuitable for open surgery, using a high dose of radiation given in one fraction. The first stereotactic gamma unit with Cobalt-60 was installed in 1968 at Sophiahemmet hospital in Stockholm. X-rays were first tried but both gamma rays and ultrasonics were included as alternatives. The word stereotactic refers to the three-dimensional coordinate system that is identified by the diagnostic images and makes it possible to create a good treatment plan. Radiosurgery is a special case of radiotherapy with only one fraction, it relies on sharp gradients of radiation which makes the dose drastically drop outside of the target. Fractionated radiotherapy on the other hand, delivers radiation in smaller amounts per fraction and instead relies on the different sensitivities of radiation in tumours and healthy tissue, allowing the healthy tissue to heal in between fractions. The company Elekta AB was founded by Lars Leksell in 1972 to commercialize this stereotactic radiosurgery system with the Leksell Gamma Knife®.

2.3 Treatment Planning

A treatment plan in radiation therapy is a specification of the number of beams and the settings in the radiation instrument that determine how the beams are to be delivered to the patient, e.g. beam sizes and beam-on times. The goal is to find a treatment plan which maximizes the probability of curative treatment without
2.4 EVALUATION OF PLAN QUALITY - DOSE VOLUME HISTOGRAM

complications. However, it is physically impossible to find an ideal treatment plan, giving a large dose of radiation to the target while the organs at risk and normal tissue is completely spared. Therefore a plan with high probability of success is approximated as one with a suitable balance between high target dose and low doses to the surrounding tissue. Modern radiation therapy treatment use inverse treatment planning as explained above, with a selected importance between tumours and other structures.

In order to optimize the treatment plan and get a dose distribution in the target and surrounding structures, the volume of all tissue is divided into small sub volumes called voxels.

2.4 Evaluation of Plan Quality - Dose Volume Histogram

The quality of a treatment plan is primarily determined by studying the quality of the resulting dose distribution. An easy way to represent the entire dose distribution in one structure is by a Dose Volume Histogram (DVH) first suggested by Bortfeld [4]. Many physical measures of the dose distribution for targets and healthy tissue can be evaluated by inspection of its dose volume histogram. For a given region of interest, the DVH shows how large fraction of the region that receives a dose at or above each dose level. Let \( F(d) \) denote the volume fraction of all voxels \( v \) in a region \( S \), that attains at least the dose \( d \). Thus, \( F(d) \) parametrizes the DVH of the region, and can be defined as [16],

\[
F(d) = \frac{V(\{ v \in S : d_v \geq d \})}{V(S)},
\]

where \( V(A) \) is the volume of the set \( A \). Some properties of the structure that can be used to evaluate the treatment plan quality and can be extracted from the DVH are:

- **Dose-at-volume:** \( D_v \), is the dose level \( d \) such that at least \( v\% \) of a region receives that dose or higher.

- **Volume-at-dose:** \( V_d \), is the fraction of the volume of a region that receives the dose \( d \) or higher.

The \( D_v \) is interesting to study for the targets to ensure that a large enough volume get a certain dose, while the \( V_d \) can be studied for the OARs and normal tissue to ensure that not a too large volume receives a certain dose. Now the maximum, minimum and median dose can be calculated from \( D_{100}, D_0 \) and \( D_{50} \). An example of DVHs are shown in figure 2.1.

Until recently, the quality of radiation treatment plans have been judged by such physical quantities, thought to correlate with biological response rather than by estimates of the biological outcome itself. However, other measures of dose may also be considered in the evaluation of the plan quality. For example biological measures
CHAPTER 2. BACKGROUND

Figure 2.1: Example of DVHs of one target and one OAR. $D_{98}$ shows that 98% of the target receives 15 Gy or more, and $V_{13}$ shows that only 1% of the OAR receives 13 Gy or more.

for tumours and normal tissue such as Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) [30]. These are the probabilities of achieving tumour control and of having any complications, more about these concepts can be found in section 2.7.2. A combination of TCP and NTCP can be used for the measure $P_+$, which represents the probability of a curative and complication free treatment. Another example is the measure of physical dose with a biological basis. The Equivalent Uniform Dose (EUD), which is the uniform dose that will give the same biological effect as a given non-uniform dose distribution, find more about this concept in section 2.7.3

2.5 Dose-Volume Based Planning and it’s Limitations

The currently most used models in treatment planning for radiotherapy are dose-volume based. These models use the concepts of the DVH. The dose delivered to each region in the patient’s body is compared directly to a dose distribution prescribed by the physician. An objective function is calculated from the difference between the actual and desired doses and it usually include maximum and minimum dose constraints for the target and the healthy tissues. The objective functions in these formulations are usually linear or quadratic functions of the beam-on times which penalizes deviations from the desired dose distribution [31]. In addition to this, there are usually Dose-Volume Constraints (DVC) which is a common way to put a constraint on the DVH. The role of the DVC is to change the shape of the DVH to possibly receive a better dose distribution. This constraint set a desired point to reach in the DVH by making sure that no more than $V_{max}$ of the volume
receives more than a dose $D_{max}$. It can be specified as $V\{v : d_v \geq D_{max}\} < V_{max}$. This is visualized in figure 2.2.

One great limitation is that objective functions based on DVC tend to be non-convex which can lead to multiple local minima [10]. This implies that a search algorithm, designed for global minimum problems, is likely to get trapped in a local minimum, potentially leading to a less favourable dose distribution. Further, DVC used for inverse treatment planning or plan evaluation are based on clinical studies of correlations between tumour control and particular dose volume metrics, which makes them an approximation of the biological outcome. The treatment planning also require skill and experience in selecting values and relative weights for constraints that would provide optimal tumour control without complications. Lastly, specifying several DVC in the optimization increases the computational complexity of the inverse treatment planning problem [1].

## 2.6 Radiobiology

Radiobiology is the study of how living matter reacts to ionizing radiation. Much research is currently being done in this field with the goal of incorporating radiobiology in treatment planning which is thought to give better individual treatments. There are three levels of important possible improvements to radiation treatment by radiobiology [33]:

- **Knowledge** - It will extend the knowledge about radiotherapy and give a wider explanation of what underlies the observed phenomena when tumours and normal tissue reacts to radiation. For example tumour cell repopulation, reoxygenation, DNA repair mechanisms and hypoxia.

- **Treatment strategy** - Development of treatment planning, including new approaches on treatment and different biological models.


- **Protocols** - Suggestions for choice of strategy in planning radiotherapy treatment. For example predicting the best treatment for the individual patient and plan quality evaluation.

It is suggested that the dose volume criteria, which are merely substitute measures of biological responses, should be replaced by biological models in order for the treatment process to more closely reflect clinical goals [1]. To achieve this, our understanding of advantages and limitations of existing dose-response models, as well as our understanding of radiobiology, must be developed. Today, only small steps have been taken in the direction of incorporating biological concepts into a routine treatment planning process. One goal of radiobiology is to develop mathematical models that for example describe the relationship between surviving fraction of cells and radiation dose, or models that link radiation sensitivity to cure rates for tumours. The new approach to treatment planning would include such models and attempts to measure the biological efficacy of the dose distribution.

Biologically Guided Radiation Therapy (BGRT) stands for the use of relevant patient-specific biological parameters in radiotherapy. These might for example be tumour and normal cell radiosensitivity, oxygenation status, proliferation rate, number of clonogenic cancer cells etc. A major part of BGRT is the ability to design dose distributions that would produce the desired balance between tumour cure and normal tissue injury based on the knowledge of biological properties of the particular tumour and surrounding normal tissues.

### 2.6.1 Radiation Effects on Cells

The general goal in radiation treatment is to kill all clonogenic cells in the tumour in order to get full tumour control and a curative treatment. The ionizing radiation damages the cellular DNA and if the damage is large enough the cell looses its ability to proliferate, which eventually leads to cell death.
2.6 RADIOBIOLOGY

The response of tissue to radiation therapy is related to the five R’s of radiobiology: Repair, Redistribution, Repopulation, Radiosensitivity and Reoxygenation. These all play a significant role in the field of radiobiology. However, not all concepts are relevant for radiosurgery since the radiation is only given in one, or possibly a few, fractions. Thus, the most important of these concepts in this study is the radiosensitivity of tissue.

When living matter is exposed to ionizing radiation, the cellular DNA is damaged by interaction with the ionizing particles. It is a long process which is divided into a physical phase, a chemical phase and a biological phase, see figure 2.3 [33]. It starts with the physical phase where the x-ray photons that pass through the tissue interact with free electrons or electrons with small binding energy compared to the photon energy. A part of the photon energy is given to the electrons and some of them is ejected from the atom (ionization) while others are raised to a higher energy level (excitation). The high energy electron resulting from the ionization may damage the DNA directly or indirectly. In direct action, the electrons interact with the DNA and produce damage. Then there is the indirect action, in which the electron interacts with other atoms or molecules in the cells, such as water. Ionization and excitation lead to the breakage of chemical bonds and the formation of broken molecules, known as free radicals. Then there is the chemical phase in which the free radicals react with and cause biological and chemical changes to the DNA. Indirect action is dominant for x-rays or gamma rays and it is possible to modify it using chemical sensitizers. These two phases, with direct and indirect action, are illustrated in figure 2.4. Lastly there is the biological phase, which include all subsequent events. A relatively large part (depending on the dose) of the lesions, including in the DNA, are repaired. However, some lesions fail to repair and these might eventually lead to cell death. The damage produced by the free radicals may be restored if molecular oxygen is available. It is the killing of stem cells.
which would have given rise to new cells that causes the early display of damage on healthy tissue. A secondary effect of cell killing is compensatory cell proliferation, which occurs both in healthy tissues and tumours. An even later effect of radiation damage is the appearance of secondary tumours.

The radiosensitivity of cells depends on many things, and one example is the supply of oxygen [33]. Oxygen is a radiosensitizer which means that it makes the tumours more sensitive to radiation. By forming DNA-damaging free radicals, it increases the effect of a given radiation dose. As a tumour grows, it may outgrow its blood supply, leaving regions of the tumour where oxygen concentration is low. This state, where tumour cells have been deprived of oxygen, is known as hypoxia. Hypoxic cells have more resistance to radiation and this can be taken into account in the treatment planning.

2.6.2 Dose Response Curves and the Therapeutic Window

One of the main limiting factors of the dose that can be delivered to the tumour is the tolerance of dose in the surrounding normal tissue. The relationship between dose and desired tumour control with undesired normal tissue complication can be represented by two dose response curves. The dose response curves can be illustrated by plotting the probability of controlling the target and the probability of normal tissue complication as a function of the radiation dose. If these two curves are plotted in the same graph one can see the therapeutic window which is the area between the two curves, as illustrated in figure 2.5. The figure shows that for 100% probability of tumour control, the probability of normal tissue complication is approximately 50%. By optimizing the treatment, the two response curves for
the target and the normal tissue will be pushed away resulting in an increase of the width of the therapeutic window. Further, by reducing the margin of the target the complication curve is shifted toward higher dose and the therapeutic window is increased.

2.7 Radiobiological Dose Response Models

Radiobiological models can be used in several fields of the treatment planning, for example to evaluate the quality of the plan as suggested above. Another potential of radiobiological modeling lies in the use of models to construct cost functions for optimization of treatment plans. For example, the concept of “complication-free cure”, denoted as $P_c$, was suggested as a cost function for unconstrained biologically based optimization [2]. A number of mathematical models have been developed over the years to better describe the biological effect of radiation, some of them are described below.

2.7.1 Linear-Quadratic Model

One of the most important contributions of radiobiology has been the theoretical description of cell death as a function of dose.

The linear quadratic (LQ) model, first proposed by Douglas and Fowler [11], is a commonly used model to describe the relationship between cell survival and a given dose of radiation, $d$. The name comes from the linear and quadratic components of the dose $d$. The cell survival curve is a continuously decreasing curve which can be fitted by the LQ-model and it is defined by the surviving fraction (SF) of cells as,

$$SF = \exp(-\alpha d - \beta d^2).$$

The shape of the curve is determined by the ratio $\alpha/\beta$, as can be seen in figure 2.6. Although the model can be regarded a purely mathematical model, it has also been possible to attach radiobiological mechanisms to it and it is an accepted mathematical description of biological response to radiation [33]. The parameters $\alpha$ and $\beta$ can be fitted to the graph and they describe the radiosensitivity of the concerned tissue. The dimensions of the parameters are for $\alpha$, Gy$^{-1}$ and for $\beta$, Gy$^{-2}$, hence the dimension of the ratio $\alpha/\beta$ is Gy. This ratio is the dose which represents equal contribution to damage from the linear term and the quadratic term. A high ratio implies that the tissue is early responding while a low ratio implies late responding tissue. As mentioned in [26][12], the LQ-model is a good estimate when considering fractionated radiotherapy but its applicability when it comes to high doses per fraction, as in radiosurgery, can be questioned. Yet no good alternatives have been developed.
2.7.2 TCP and NTCP

A common way to incorporate radiobiology in treatment planning optimization is by using the concepts of Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). The TCP model assumes that a tumour is only controlled when all clonogenic cells have been killed. The models include the Poisson-based expression of the probability that no cells survive a certain dose, first suggested by Brahme [5],

\[ P = \exp(-N_f). \]

Where \( N_f \) is the number of clonogenic cells left at the end of the treatment. Assuming there are \( N_0 \) clonogenic cells in each voxel to begin with the expression can be defined as,

\[ P = \exp(-N_0 \cdot SF), \]

where SF is the LQ model of the surviving fraction of cells. This allows the TCP function for a tumour to be written as,

\[
TCP(V_t d) = \prod_{i=1}^{n_t} P_i = \prod_{i=1}^{n_t} \exp \left( -N_0 \exp(-\alpha d_i - \beta d_i^2) \right),
\]

(2.2)

where \( n_t \) is the number of voxels in the tumour, \( d_i \) is the dose in voxel \( i \) and \( d \) is the vector of all doses \( d_i \). \( V_t \) is a selection matrix of size \( n_t \times |d| \) consisting of rows of unit vectors \( e_j \), for all indices \( j \) of voxels which belong to the tumour. Hence, \( V_t d \) is the vector of doses to all voxels in the tumour \( t \).

The most well known NTCP model is the relative seriality \( s \)-model, also based on SF [21]. For an OAR or other normal tissue it is defined as,

\[
NTCP(V_r d) = \left( 1 - \prod_{i=1}^{n_r} (1 - P_i^s)^{1/n_r} \right)^{1/s},
\]

(2.3)
Figure 2.7: DVHs for three dose plan optimizations involving TCP and NTCP, using \( \alpha = 0.1 \) (dashed lines), \( \alpha = 0.2 \) (solid lines) and \( \alpha = 0.3 \) (dotted lines) for the target.

\[ n_r \text{ is the number of voxels in the normal tissue or organ at risk and } s \in (0,1] \text{ is the relative seriality parameter that characterizes the internal organization of the tissue. A value of } s \approx 0 \text{ represents a largely parallel organ (the function of which is proportional to the fraction of its volume that is undamaged), whereas } s \approx 1 \text{ corresponds to a serial organ (which loses its function if one of its functional subunits is damaged). } V_r \text{ is defined as } V_t \text{ above but instead it specifies the voxel indices for normal tissue or an organ at risk, } r. \text{ It will later be specified that the TCP and NTCP are convex under some logarithmic transformations.}

In both the TCP and NTCP functions there are several radiobiological parameters, \( \alpha, \beta, N_0 \) and \( s \), which differ between tumours and normal tissue as well as in each individual case [9].

Figure 2.7 illustrates an example of how much a dose plan depend on the biological parameters, by showing a DVH for some plans optimized with an objective function involving TCP and NTCP. The considered patient structure consist of one tumour, one OAR and some normal tissue around the tumour (the same patient data is used later in this project to test models). The figure shows DVHs for three different values of \( \alpha \) for the tumour (\( \alpha \) in the TCP function), always with a constant \( \alpha/\beta \)-ratio.

### 2.7.3 Equivalent Uniform Dose

The concept of Equivalent Uniform Dose (EUD) for tumours was originally introduced by Niemierko [28] as the uniform dose that will give the same radiobiological...
effect as a given non-uniform dose. It was constructed under the assumption that two dose distributions are equivalent if they give the same probability for tumour control. It is a simplification to the TCP and NTCP models that only have one biological parameter and it maps the dose distribution into one value. The EUD for a target is defined as,

$$EUD(\bar{d}) = -\frac{1}{a'} \ln \left( \frac{1}{|V|} \sum_{i=1}^{|V|} e^{-a'd_i} \right),$$  \hspace{1cm} (2.4)

where $V$ is the set of all voxels in the target and $d_i$ is the dose to voxel $i$. The parameter $a'$ is tissue-specific with unit Gy$^{-1}$ and describe the radiosensitivity, which depends on the seriality of the tissue. This function was originally constructed by equating the TCP function of an equivalent homogeneous distribution and solving for EUD. Hence, the EUD can also be expressed as,

$$EUD(\bar{d}) = -\frac{\alpha}{2\beta} n \left[ 1 - \sqrt{1 - \frac{4\beta}{\alpha^2 n} \ln SF(\bar{d})} \right],$$  \hspace{1cm} (2.5)

where $n$ is the number of fractions. The concept was later generalized by Niemierko to also apply to normal tissues and risk organs [29]. This model is called the generalized Equivalent Uniform Dose and is a generalized mean function defined as,

$$gEUD(\bar{d}) = \left( \frac{1}{|V|} \sum_{i=1}^{|V|} d_i^a \right)^{\frac{1}{a}}.$$  \hspace{1cm} (2.6)

Note that $a$ in this function is also a tissue specific parameter which in this case is dimensionless. The gEUD function is easy to handle because it is convex for $a \geq 1$ and concave for $a \leq 1$ [6]. For $a = 1$, the gEUD measures the average dose to the voxels in the region, while for $a \to \infty$, gEUD approaches the maximum dose taken over all the voxels in $V$. For negative values of $a$, the gEUD function is defined only when $d_i > 0$ for all $i \in V$, and as $a \to -\infty$, gEUD approaches the minimum dose in all voxels.

Hence, $a$ is generally negative for tumours while large and positive for serial organs at risk or normal tissues and small and positive for parallel organs at risk or normal tissues [31]. In general the value of gEUD is between the mean and minimum dose of the non-uniform distribution for tumours and between mean and maximum dose of the non-uniform distribution for normal tissues. The concept of generalised equivalent uniform dose has been employed in biological treatment plan optimization, where gEUD of both target structures and healthy structures are used in the objective function. Then, ‘soft’ upper and lower bounds on the dose to each region can be defined by enforcing some constraint on gEUD in comparing it to a pre-determined dose $EUD_0$. $EUD_0$ is related to the desired minimum dose
2.8 Uncertainties in Radiation Treatment

All types of radiation treatments involve some sort of uncertainties that may affect the outcome. The treatment planning takes a wide range of input parameters and many of these have a significant uncertainty. Yet the inverse planning algorithms use fixed values for many of these parameters. Some sources of uncertainty include positioning of the patient relative to the beams and location and density of clono-
genic cancer cells. However, in this thesis only uncertainties in biological parameters are considered. These are the parameters found in the radiobiological models which are used in the plan optimization. Yet another important problem is involving the geometric uncertainties in the treatment planning, this is done in e.g., [19].

Commonly, uncertainties are handled by using margins. The clinical target volume might then be expanded into a planning target volume (PTV) and planning is performed to irradiate the latter. Another example is that margins on dose can be added in the physical constraints in non-biological optimization models. Unless uncertainties are accounted for in the treatment planning process, the resulting plan might have a severe degradation of quality in comparison to the goal plan.

2.8.1 Biological Parameter Uncertainties

If it was possible to precisely describe the reactions of an individual tumour and normal tissue for a given dose distribution, the highest quality treatment configuration from a biological perspective, for each individual patient, could be judged and an optimal solution obtained. However, radiobiological models are yet far from this ideal scenario. The most common biologically based optimization functions include the previously discussed concepts of TCP, NTCP and EUD. In the optimization techniques involving these models there will always be at least one biologic parameter. Most of these vary significantly between individual cases and are difficult to decide in each case. Values of the parameters are at best available for the “average” patient or they are based only on in vitro studies. No good methods are today available to better determine these parameters. The TCP and NTCP functions involve several uncertain parameters, \( \alpha, \beta, N_0 \) and \( s \). These functions are solely based on these biological measures and hence the dose plan will depend only on them. The parameters \( \alpha \) and \( \beta \) describe how fast the tissue responds to radiation while \( N_0 \) is the number of clonogenic cells, which can vary a lot in magnitude between voxels and structures. A larger density of clonogenic cells will yield a higher dose to the tumour in order to get tumour control. The EUD function however, only has the one biologic parameter \( a \), while the model also involve physical dose properties via \( \text{EUD}_0 \). The parameter \( a \) will therefore include all biological properties described by several parameters in the other functions.

If these biological models are included in the optimization objective function, some studies show that small changes in the biological parameters, such as \( \alpha \) and \( \beta \), have a large effect on the outcome of the treatment plan [18]. Even though it is commonly mentioned that the treatment plans will be greatly improved if they are biologically optimized the parameter knowledge is yet too poor to use in biological optimization models in practice. Possible solutions to account for these uncertainties have been suggested in the form of assuming some distribution of parameter values and including that in the optimization process. This have been discussed in for example [34][36][25][37].
2.9 Mathematical Background

This section shortly describes how the optimization problem in radiation treatment can be formulated and how to include robust optimization given some uncertainties.

2.9.1 Optimization Problem

The dose distribution, \( d \), is a mapping that takes each voxel \( i \) in the patient to a dose \( d_i \in \mathbb{R}_+ \). \( d \) depends on the optimization variables \( x \) which are determined in the inverse planning. The optimization problem in the inverse planning include an objective function and possibly some constraint functions. These functions specify the desired objectives and relevant trade offs for the treatment plan. The objective function \( f \) penalize deviations from these objectives and is to be minimized. Usually, the objective function is a linear combination of several functions \( f_1, f_2, \ldots, f_n \) that each reflect a desired objective of the plan. Often these functions represent conflicting objectives such as a high dose to the target and a low dose to the healthy tissues. A trade off between these functions \( f_i \) is possible by the introduction of non-negative importance weights \( \lambda_1, \lambda_2, \ldots, \lambda_n \). The objective function can be defined as,

\[
f(d) = \sum_{i=1}^{n} \lambda_i f_i(d).
\]

The constraints are either physical constraints or planning constraints. The physical constraints are limitations of the set up and laws of nature, e.g., non negative beam-on times, these are represented by the set \( \mathcal{X} \) of feasible variables. While the planning constraints are requirements of the treatment plan and set by the user. The inverse planning optimization problem can be formulated as

\[
\begin{align*}
\text{minimize} & \quad f(d(x)) & \quad \text{(Objective function)} \\
\text{subject to} & \quad c_j(d(x)) \leq 0, \quad j = 1, \ldots, m & \quad \text{(Planning constraints)} \\
& \quad x \in \mathcal{X}. & \quad \text{(Physical constraints)}
\end{align*}
\]

The optimization functions steer the optimization towards plans that will perform the best given the conditions. To be sure that the optimization finds a global minima, the problem must be convex. This optimization problem is convex whenever the objective function is a convex function and the constraints define a convex feasible space of solutions. Note that since the objective function is a sum of several functions, it is enough that each of these functions, \( f_1, f_2, \ldots, f_n \) is convex, since the sum of convex functions is also convex.

2.9.2 Optimization Under Uncertainty

Optimization problems may sometimes include uncertainties that can be represented as deterministic variability in the value of the problem parameters. Usually, optimization problems are considered with precisely specified parameters. The solution
to such problems may be very sensitive to errors in the parameter values and the
resulting solution may be far from optimal if the true value differ from the one
used in the optimization. Thus, if the problem have some uncertainty, it must be
taken into consideration in the problem formulation for the solution to be robust.
This can be done in different ways depending on the type of uncertainty and the
degree of robustness needed. For computational optimization problems, the possible
realizations of the uncertainty is denoted by the set $S$ of scenarios. In this thesis,
each scenario $s \in S$ will be a combination of possible biological parameter values in
the objective function.

Stochastic programming is often used to account for uncertainties in radiation
treatment planning [16] [25] [37] [36] [20]. This method minimizes the expected
value of the objective function and is called expected value optimization. It can be
formulated as

$$\min_{x \in X} \mathbb{E}_S[f(d(x), s)], \tag{2.8}$$

where $S$ is the random variable picking a scenario $s$ from $S$ with a probability
depending on the probability distribution of $S$. Another optimization method used
to account for errors is worst case, or minimax, optimization [15]. It minimizes the
objective function assuming that the worst case scenario occur, with no regard to
the probabilities of the scenarios. The minimax problem is formulated as

$$\min_{x \in X} \max_{s \in S} f(d(x), s). \tag{2.9}$$

Lastly, there is conditional value at risk (CVaR) optimization [15] [8]. It measures
the expected value of a fraction of the worst case scenarios conditioned on that
one of those scenarios will occur. Thus, it is a generalization of the expected value
optimization and the worst case optimization and it is formulated as

$$\min_{x, \lambda} \lambda + \frac{1}{\gamma} \mathbb{E}_S[\max\{f(d(x), s) - \lambda, 0\}] \tag{2.10}$$

subject to $x \in X$,

where $0 < \gamma \leq 1$ is the fraction of worst scenarios. These methods are similar but
with different levels of conservativeness, the expected value optimization method is
least conservative and the minimax optimization method is most conservative.
This chapter describes the context of this thesis work. As mentioned, the work is performed at Elekta AB and in consideration of potential use in the Gamma Knife. The goal of the project is to use robust optimization in the creation of biologically based dose plans to account for the uncertainties that lies in the biological parameters. Thus possibly improve the dose plan process and taking a step closer to being able to use biological models in the plan optimization. Therefore all optimization models in this thesis will be based on radiobiological models with uncertain biological parameters, as those presented in section 2.8.1.

With the non robust methods the optimization is performed with a fixed value of the biological parameters. The resulting treatment plan will then be optimal for this value. However, we do not know the quality of the plan if the real case is that the parameter slightly deviates from that value. There could be a drastic decrease of plan quality just a small step away from the used parameter value. Robust optimization will make sure that the plan is good for a larger span of parameter values. Hence, the overall result should improve given the possibility of uncertainty in the parameter.

The currently used treatment planning for the Gamma Knife is done in the software Leksell Gamma Plan, described in section 1.2. To enable a simple way of testing new optimization models and methods, Svedberg [35] implemented a graphical user interface (GUI) in MATLAB. This is a “test bench” for the Leksell Gamma Plan in which the treatment planning method can be altered. The work of this thesis is implemented as a development of this GUI. An overview of its functionality is given below.

The main GUI window with the added robust optimization options can be seen in figure 3.1. The treatment planning works similar to the one used in the Gamma Plan, with some simplifications. The user starts with choosing a patient and loading the corresponding data. The patient data is stored in voxels and based on DICOM files, common in medical imaging. When the data is loaded in to MATLAB, structures are created for all regions of interest (targets and OARs) in the data, including voxel coordinates, type, etc. Then, a system is chosen with all regions of interest the user wants to include in the treatment plan optimization. It is possible to add hypoxic areas to the tumour in order to incorporate the radiation resistance in the hypoxic cells. These areas will then have modified radiosensitivity parameters. This choice is presently not compatible with robust optimization options.
Figure 3.1: Main window of the MATLAB GUI including robust optimization choices.
Next, isocenters are placed in the targets by an algorithm that is described in the next section. The user now chooses whether or not to involve robust optimization. There are different robust optimization possibilities, such as considering geometric uncertainties (added by Josefsson [19]), or biological parameter uncertainties (added in this work). Then, an objective function model is chosen (DVH based or other radiobiological based model). Parameter values for the chosen model must be provided under 'set parameters'. The optimization is carried out by the MATLAB function \texttt{fmincon} using either an interior-point, SQP, active-set, or trust region-reflective algorithm, chosen by the user. Input on maximum iterations, maximum objective function evaluations, and numerical tolerance level can also be set to some values. Some pre-calculations must be done before the optimization can start. These are mostly correlated to the geometrical uncertainties. Finally, the optimization can be run. The results panel show different results of the optimal dose distribution, such as DVH and isodose areas. The mathematical models that are used are detailed in the next chapter.
4 | Models

This chapter describes all optimization models used in this thesis work. The treatment is steered by the beam-on times as described in section 1.1. Hence, the goal of the treatment planning is to optimize the beam-on times in order to get the best possible plan. Here follows a description of all different, robust and non-robust, optimization models that have been used, as well as the problem set-up used for the implementation.

4.1 Problem Set-up

The way to find the optimal treatment plan can be divided into a few steps as specified in the previous chapter about the GUI. After the tumour, organs at risk and normal tissue to be considered are specified, the isocenters can be found by the grass-fire algorithm. This algorithm computes the distance to the surface of the tumour to decide the center as the largest distance from the surface. The coordinates of this center will be the first isocenter, then the algorithm is iterated with the volume of the previous isocenters subtracted from the target volume. A cut-off distance is set beforehand to decide a smallest distance between isocenters and hence limit the number of them. Three different isocenter shapes can be used in the GUI, these are spheres with radii of 3, 5 or 10 mm. The number of isocenters and their positions will be fixed throughout the optimization. This will simplify the optimization and make the problem convex given a convex objective function.

For planning purposes, the treatment region in the patient’s body is divided into box-shaped regions known as voxels, indexed as $i = 1, 2, ..., n$. Recall that there are eight sectors from which the beams originate, three different collimator settings for beam size and a number, $N$, of isocenter positions. Each different beam that can be delivered to the target is hence indexed as $j = 1, 2, ..., m$, where $m = \text{number of sectors} \times \text{number of beam sizes} \times \text{number of isocenters}$. The planning variable $\omega$ to be determined in the optimization is the beam-on time for all these
different beams and it can be written as

\[
\omega = \begin{bmatrix}
\omega_{1,1,1} \\
\omega_{1,1,2} \\
\omega_{1,1,3} \\
\omega_{1,2,1} \\
\vdots \\
\omega_{N,8,3}
\end{bmatrix} = \begin{bmatrix}
\omega_1 \\
\omega_2 \\
\omega_3 \\
\vdots \\
\omega_m
\end{bmatrix}.
\]

The dose of radiation delivered to voxel \(i\) by a unit time weight in beamlet \(j\) is denoted by \(D_{ij}\). These quantities can be assembled into a dose rate matrix \(D\) of dimension \(n \times m\). The dose distribution \(d\) is a linear mapping of the beam-on times \(\omega\) by \(D\),

\[
d(\omega) = D \cdot \omega.
\]

Hence, the dose in voxel \(i\) can be denoted as

\[
d_i(\omega) = \sum_{j=1}^{m} D_{ij}\omega_j, \quad \forall i = 1, \ldots, n.
\]

This represents the discretized form of the Fredholm integral of the first kind [17] that is encountered when solving the inverse planning problem.

The elements of \(D\) is pre-calculated using information of the isocenter positions. Given the matrix \(D\), the optimization of \(\omega\) can be performed. The objective function is a cost function, \(f(\omega) : \mathbb{R}^m_+ \to \mathbb{R}_+\), which penalizes deviations from a pre-determined goal and is to be minimized. The objective function and the constraints are usually constructed from the dose rate matrix \(D\). Hence, the size of the planning problem depends on the size of \(D\), the number of different beams and the number of voxels, and it varies significantly from case to case.

In treatment planning, the set of voxels is partitioned into one or more target volumes \(T\) and one or more risk organs or normal tissues \(R\). To get radiation dose in the regions \(R\) is usually unavoidable, because they are adjacent to the target or because the radiation must travel through them to reach the target. The planner may specify penalties and constraints of varying types to discourage excessive dosage to these regions.

### 4.2 Non-Robust Models

Two radiobiological optimization models are studied, one including the TCP and NTCP functions and the other including the EUD function. Note that the function defined as \(gEUD\) in the background chapter will now be called EUD. The general formulation of the optimization problems will now be,

\[
\begin{align*}
\text{minimize} & \quad f(\omega) \\
\text{subject to} & \quad \omega_j \geq 0, \quad j = 1, \ldots, m.
\end{align*}
\]
4.2 NON-ROBUST MODELS

Where \( f(d(\omega)) \) is the objective function depending on the beam-on times \( \omega \) and the constraint makes sure that all times are non-negative. A time penalty is used in all objective functions, as a simple way of penalizing large beam-on times,

\[
\lambda \sum_{j=1}^{m} \omega_j. \tag{4.2}
\]

All terms of the objective function have individual weights, \( \lambda_t, \lambda_r \) and \( \lambda \), which can be used to weigh the importance of the terms.

4.2.1 TCP-NTCP-Model

First, the problem formulation of the TCP-NTCP optimization model will be described. The objective function \( f(d(\omega)) \) of this model will be a measure of \( P^+ \) which stands for a curative and complication free treatment. It will include the sum of the TCP function, defined as (2.2), for all targets, the sum of the NTCP function, defined as (2.3), for all risk organs and normal tissues and finally the sum of the beam-on times \( \omega_j \).

The TCP and NTCP are sigmoidal functions of dose and hence are inherently nonlinear and nonconvex. Consequently, their direct implementation leads to nonconvex optimization problems. However, the concavity of the logarithmically transformed TCP function has been investigated by Hoffman et al. [17]. They showed that TCP, defined as

\[
\text{TCP}(d) = \prod_{i=1}^{n_t} P_t = \prod_{i=1}^{n_t} \exp \left( -N_0 \exp(-\alpha d_i - \beta d_i^2) \right) \tag{4.3}
\]

with \( P_t = e^{-N_0 e^{-\alpha d_i - \beta d_i^2}} \) and where \( d \) is a \( n_t \times 1 \) vector, is strictly log-concave under the condition that,

\[
d_i > \sqrt{\frac{1}{2\beta} - \frac{\alpha}{2\beta}}. \tag{4.4}
\]

Since the dose is always non-negative, the constraint (4.4) is satisfied whenever \( \alpha^2 > 2\beta \). In the opposite case where \( \alpha^2 < 2\beta \), the constraint (4.4) must always be fulfilled to achieve concavity. Further, the NTCP function, defined as

\[
\text{NTCP}(d) = \left( 1 - \prod_{i=1}^{n_r} (1 - P_i^s)^{1/n_r} \right)^{1/s}, \tag{4.5}
\]

is strictly convex under the transformation \( x \to -\ln(1-x) \), and the condition that \( 0 < s < 1 \) [17] [21]. Since the sum of convex functions is also convex, the following is a convex objective function,

\[
f_{\text{TCP-NTCP}}(\omega) = -\sum_{t \in T} \lambda_t \ln [\text{TCP}(V_t d(\omega))] - \sum_{r \in R} \lambda_r \ln [1 - \text{NTCP}(V_r d(\omega))] + \lambda \sum_j \omega_j. \tag{4.6}
\]
While minimized, this objective function will maximize the tumour control for all studied tumours, while minimizing the normal tissue complication probability for all such structures. The resulting convex optimization problem is formulated as,

\[
\begin{align*}
\text{minimize} & \quad f_{\text{TCP-NTCP}}(\omega) \\
\text{subject to} & \quad \omega_j \geq 0, \quad j = 1, \ldots, m \\
& \quad d_i(\omega) \geq d_K, \quad i = 1, \ldots, n,
\end{align*}
\]

where the last constraint ensures that (4.4) always holds. Depending on the values of \(\alpha\) and \(\beta\) in the TCP function, different values of the constant \(d_K\) can be used. If \(\alpha^2 < 2\beta\), the constraint is redundant and can be removed.

### 4.2.2 EUD-Model

The objective function of the EUD-model include the EUD function (2.6) for all tumours, normal tissues and OARs that are being studied. EUD is compared to a reference level \(\text{EUD}_0\), which is the desired dose parameter for tumours and the maximum tolerable dose for normal tissue and OARs. EUD values under \(\text{EUD}_0\) is penalized for tumours and EUD values over \(\text{EUD}_0\) is penalized for normal tissue and OARs. Recall that EUD is convex for \(a \geq 1\) and concave for \(a \leq 1\) and the composition of two convex functions is convex. Hence, the following is a convex objective function,

\[
f_{\text{EUD}}(\omega) = \sum_{t \in T} \lambda_t \left( (\text{EUD}_0 - \text{EUD}_t(V_t d(\omega)))_+ \right)^2 + \sum_{r \in R} \lambda_r \left( (\text{EUD}_r(V_r d(\omega)) - \text{EUD}_0)_+ \right)^2 + \lambda \sum_j \omega_j,
\]

where \((x)_+ = \max(x, 0)\). Finally, the following optimization problem is a convex problem based on the EUD function,

\[
\begin{align*}
\text{minimize} & \quad f_{\text{EUD}}(\omega) \\
\text{subject to} & \quad \omega_j \geq 0, \quad j = 1, \ldots, m.
\end{align*}
\]

This problem will make the EUD functions strive towards their respective \(\text{EUD}_0\) values.

### 4.3 Robust Models

When creating the robust optimization models with respect to uncertainties, the concepts of section 2.9.2 are considered. Robust options will be given for both the TCP-NTCP-model and the EUD-model. In the TCP-NTCP-model, the parameter
4.3 ROBUST MODELS

α of the target will be considered uncertain and given some distribution. In the EUD-model the single biological parameter a will be given a distribution for the target and then also for an OAR.

4.3.1 TCP-NTCP-Model

The first considered robust optimization approach is to use the expected value optimization method. This method minimizes the expected value of the objective function as,

\[
\min_{\omega} E_S[f_{TCP-NTCP}(d(\omega), s)],
\]

where \( S \) is the random variable picking a scenario \( s \) from \( S \) with some probability. The scenarios in this case will be different values of the biological parameters. Furthermore, the CVaR optimization method will be used considering 50% of the worst case scenarios. Worst case optimization will not be a good model in this work since the worst case will always be generated by the lowest value of \( \alpha \) in the distribution.

In this model, the uncertain parameters are \( \alpha, \beta \) and \( N_0 \) for the tumours with the addition of \( s \) for the OARs and normal tissue. The focus of this study will be on considering the uncertainty in \( \alpha \) in the TCP function. The variation of \( \beta \) will always be assumed to correlate with a constant value of \( \alpha/\beta \).

To only include a distribution on \( \alpha \) for the TCP function can be regarded a valid model considering that the goal of the optimization is to destroy all of the tumour. Hence, the importance of the treatment lies in using a good model for the tumour control value, while the NTCP value will be minimized to some degree regardless if the parameters are precise or vary a little. The expectation of the objective function will in this case include the expectation of the TCP function, defined as

\[
E_S[TCP(d(\omega))] = \int_{-\infty}^{\infty} \phi(\alpha)TCP(d(\omega), \alpha) d\alpha,
\]

where \( \phi(\alpha) \) is the probability density function of the parameter \( \alpha \). It is commonly assumed that \( \alpha \) follows a normal (Gaussian) distribution with mean \( \mu \) and variance \( \sigma^2 \) [30]:

\[
\phi(\alpha) = \frac{1}{\sigma \sqrt{2\pi}} \exp\left(-\frac{(\alpha - \mu)^2}{2\sigma^2}\right).
\]

Others have used the log-normal distribution in order to limit the range of the parameter \( \alpha \) to more biologically relevant values, see e.g., [22]. The concavity of the new function of TCP to be incorporated in the objective function must be studied. It has been proven by Hoffman et. al. [17] that \( E[TCP] \) is log-concave when \( \alpha \) is normally distributed, provided that the dose in each voxel satisfies the condition

\[
d_i > \sqrt{\left(\frac{\alpha}{2\beta}\right)^2 + \frac{1}{2\beta} - \frac{\alpha}{2\beta}}.
\]
However, this is not necessarily the case for the log-normal distribution since \( \phi(\alpha) \) is not log concave \([3]\). Hence, only the normal distribution of \( \alpha \) will be used in this work. The resulting objective function is,

\[
f_{\text{TCP-NTCP}}^{\text{exp}}(\omega) = \sum_{t \in T} \lambda_t \ln [\mathbb{E}_S\{\text{TCP}(V_t d(\omega))\}] \\
+ \sum_{r \in R} \lambda_r \ln [1 - \text{NTCP}(V_r d(\omega))] \\
+ \lambda \sum_{j} \omega_j. \tag{4.11}
\]

Finally, the robust optimization problem using expected value optimization is,

\[
\begin{align*}
\text{minimize} & \quad f_{\text{TCP-NTCP}}^{\text{exp}}(\omega) \\
\text{subject to} & \quad \omega_j \geq 0, \quad j = 1, ..., m \\
& \quad d_i(\omega) \geq d_R, \quad i = 1, ..., n.
\end{align*} \tag{4.12}
\]

The last constraint ensures that (4.10) always holds. Since \( \alpha \) has some distribution \( \phi(\alpha) \), (4.10) must hold for the lowest value of the distribution and the constraint in the problem will therefore always be needed.

Now the CVaR optimization method will be specified. This method optimizes the expected value of some percent of the worst case scenarios. In this case, this means using the expectation of TCP with the biological parameters that will result in the largest objective function values. Since we know that a smaller \( \alpha \) and \( \beta \) will give a larger value of TCP, the task of deciding the worst cases is simplified to choosing the smallest values of \( \alpha \). The normal distribution \( \phi(\alpha) \), will be transformed into an alternate form \( \phi_x(\alpha) \) of the same distribution, with only the lowest \( x\% \) of the values, normalized. Hence, the objective function can be written as,

\[
f_{\text{TCP-NTCP}}^{\text{CVaR}}(\omega) = \sum_{t \in T} \lambda_t \ln [\mathbb{E}_S\{\text{TCP}(V_t d(\omega))\}] \\
+ \sum_{r \in R} \lambda_r \ln [1 - \text{NTCP}(V_r d(\omega))] \\
+ \lambda \sum_{j} \omega_j. \tag{4.13}
\]

The final robust optimization problem with CVaR optimization is,

\[
\begin{align*}
\text{minimize} & \quad f_{\text{TCP-NTCP}}^{\text{CVaR}}(\omega) \\
\text{subject to} & \quad \omega_j \geq 0, \quad j = 1, ..., m \\
& \quad d_i(\omega) \geq d_R, \quad i = 1, ..., n,
\end{align*} \tag{4.14}
\]

where the last constraint is added for the same purpose as in the expected value model.
4.3 ROBUST MODELS

4.3.2 EUD-Model

For the EUD-model, only expected value optimization is studied. In this model, the only uncertain parameter is $a$. Since the parameter can vary within very large intervals, two different distributions will be used for $a$, and compared. These are described in the next chapter. Two approaches are used, the first one only consider the uncertain parameter of targets and the second one also include the uncertain parameter of risk organs and normal tissues.

Parameter $a$ of Targets

The expected value optimization will involve a distribution of $a$ for the tumours, and hence the expected value of EUD,

$$
\mathbb{E}_S [\text{EUD}_t(d(\omega))] = \int_{-\infty}^{\infty} \phi_t(a)\text{EUD}_t(d(\omega), a)da,
$$

where $\phi_t(a)$ is the probability density function of $a$ for the target. The new robust objective function is then,

$$
f^{\text{Rob}T}_{\text{EUD}}(\omega) = \sum_{t \in T} \lambda_t \mathbb{E}_S \left[ \left( (\text{EUD}_0 - \text{EUD}_t(d(\omega)))_+ \right)^2 \right] + \sum_{r \in R} \lambda_r \left( (\text{EUD}_r(V_r d(\omega)) - \text{EUD}_0)_+ \right)^2 + \lambda \sum_j \omega_j. \tag{4.15}
$$

Hence, the following is a convex optimization problem,

$$
\begin{align*}
\text{minimize} & \quad f^{\text{Rob}T}_{\text{EUD}}(d(\omega)) \\
\text{subject to} & \quad \omega_j \geq 0, \quad j = 1, ..., m. \tag{4.16}
\end{align*}
$$

The superscripted Rob$T$ stands for a robust formulation considering the uncertain parameter in the target EUD function.

Parameter $a$ of the Target, OARs and Normal Tissue

When also considering the uncertain parameter of the organs at risk (OAR) and normal tissue the only change from the above formulation is the addition of the expected value of EUD$_r$,

$$
\mathbb{E}_S [\text{EUD}_r(d(\omega))] = \int_{-\infty}^{\infty} \phi_r(a)\text{EUD}_r(d(\omega), a)da,
$$
where $\phi_r(a)$ is the probability density function of $a$ an OAR or normal tissue. Thus, the robust objective function will be,

$$
\begin{align*}
    f_{\text{R}^{\text{TR}^{\text{EUD}}}}(\omega) &= \sum_{t \in T} \lambda_t \mathbb{E}_S \left[ (EUD_{0t} - EUD_t(d(\omega)))_+^2 \right] \\
    &+ \sum_{r \in R} \lambda_r \mathbb{E}_S \left[ (EUD_r(Vrd(\omega)) - EUD_{0r})_+^2 \right] \\
    &+ \lambda \sum_j \omega_j,
\end{align*}
$$

with the associated optimization problem,

$$
\begin{align*}
    \text{minimize} & \quad f_{\text{R}^{\text{TR}^{\text{EUD}}}}(d(\omega)) \\
    \text{subject to} & \quad \omega_j \geq 0, \quad j = 1, \ldots, m.
\end{align*}
$$
5 | Implementation

This chapter describes the method of how the models were implemented and tested and how parameters were selected. Patient data files for two previous patients of the Gamma Knife, with different disorders, were provided in order to test the models. The first case (patient 1) has vestibular schwannoma (acoustic neuroma) which is a tumour on the nerve connecting the ear to the brain. The brain stem is considered as an OAR, it slightly surrounds the tumour making it impossible to spare the organ to a larger extent. The second case (patient 2) has meningioma with thalamic fibres considered as an OAR. This is an easier problem, with large parts of the OAR on a relatively large distance from the tumour. In both cases, a fairly small region of healthy tissue around the tumour is considered as “normal tissue” (NT). Pictures of the two cases can be seen in figure 5.1, and some problem parameters and settings are given in table 5.1.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. voxels $n$</td>
<td>3,095</td>
<td>1,549</td>
</tr>
<tr>
<td>No. isocenters</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>No. variables $m$</td>
<td>216</td>
<td>120</td>
</tr>
<tr>
<td>Voxel size [mm$^3$]</td>
<td>4.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Target volume [cm$^3$]</td>
<td>2.1</td>
<td>6.6</td>
</tr>
<tr>
<td>OAR volume [cm$^3$]</td>
<td>10.3</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 5.1: Information of the two patients.

All models presented in the previous chapter are tested, the non-robust models are run in order to compare the robust models with. Firstly, the robust TCP-NTCP model where $\alpha$ in TCP takes a normal distribution was implemented and tested with both expected value optimization and CVaR optimization. Then the robust EUD-model where $a$ of the target takes two different distributions was implemented and tested with expected value optimization. And lastly, the robust EUD-model was extended to also include two distributions of $a$ of the OAR. How this was done can be seen in the following sections. All optimizations were run through the MATLAB GUI presented in the previous chapter. The interior point (IP) algorithm was used with the first order error tolerance set to $10^{-7}$ in all models. The parameters used in the treatment plan optimization for the tumour, NT and OAR in the non-robust
case are presented in table 5.2. The weight term $\lambda$ of the total time, used in the objective function, can be found in table 5.3. The parameter values are based on the ones used in [35], which also studied patient 2 and a case of acoustic neuroma. However, some were influenced from values specified in [1], [27] (parameter $a$ of EUD), and [37], [9] (parameters $\alpha$ and $\beta$ of TCP). The values of EUD$_0$ was chosen by studying the DVH of the patients Gamma Knife treatment plans, in order to get values that correspond to a treatment using the Gamma Knife and that provides enough dose to each tumour. In the case of clonogenic cells, $N_0$, the value depend on the voxel size and the tumour and is very hard to decide as mentioned earlier. The used value was approximated and based on the ones used in [35], as well as the voxel size. The parameter values used in the robust optimization that differ from the ones used in the non-robust case, will be presented in each model below.

Further, the convexity of the non-robust TCP-NTCP model must be checked for the used parameter values of $\alpha = 0.2 \text{ Gy}^{-1}$ and $\beta = 0.025 \text{ Gy}^{-2}$. The reduced constraint $\alpha^2 > 2\beta$ is not fulfilled and the constraint (4.4) imposes that problem is convex whenever $d_i > 0.05 \text{ Gy}$ for all voxels $i$. To ensure convexity, the last constraint in the non-robust optimization problem (4.7) will be used with the constant $d_K = 1 \text{ Gy}$.

5.1 Robust TCP-NTCP-Models

Here follows a description of how the robust TCP-NTCP-model with respect to the uncertain target parameter $\alpha$ in the TCP function was implemented. The robust model described in section 4.3.1 is considered. The dose constraint in the optimization problem will be given the constant value $d_R = 10 \text{ Gy}$. This constraint
5.1 ROBUST TCP-NTCP-MODELS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Tumour</th>
<th>NT</th>
<th>OAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda$</td>
<td>1</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>$\alpha$ [Gy$^{-1}$]</td>
<td>0.22</td>
<td>0.05</td>
<td>0.0491</td>
</tr>
<tr>
<td>$\beta$ [Gy$^{-2}$]</td>
<td>0.0268</td>
<td>0.02</td>
<td>0.02338</td>
</tr>
<tr>
<td>$s$</td>
<td>-</td>
<td>0.64</td>
<td>1</td>
</tr>
<tr>
<td>$N_0$</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>$EUD_0$ [Gy]</td>
<td>16</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>$a$</td>
<td>-10</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\lambda$</td>
<td>1</td>
<td>0.01</td>
<td>0.5</td>
</tr>
<tr>
<td>$\alpha$ [Gy$^{-1}$]</td>
<td>0.2</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>$\beta$ [Gy$^{-2}$]</td>
<td>0.025</td>
<td>0.024</td>
<td>0.025</td>
</tr>
<tr>
<td>$s$</td>
<td>-</td>
<td>0.64</td>
<td>1</td>
</tr>
<tr>
<td>$N_0$</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>$EUD_0$ [Gy]</td>
<td>15</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>$a$</td>
<td>-10</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 5.2: Parameter values of the non-robust cases for patient 1 and patient 2.

<table>
<thead>
<tr>
<th>Model</th>
<th>TCP-NTCP</th>
<th>EUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.0015</td>
<td>0.01</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.0005</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 5.3: Parameter values of the weight term of the total time for all models.

grants the usage of parameter values as low as $\alpha = 0.02$ Gy$^{-1}$ with $\alpha/\beta = 8$ Gy.

For implementation reasons, the normal distribution is discretized and normalized over some interval of reasonable values, $\alpha \in [\alpha_{\text{min}}, \alpha_{\text{max}}]$. A step length, $l$, is chosen in order to generate a number of robust optimization scenarios $S$ which will be a uniform grid of $[\alpha_{\text{min}}, \alpha_{\text{max}}]$. The probability $P_s$ to each scenario $s$ will hence follow a discrete approximation of a Gaussian distribution with mean value $\mu$ and standard deviation $\sigma$. It will be conditioned on the event $H$; that the parameter $\alpha$ is in the chosen interval as,

$$P_s = \Pr(\alpha_s | H) = \frac{\Pr(\alpha_s \cap H)}{\Pr(H)}.$$

The probabilities for each $\alpha_s$ is approximated as the probability of $\alpha_s$ being within a small interval of the step length $l$, defined as,

$$\Pr(\alpha_s) \approx \Pr(\alpha - l/2 \leq \alpha_s \leq \alpha + l/2) = \int_{\alpha - l/2}^{\alpha + l/2} f(x_s) \, dx,$$
where \( f(x_s) \) is the probability density function of a normal distribution,

\[
f(x_s) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(x_s - \mu)^2}{2\sigma^2}}.
\]

Note that this is only a good approximation if \( l \) is small and \( \Pr(H) \) is large. The expectation of the objective function can now be calculated. The mean value \( \mu \) and standard deviation \( \sigma \) of the parameter is chosen by the user in the GUI before the optimization. The parameter values used to test this robust model for the two patients can be seen in table 5.4.

### Table 5.4: Parameter values used in the robust TCP-NTCP optimization model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>( \alpha_{\text{min}} )</th>
<th>( \alpha_{\text{max}} )</th>
<th>( \mu )</th>
<th>( \sigma )</th>
<th>( \alpha/\beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.04</td>
<td>0.4</td>
<td>0.22</td>
<td>0.05</td>
<td>8.2</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.04</td>
<td>0.4</td>
<td>0.2</td>
<td>0.05</td>
<td>8</td>
</tr>
</tbody>
</table>

In each step in the optimization, with the corresponding dose distribution, the evaluation of the objective function consists of the following steps:

- Calculate NTCP for each OAR and NT structure,
- Calculate TCP for the target structure corresponding to each possible scenario (different values of \( \alpha \)),
- Calculate the probability for each scenario,
- Sum the TCP value times the corresponding probability for all scenarios to get the expected value of TCP,
- Sum TCP and NTCP for all structures and the beam-on time to get the objective function value.

After the dose optimization, DVHs and other measures of plan quality are available. Both expected value optimization and CVaR optimization, considering the worst 50\% of the scenarios, were used. The expected value model used a step length that generated 73 different scenarios. In the CVaR model, the interval \([\alpha_{\text{min}}, \alpha_{\text{max}}]\) is changed to apply to the worst case scenarios, however, the rest of the calculations regarding the scenario probability \( P_s \) are the same. Hence, the number of scenarios in this optimization was 37. The results can be found in the next chapter.

### 5.2 Robust EUD-Models

Next is the robust EUD-models and here follows a description of how they were implemented.
5.2 ROBUST EUD-MODELS

5.2.1 Parameter $a$ of the Target

To investigate the behaviour of the dose plan when using robust optimization in this model, the parameter $a$ of the target EUD takes two different distributions as in the work of Lian et. al. [25]. The first distribution (D1) is a discretized normal distribution, and the second one (D2) is another discrete distribution which is shifted a bit toward smaller negative values. Both distributions can be seen in figure 5.2. The expected value of EUD for the target is calculated using the probabilities for each scenario. Hence, the parameter $a$ is given an interval $a \in [a_{\text{min}}, a_{\text{max}}]$ of reasonable values and the distributions are normalized so that $\sum_s P_s = 1$. It can be seen in the distribution figures that there are 21 different scenarios for each distribution. Only the first distribution, D1, is implemented in the GUI for later use, and as before, the user may choose relevant values of the mean value and standard deviation. As mentioned, the $a$-parameter of targets is negative and sometimes very large. Since it should combine all the biologic parameters of the TCP function, it is also very hard to decide and have a larger interval of possible values. The parameters used to test the model with D1 can be seen in table 5.5, and for D2, the same $a_{\text{min}}$ and $a_{\text{max}}$ were used.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$a_{\text{min}}$</th>
<th>$a_{\text{max}}$</th>
<th>$\mu$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>-65</td>
<td>-5</td>
<td>-35</td>
<td>8</td>
</tr>
<tr>
<td>Patient 2</td>
<td>-65</td>
<td>-5</td>
<td>-35</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 5.5: Parameter values used in D1 for the uncertain target parameter $a$ in EUD.
5.2.2 Parameter $\alpha$ of the OAR

Following the work of Lian et. al. [25], the robust model was developed to also include the uncertainty in the OAR parameter $\alpha$. This parameter takes two different distributions, similar in shape as the ones used for the target, and with equal amount of discrete values. The distributions D3 and D4 can be seen in figure 5.3. The inclusion of a distribution of the OAR parameter was only tested for patient 1 to keep the report at a moderate length, and the parameter values used for D3 can be found in table 5.6. The same $a_{\text{min}}$ and $a_{\text{max}}$ were used in D4. The optimization steps to find the objective function value are similar as those described for the TCP-NTCP model but instead the EUD function is calculated for all structures. Firstly, the robust EUD model that only consider a distribution of the target $\alpha$, with both D1 and D2 was tested. Then, to include the distributions of $\alpha$ for the OAR, some combinations of the distributions D1, D2, D3 and D4 was run together. All results can be found in the next chapter. Note that in these last optimizations, the number of scenarios is increased to $21^2$.

Table 5.6: Parameter values used in D3 for the uncertain OAR parameter $\alpha$ in EUD.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>$a_{\text{min}}$</th>
<th>$a_{\text{max}}$</th>
<th>$\mu$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>2</td>
<td>42</td>
<td>22</td>
<td>6</td>
</tr>
</tbody>
</table>
6 | Results and Discussion

In this chapter, results obtained with the robust models will be presented and discussed, as well as compared to the non-robust results. As mentioned before, there is no perfect way of determining the quality of a dose plan and thus deciding which of several plans is superior. The results of the different dose plans for different models will be presented first by DVHs, followed by an attempt of measuring the quality quantitative using the TCP and NTCP functions. All results are presented for patient 1, but the results of patient 2 are only presented in some tables of TCP and NTCP values.

Table 6.1 represents summary statistics for some optimization trials whose results are presented later in this chapter. These statistics concern the models which include only a target parameter uncertainty, and are presented for trials with patient 1.

<table>
<thead>
<tr>
<th>Obj. function</th>
<th>TCP/NTCP</th>
<th>EUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opt. model</td>
<td>Non-rob.</td>
<td>Exp.</td>
</tr>
<tr>
<td>Run-time [sec]</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>No. iter</td>
<td>982</td>
<td>1009</td>
</tr>
<tr>
<td>F. count</td>
<td>983</td>
<td>1010</td>
</tr>
<tr>
<td>F. Value</td>
<td>0.726</td>
<td>0.897</td>
</tr>
<tr>
<td>First-order opt.</td>
<td>1 \times 10^{-7}</td>
<td>1 \times 10^{-7}</td>
</tr>
</tbody>
</table>

Table 6.1: Summary data from some of the optimization runs.

6.1 Considering Uncertain \( \alpha \) in TCP

The TCP-NTCP model with expected value optimization and CVaR optimization with 50% of the worst scenarios was tested first. In these models the target parameter \( \alpha \) was given a normal distribution. Hence, there are two robust models to test against one non-robust model which assumes a fixed value of the uncertain parameter. As shown in the background chapter, the resulting dose distribution depends a lot on the value of \( \alpha \). In figure 6.1 some target DVHs are presented for three different values of \( \alpha \) in the non-robust model, and for both of the robust
models. As can be expected, the DVHs for the robust models tend to be close to the non-robust case with the parameter used as mean value in the distribution. However, they strive toward higher dose values to ensure that the TCP value gets high enough, even for the worst scenarios.

The resulting dose volume histograms of the expected value model, the CVaR model and the non-robust case can be seen in figure 6.2 for all structures. All parameter values used are found in the previous chapter. This figure shows an improvement in the target dose distribution in the robust cases, with the cost of more radiation in larger volumes for the OAR and NT. However, for the expected value model, the gain in radiation dose in the tumour is much greater than the dose increase in the OAR and NT. This shows a great improvement in treatment for the target structure with only a little sacrifice in the other structures. The CVaR model however, tend to increase the dose significantly in all structures, yet still not as much in the OAR as in the target. This behaviour is also expected since the model strives towards full tumour control with parameter values that enforce larger doses to do so. It is well known that there generally is no net gain in dose optimization, an improvement in dose to a structure is often accompanied by adverse effects in another structure. The results here however suggest that it is possible to have a great gain in one structure with only a little sacrifice in another structure. The important problem lie in finding the optimal trade off. Note that for all models, the dose distribution in all structures is almost equally homogeneous, as seen by the equal slope of the DVHs.
6.1 UNCERTAIN PARAMETER IN TCP

The TCP and NTCP functions were used to evaluate and compare the quality of the resulting dose plans with all models. In table 6.2 the resulting TCP and NTCP values for the tumour and organ at risk (OAR) are displayed for all models and both patient. The resulting total treatment time can also be found there. These results suggest that a more conservative robust model generates higher tumour control with the effect of a little more OAR complication, as expected from studying the DVHs. The treatment time however, does not vary much between models. This might be due to small changes in which sectors of the collimator that have the largest

![Graph showing DVHs for the Tumour, OAR, and NT for patient 1, using different models.](image)

Table 6.2: TCP and NTCP values for the tumour and OAR in both patients and for all used TCP-NTCP-models.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>TCP</th>
<th>NTCP</th>
<th>Beam-on time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-rob.</td>
<td>88%</td>
<td>14%</td>
<td>54 min</td>
</tr>
<tr>
<td>Exp.</td>
<td>92%</td>
<td>15%</td>
<td>55 min</td>
</tr>
<tr>
<td>CVaR</td>
<td>98%</td>
<td>19%</td>
<td>59 min</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-rob.</td>
<td>95.8%</td>
<td>0.52%</td>
<td>56 min</td>
</tr>
<tr>
<td>Exp.</td>
<td>97.3%</td>
<td>0.54%</td>
<td>57 min</td>
</tr>
<tr>
<td>CVaR</td>
<td>99.3%</td>
<td>0.56%</td>
<td>63 min</td>
</tr>
</tbody>
</table>
beam-on times. With large uncertainties in some parameters, it might no longer be optimal to irradiate as much from certain angles and sectors. As mentioned, patient 2 by most standards is an easier problem, dose planning-wise, than patient 1. This results in an overall high TCP value and low NTCP value for all models for patient 2. The robust plans again perform better when it comes to the TCP values, and the differences in NTCP value for the OAR are almost negligible.

The TCP function was used to estimate how robust the three optimal dose plans would be to changes in the target TCP parameter $\alpha$, assuming again a constant $\alpha/\beta$ ratio. Figure 6.3 show how the TCP percentage changes in the optimal plans with different “real” $\alpha$ values. The other parameters of the TCP function was selected according to table 5.2. These plots show that if the $\alpha$ value for the target is around 0.2 Gy$^{-1}$, the expected value model generates a tumour control probability of approximately 13 percentage greater that the non-robust model does. As for the CVaR model, the TCP value is approximately 24 percentage greater. The TCP value is better for the robust models in the entire interval of $\alpha$ values. These results show a drastic increase in dose plan quality (when considering the target) for the robust models in comparison to the non-robust model.

To estimate the degree of sensitivity of the solutions against the variable $\alpha$, the objective function, $f_{TCP-NTCP}$, was computed as a function of $\alpha$ for the non-robust and the two robust resulting optimal dose distributions. The results are found in figure 6.4. As expected, this figure suggest that the robust models become much
6.2 UNCERTAIN PARAMETER IN EUD$_T$

Firstly, the behaviour of the system when the parameter $a$ of the target takes two different distribution (D1 and D2) was investigated. These robust results were compared to the non-robust case where the parameter $a$ was given a constant value according to table 5.2. This was done while keeping the parameter $a$ of the OAR and NT at constant values. Recall that in the background chapter, a DHV was shown for three cases of different constant values of the target $a$ parameter. In figure 6.5 some target DVHs are presented for three different values (same as in the DVH in the background) of $a$ in the non-robust model, and for both of the robust models. As can be expected from the shape of the distributions, the DVHs of the robust models tend to lay close to the non-robust models using the lower negative values of $a$. This is due to the higher parameter values in the distributions which would worsen the dose results and hence must be taken into account in a larger sense in the robust optimization. We know that a lower negative value of $a$ is associated with an EUD value representing a smaller dose considering all voxels. This would make the resulting dose plan to the target more homogeneous while still keeping a high enough dose, hence, a better result from the target perspective. Similar results

Figure 6.4: Objective function value plotted versus $\alpha$ for the two robust models and the non-robust model, for patient 1.

less sensitive to variations in the parameter $\alpha$. The CVaR model is a bit more conservative when it comes to changes in the parameter value. Hence, as expected, the difference in results are greater for this robust model, when compared to the non-robust.
can be seen in the robust cases which improve the target dose whilst slightly raising the dose in the OAR and NT.

Figure 6.6 show the DVHs for all structures in the two robust model and the one non-robust model using a target $a = -10$. The results show a significant difference in optimal dose distributions for the three models. Both robust models generate better dose distributions for the target than the non-robust model, with the robust model using D1 achieving better than the robust model using D2. The cost of these improvements is a slightly increased dose large parts of the OAR and NT. For the D1 model, the target dose homogeneity is significantly improved. The minimum dose increases from 11 Gy to 13 Gy and the maximum dose is slightly decreased, generally the slope of the DVH curve is increased. The improvement of target coverage and compromise of OAR sparing is a natural outcome of the competitive requirements for targets and healthy structures imposed on the system.

Again, the TCP and NTCP functions were used to evaluate and compare the quality of the resulting dose plans with these models. Note that this is only valid in the sense of comparing different treatment plans since the parameters of the TCP and NTCP functions are also uncertain. In table 6.3 the resulting TCP and NTCP values for the tumour and OAR are displayed for all models and both patient. The resulting total treatment time can also be found there. As in the DVHs, the table shows that the robust models improve the target dose resulting in a higher TCP value, to some cost. However, the increase from 67% to 88% in tumour control for patient 1 is a much greater gain than the loss in an NTCP value of 4.3% to
Figure 6.6: DVHs for the Tumour, OAR and NT in patient 1, using the non-robust model (solid lines), robust with D1 (dashed lines) and robust with D2 (dotted lines).

<table>
<thead>
<tr>
<th></th>
<th>TCP</th>
<th>NTCP</th>
<th>Beam-on time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-rob.</td>
<td>67%</td>
<td>4.3%</td>
<td>76 min</td>
</tr>
<tr>
<td>D1</td>
<td>88%</td>
<td>6.6%</td>
<td>78 min</td>
</tr>
<tr>
<td>D2</td>
<td>77%</td>
<td>5.0%</td>
<td>81 min</td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-rob.</td>
<td>32%</td>
<td>0.16%</td>
<td>64 min</td>
</tr>
<tr>
<td>D1</td>
<td>82%</td>
<td>0.18%</td>
<td>84 min</td>
</tr>
<tr>
<td>D2</td>
<td>53%</td>
<td>0.17%</td>
<td>68 min</td>
</tr>
</tbody>
</table>

Table 6.3: TCP and NTCP values the target and OAR in both patients and for all used EUD\_T-models.
6.6%. From a clinical point of view it is hence possible to have a large gain in one structure with a little sacrifice in another. The difference in beam-on time is very small, suggesting that instead of longer times in one sector of beams in the collimator, the time is more spread out on the different sectors. Perhaps because of the uncertain radiosensitivity in the robust cases. Similar results as those for patient 1 are seen in patient 2. A very large increase in TCP for the robust cases results in a small increase in NTCP. However, the results for patient 2 also indicate that the start parameters chosen, either in the TCP evaluation function or in the EUD objective function, are not perfect. This show for instance in the very low TCP value for the non-robust case.

The TCP function was again used to estimate how robust the three optimal dose plans would be to changes in the target TCP parameter $\alpha$, assuming again a constant $\alpha/\beta$ ratio. Figure 6.7 show how the TCP percentage changes in the optimal plans with different $\alpha$ values. The other biological parameters of the TCP function was according to table 5.2. These figures show that the robust optimal dose distributions generates higher or equal TCP values for all possible target $\alpha$ values. The difference is seen when drawing vertical lines in the figure. If the “real” value of $\alpha$ is around $0.2 \text{ Gy}^{-1}$, the increase of tumour control probability would be approximately 22 percentage in the robust case with D1 and 11 percentage in the robust case with D2, compared to the non-robust case.

To estimate the degree of sensitivity of the solutions against the variable $\alpha$, the target EUD and the objective function, $f_{EUD}$, was computed as a function of $\alpha$.
6.3 UNCERTAIN PARAMETER IN EUD\textsubscript{T} AND EUD\textsubscript{R}

Lastly, robust models were created which include distributions in both the target parameter and the OAR parameter. The distribution D1 of the target parameter was combined with the distribution D3 of the OAR parameter into one robust model, while the distributions D2 and D4 was combined to another robust model. The resulting DVHs can be seen in figure 6.9 for the tumour, OAR and NT. The resulting target dose is better and more homogeneous in the first robust case with D1 and D3, compared to the non-robust case. The volumes receiving radiation dose in the OAR and NT increases slightly though the maximum dose remains similar. However, the OAR DVH in this case has not worsen to the same extent as in the previous section because parameter \( a \) of the OAR EUD was also allowed to take a spectrum of values. In the other robust case with D2 and D4 however, the results are opposite, with a less homogeneous dose to the target and an increase in maximum dose, while the dose distributions in the OAR and NT remain quite similar to the non-robust case. This shows that the distribution of the OAR of this robust model dominates and hence the trade off between distributions and other parameter values are not very good. Because of the relatively poor results in these models, one last

Figure 6.8: Objective function value and EUD value plotted versus \( a \) for the two robust models and the non-robust model, for patient 1.

for the non-robust and the two robust optimal dose distributions. The results are found in figure 6.8. These results suggest that the EUD model become much less sensitive to the variation in parameter \( a \) in the robust plans.

6.3 Considering Uncertain \( a \) in EUD\textsubscript{T} and EUD\textsubscript{R}


model is tested, with the distribution D1 of the target parameter and D4 of the OAR parameter. The resulting DVHs, in comparison to the non-robust model and the model with D1 and D3 DVHs, can be seen in figure 6.10. The DVHs for the last robust model, (D1,D4), show a more homogeneous dose distribution to the target and better dose levels compared to the other models. Furthermore, the dose to the OAR is not increased compared to the other models with the exception of a marginally larger maximum dose. For the NT, the dose increase in the volume is small compared to the other models. In table 6.4 the resulting TCP and NTCP values for the target and OAR are shown together with the beam-on times, for all three robust models and the non-robust model. These results are consistent with the expectations from the DVHs. An increase in TCP value in the first and

<table>
<thead>
<tr>
<th>TCP</th>
<th>NTCP</th>
<th>Beam-on time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-rob.</td>
<td>67%</td>
<td>4.3%</td>
</tr>
<tr>
<td>D1,D3</td>
<td>75%</td>
<td>5.4%</td>
</tr>
<tr>
<td>D2,D4</td>
<td>59%</td>
<td>3.9%</td>
</tr>
<tr>
<td>D1,D4</td>
<td>86%</td>
<td>6.4%</td>
</tr>
</tbody>
</table>

Table 6.4: TCP and NTCP values for the Target and OAR, for all EUD-models with uncertainty in \( a \) for target and OAR, as well as the non-robust model.
third robust models and a decrease in the second robust model. While there are only small changes in the NTCP value of the OAR. The last robust model with the combination of distributions D1 and D4 is clearly superior to all other models. This model have a significantly better dose distribution in the sense of tumour control, with a TCP value of 86\%. The cost of this is an almost insignificant increase in OAR damage. Hence, the trade off between tumour control and OAR sparing is the most optimal of all tested models. Another advantage with this model is the decrease in treatment time. This can be explained by larger changes in which sectors are active the most, compared to the other robust models. This most likely depend on that the specific uncertainty set up in the model parameters makes it no longer worth it to irradiate from certain angles with certain sectors.

Figure 6.10: DVHs for the Tumour, OAR and NT of patient 1, using the non-robust model (solid lines), robust with D1 and D3 (dashed lines) and robust with D1 and D4 (dotted lines).
Now the main objective of this thesis can be addressed: how well do robust optimization methods improve the performance of biologically optimized dose plans, in a Gamma Knife context? In this chapter, conclusions from the results presented in the previous chapter are drawn, some model flaws are acknowledged and suggestions for further research are presented.

With the increasing interest in the radiation therapy community to use biologically based models for treatment planning, this work provides an effective way to account for the known uncertainties in the model parameters and allows us to maximally utilize the available radiobiology knowledge to facilitate patient care. Overall it is concluded that including robust optimization to account for parameter uncertainties is a step toward being able to use radiobiological models in treatment plan optimizations to a larger extent. It can be discussed whether or not it is optimal to fully replace physical dose constraints with radiobiological models. But if that were the case, including parameter uncertainties by assuming distributions will in most cases generate dose plans of higher quality and which are more robust to uncertain parameter settings. The final solutions will in all cases be less likely influenced by inter-patient variation of biological characteristics.

As, mentioned, it can be discussed whether or not the LQ model is a good approximation in the case of radiosurgery, which involve larger doses per fraction. This in turn make the TCP and NTCP function questionable in this case. But, if one were to use a model including these functions, accounting for parameter uncertainties is essential for the plan quality. Recall the large increase in tumour control probability when the robust models were used. A more accepted model choice is to use the EUD function in the optimization, since this is a combination of a biological and physical model with only one radiobiological parameter. This make the model a little more robust in opposite to the TCP and NTCP models where all parameters may affect the results. For the EUD-model used in this thesis work, the result show increased quality in dose plans when accounting for the uncertainties in α with different probability distributions. Which distributions are optimal to use depend on course of which structure the parameter represents and how uncertain one are of the “real” value of this tissue specific parameter.

In general, the results show that it is possible to have a gain in dose distribution quality in one structure with a smaller sacrifice in another structure. How to find the optimal trade off is a question that is worth studying in the future. This include
investigating which parameter distributions to use and what weights to use for all structures as well as the time component. A possible model improvement would be to use distribution based on statistics from relevant, perhaps previously treated, patients.

From the results of patient 2, it can be noted that in the case of a larger distance between tumour and OAR, it might be better to use a more conservative optimization model. Furthermore, the results of using distributions on both the target and OAR parameter \( a \) in an EUD-model show promising results. Especially in the case of the combination of distributions D1 and D4 used in this thesis, since the TCP and NTCP values and the DVHs of this plan showed better results than the other distribution combinations.

The resulting dose plans were compared to the original plan created for use in the Gamma Knife for each patient by studying the DVHs. Reasonable results with high enough dose to the tumours while the dose to the other structures were at least as spared as in the Gamma Knife treatment was found.

The model representations in this thesis fails to take into account the likely variations of sensitivity in different parts of the structures. It is assumed that the parameter values in each structure are the same in all voxels in that structure. Ideally, different parameter values, and in some cases distributions, would be used for each voxel. This includes adding the possibility of delineating hypoxic regions in the target, where parameters would be altered. Furthermore, an additional improvement could be to test other distributions which are more dense with more scenarios. In the case of the TCP and NTCP model, the other biological parameters could also be addressed as uncertain and given some distributions. Especially the parameter \( N_0 \) which measure the clonogenic cell density in each voxel would optimally take different values in different regions, however, this number is very hard to decide.
Bibliography


BIBLIOGRAPHY


