Linköping Studies in Science and Technology
Licentiate Thesis No. 1831

Mathematical Modelling of Dose Planning in High Dose-Rate Brachytherapy

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Abstract

Cancer is a widespread type of diseases that each year affects millions of people. It is mainly treated by chemotherapy, surgery or radiation therapy, or a combination of them. One modality of radiation therapy is high dose-rate brachytherapy, used in treatment of for example prostate cancer and gynecologic cancer. Brachytherapy is an invasive treatment in which catheters (hollow needles) or applicators are used to place the highly active radiation source close to or within a tumour.

The treatment planning problem, which can be modelled as a mathematical optimization problem, is the topic of this thesis. The treatment planning includes decisions on how many catheters to use and where to place them as well as the dwell times for the radiation source. There are multiple aims with the treatment and these are primarily to give the tumour a radiation dose that is sufficiently high and to give the surrounding healthy tissue and organs (organs at risk) a dose that is sufficiently low. Because these aims are in conflict, modelling the treatment planning gives optimization problems which essentially are multiobjective.

To evaluate treatment plans, a concept called dosimetric indices is commonly used and they constitute an essential part of the clinical treatment guidelines. For the tumour, the portion of the volume that receives at least a specified dose is of interest while for an organ at risk it is rather the portion of the volume that receives at most a specified dose. The dosimetric indices are derived from the dose-volume histogram, which for each dose level shows the corresponding dosimetric index. Dose-volume histograms are commonly used to visualise the three-dimensional dose distribution.

The research focus of this thesis is mathematical modelling of the treatment planning and properties of optimization models explicitly including dosimetric indices, which the clinical treatment guidelines are based on. Modelling dosimetric indices explicitly yields mixed-integer programs which are computationally demanding to solve. The computing time of the treatment planning is of clinical relevance as the planning is typically conducted while the patient is under anaesthesia. Research topics in this thesis include both studying properties of models, extending and improving models, and developing new optimization models to be able to take more aspects into account in the treatment planning.

There are several advantages of using mathematical optimization for treatment planning in comparison to manual planning. First, the treatment planning phase can be shortened compared to the time consuming manual planning. Secondly, also the quality of treatment plans can be improved by using optimization models and algorithms, for example by considering more of the clinically relevant aspects. Finally, with the use of optimization algorithms the requirements of experience and skill level for the planners are lower.

This thesis summary contains a literature review over optimization models for treatment planning, including the catheter placement problem. How optimization models consider the multiobjective nature of the treatment planning problem is also discussed.

Populärvetenskaplig sammanfattning

Cancer är en grupp av sjukdomar som varje år drabbar miljontals människor. De vanligaste behandlingsformerna är cellgifter, kirurgi, strålbehandling eller en kombination av dem. Högdosrat brachyterapi är en form av strålbehandling och används till exempel till att behandla prostatacancer och gynekologisk cancer. För brachyterapi används ihåliga nålar för att placera strålkällan antingen inuti eller intill en tumör. I varje nål finns det ett antal så kallade dröjpositioner där strålkällan kan stanna en viss tid för att bestråla den omkringliggande vävnaden.

Planeringen av en behandling med brachyterapi omfattar hur många nålar som ska användas, var de ska placeras samt hur länge strålkällan ska stanna i de olika dröjpositionerna (som kan vara flera hundra stycken). Dessa komponenter utgör en dosplan och i den anges hur hög stråldos som tumören och intilliggande frisk vävnad och riskorgan utsätts för. Dosplaneringen kan formuleras som ett matematiskt optimeringsproblem vilket är ämnet för avhandlingen. De övergripande målsättningarna för behandlingen är att ge en tillräckligt hög stråldos till tumören, för att ha ihjäl alla cancerceller, samt att undvika att bestråla riskorgan eftersom det kan ge allvarliga biverkningar. Då alla målsättningarna inte kan uppnås fullt ut så fås optimeringsproblem där flera målfunktioner behöver prioriteras mot varandra. Utöver att dosplanen uppfyller de kliniska behandlingsriktlinjerna så är också tidsaspekten viktig eftersom att det är vanligt att planeringen sker när patienten är under bedövning.

Vid utvärdering av en dosplan så används dos-volymmått. För en tumör så anger ett dos-volymmått hur stor andel av tumören som får en stråldos som är högre än en specificerad nivå. För riskorgan så är innebörden istället hur stor andel av volymen som får en stråldos som lägre än en specificerad nivå. Dos-volymmått utgör en viktig del av de mål för dosplaner som tas upp i kliniska behandlingsriktlinjer och ett exempel på ett sådant mål vid behandling av prostatacancer är att 95% av prostatan ska få en stråldos som är högre än den föreskrivna dosen. Dos-volymmått är nära besläktade med de kliniskt viktiga dos-volym histogrammen som för varje stråldosnivå anger motsvarande volym som erhåller den dosen.

I avhandlingen så ligger fokus på hur dos-volymmått kan användas och modelleras explicit i optimeringsmodeller, så kallade dos-volymmodeller. Det omfattar såväl analys av egenskaper hos befintliga modeller, utvidgningar av använda modeller samt utveckling av nya optimeringsmodeller. Eftersom dos-volymmodeller modelleras som heltalsproblem, vilka tar lång tid att lösa, så är det också viktigt att kunna lösa dem snabbare. Ett annat mål med modellutvecklingen är att kunna ta hänsyn till fler kriterier som är kliniskt relevanta men som inte ingår i dos-volymmodeller. Ett exempel är hur dosen är fördelad rumsligt och ett relaterat mål är att volymen av sammanhängande områden som får en alldeles för hög dos ska vara liten. Sådana områden går dock inte att undvika helt eftersom det är typiskt för dosplaner för brachyterapi att stråldosen fördelar sig ojämnt, med väldigt höga doser till små volymer precis intill strålkällorna.

En fördel med att använda matematisk optimering för dosplanering är att det kan spara tid jämfört med manuell planering. Med väl utvecklade modeller så finns det också möjlighet att skapa en bättre dosplan, till exempel genom att ge en lägre dos till riskorgan med bibehållen dos till tumören. Vidare så finns det också fördelar med en process som inte är lika personberoende och som inte kräver erfarenhet i lika stor utsträckning som manuell dosplanering gör.

Utöver en sammanfattning av de egna forskningsbidragen så innehåller kappan också en genomgång av optimeringsmodeller för dosplanering av högdosrat brachyterapi och ett tema är hur optimeringsmodellerna hanterar de motstridiga målfunktionerna.

Acknowledgments

When I discussed writing with Paul, about fourteen years ago, my imagined publication back then was far from this thesis. Despite that, I am very happy with this result and the long process leading to it. Fortunately I have not been alone in this and there are many to whom I am grateful, there is not enough space here to thank you all.

First of all I would like to thank my supervisors, Torbjörn Larsson and Åsa Carlsson Tedgren whom I have much enjoyed working with in this project. Torbjörn has been a great source of inspiration and joy for a very long time, from my first course in optimization, via several optimization courses, the master thesis, the work at Schemagi, to the current doctoral studies. Åsa is an inexhaustible source of enthusiasm and has done an excellent job introducing me to the field of radiation therapy.

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Furthermore, I want to dedicate a few words to the members of KPS — each of you have influenced me greatly over a long period of time and during very important years.

Last, but certainly not least, I would like to express my gratitude to my parents who always have been very supportive and encouraging!

Contents

Abstract	i
Populärvetenskaplig sammanfattning	iii
Acknowledgments	v
Contents	vii
List of Figures	ix
List of Tables	x
1 Introduction	1
1.1 Outline	1
1.2 Contributions	2
1.3 Presentations	3
2 Background	5
2.1 High dose-rate brachytherapy	6
2.2 Clinical treatment evaluation	9
3 Mathematical modelling	15
3.1 Conflicting aims	16
3.2 Why use optimization?	17
3.3 Uncertainty	17
3.4 Mathematical notation	18
3.5 Linear penalty model	18
3.6 Dose-volume model	22
3.7 Mean-tail-dose model	25
3.8 Radiobiological models	29
3.9 Multi-objective models	30
3.10 Model analysis	33
3.11 Modelling of spatial aspects	39
3.12 Catheter placement	40

3.13 Future research	42
4 Contributions of our research	45
4.1 DVH based modelling	45
4.2 Patient data	46
4.3 Relationships between models	46
4.4 A modelling extension using mean-tail-dose	48
4.5 A new optimization model for spatiality	49
Bibliography	53
Paper A	67
Paper B	81
Paper C	95

List of Figures

2.1	Ultrasound contours of structures	7
2.2	Tumour contouring	8
2.3	Clinical work flow	9
2.4	Differential DVH curve	10
2.5	Cumulative DVH curve	11
3.1	Linear penalty functions	21
3.2	Heaviside approximation	25
3.3	Differential DVH curve and CVaR	26
3.4	Pareto front	31

List of Tables

3.1	Common notation	19
3.2	Notation in the linear penalty model	19
3.3	Small example	23
3.4	Notation in the dose-volume model	24
3.5	Notation in the mean-tail-dose model	27
3.6	Notation in the EUD and TCP models	29
3.7	Notation in the MTDM	35
3.8	Notation in the spatial optimization model	40
3.9	Notation in the catheter placement model	41

Introduction

The topic of this thesis is automated treatment planning of high dose-rate brachytherapy using mathematical optimization. Brachytherapy is a modality of radiation therapy in which the radiation source is placed within the body. The aim with the treatment is to give the tumour a dose that is high enough while at the same time keep the dose to healthy tissue at a level that is low enough to avoid severe complications. For modern external beam treatment techniques, such as intensity modulated radiation therapy and volumetric arc therapy, manual planning is not possible because the degrees of freedom are too many. Hence, the use of mathematical optimization for the treatment planning is vital. Manual planning in brachytherapy is still manageable but mathematical optimization is a growing field of research and the clinical usage of automated treatment planning has also been increasing. There is a need to study and analyse the models recently developed for brachytherapy to get a deeper understanding on how a specific model affects the resulting treatment plans. Therefore, a focus of this thesis summary is to summarise and present an overview of optimization models for treatment planning of high dose-rate brachytherapy. The work for this thesis include both studying properties of optimization models for treatment planning, extending and improving models, and developing new optimization models to be able to take more aspects into account in the treatment planning.

1.1 Outline

This thesis is divided into two parts, being a thesis summary followed by the own work. The thesis summary contains an extensive review of the research field (Chapter 3). The thesis is organized as follows.

In the first part of the thesis, Chapter 2 gives an introduction to radiation therapy and brachytherapy and introduces the relevant concepts. The text does not assume any background in radiation therapy. The use of mathematical optimization in the treatment planning of high-dose-rate brachytherapy is discussed in Chapter 3. It contains a broad discussion about modelling and multi-objective aspects as well as a literature review of optimization models for treatment planning. It also contains analyses of the presented models and how they are related mathematically. Chapter 4 describes the contributions from the papers of this thesis.

In the second part three papers are appended. Paper A considers two common optimization models and derive mathematical relationships between them. Paper B presents an extension to a sophisticated optimization model to remediate a weakness of the original formulation. The third paper, Paper C, proposes an optimization model for taking the spatial dose distribution into account. The purpose is to further improve spatial properties of a treatment plan, approved with the so-called dosimetric indices, to make it more homogeneous.

1.2 Contributions

The following papers are appended.

Paper A - Mathematical Optimization of High Dose-Rate Brachytherapy - Derivation of a Linear Penalty Model from a Dose-Volume Model

Two optimization models for treatment planning are considered, the linear penalty model and the dose-volume model. Although they are seemingly different, this study shows that there is a precise mathematical relationship between the two models.

Paper B - An Extended Dose-Volume Model in High Dose-Rate Brachytherapy - Using Mean-Tail-Dose to Reduce Tumour Underdosage

A weakness of the dose-volume model is identified; the model does not take the dose to the coldest volume of the tumour into account. Research indicates that underdosage to only a small portion can have an adverse treatment effect. This study extends a standard formulation of the dose-volume model to also consider the dose to the coldest part of the tumour, and the additional component have the role of a safeguard against underdosage.

Paper C - Preventing Hot Spots in High Dose-Rate Brachytherapy

Proposes a new optimization model that adjusts a given dose plan to also take spatial aspects into account, with the aim to reduce dose heterogeneities

in the tumour. While improving the spatial aspects, aggregate aspects are also considered and maintained in the adjustment step.

1.2.1 Publication status

Paper A has been published as B. Morén, T. Larsson, and Å. Carlsson Tedgren. 2018 “Mathematical optimization of high dose-rate brachytherapy - Derivation of a linear penalty model from a dose-volume model”. *Physics in Medicine & Biology* **63.6**

Paper B is submitted and revised.

Paper C has been published as B. Morén, T. Larsson, and Å. Carlsson Tedgren. 2018 “Preventing hot spots in high dose-rate brachytherapy”. In: *Operations Research Proceedings 2017*. Ed. by N. Klierer, J. F. Ehmke, and R. Borndörfer. Cham: Springer International Publishing

1.2.2 Other publications

B. Morén. 2016 “Using optimization to make better plans for cancer treatment”. *ORbit* **27**

1.2.3 Contributions by co-authors

All papers are co-authored with Torbjörn Larsson and Åsa Carlsson Tedgren. I have been responsible for implementation and writing. The focus of Torbjörn Larsson has been mathematical optimization and the focus of Åsa Carlsson Tedgren on aspects related to radiation therapy.

1.3 Presentations

During my doctoral studies I have attended and presented at the following conferences.

MBM, Mathematics in Biology and Medicine Linköping, Sweden, May 2017. I presented an early version of Paper C.

OR2017, The annual international conference of the German Operations Research Society (GOR) Berlin, Germany, September 2017. I presented Paper C.

SOAK2017, The bi-annual conference of the Swedish Operations Research Association (SOAF) Linköping, Sweden, October 2017. I presented Paper C.

ISMP, International Symposium on Mathematical Programming Bordeaux, France, July 2018. I presented Paper B.

I have also attended the following conference.

Sixth International Workshop on Model-based Metaheuristics
Brussels, Belgium, September 2016.

Furthermore, I have given the following presentations.

KU Leuven, Research Centre for Operations Management Brussels, Belgium, June 2016. I presented an early version of Paper A.

Linköping University, Department of Science and Technology Norrköping, Sweden, November 2016. I presented Paper A.

KTH Royal Institute of Technology, Optimization and Systems Theory Stockholm, Sweden, September 2018. I presented parts of Paper B and Paper C.

National brachytherapy meeting for oncologists, medical physicists and oncology nurses Örebro, Sweden, January 2019. I talked about advantages and the potential of using optimization for dose planning.

Background

Cancer is a widespread type of diseases. In 2018 17 million new cases were diagnosed worldwide and there were 9.6 million deaths [19]. In 2016, the number of new cancer cases in Sweden was 64 000 and the number of deaths 23 000 [5]. However, positive trends can be seen. In the United States the cancer death rates have declined by approximately 26% between 1991 and 2015, and both cancer incidence rates and death rates have dropped continuously for the whole population [99]. Survival rates have also increased in Sweden during the period 1980–2015, with the five-year relative survival rate increasing from 35% to 75% for men and from 48% to 74% for women [5]. Furthermore, in 2016 the most common cancer type in Sweden in men and women combined was prostate cancer [5].

The common treatment modalities of cancer are surgery, radiation therapy and chemotherapy and also combinations of them. Radiation therapy can in turn be divided into external beam radiation therapy (EBRT), of which photon-based intensity modulated radiotherapy (IMRT) is one modality, and brachytherapy (BT) another. Brachytherapy, which is the subject of this thesis, is described in this chapter along with important concepts that will be used later on. The aim is to provide enough introduction for the literature review of mathematical models for treatment planning in Chapter 3. The introduction and the examples are written with prostate cancer in mind but are to a large extent also applicable to other types of cancer.

The literature review covers the optimization models that have been proposed for high dose-rate (HDR) BT. References for low dose-rate (LDR) BT and in EBRT are included when they precede or have a close resemblance to HDR BT models. A literature review of optimization models for HDR BT dose planning can be found in [26], covering the time period 1990–2010, and reviews of optimization models in IMRT can be found in [93, 35, 16].

2.1 High dose-rate brachytherapy

In BT the radiation is delivered from within the body, by placing small, sealed radiation sources close to or within a tumour. The radiation sources reach the treatment sites by being placed in the body through the use of catheters/needles/applicators. In this presentation all three are referred to as catheters. In prostate cancer the catheters can be thought of as hollow needles. See [55] for treatment guidelines on catheter placement in HDR BT for prostate cancer. The placement of the radiation source within the body is in contrast to EBRT in which the radiation is delivered from the outside using large linear accelerators. An advantage with BT compared to EBRT is that it can deliver a very high radiation dose conformal to the tumour while sparing nearby healthy tissue and organs at risk (OAR). A disadvantage is that it is invasive which requires the patient to be under some form of anaesthesia. While common applications of BT are in cervical and prostate cancer, it is also used to treat for example head and neck, and breast cancer. There are three types of BT: (i) high dose-rate in which the radiation source is placed temporarily in the body for a short time (minutes), (ii) low dose-rate in which the radiation sources are placed permanently in the body (or temporarily but for a longer time than in HDR), and (iii) pulse dose-rate (PDR). In PDR the dose is given in pulses, typically once per hour, with the purpose to simulate the radiobiological effects from LDR.

A small single radiation source, of mm dimension, is used in HDR BT, most commonly of the isotope ^{192}Ir , emitting photons with a mean energy of 400 keV. For dose delivery, each catheter is discretised into a number of dwell positions in which the source can dwell for a short time. After the catheters have been implanted into the patient using a catheter template, and the treatment planning is finished, the template is connected to a remote radiation-safe afterloader where the source is stored. At the time of the delivery, the personnel leave the room, and the radiation source steps through each catheter. At each possible dwell position it either dwells for a predetermined time, irradiating the surrounding tissue, or continues to the next.

2.1.1 Clinical process

The treatment is planned individually for each patient with the patient specific anatomy taken into account. The first step in the treatment planning is thus to acquire images of the treatment structures. The image modalities that are used in this step are typically ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI). Positron emission tomography (PET) can also be used, as in [61]. For an overview of the imaging modalities and their differences, see [84]. Planning images are generally acquired during (or in close conjunction to) the treatment session as they must incorporate the various catheters used. Figure 2.1 illustrates how a two-dimensional cross

Figure 2.1: Shows a dose plan for prostate cancer with an ultrasound image as the background. The structures of interest, the prostate, the urethra and the rectum, are delineated on the image, while the radiation doses are shown in colours. Red indicates a high dose while blue indicates a lower dose.

section of the treated structures related to prostate cancer are delineated on an ultrasound image. The large volume, with the green contour, is the target (the prostate) and the urethra is delineated within the prostate. Further, the rectum is below the other structures, at the bottom of the image. The figure also shows radiation doses in a colour scale, where red indicates a high dose and blue a lower dose.

The medical images are used to manually contour and define the structures of interest, which includes both the target (tumour, tumours, or other regions of interest such as a cavity after surgery due to suspected microscopic spread) and OAR in the proximity. There are several interrelated volume definitions regarding the tumour [12]. First, the gross tumour volume (GTV) contains the tumour cells that have been identified. Secondly, the clinical target volume (CTV) contains the GTV as well as an extra margin based on clinical experience. Thirdly, the planning target volume (PTV) contains the CTV and an extra margin because of uncertainties due to movements (e.g. breathing) or technical reasons. See Figure 2.2 for an illustration of how these definitions are related. In this presentation PTV will generally be used to denote the target. However, even though PTV is typically used in BT, there are arguments that the extra margins of the CTV lead to unnecessary dose escalation [103]. Compared to EBRT, smaller CTV margins are in general used in BT because the organ motion is less problematic as the radiation sources move with the irradiated target.

For prostate cancer, HDR BT is most frequently used in combination with EBRT, with the purpose of giving an extra boost to the PTV [111]. The HDR BT treatment is commonly given in one to six fractions, while if the treatment

Figure 2.2: Shows the various volume definitions of the tumour with emphasis on how they are related.

only consists of HDR BT (monotherapy) the treatment is commonly given in three to six fractions [111].

For a more thorough introduction to cancer, radiobiology and radiotherapy, see for example [45, 46].

2.1.2 Treatment planning

The treatment planning is a rigorous process. First, a dosimetrist or a physicist prepares the dose plan. Then it is reviewed and approved by the treating physicist. Finally, there is an independent review by a second physicist [111].

The term treatment planning refers to the full process of planning the treatment while dose planning refers to the process of deciding the dwell times. Further, the result of the dose planning is referred to as the dose distribution or the dose plan.

During the treatment session the patient is under some form of anaesthesia (spinal, general) as the catheters are inserted invasively. The treatment planning is often performed during the treatment session (“on-line”) to plan the treatment using up to date anatomy information. The overall time for the treatment is hence an important aspect, so it is beneficial to be able to perform the treatment planning fast. An illustration of the clinical process is shown in Figure 2.3.

The dose planning can either be performed with forward planning or with inverse planning. Forward planning is typically a manual trial-and-error process in which the planner first constructs a dose plan. This is evaluated and if it is not good enough, the planner adjusts the dose distribution. This process is repeated until the planner is satisfied, which can be time consuming. In [85] it is reported that the manual treatment planning takes 20–35 minutes for experienced planners. The forward planning is conducted with graphical aid from a treatment planning system (TPS). In inverse planning, the starting point is the treatment goals and in the planning step, a dose distribution is constructed to be as close as possible to these goals. Due to the computational

Figure 2.3: Illustration of the clinical work flow. The steps in the upper part of the figure are related to the planning phase and the steps in the lower part are related to the delivery phase. During all these steps the patient is under some form of anaesthesia.

complexity of inverse planning, optimization models and algorithms are used to construct the dose distribution.

2.2 Clinical treatment evaluation

The main decisions in the treatment planning is the catheter placement, how many to use and where to insert them, and how long the source dwells at each dwell position. When these are decided, the dose distribution in the PTV and OAR can be calculated. But how should such a treatment plan be evaluated? What properties do the clinical treatment guidelines promote in a dose distribution?

2.2.1 Dose points and dose calculation

The concept of dose points are used in the evaluation of dose plans. The dose points constitute a discretisation of the treatment structures and each dose point corresponds to a small volume. Instead of calculating the received dose in every single cell, which would be impossible, dose points allow for calculating the received dose only in a much smaller number of volumes. The dose points are commonly generated according to [56]. Clinical treatment guidelines for HDR BT of prostate cancer [111] suggests that the number of dose points used for evaluating a dose plan should be at least 5000.

To calculate the received dose in a dose point we first need to know the dose-rate contribution, per second, from each dwell position, see [78, 88]. The received dose is also scaled with respect to the strength of the radiation source, which depends on how long time the source has been in use at the clinic. With this information, as well as the dwell times, the total received dose in each dose point is then calculated by summing the dose contribution from each dwell position, which is the dwell time multiplied with the dose-rate contribution scaled with the strength of the radiation source.

2.2.2 Dose-volume histogram

A concept that is essential in clinical treatment guidelines and dose plan evaluation is the dose-volume histogram (DVH), which plots portions of a structure against dose levels. The DVH curve can be presented in a differential version, in which the portion that receives exactly a dose level is shown for each dose level, or in a cumulative version, in which, for the PTV, the portion that receives at least a radiation dose is shown for each dose level, or for an OAR, the portion that receives at most a radiation dose is shown. See Figures 2.4 and 2.5 for examples of these two types of DVH curves. In the following, the expression DVH curve refers to the cumulative DVH curve (unless otherwise specified). Each point on the DVH curve corresponds to a dosimetric index (DI), which can be formulated in two ways. These are either denoted V_x^s or D_y^s , where x is a dose level (in Gy), y is a portion of the volume or a volume (commonly cubic centimetres, cc), and s is a structure, either PTV or part of the PTV, or an OAR. The meaning of the DI V_x^s differs depending on if the structure is the PTV or an OAR. For the PTV, it is the portion of the volume that receives at least the specific dose level x and for an OAR, it is the portion that receives at most the specific dose level x . The DI D_y^s , for a structure s , is the lowest dose that is received by either a portion of a volume or a volume that receives the highest dose.

Figure 2.4: Example of a differential DVH curve.

Figure 2.5: Example of a cumulative DVH curve.

2.2.3 Dose homogeneity

A measure that is related to the DVH curve is the dose homogeneity index (DHI) [109], which is defined for the PTV as

$$DHI = \frac{V_{100}^{PTV} - V_{150}^{PTV}}{V_{100}^{PTV}}, \quad (2.1)$$

where 100 and 150 refer to percentages of the prescription dose. The measure takes a value between zero and one, and in an ideal situation the DHI equals one. This means that the full volume receives at least the prescribed dose and no portion of the volume receives more than 150% of the prescription dose.

The conformation number (CN) [87] is a measure related to the DHI. In addition to the dose to the PTV it also takes the portion of the OAR that receives a dose that is higher than the prescription dose into account. However, the part of the PTV that receives a dose that is too high is not included in this measure. Mathematically, CN is calculated as

$$CN = V_{100}^{PTV} \cdot \frac{PTV_{ref}}{Tot_{ref}}, \quad (2.2)$$

where PTV_{ref} is the PTV volume which receives at least the prescription dose and Tot_{ref} is the total volume (PTV and OAR included) which receives at least the prescription dose.

The conformal index (COIN) [7] is an extension of the CN which in addition has an extra OAR specific term. COIN is defined as

$$COIN = V_{100}^{PTV} \cdot \frac{PTV_{ref}}{Tot_{ref}} \cdot \prod_{s \in S_O} V_{100}^s, \quad (2.3)$$

where S_O is the set of OAR. Each factor in both CN and COIN takes a value between zero and one, with one as the best possible value in the two

measures. This corresponds, for both measures, to the whole PTV receiving the prescription dose and no portion of any OAR receiving a dose that is higher than the prescription dose.

2.2.4 Radiobiological concepts

In contrast to the DIs, which are based solely on the physical dose, radiobiological indices are meant to explicitly capture the radiobiological treatment effect from a dose distribution. One such index is the tumour control probability (TCP) which is an estimate of the probability of local tumour control. To give some examples from the literature, introductions to TCP models are given in [113, 77] and TCP models are analysed in [114]. Furthermore, a guide implementing a TCP model is presented in [82].

For the suggested TCP models there are several parameters that must be estimated, which is not easy. For some parameters there are also individual variations to consider, making it even more difficult to get accurate results from TCP models. In [29] and [28] these uncertainties and difficulties with the use of TCP are discussed.

The corresponding radiobiological index for OAR is normal tissue complication probability (NTCP) which estimates the probability that complications occur in an OAR. A summary of how NTCP is used is given in [69].

Another radiobiological concept is the equivalent uniform dose (EUD) which was introduced in [81]. It captures the radiobiological treatment effect of the tumour, as a single value, with the purpose of comparing the treatment effect from inhomogeneous dose distributions. The EUD value is meant to be the homogeneous radiation dose (the same dose to all dose points) that gives the same treatment effect as the evaluated inhomogeneous dose distribution. The EUD was further developed with the generalized EUD (gEUD) [80] that can also be used for OAR. One way to define the gEUD is given in [110] as

$$gEUD = \left(\frac{1}{N} \sum_{i=1}^N Dose_i^a \right)^{1/a}, \quad (2.4)$$

where N is the number of dose points in the structure, $Dose_i$ is the dose to dose point i and a is a parameter depending on the structure. Compared to TCP and NTCP the gEUD has fewer parameters, in this formulation only one, but this parameter is supposed to capture both effects from the treatment method and from the structure.

Finally, a concept that considers both tumour control probability and risk for complications in OAR is P^+ , introduced in [15]. It estimates the probability of tumour control without any complications.

2.2.5 Clinical treatment guidelines

There are guidelines for the different steps in the treatment and the dose planning, see [52, 111] for HDR BT guidelines for prostate cancer, which is the main topic of this thesis. These guidelines include planning aims for the PTV and OAR, which are typically expressed in terms of DIs. For example, the DI V_{100}^{PTV} should be at least 90% with the recommended goal for the DI to be above 95%. The guidelines in [52] also recommend reporting a value that is equivalent to the DHI, see equation (2.1).

Similar clinical treatment guidelines are also published for other cancer types and treatments, see for example [11] for BT guidelines for vaginal cancer and [107] for HDR BT guidelines for cervical cancer.

Mathematical modelling

The general nature of the treatment planning problem, to deliver a high enough dose to the tumour while sparing OAR as much as possible, tells us a lot about the problem that is modelled and solved. The formulation is in itself vague, with expressions such as “high enough” and “sparing OAR as much as possible”. Even though there are goals for the clinical evaluation criteria in the treatment guidelines it is hard to a priori decide which is the best treatment plan for a specific patient, because the anatomy and the catheter placement determine what is achievable. The treatment planning problem can therefore be seen as a soft optimization problem. From a modelling point of view there is no obvious objective function and this also becomes apparent from the broad variety of dose planning models presented in this chapter.

The lack of a standard problem formulation makes this problem different to many other optimization problems. A basic example of a standardized optimization problem is the travelling salesman problem. The aim of this problem is to find a minimum cost tour that visits all nodes in a graph, where both the feasibility constraints, to visit all nodes in one cycle, and the objective function, to minimise the total cost for the used arcs, are well-defined.

Nevertheless, all the proposed dose planning models are capable of delivering dose plans that are clinically relevant (possibly including a trial-and-error process of parameter tuning or manual adjustments of the resulting dose plan). The softness of the treatment planning problem is also apparent from the fact that feasibility is here not a strict property and for most of the presented models, feasibility is considered differently. This is because even though there are important goals for the clinical evaluation criteria, there are cases which are extra difficult and for which not all these goals are attainable. For such a case, the treatment goals must be relaxed to find a dose plan at all. The other way

around, that it is possible to find a dose plan with much better values than the goals, can also occur.

The optimization models for dose planning that are presented in Sections 3.5–3.9 have the dwell times as the main decision variables and the objective (each objective term) is based on an evaluation of the dose that each dose point receives. In the models for dose planning in Sections 3.5–3.9, the catheter placement is predetermined but these decisions can also be studied in combination with the dwell times. When the dose planning is combined with the catheter placement, another type of objective is introduced and it is commonly to use as few catheters as possible. Such models are discussed in Section 3.12.

3.1 Conflicting aims

The main treatment goal is to find a dose plan which is a good trade-off between what is attainable in PTV coverage and in sparing of OAR. Trade-offs are not only present between different structures but can also be relevant within a structure, to deliver a dose that is sufficiently high but not too high, or if for example the PTV is divided into two structures with different priorities (due to the cancer spread). Homogeneity of the dose distribution is also of interest.

The optimization problem to construct a dose distribution is therefore fundamentally multi-objective. The property is handled in a number of ways which does not explicitly consider the problem as multi-objective. The proposed models from the literature are primarily based on one of the following reformulations of multi-objective models to single objective models: (i) to consider a weighted sum of the objective terms, (ii) to put a hard constraint on an objective term, or (iii) to minimise the penalty from the worst objective term, as a pessimistic approach. A property in common for these is that the result is a single solution (dose distribution) while the result from a multi-objective formulation typically is a set of solutions. There are also multi-objective approaches to dose planning, and these are discussed in Section 3.9. The literature review for IMRT dose planning [16] is focused on multi-objective formulations and decision making.

The components of the optimization models presented in this chapter can be divided into three categories depending on how closely they are related to the evaluation criteria in the clinical treatment guidelines. There are components that are explicitly based on an evaluation criterion, that approximates or in some other way include a clinical evaluation criterion, and there are components that are not based directly on any clinical evaluation criteria. Examples of this are given in the following sections. The different ways of considering clinical evaluation criteria are typically related to a trade-off between comput-

ing time and solution quality. Measures that are closer to clinical evaluation criteria tend to be more expensive computationally.

3.2 Why use optimization?

Manual planning is a time consuming task of trial-and-error and the usage of optimization models has the potential of saving time, which is beneficial for the patient. Also treatment plan quality can be improved with the use of optimization; there is a number of examples of this, such as [31, 75, 44, 68]. In the study [68], planners were presented with a manually constructed dose plan and five dose plans which were constructed with an optimization model. It turned out that they preferred an optimized dose plan in 53 out of 54 cases. Nevertheless, to fully utilise the potential of optimization models it is important to further develop the dose planning models to include all relevant aspects that are considered in manual planning. Further, manual construction of dose plans requires a lot of experience [85] and the use of optimization can make the planning process less dependent of individual varying skills.

A reason why it is important to develop optimization models and algorithms is because of the computing time limitation in the treatment planning. Since the treatment planning typically is conducted when the patient is under anaesthesia, any decrease in the planning time is beneficial. There are no hard limits on how much computing time that an optimization algorithm is allowed to use, but finding a dose plan within minutes is a reasonable aim. The allowed computing time also depends on the need for manual adjustments of the dose plan or changes of parameter values, both which depend on the optimization model. Further, even if an improvement in computing times might not be of direct clinical importance, it instead allows solving a harder problem, for example with an increased number of dose points.

3.3 Uncertainty

An inherent part of the treatment is a wide range of uncertainties. The sources of uncertainty are reviewed in [54]. The following list is a non-exhaustive review of uncertainties that are present (without ordering).

- The strength of the source declines over time and needs to be measured before a treatment.
- The dose-rate contribution contains a number of parameters which are estimated.
- Dose calculations are based on simulations on a water phantom, which approximates the tissue of the treated structures.

- The dose calculations depend on the exact position of the radiation source (within the catheter).
- The dose calculations also depend on the orientation of the source within the catheter.
- The delineation of the treated structures depends on the type of images (e.g. ultrasound, MRI, CT) and also on the physician. Two physicians might delineate the structures slightly different or a single physician might delineate the structures slightly different on two separate occasions. Furthermore, the clinical practice might differ between clinics.

The total dosimetric uncertainty differs between disease sites and varies from 5% to 13% according to [54].

The uncertainty in the target volume delineation was studied in [9]. Instead of the standard margin around CTV to construct the PTV they considered scenarios corresponding to different delineations of the PTV. This is motivated by the previously mentioned observations of [103], that the extra margins of the CTV lead to dose escalation. The approach in [9] is formulated as a mathematical optimization model which optimize the worst-case scenario.

A model for handling uncertainties in the source position is proposed in [38]. The uncertainty is handled by optimizing the worst-case scenario, where each scenario is based on possible inaccuracies in the catheter placement.

In addition to OAR, artificial healthy tissue, in which the radiation doses should be sufficiently low, are typically added. The reason is to avoid unreasonable high dwell times in the outskirts of the PTV where the distances to OAR are large. No artificial healthy tissue is added in [70] and it is described to result in clinically undesirable properties of the dose distribution.

3.4 Mathematical notation

Table 3.1 introduces the common notations for the mathematical models presented in this section. Subscript T refers to the PTV and O to OAR. The set S contains all structures including both PTV and OAR. Some optimization models in this chapter, in their general form, contain objectives which strive to irradiate each dose points with at least a specified level of radiation. For an OAR $s \in S$ such an objective might not be relevant but the set S is still used for the purpose of generality.

3.5 Linear penalty model

The optimization model most used in clinical practice (implemented in several commercially available treatment planning systems) gives a penalty for each

Table 3.1: Common sets, parameters and variables that are used in the optimization models.

Indices	
i	Index for dose points
j	Index for dwell positions
s	Index for structures
Sets	
S	Set of structures, including PTV and OAR
S_O	Set of OAR, including artificial normal tissue, $S_O \subset S$
P_s	Set of dose points in structure $s \in S$
J	Set of dwell positions
Parameters	
d_{ij}	Dose-rate contribution from dwell position $j \in J$ to dose point $i \in \cup_{s \in S} P_s$
L^s	Prescription dose to structure $s \in S$
U^s	Upper dose bound for structure $s \in S$
M^s	Maximum allowed dose to structure $s \in S$
$Dose_i$	Radiation dose received at dose point i
Variables	
t_j	Dwell time for dwell position $j \in J$

Table 3.2: Notation used in the linear penalty model.

Parameters	
w_s^l	Penalty for dose being too low in structure $s \in S$
w_s^u	Penalty for dose being too high in structure $s \in S$
Variables	
x_i^l	Penalty variable for dose being too low at dose point $i \in P_s$, $s \in S$
x_i^u	Penalty variable for dose being too high at dose point $i \in P_s$, $s \in S$

dose point in which the dose is outside a specified interval. This penalty increases linearly with the distance to the interval. In HDR BT, such a model, known as IPSA (inverse planning simulated annealing), was first proposed in [62], where the model was solved heuristically with simulated annealing (see e.g. [102] for a description of simulated annealing). The same model was formulated as a linear program in [4], which made it possible to find and prove global optimality. This model is referred to as the linear penalty model (LPM).

3.5.1 Optimization model

Table 3.2 introduces the specific notation that is used in the linear penalty model.

The dashed line in Figure 3.1 shows the dose-penalty relationship for one dose point. There is no penalty when the dose is within the specified interval (that is, between L^s and U^s), and outside this interval the penalty increases linearly. The linear penalty model is mathematically formulated as follows.

$$\min \sum_{s \in S} w_s^l \sum_{i \in P_s} x_i^l + \sum_{s \in S} w_s^u \sum_{i \in P_s} x_i^u \quad (3.1a)$$

subject to

$$\sum_{j \in J} d_{ij} t_j \geq L^s - x_i^l, \quad i \in P_s, s \in S \quad (3.1b)$$

$$\sum_{j \in J} d_{ij} t_j \leq U^s + x_i^u, \quad i \in P_s, s \in S \quad (3.1c)$$

$$x_i^l \geq 0, \quad i \in P_s, s \in S \quad (3.1d)$$

$$x_i^u \geq 0, \quad i \in P_s, s \in S \quad (3.1e)$$

$$t_j \geq 0, \quad j \in J \quad (3.1f)$$

Constraints (3.1b) and (3.1d) in combination with the objective function ensure that the penalty variables for the lower dose bound take the correct values, while constraints (3.1c) and (3.1e) in combination with the objective function ensure that the penalty variables for the upper dose bound take the correct values. Moreover, in this formulation, any combination of non-negative dwell times, t_j , $j \in J$, correspond to a feasible solution.

The LPM is connected to clinical practice through the use of prescription doses, but it does not correspond to the clinical evaluation criteria in any way, and neither the penalty parameters nor the objective value in itself have direct clinical interpretations. This model can thus be regarded as an ad-hoc model and rather a forward planning model than an inverse planning model (see Section 2.1.2). Still, practice has shown that it can be a useful model because, with tuning of the penalty parameters, dose plans that are adequate can be obtained within a clinically acceptable time. However, the parameter tuning is a manual task and can itself be time consuming.

3.5.2 Properties and extensions

It has been observed that the LPM produces dose plans with less homogeneous dwell times than manual planning [20]. In [50] it was shown that the inhomogeneous dwell times is a property of the linear programming (LP) model and the Simplex method. (See e.g. [76] for an introduction to LP and the Simplex method.) For a basic feasible solution to the LPM, there is a maximal number of dwell positions that can be active, that is positions with a positive dwell time, and it is therefore not surprising that solutions to the LPM from the Simplex method tend to use few active dwell positions compared to manual planning. In [50] they also propose a remedy by using piecewise linear

Figure 3.1: The dashed line is the linear penalty function for one dose point for each feasible dose level. The dotted line is the piecewise linear penalty function, here with six segments (the flat segment included).

penalties, which give increased penalties for dose deviations further from the specified interval. Such a model is shown to produce dose plans with more homogeneous dwell times and shorter maximum dwell times compared to the LPM [50]. An example of a convex piecewise linear penalty function can be seen in Figure 3.1, where the dotted line corresponds to a penalty function with six segments.

An extension of the LPM that increases the degrees of freedom is to allow penalty parameters in a structure to be set differently for individual dose points. It was suggested in [91] to be able to put a higher penalty on points in the middle of the PTV, but this has to our knowledge not been clinically evaluated yet.

Because the objective function in the LPM has no clinical meaning in itself, criteria such as dosimetric indices are instead used to evaluate and compare dose plans. Solutions from IPSA and solutions from the LP formulation were compared in [4]. Even though the objective function value was improved significantly by using linear programming, the DIs were not significantly different. An example that two dose plans with similar DVH curves can differ a lot in terms of linear penalty values is also given in [39], where it is shown that the objective values of two similar plans differ by a factor of 12. To further strengthen this observation, the correlation between the objective value of the LPM and the DIs was studied in [51], in which it was shown that the correlation is poor.

3.5.3 Dwell time modulation restriction

To make the dwell times more homogeneously distributed the concept of dwell time modulation restriction (DTMR) was introduced in [6]. However, their

DTMR formulation was not explicitly defined. The model studied in [6], with DTMR, gives similar results, compared to the model without DTMR, in terms of PTV coverage (V_{100}), but a reduction in dose to urethra, and also more homogeneous dwell times. Three implementations of DTMR are suggested and evaluated in [8], in which the formulations extend both an LPM and a model which explicitly includes constraints on dosimetric indices (see the next section),

$$t_{j_1} \leq (1 + \gamma)t_{j_2}, \quad j_1 \in J, j_2 \in \Gamma(j_1), \quad (3.2a)$$

$$t_{j_1} - t_{j_2} \leq \theta, \quad j_1 \in J, j_2 \in \Gamma(j_1), \quad (3.2b)$$

$$\frac{1}{2} \sum_{j_1 \in J} \sum_{j_2 \in \Gamma(j_1)} (t_{j_1} - t_{j_2})^2 \leq \rho, \quad (3.2c)$$

where Γ denotes the set of adjacent dwell positions in the same catheter, and γ, θ , and ρ are parameters. For each of these constraints, there is a significant deterioration of V_{100}^{PTV} . A component to reduce the variance in dwell times was also added to IPSA [24] and the effects were studied in [100], also showing a reduction in PTV coverage.

Adding a constraint to a model imposes a restriction and the objective value of the restricted model can be expected to be worse than the objective value of the original model. The results from the studies, for example [6, 8, 100], are inconclusive about the size of this effect but there is an evident trade-off between imposing a more restrictive DTMR and keeping the PTV coverage at a high level. Both [6] and [100] have a parameter between zero and one to control the DTMR, where zero is the least restrictive choice, and [6] suggests the value of their parameter to be in the range 0.1–0.2.

3.6 Dose-volume model

Since dosimetric indices are the primary evaluation criteria for dose plans in the clinical treatment guidelines it is logical to include them explicitly in the optimization model. By doing so we obtain a dose-volume model (DVM). The first optimization model in HDR BT to explicitly include a DI was proposed in [10], in which a linear penalty model is extended with a constraint on a DI for one OAR. A dose-volume model was however studied earlier in EBRT in [59]. Such models for HDR BT were further developed and studied in [97, 39, 30].

The dosimetric index is also related to concepts in other fields of research; the counterpart in finance is called value-at-risk (VaR), see [32], and concepts similar to DIs also appear in the field of chance constraints, see for example [3].

3.6.1 Numerical example

To illustrate how the DIs are calculated a small numerical example of a dose distribution in the PTV is given in Table 3.3. With a prescription dose equal to 9 Gy, V_{100}^{PTV} (that is the portion of the PTV volume that receives at least the prescription dose) is 80%, and D_{10}^{PTV} (that is the lowest dose to the 10% of the dose points that receives the highest dose) and D_{80}^{PTV} equals 18 Gy and 9 Gy, respectively.

Table 3.3: Small numerical example of a dose distribution.

dose point i	1	2	3	4	5	6	7	8	9	10
received dose (Gy)	5	6	9	9	9.5	10	10.5	12	15	18

3.6.2 Optimization model

Table 3.4 introduces the notation that is used in the dose-volume model.

The following model is adapted from [97] and [30] (but without the DTMR constraints from the latter reference).

$$\max \quad \frac{1}{|P_T|} \sum_{i \in P_T} y_i \quad (3.3a)$$

subject to

$$\sum_{j \in J} d_{ij} t_j \geq L^T y_i, \quad i \in P_T \quad (3.3b)$$

$$\sum_{j \in J} d_{ij} t_j \leq M^s - (M^s - U^s) v_i^s, \quad i \in P_s, s \in S_O \quad (3.3c)$$

$$\sum_{i \in S_O} v_i^s \geq \tau^s |P_s|, \quad s \in S_O \quad (3.3d)$$

$$y_i \in \{0, 1\}, \quad i \in P_T \quad (3.3e)$$

$$v_i^s \in \{0, 1\}, \quad i \in P_s, s \in S_O \quad (3.3f)$$

$$t_j \geq 0, \quad j \in J \quad (3.3g)$$

The notation $|\cdot|$ is used for the cardinality of a set. The objective function value is the V_{100}^{PTV} value and the set of constraints (3.3b) ensures that each binary indicator variable y_i takes the correct value, that is, one if the dose is sufficiently high and zero otherwise. Therefore, to calculate the value of the DI V_{100}^{PTV} it is enough to count the indicator variables which take the value one, and scale the objective function with the number of dose points to get a value between zero and one. Similarly, the set of constraints (3.3d) ensures that the value V_{100}^s is at least τ^s . The set of constraints (3.3c) ensures

Table 3.4: Notation used in the dose-volume model.

Parameters	
τ^s	Portion of OAR $s \in S_O$
Variables	
y_i	Indicator variable for PTV dose points, $i \in P_T$, that takes the value one if the dose is high enough and zero otherwise
v_i^s	Indicator variable for OAR dose points, $i \in P_s$, $s \in S_O$, that takes the value one if the dose is low enough and zero otherwise

that each binary indicator variable v_i^s takes the value one only if the dose is sufficiently low. These constraints, referred to as “Big M” constraints, also impose a hard upper bound, M^s , on the dose received in each dose point. This upper bound can be chosen to be large enough to not cut off any feasible solutions or take the value of a clinically relevant upper bound, if available.

3.6.3 Properties and solutions methods

The model is a mixed-integer programming (MIP) model (for an introduction to integer programming, see e.g. [108]) and its non-convexities were studied in the field of IMRT in [27], showing that there can be multiple local minima which must be handled (the definition of a local minimum is however not explicit). Solving the model directly with a MIP-solver, which is based on branch-and-bound, has proved to be hard [10, 97, 30] and due to time constraints the MIP-solver has to be stopped prematurely, before proving optimality. The computational difficulties of this model are not surprising because models with indicator constraints are known to have weak linear programming relaxations and to be hard to solve [13]. However, in [36] it is argued that Big M formulations remains the most practical way for solving DI problems (they use the term VaR problems). A common alternative approach is to use the heuristic simulated annealing to find good results within a short time. This has been studied in [10, 97, 30].

Another approach to handle dose-volume models is to approximate the Heaviside step functions (corresponding to the binary indicator variables) with smooth non-linear sigmoid functions [53, 44],

$$f(Dose_i) = 0.5(1 + \tanh(\beta(Dose_i - L^T))),$$

where β is a parameter to control the steepness. See Figure 3.2 for an illustration. Good results compared to manual planning, LPM and IPIP [97] are shown in [44], and in addition within very short computing times, in the order of seconds. However, because of the approximations there are no guarantees that the constraints on the DIs are satisfied. Also, it is neither known if the solution is the global optimum nor are any optimistic bounds on the optimal objective value known. Approximations of the Heaviside step functions

Figure 3.2: Shows the Heaviside step function (the solid line) and the smooth non-linear sigmoid approximation (the dashed line).

have been studied also in IMRT [63]. They were approximated with concave functions, and in addition to constraints on DIs the model has an objective function with the aim to find homogeneous dose distributions.

An advantage with the use of a MIP-solver to solve an exact formulation is that optimistic bounds on the objective value is available during the solution process. Combining the optimistic bound with the pessimistic bound from the best found feasible solution gives an interval for the optimal V_{100}^{PTV} value. This is useful because the planning process includes decisions on the necessary trade-offs between the multiple criteria, and to make an informed decision it is relevant to know what is attainable for each evaluation criteria. However, with computing time as a limiting factor, improvements of the solution methods are necessary to fully capitalise on this potential.

3.7 Mean-tail-dose model

A measure that is related to the dose-volume histogram and the dosimetric indices is the conditional value-at-risk (CVaR), which was introduced as a financial risk measure [90]. In the financial context, CVaR can be used to limit the mean loss in a specified portion of the scenarios with the worst outcome. In the context of radiation therapy the CVaR value either quantifies the mean dose to the $\alpha\%$ of the structure that receives the lowest dose or the mean dose to the $\beta\%$ of the structure that receives the highest dose. To distinguish between them, $LCVaR_{\alpha}^s$ denotes the CVaR value for the portion α of the structure $s \in S$ that receives the lowest dose and $UCVaR_{\beta}^s$ denotes the CVaR value for the portion β of the structure $s \in S$ that receives the highest dose. In radiation therapy CVaR has also been referred to as mean-tail-dose. It has been shown that CVaR can be modelled with a linear formulation [90], either to maximise (or lower bound) $LCVaR_{\alpha}^s$ or to minimise (or upper bound) $UCVaR_{\beta}^s$.

Figure 3.3 shows how these CVaR values are related to the differential DVH curve. This curve shows, for each dose level, the portion of the volume that receives exactly this radiation dose. The mean value of the area in grey is $LCVaR_\alpha^s$, which mathematically is calculated as

$$LCVaR_\alpha^s = \frac{1}{\alpha|P_s|} \sum_{i \in P_s: Dose_i \leq D_{1-\alpha}^s} Dose_i. \quad (3.4)$$

The mean value of the area in black is $UCVaR_\beta^s$ which is calculated as

$$UCVaR_\beta^s = \frac{1}{\beta|P_s|} \sum_{i \in P_s: Dose_i \geq D_\beta^s} Dose_i. \quad (3.5)$$

The measure CVaR can be regarded and used as a convex approximation of dosimetric indices. This convex approximation is shown, in a certain sense, to be the most accurate approximation of VaR in [79]. Even though CVaR is related to the DVH curve and its meaning is tangible, in contrast to the objective of the LPM, it is only an approximation of measures in the clinical treatment guidelines.

Figure 3.3: Example of a differential DVH curve. The mean value of the area in grey is the $LCVaR$ value and the mean value of the area in black is the $UCVaR$ value.

3.7.1 Numerical example

To continue the numerical example in Section 3.6.1, one can also calculate the CVaR values. From the dose distribution in Table 3.3 we get $LCVaR_{20}^{PTV} = \frac{5+6}{2} = 5.5$ Gy (the mean dose to the 20% dose points that receive the lowest dose is 5.5 Gy) and $UCVaR_{10}^{PTV} = \frac{18}{1} = 18$ Gy.

3.7.2 Optimization model

An optimization model for dose planning of IMRT with CVaR constraints was first formulated in [92]. An optimization model for HDR BT with CVaR constraints has been proposed [49].

Table 3.5: Notation used in the mean-tail-dose model.

Indices	
k	Index for a segment in the piecewise linear penalty function
Sets	
K^{sl}	Set of penalty segments for dose being too low in structure $s \in S$
K^{su}	Set of penalty segments for dose being too high in structure $s \in S$
Parameters	
α^s	Denotes a portion of the structure $s \in S$
β^s	Denotes a portion of the structure $s \in S$
$L_{\alpha^s}^s$	Lower bound on the value of $LCVaR_{\alpha^s}^s$, $s \in S$
$U_{\beta^s}^s$	Upper bound on the value of $UCVaR_{\beta^s}^s$, $s \in S$
w_{sk}^l	Penalty of segment $k \in K^{sl}$ for a too low dose in structure $s \in S$
w_{sk}^u	Penalty of segment $k \in K^{su}$ for a too low high in structure $s \in S$
L^{sk}	Lower bound of segment $k \in K^{sl}$ for structure $s \in S$
U^{sk}	Upper bound of segment $k \in K^{su}$ for structure $s \in S$
Variables	
$\bar{\zeta}^s$	Auxiliary variable
$\underline{\zeta}^s$	Auxiliary variable
$\bar{\xi}_i^s$	Auxiliary variable to take the maximum of two expressions
$\underline{\xi}_i^s$	Auxiliary variable to take the maximum of two expressions
x_{ik}^l	Penalty variable for segment $k \in K^{sl}$ for dose being too low at dose point $i \in P_s$, $s \in S$
x_{ik}^u	Penalty variable for segment $k \in K^{su}$ for dose being too high at dose point $i \in P_s$, $s \in S$

The following model, based on the model formulated in [91], shows an example of a mean-tail-dose model with constraints that impose upper bounds on $UCVaR_{\beta^s}^s$, $s \in S$, and lower bounds on $LCVaR_{\alpha^s}^s$, $s \in S$. The objective function is based on the LPM (presented in Section 3.5) but with piecewise linear penalties. The notation is given in Table 3.5.

$$\min \sum_{s \in S} \sum_{k \in K^{sl}} w_{sk}^l \sum_{i \in P_s} x_{ik}^l + \sum_{s \in S} \sum_{k \in K^{su}} w_{sk}^u \sum_{i \in P_s} x_{ik}^u \quad (3.6a)$$

subject to

$$\sum_{j \in J} d_{ij} t_j \geq L^{sk} - x_{ik}^l, \quad i \in P_s, k \in K^{sl}, s \in S \quad (3.6b)$$

$$\sum_{j \in J} d_{ij} t_j \leq U^{sk} + x_{ik}^u, \quad i \in P_s, k \in K^{su}, s \in S \quad (3.6c)$$

$$\bar{\zeta}^s + \frac{1}{\beta^s |P_T|} \sum_{i \in P_T} \bar{\xi}_i^s \leq U_{\beta^s}^s, \quad s \in S \quad (3.6d)$$

$$\underline{\zeta}^s - \frac{1}{\alpha^s |P_T|} \sum_{i \in P_T} \underline{\xi}_i^s \geq L_{\alpha^s}^s, \quad s \in S \quad (3.6e)$$

$$\bar{\xi}_i^s \geq \sum_{j \in J} d_{ij} t_j - \bar{\zeta}^s, \quad i \in P_s, s \in S \quad (3.6f)$$

$$\underline{\xi}_i^s \geq \underline{\zeta}^s - \sum_{j \in J} d_{ij} t_j, \quad i \in P_s, s \in S \quad (3.6g)$$

$$\bar{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.6h)$$

$$\underline{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.6i)$$

$$\sum_{j \in J} d_{ij} t_j \leq M^s, \quad i \in P_s, s \in S \quad (3.6j)$$

$$x_{ik}^l \geq 0, \quad i \in P_s, k \in K^{sl}, s \in S \quad (3.6k)$$

$$x_{ik}^u \geq 0, \quad i \in P_s, k \in K^{su}, s \in S \quad (3.6l)$$

$$t_j \geq 0, \quad j \in J \quad (3.6m)$$

The objective function (3.6a) and constraints (3.6b), (3.6c), (3.6k) and (3.6l) are similar to those presented and explained in Section 3.5. The difference is that the penalties here are piecewise linear with a number of segments. See Figure 3.1 for an illustration of a piecewise linear penalty function. The constraints (3.6d), (3.6f) and (3.6h) form the linear formulation of $UCVaR_{\beta^s}^s$, as presented in [89]. The auxiliary variables $\bar{\zeta}^s$ take the values of the dosimetric indices $D_{\beta^s}^s$. The variables $\bar{\xi}_i^s$ are used only to linearise the maximum function of the two right-hand-side values in constraints (3.6f) and (3.6h) (that is, the positive part of the right-hand-side of (3.6f)). The linear formulation of $LCVaR_{\alpha^s}^s$ is similarly defined with constraints (3.6e), (3.6g) and (3.6i). The resulting feasible region for constraints (3.6d)–(3.6i) is a convex set, as shown in [90]. Furthermore, this model is a restriction of the LPM, as the feasible set is made smaller by adding constraints (3.6d)–(3.6i).

The latter CVaR constraints are combined with an objective function to maximise an approximation of the dose homogeneity index (see equation (2.1)) in [49], and the resulting model is formulated and solved as an LP.

3.8 Radiobiological models

Instead of taking the detour of evaluating the dose plan based on physical dose, an alternative approach is to incorporate the anticipated radiobiological effects explicitly in an optimization model. Examples of this are optimization models based on EUD (see equation (2.4)) and on TCP. Also this direct approach has drawbacks however, a major one being difficulties in estimating values of parameters in radiobiological models. See [28] for a discussion about replacing dosimetric indices, which are the primary clinically used evaluation criteria, with criteria the instead are based on radiobiological models.

In [37] a non-linear optimization model based on the radiobiological index gEUD is proposed, with the aim of sparing OAR. A more homogeneous dose distribution with respect to COIN is also obtained. The index gEUD is also used in an optimization model in [112]. In both these BT studies, the objective function used is the gEUD formulation that was proposed in the context of IMRT in [110]. Equation (3.7) shows this formulation using the notation given in Table 3.6.

$$F = \frac{1}{\left(1 + \frac{EUD_0^T}{EUD^T}\right)^{n_T}} \cdot \prod_{s \in S_O} \frac{1}{\left(1 + \frac{EUD^s}{EUD_0^s}\right)^{n_s}} \quad (3.7)$$

Table 3.6: Notation used in the models with radiobiological indices, EUD and TCP.

Parameters	
EUD_0^s	Is a structure specific parameter for $s \in S$, estimated from dose-response data
n_s	A penalty factor, specific for each structure $s \in S$
b	Birth rate of tumour cells
d	Death rate of tumour cells
Variables	
EUD^s	The value of EUD for structure $s \in S$, as calculated by expression (2.4)
t	Time, during or after the treatment
Functions	
$S(t)$	Survival probability of the tumour cells, with $t = 0$ it gives the initial probability

Furthermore, in [112] it is observed that overdosage of the tumour has only a small impact on the gEUD while gEUD is very sensitive to underdosing of the tumour. In IMRT there has been a larger interest in the optimization models based on gEUD, possibly because non-linear models are more common in IMRT, while linear models, such as the LPM and the DVM, are more common in HDR BT.

The radiobiological index TCP is included in a bi-objective model in [61]. The objective function contains two parts, one weighted sum over binary indicator variables (for dose points), each of which equals one if the dose is sufficiently high or sufficiently low, and the TCP, which is based on the TCP value calculated as in [113],

$$TCP(t) = \left[1 - \frac{(S(t)e^{(b-d)t})}{\left(1 + bS(t)e^{(b-d)t} \int_0^t \frac{dt'}{S(t')e^{(b-d)t'}}\right)} \right]^{|P_T|}, \quad (3.8)$$

using the notation given in Table 3.6. This formulation is both non-linear and non-convex. In the solution process in [113] primary goals are the DIs and the model is solved as a MIP, using branch-and-cut, without the TCP component. When an integer solution is found, a local search is initiated to improve the TCP value.

Moreover, in an LDR BT study [42], estimates of TCP and NTCP are included. Because the OAR have different radiobiological sensibility, small changes in the DVH curve for the rectum had a big impact on the NTCP, while a large change in the DVH curve for the urethra gave only a small change in the NTCP.

On the topic of underdosing the tumour, it was shown in [105] that cold volumes reduces the TCP value significantly even when the cold volumes is only 1% of the tumour. Related to this is an IMRT study on a version of EUD [14], denoted tail EUD, focused on increasing the dose to the coldest part of the tumour. Hence, the purpose of the tail EUD is the same as of LCVaR.

3.9 Multi-objective models

Because the evaluation of treatment plans takes multiple criteria into account, a reasonable modelling approach to dose planning is multi-objective optimization. In HDR BT there are several studies on multi-objective models, see [58, 71, 57, 64, 65, 95, 70]. For all of them, the final result is a set of dose plans that satisfy the Pareto optimality conditions, and there is no decision on which plan that is the best one. The Pareto optimality front is defined as follows. With the goal to minimise a number of objective functions $f_i(x)$, $i = 1, \dots, n$, a dose plan x dominates a dose plan y if the following two criteria are satisfied.

1. $f_i(x) \leq f_i(y)$, $i = 1, \dots, n$,
2. $f_k(x) < f_k(y)$ holds for some $k \in \{1, \dots, n\}$.

The Pareto front is the set of all non-dominated dose plans, or in other words, solutions on a Pareto front cannot be improved in one objective without deteriorating another.

Figure 3.4 shows an example of a solution space, where each solution is plotted according to the values of two objectives, f_1 and f_2 , which both should

be minimised. The solutions that are plotted with filled circles belong to the Pareto front. For these points it is not possible to improve the value of one objective without making the other worse.

Figure 3.4: Example of a Pareto front. All points (circles) correspond to a solution plotted according to two objective values, f_1 and f_2 , which both should be minimised. The Pareto front consists of the filled circles.

An advantage of presenting a set of solutions instead of a single solution is that the trade-offs can be made clear, for example as shown in Figure 3.4. Such an illustration is also useful when choosing a treatment plan as it is important to know what objective values that are attainable.

Both [71] and [57] consider a composite objective function which is a weighted sum of the multiple objectives. These objectives are referred to as variance based objectives. The three types of objectives they consider are the following:

$$\frac{1}{|P_E|} \sum_{i \in P_E} \frac{(Dose_i - m_E)^2}{m_E^2}, \quad (3.9a)$$

$$\frac{1}{|P_V|} \sum_{i \in P_V} \frac{(Dose_i - m_V)^2}{m_V^2}, \quad (3.9b)$$

$$\frac{1}{|P_o|} \sum_{i \in P_o} \frac{\Theta(Dose_i - D_C^o m_E) (Dose_i - D_C^o m_E)^2}{(D_C^o m_E)^2}, o \in OAR, \quad (3.9c)$$

where the sets P_E and P_V are PTV dose points on the surface and in the volume, respectively, and m_E and m_V are the average PTV dose to the surface and the volume, respectively. The function Θ is the Heaviside step function, with $\Theta(0) = 1/2$, and D_C^o is a fraction of the prescription dose for $o \in OAR$. They solve a large number of non-linear optimization problems with different weights (in the composite objective function), each of them giving a candidate to the Pareto front.

Simulated annealing, which is popular in HDR BT dose planning, belongs to a class of metaheuristics which only considers a single solution at each iteration. Contrary to simulated annealing and the previously described approaches based on composite objective functions, genetic algorithms belong to the class of population-based metaheuristics, which means that there is a set of solutions which are updated at each iteration [102]. Genetic algorithms are the most commonly studied metaheuristic method in HDR BT that allow for dealing with the objectives in a truly multi-objective manner [58, 57, 64, 65, 95, 70], since by having a fitness criterion that is based on domination it is not necessary to combine all objectives into a single value. Further, in the case of non-convex objectives, a weighted sum method might not be able to find all solutions on the Pareto front which is a disadvantage compared to dominance based methods [34, p. 73]. However, with convex objectives, a weighted sum formulation can be seen as equivalent to a formulation in which the objectives are constrained [18].

With multiple objectives, it is not easy to visualise the set of possible solutions and the trade-offs that have to be made. In [71, 57] the trade-offs are mainly illustrated by plotting the Pareto front with respect to two objectives at a time.

Another approach to visualise the trade-offs is taken in the studies [64, 65, 68] (which are based on the evolutionary algorithm presented in [66]). Here, the multi-objective problem is reduced to a bi-objective by partitioning the objectives into two categories, either related to PTV coverage or to OAR sparing, and for each category the objective value is the worst objective term, in comparison to a target value for each objective. Dosimetric indices for high doses to the PTV (V_{200}^{PTV} and V_{150}^{PTV}) are considered as hard constraints.

The objective related to coverage, least coverage index (LCI), is formulated as

$$LCI = \min\{V_{100}^{prostate} - 95\%, V_{80}^{vesicles} - 95\%\}, \quad (3.10)$$

where 95% is the target value in the clinical treatment protocol used. The objective related to OAR sparing, least sparing index (LSI), is formulated as

$$LSI = \min\{\delta(D_{1cc}^{bladder}), \delta(D_{2cc}^{bladder}), \delta(D_{1cc}^{rectum}), \delta(D_{2cc}^{rectum}), \delta(D_{0.1cc}^{urethra})\}, \quad (3.11)$$

where D_y^s is the DI introduced in Section 2.2.2. (D_y^s is the lowest dose that is received by the y cc of the structure s that receives the highest dose.) The function δ is defined as

$$\delta = D_y^{s,max} - D_y^s, \quad (3.12)$$

where $D_y^{s,max}$ is a threshold value from the clinical treatment protocol for structure s and for volume y . The value of LCI is a portion and the value

of LSI is in Gy. The formulations (3.10)–(3.12) are taken from [65]. For both LCI and LSI a positive value indicates that the clinical requirements are satisfied, and thus it is easy to verify for which solutions, on the Pareto front, the requirements are satisfied.

The bi-objective formulation described above allows for an easier visualisation but also reduces the possibilities for the planner to select a dose plan, because a dose plan not on the Pareto front might be the preferred one. Related approaches are presented in [95, 70], but in addition to the two objectives for PTV coverage and OAR sparing, these also consider the number of catheters as an objective to minimise (see Section 3.12).

A multi-objective approach different from the ones presented previously in this section is proposed in [94]. Instead of providing the planner with a set of dose plans to choose among, the planner is active during an iterative and interactive optimization process. In each iteration the planner has five options for each objective:

1. to improve it,
2. to improve it up to a specified level,
3. to allow for a deterioration to a specified level,
4. to keep it fixed, or,
5. to not bound it at all.

The result of an iteration can either be a single dose plan or a set of dose plans based on convex combinations of two previous dose plans.

3.10 Model analysis

We have presented a broad variety of optimization models for dose planning and we continue by discussing mathematical properties of these models and mathematical relationships between them.

3.10.1 Multi-objective interpretation of single objective models

Since the inherent treatment planning problem is multi-objective the single-objective models presented in this chapter should be viewed also in that perspective.

An optimal solution to the LPM with positive penalty weights belongs to the Pareto front of the multi-objective formulation

$$\min \left(\min_{s \in S} \sum_{i \in P_s} x_i^l, \min_{s \in S} \sum_{i \in P_s} x_i^u \right).$$

Because each objective is convex, there exists weights of the LPM such that any solution on the Pareto front can be found by solving an instance of the LPM [34].

3.10.2 Dosimetric indices and mean-tail-dose

The dosimetric index D_y^s (which is similar to value-at-risk) is related to the CVaR value. From the definition of $UCVaR_\beta^s$ (which is the mean dose to the $\beta\%$ of the structure $s \in S$ that receives the highest dose, see equation (3.5)) it is clear that $UCVaR_\beta^s \geq D_\beta^s$, and similarly that $LCVaR_\alpha^s \leq D_{1-\alpha}^s$. Further, if $LCVaR_\alpha^{PTV} = x$, then $V_x^{PTV} \geq 1 - \alpha$, or in words, the portion of the volume that receives at least x Gy is at least $1 - \alpha$. Therefore, one way to model the treatment goal $V_{100}^{PTV} \geq 95\%$, from the clinical guidelines, is with the constraint $LCVaR_{5\%}^{PTV} \geq 100\%$ (of the prescription dose). If this constraint is fulfilled, some dose point among the 5% dose points that receive the lowest dose receives a dose at least as high as the prescription dose. Thus, at least 95% of the dose points receive a dose that is at least as high as the prescription dose, and the constraint $V_{100}^{PTV} \geq 95\%$ is satisfied. The LCVaR constraint is a more restrictive formulation than the constraint $V_{100}^{PTV} \geq 95\%$, that is, if the LCVaR constraint is fulfilled then also the constraint $V_{100}^{PTV} \geq 95\%$ is fulfilled. However, the advantage of using CVaR constraints is that they can be modelled with a convex and linear formulation. Similarly for an OAR o , the constraint $UCVaR_\beta \leq x$, implies that $V_x^o \geq 1 - \beta$. A formal proof of the relationship between VaR and CVaR is given in [89].

3.10.3 Relationship between model LPM and mean-tail-dose

The optimization model, with CVaR constraints, presented in Section 3.7 can be reformulated by removing the CVaR constraints and instead adding CVaR terms to the objective, with the aim of maximising LCVaR terms and minimising UCVaR terms. These CVaR terms are prioritised using weights. The resulting formulation, given by expressions (3.13a)–(3.13h), is referred to as the mean-tail-dose model (MTDM). Explanations of the notation introduced in the objective function are given in Table 3.7 and explanations of the previously introduced notation used in the expressions (3.13a)–(3.13h) are given in Table 3.5 (see Section 3.7).

Table 3.7: Notation used in the MTDM.

Parameters	
ω_s^u	Objective weight for the UCVaR term for structure $s \in S$
ω_s^l	Objective weight for the LCVaR term for structure $s \in S$
Variables	
$\bar{\phi}_{\beta^s}^s$	Takes the value of $UCVaR_{\beta^s}^s$, $s \in S$
$\underline{\phi}_{\alpha^s}^s$	Takes the value of $LCVaR_{\alpha^s}^s$, $s \in S$

$$\min \sum_{s \in S} \omega_s^u \bar{\phi}_{\beta^s}^s - \sum_{s \in S} \omega_s^l \underline{\phi}_{\alpha^s}^s \quad (3.13a)$$

subject to

$$\bar{\zeta}^s + \frac{1}{\beta^s |P_s|} \sum_{i \in P_s} \bar{\xi}_i^s = \bar{\phi}_{\beta^s}^s, \quad s \in S \quad (3.13b)$$

$$\underline{\zeta}^s - \frac{1}{\alpha^s |P_s|} \sum_{i \in P_s} \underline{\xi}_i^s = \underline{\phi}_{\alpha^s}^s, \quad s \in S \quad (3.13c)$$

$$\bar{\xi}_i^s \geq \sum_{j \in J} d_{ij} t_j - \bar{\zeta}^s, \quad i \in P_s, s \in S \quad (3.13d)$$

$$\underline{\xi}_i^s \geq \underline{\zeta}^s - \sum_{j \in J} d_{ij} t_j, \quad i \in P_s, s \in S \quad (3.13e)$$

$$\bar{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.13f)$$

$$\underline{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.13g)$$

$$t_j \geq 0, \quad j \in J \quad (3.13h)$$

The objective is a weighted sum of UCVaR and LCVaR terms. The second objective term has a negative sign, because the mean dose to a specified portion that receives the lowest dose should be maximised.

Starting with the MTDM with arbitrary parameter values, we can formulate an instance of the LPM (see Section 3.5), with specific choices of parameters values, which yields the same set of optimal solutions. This is stated formally in Theorem 1.

Theorem 1. *For an instance of the MTDM, let $\bar{\zeta}^{s*}, s \in S$, and $\underline{\zeta}^{s*}, s \in S$, be values in an optimal solution. Consider an instance of the LPM with parameter values $U^s = \bar{\zeta}^{s*}, s \in S$, $L^s = \underline{\zeta}^{s*}, s \in S$, $w_s^u = \frac{\omega_s^u}{\beta^s |P_s|}, s \in S$, and $w_s^l = \frac{\omega_s^l}{\alpha^s |P_s|}, s \in S$. Then optimal dwell times for the LPM are optimal also for the MTDM.*

Proof. We formulate an instance of the LPM and we draw conclusions about optimal solutions to this LPM.

We can note that fixing variable values to the values in an optimal solution do not change the optimal objective value, that is, $\min_{\bar{\phi}, \bar{\phi}, \bar{\zeta}, \bar{\zeta}, \bar{\xi}, \bar{\xi}, t} MTDM(\bar{\phi}, \bar{\phi}, \bar{\zeta}, \bar{\zeta}, \bar{\xi}, \bar{\xi}, t) = \min_{\bar{\phi}, \bar{\phi}, \bar{\xi}, \bar{\xi}, t} MTDM(\bar{\phi}, \bar{\phi}, \bar{\zeta}^*, \bar{\zeta}^*, \bar{\xi}, \bar{\xi}, t)$, where $\bar{\zeta}^{s*}, s \in S$, and $\bar{\zeta}^{s*}, s \in S$, are values from an optimal solution. Further, optimal dwell times, $t_j, j \in J$, in the MTDM with fixed variables, $\bar{\zeta}^{s*}, s \in S$, and $\bar{\zeta}^{s*}, s \in S$, are optimal also in the original MTDM.

We next consider the formulation

$$\min \sum_{s \in S} \omega_s^u \left(\bar{\zeta}^{s*} + \frac{1}{\beta^s |P_s|} \sum_{i \in P_s} \bar{\xi}_i^s \right) - \sum_{s \in S} \omega_s^l \left(\bar{\zeta}^{s*} - \frac{1}{\alpha^s |P_s|} \sum_{i \in P_s} \bar{\xi}_i^s \right) \quad (3.14a)$$

subject to

$$\bar{\xi}_i^s \geq \sum_{j \in J} d_{ij} t_j - \bar{\zeta}^{s*}, \quad i \in P_s, s \in S \quad (3.14b)$$

$$\bar{\xi}_i^s \geq \bar{\zeta}^{s*} - \sum_{j \in J} d_{ij} t_j, \quad i \in P_s, s \in S \quad (3.14c)$$

$$\bar{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.14d)$$

$$\bar{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.14e)$$

$$t_j \geq 0, \quad j \in J \quad (3.14f)$$

We obtain the formulation by starting with the MTDM given by expressions (3.13a)–(3.13h), fixing variables $\bar{\zeta}^s$ to $\bar{\zeta}^{s*}, s \in S$, and $\bar{\zeta}^s$ to $\bar{\zeta}^{s*}, s \in S$, and replacing variables $\bar{\phi}_{\beta^s}^s, s \in S$, and $\bar{\phi}_{\alpha^s}^s, s \in S$, with the expressions from the equality constraints (3.13b) and (3.13c). Because of the observation in the previous paragraph, optimal dwell times to the formulation given by expressions (3.14a)–(3.14f) are optimal also in the MTDM.

Rewriting this formulation as

$$\sum_{s \in S} \omega_s^u \bar{\zeta}^{s*} - \sum_{s \in S} \omega_s^l \bar{\zeta}^{s*} + \min \sum_{s \in S} \frac{\omega_s^u}{\beta^s |P_s|} \sum_{i \in P_s} \bar{\xi}_i^s + \sum_{s \in S} \frac{\omega_s^l}{\alpha^s |P_s|} \sum_{i \in P_s} \bar{\xi}_i^s \quad (3.15a)$$

subject to

$$\sum_{j \in J} d_{ij} t_j \leq \bar{\zeta}^{s*} + \bar{\xi}_i^s, \quad i \in P_s, s \in S \quad (3.15b)$$

$$\sum_{j \in J} d_{ij} t_j \geq \bar{\zeta}^{s*} - \bar{\xi}_i^s, \quad i \in P_s, s \in S \quad (3.15c)$$

$$\bar{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.15d)$$

$$\bar{\xi}_i^s \geq 0, \quad i \in P_s, s \in S \quad (3.15e)$$

$$t_j \geq 0, \quad j \in J \quad (3.15f)$$

does neither change the set of optimal solutions nor the optimal objective value. This problem is of the same format as the LPM and we conclude that optimal solutions to this problem are optimal also in the MTDM. $\square$

In general the converse of Theorem 1 is *not* true, that is, starting with an instance of the LPM, it is not always possible to create an instance of the MTDM, such that optimal solutions to the LPM are optimal also in the MTDM. To motivate why, first note that the parameters α^s and β^s , $s \in S$, are not present in the LPM but must be specified in the MTDM. A solution to the LPM minimises the total underdosage, below L^s , $s \in S$, and the total overdosage, above U^s , $s \in S$. If these underdosages and overdosages in the LPM solution are distributed over $\alpha^s\%$ and $\beta^s\%$, $s \in S$, of the volumes of the structures respectively, there is possibly another solution in which the underdosages and overdosages are distributed over larger portions of the volumes. In that case the CVaR values, for $\alpha^s\%$ and $\beta^s\%$, $s \in S$, respectively, can be improved compared to the values from an optimal solution to the LPM, possibly with higher total underdosages and overdosages. Therefore, it is not certain that there are parameter values in the MTDM such that the optimal solution to the LPM is optimal also in the specified instance of the MTDM.

This reasoning can be illustrated with the following numerical example. Assume for simplicity that there are only penalties for the PTV, which consists of five dose points. The prescription dose L is 10 Gy and the optimal dose distribution from an LPM is (8, 9, 10, 11, 13) Gy with a total underdosage, below L , of 3 Gy. If we specify α to be 40%, $LCVaR_{40}$ equals 8.5 Gy. Another possible dose distribution with the same total dose and the same total underdosage is (9, 9, 9, 11, 13) Gy. If the aim is to maximise $LCVaR_{40}$ this solution, with $LCVaR_{40} = 9$ Gy, is better than the LPM solution, which therefore is not optimal in the MTDM with $\alpha = 40\%$. Also for $\alpha = 60\%$, with $LCVaR_{60} = 9.5$ in the LPM dose distribution, there is another possible dose distribution of (8, 9, 10, 12, 12) Gy, with the same total dose and the same total underdosage. In the latter dose distribution the $LCVaR_{60}$ value is 9.75 Gy, which is an improvement compared to the CVaR value of the LPM dose distribution. An interpretation of this is that there is a lack of coordinability in the LPM compared to the MTDM. Only linear penalties are not enough to control results in terms of CVaR values.

3.10.4 Number of active dwell positions

The impact of the choice of model on the number of active dwell positions was discussed briefly in Section 3.5.2, based on the analysis in [50], in which the piecewise linear penalty model is presented as one way to increase the number of active dwell positions compared to the LPM. The analysis is continued here for the other two linear models, the dose-volume model and the mean-tail-dose model. The underlying observation is that in a basic feasible solution the number of non-zero variables are limited by the number of constraints. The impact of the linear dwell time modulation restrictions (see Section 3.5.3) on the number of active dwell positions is also discussed. Advantages of increasing the number of active dwell positions are not well-studied, but there

are indirect effects such as shorter maximum dwell times and lower radiation doses to the most irradiated dose points, which are considered as beneficial. There is also a lower risk that there is a large hot spot which encloses two adjacent dwell positions, that is, a volume where the 200% isodose curves enclose two dwell positions.

Starting from the MTDM presented in Section 3.10.3, we conduct a similar analysis as the one in [50], where the LPM and the piecewise linear penalty model are studied. The structure of the constraints (3.13d)–(3.13g) is the same as that of the constraints (3.6b)–(3.6k) in the LPM. The sizes of the two other sets of constraints, (3.13b) and (3.13c), are much smaller and do not to any large extent affect the number of basic variables, and in turn the number of active dwell positions. Thus, the inherent property of the LPM activating few dwell positions is also an inherent property of the MTDM, assuming that the Simplex method is used to find solutions.

The structure of the LP relaxation of the DVM is similar to the structure of the LPM. (This is further discussed in Paper A.) In the formulation given in Section 3.6 there is one constraint for each indicator variable (that is, one per dose point) and one constraint per structure. Thus, in the LP relaxation the number of active dwell positions is about as many in the LPM and in the MTDM. However, in the branch-and-bound algorithm used to solve the mixed-integer program there are aspects that can affect the number of active dwell positions. First, when branching on a binary variable y_i (which takes a fractional value in the LP solution), new constraints, such as $y_i = 1$ and $y_i = 0$ are added. Such a constraint allows one more dwell time to become positive. Secondly, valid inequalities are used in the branch-and-bound algorithm to cut off fractional solutions, and such constraints also allow more dwell time variables to become positive. Thirdly, in practice, mixed-integer solutions are often found using a heuristic algorithm. These solutions do not necessarily correspond to basic feasible solutions and thus more dwell positions can be active. The conclusion is that solutions from the dose-volume model typically can have more active dwell positions than solutions from the linear penalty model. It is however not certain that this is always the case.

The dwell time modulation restrictions were introduced in Section 3.5.3. The following analysis is based on the DTMR formulation with constraints (3.2a) and (3.2b). The number of extra constraints is of the order of two times the number of dwell positions. For each such constraint that is satisfied with equality, one extra dwell time variable can become positive. Thus, one effect from using DTMR constraints is that more dwell positions can be active in a basic feasible solution. Typically, with tighter bounds (smaller parameter values of γ or θ) more DTMR constraints are satisfied with equality, which allows more dwell positions to be active.

3.10.5 User perspective

From a user perspective it is relevant whether the parameters and entities involved in the treatment planning are based on well-known concepts and therefore are tangible, or if the parameters and entities are superficial constructions. An example of the former is the DVM, where the parameters (τ^s) are values of the dosimetric indices that should be fulfilled. Thus it is easy to interpret the meaning of this model. In contrast, the LPM has penalty parameters in the objective function which has no clinical interpretation, and which only indirectly affect entities of clinical importance.

3.11 Modelling of spatial aspects

The optimization models and evaluation criteria that have been presented so far evaluate the dose distribution on an aggregate level only. How the doses are spatially distributed are not in any way considered in the evaluation. For example, dosimetric indices only count the number of dose points in which the dose is high enough or low enough, and no consideration is given to how these dose points are spatially distributed in the volume.

An optimization model that takes also the spatial dose distribution into account is proposed in an IMRT study [101]. Its aim is to improve a given dose plan by removing “critical spots”, which are either regions in the PTV where the radiation doses are too low (“cold spots”) or regions in OAR where the radiation doses are too high (“hot spots”). In their model, there are constraints to adjust the doses in the critical spots while the objective strives for maintaining certain properties of the given plan, including objective function values, constraint values and the dose at each dose point. The complete model is as follows, with the notation introduced in Table 3.8.

$$\min_x \sum_{i \in I_f} (f_i(x) - f_i^A)^2 \quad (3.16a)$$

$$+ \sum_{j \in I_c} \pi_j \max(0, g_j(x)) \quad (3.16b)$$

$$+ \sum_{k \in I_k} r_k (Dose_k(x) - dose_k^A)^2 \quad (3.16c)$$

subject to

$$l_c \leq Dose_c(x) \leq u_c, \quad c \in I_s \quad (3.16d)$$

$$x \in \mathcal{X} \quad (3.16e)$$

The dose received at dose points k and c are denoted $Dose_k(x)$ and $Dose_c(x)$ respectively, where x denotes the treatment plan parameters. The set of constraints (3.16d) ensures that the doses are adjusted in the critical spots,

Table 3.8: Notation used in the spatial optimization model.

Indices	
i	Index for objective functions
j	Index for constraints
k	Index for dose points
c	Index for dose points in the critical spot
Sets	
I_f	Set of objective functions
I_c	Set of constraints
I_d	Set of all dose points
I_s	Set of dose points in the critical spot
$\mathcal{X}$	Set of feasible dwell times
Functions	
f_i	Objective function $i \in I_f$, in original model formulation
g_j	Constraint $j \in I_c$, in original model formulation
Parameters	
$dose_k^A$	Received dose at dose point $k \in I_d$, in the given dose plan
f_i^A	Objective value of function f_i , $i \in I_f$, in the given dose plan
π_j	Penalty parameter for infeasibility in constraint g_j , $j \in I_c$
r_k	Penalty parameter for dose deviation at dose point $k \in I_d$
l_c	Lower dose bound for dose point $c \in I_s$
u_c	Upper dose bound for dose point $c \in I_s$
Variables	
x	Treatment plan parameters (for IMRT)

to respect the bounds l_c and u_c (which are possibly equal to zero and infinity respectively, if a bound is not active).

3.12 Catheter placement

So far we have assumed that the catheter placement is predetermined with the dwell times being the only decisions. The question of how to place the catheters has, however, also been included in the treatment planning. A complete formulation of the treatment planning problem includes both the number of catheters to use and where to place them as well as the decisions regarding the dwell times. Most studies presented in this section are on prostate cancer, with a few exceptions such as gynaecological cancer [43] and breast cancer [86]. In clinical treatment the standard way to insert catheters is by using a template. However, there are several studies [95, 70, 98, 86, 25] that investigate catheter placements which are not possible with the standard template. One possibility to allow for such insertions is with robotic assistance, see for example [98].

Table 3.9: Notation used in the catheter placement model.

Indices	
k	Index for catheters
Sets	
K	Set of possible catheter positions
J_k	Set of dwell positions in catheter $k \in K$
Parameters	
N	Maximum number of catheters that can be used
t_{max}	Maximal allowed dwell time
Variables	
b_k	Binary indicator variable that equals one if catheter position $k \in K$ is used, and zero otherwise

The treatment planning problem can either be modelled separately for the catheter placement and the dwell times [43, 98, 86, 25], or as one integrated formulation [95, 39, 70, 53, 48]. While the composite models can have various objectives and formulations for the dose distribution, see Sections 3.5–3.9, there is a standard formulation for connecting the dwell times and the catheters. The notation used for these constraints is given in Table 3.9 and the constraints are stated in equations (3.17a)–(3.17c):

$$t_j \leq t_{max} b_k, \quad k \in K, j \in J_k, \quad (3.17a)$$

$$\sum_{k \in K} b_k \leq N, \quad (3.17b)$$

$$b_k \in \{0, 1\}, \quad k \in K. \quad (3.17c)$$

The dwell times and the catheters are linked through the Big M constraints (3.17a), where t_{max} is supposed to be a large enough value, or if available, a clinically relevant upper bound for the dwell times. Constraint (3.17b) ensures that not too many catheters are used; it can also be formulated as an equality constraint. Because of the binary variables b_k , $k \in K$, the integrated model is a MIP, even if the objective is not (e.g. the LPM).

There are several examples of approaches that consider the catheter placement and the dose planning as an integrated problem. In [39, 53] the models (based on the DVM) are solved with a MIP solver. In [48] it is concluded that a heuristic (variable neighbourhood search) performs better than the MIP solver (on a model based on the piecewise LPM). To get tractable MIP formulations, in two studies, [39] and [47], artificial restrictions are added for which catheters that can be used together, which limits the number of possible catheter combinations. The integrated models in [95, 70] are solved with multi-objective evolutionary algorithms.

One of the main questions that catheter placement studies tries to answer is: can the number of catheters be reduced compared to clinical practice? The

reason for this question is that fewer catheters lower the risk for treatment complications. The number of catheters is correlated to the risk for acute urinary toxicity [33, 106] and is also an independent predictor for erectile dysfunction [67]. An important aim with the study in [98] is to avoid puncturing the penile bulb and it shows improvements compared to manual planning. In this study the standard template is used for catheter insertion.

Several studies conclude that the treatment plan quality can be as good with fewer catheters than what is typically used in clinical practice [95, 43, 98, 86]. In a study on prostate cancer, [21], results from using different numbers of catheters are compared. It is found that there is no significant difference in treatment plan quality between using 15, 18 or 21 catheters, but fewer catheters, 9 or 12, is significantly worse. Similarly, it is suggested in [86] that 14 catheters is enough to construct a clinically acceptable dose distribution.

3.13 Future research

In the last part of the chapter we present suggestions for future research.

3.13.1 Standard set of patient data

Comparing optimization models and methods is difficult because differences in computing times and evaluation criteria might be a result of particular properties in the data set and differences in clinical practice. These differences can be due to the treatment protocol, the number of catheters, which structures that are delineated and how, or how the dose points for the evaluation are generated. Thus, it is not obvious that results from studies are generally valid. Having a standard, freely available test set with patient data (anatomy, dose points, catheters, and dose-rate contribution) in combination with a clinical treatment protocol would greatly improve the scientific level of this field of research. In IMRT standard data sets have been introduced, such as CORT (common optimization for radiation therapy) [23] and TROTS (the radiotherapy optimisation test set) [17].

3.13.2 Distribution of dose points

The dose points are typically distributed according to [56]. To our knowledge there is no comparative study between methods of distributing the dose points and how it might affect the resulting dose plans. A related question is how artificial normal (healthy) dose points should be distributed.

3.13.3 Radiobiological models

While the clinical treatment guidelines and most evaluation criteria are based on physical dose, which only indirectly estimates the treatment effect, it would

be to prefer to use radiobiological indices, which directly estimate the treatment effects. However, more clinical development is needed before radiobiological models can replace the current physical ones, see the discussion in [83] on this subject. At the same time, there is room for improvements in radiobiological optimization models for dose planning, both in the modelling and in algorithms and solution methods.

3.13.4 Spatial dose distribution

As mentioned in Section 3.11, the spatial aspects of the dose distribution has not yet seen a wide interest in research. These aspects are relevant to study further because spatial aspects are considered to be of clinical importance, and in clinical practice dose plans are sometimes adjusted manually to reduce the spatial heterogeneities of the dose distribution. See [68] for a description of the manual planning process. The importance of spatial properties motivates more research, including both studying how spatial aspects affect clinical treatment results and the development of optimization models for dose planning, which take the spatial aspects into account. Paper C presents an optimization model which considers spatial aspects, and automates the manual adjustment step.

3.13.5 Rotating shield brachytherapy

A recently proposed treatment technique is the interstitial rotating shield brachytherapy (RSBT), which allows a dose distribution that is not radially symmetric around the source [1]. This technique has the potential of a significant sparing of the OAR [1, 2]. However, it comes at the cost of longer treatment times, on average the dose delivery for prostate cancer took 217 minutes versus 15 minutes for standard HDR BT [2]. The long treatment times can possibly be shortened by combining radiation sources of different isotopes. See [96] for an example of such a study on HDR BT treatment of cervical cancer.

From an optimization point of view the use of rotating shields is also very interesting. To take advantage of the flexibility offered by using the rotating shield and handle the increased complexity, optimization is an important tool. Even more so if multiple radiation sources are combined in one treatment, further increasing the degrees of freedom in the dose planning problem. An optimization model for RSBT is proposed in [22]. The considered objective function is a weighted sum of two components, one being a sum of quadratic penalties for dose deviations from a prescription dose over the set of dose points, and one being a sum of the dwell time deviations in all pairs of adjacent dwell positions. The latter objective term is similar to the DTMR concept given in equation (3.2b), which is described in Section 3.5.3.

3.13.6 Dose fractionation

In this presentation the fractionation schedule has only been considered indirectly through the use of parameters (such as prescription dose). One could also consider the decisions about the fractionation schedule, including the number of treatments, together with time between treatments and prescription doses, and formulate an optimization model that includes these aspects. This is discussed in [40] and such a model of the treatment planning of a type of a brain tumour (glioblastomas) is studied in [60]. To be able to formulate accurate models for the full treatment, and to compare fractionation schedules, it is also important to further develop and improve radiobiological models.

Contributions of our research

The common theme of the contributions from our research is the study of mathematical optimization models for automated dose planning. First, described in Section 4.3, we study mathematical relationships between two commonly studied models. Secondly, described in Section 4.4, we present an extension of the well-studied dose-volume model, with the purpose of providing a remedy to an inherent weakness of the model, which is that cold volumes in the PTV is not considered. Thirdly, described in Section 4.5, we propose an optimization model that takes the spatial distribution of the doses into account. The aim with this model is to adjust a given dose plan, by reducing the prevalence of hot spots, to make the dose distribution more spatially homogeneous.

4.1 DVH based modelling

Our starting point in this research project is to study the use of dosimetric indices in the modelling. The main motivation for this is the clinical treatment guidelines and the fact that dose plan evaluation to a large extent is based on the DVH curve and the DIs. From an optimizers perspective it is therefore natural to include the clinically used evaluation criteria in the modelling explicitly instead of the ad-hoc criteria widely present in clinically used optimization models. Therefore, models including dosimetric index constraints are present in all of our contributions.

4.2 Patient data

In Paper B and Paper C we use patient data from ten patients that have been treated for prostate cancer. This data includes the anatomical structures, with the PTV, the rectum and the urethra outlined, and the placements of the catheters. According to the standard procedure, we also add artificial, healthy tissue surrounding the PTV. The dose points are distributed differently when used in the optimization models and when used in dose plan evaluation. The number of dose points for the former usage is in the range 4369 – 7939 and distributed according to [56], while the number of dose points for latter usage is in the range 51 974 – 134 509 and distributed uniformly with a volume of 1 mm^3 per dose point. The number of dwell positions is between 190 and 352, and the number of catheters between 14 and 20.

4.3 Relationships between models

The two models which we study in Paper A are the linear penalty model, which is the clinically most commonly used model, and the dose-volume model, which explicitly includes DVH based targets. Even though the two optimization models seemingly are very different, we formulate precise mathematical relationships between the two models. Properties of the LPM have been studied by analysing solutions (see e.g. [20, 51]) and by deriving the maximum number of active dwell positions [50]. The correlation of the LPM with DIs has been studied in [39] and [51] and found to be weak. This observed correlation is one motivation to study mathematical relationships between the LPM and the DVM, thus complementing these studies which are based on empirical observations. See Section 3.5.2 for more details about LPM properties.

The notation DVM^{LP} is used for the LP relaxation of the DVM presented in Section 3.6 and the linear penalty model is a variant of the formulation in Section 3.5, here given by expressions (4.1a)–(4.1g).

$$\min w_T^l \sum_{i \in P_T} x_i^l + \sum_{s \in S_O} w_s^u \sum_{i \in P_s} x_i^u \quad (4.1a)$$

subject to

$$\sum_{j \in J} d_{ij} t_j \geq L^T - x_i^l, \quad i \in P_T \quad (4.1b)$$

$$\sum_{j \in J} d_{ij} t_j \leq U^s + x_i^u, \quad i \in P_s, s \in S_O \quad (4.1c)$$

$$x_i^u \leq M^s, \quad i \in P_s, s \in S_O \quad (4.1d)$$

$$x_i^l \geq 0, \quad i \in P_T \quad (4.1e)$$

$$x_i^u \geq 0, \quad i \in P_s, s \in S_O \quad (4.1f)$$

$$t_j \geq 0, \quad j \in J \quad (4.1g)$$

The main difference with the formulation in Section 3.5 is that the penalty functions here are only one-sided, for each PTV dose point there is a penalty if the dose is too low and for each dose point in OAR there is a penalty if the dose is too high. The presented results can easily be extended to the case with two-sided penalty functions. In this section LPM refers to the model given by expressions (4.1a)–(4.1g).

The main results of Paper A are Theorems 2 and 3. The first theorem considers an instance of the DVM^{LP} and states that an instance of the LPM can be formulated, with specified parameter values, such that the two instances have the same objective value and an optimal solution to DVM^{LP} is also optimal in the LPM. The second theorem instead considers an instance of the LPM and states that an instance of the DVM^{LP} can be formulated, with specified parameter values. Similar conclusions can be drawn as in the first theorem, the two instances have the same objective value and any optimal solution to the DVM^{LP} is also optimal in the LPM.

Theorem 2. *For an instance of DVM^{LP} , let $\mu^{s*} = -\pi^{s*} \geq 0$, $s \in S_O$, where π^{s*} , $s \in S_O$, are optimal dual variables associated with constraints (3.3d). Consider an instance of LPM with parameter values $p = 1/L^T$ and $w_s^u = \mu^{s*}/(M^s - U^s)$, $s \in S_O$. Then,*

1. *optimal solutions to DVM^{LP} are also optimal in LPM, and*
2. *the optimal objective value in LPM equals that of DVM^{LP} .*

Theorem 3. *For an instance of LPM, let x_i^{u*} , $i \in P_s$, $s \in S_O$ be optimal values. Consider an instance of the DVM^{LP} with parameter values $\tau^s = 1 - 1/[(M^s - U^s)|P_s|] \sum_{i \in P_s} x_i^{u*}$, $s \in S_O$. Then,*

1. *optimal solutions to DVM^{LP} are also optimal in LPM, and*
2. *the optimal objective value in LPM equals that of DVM^{LP} .*

The proofs are given in Paper A (with slightly different notation).

An implication from these theorems is that the LPM is in some sense equivalent with the LP relaxation of the DVM. Because LP relaxations of models with indicator constraints, as the ones in the DVM, are known to be weak (see e.g. [13]) the results indicate that the correlation of the LPM with the DIs is also weak. This is in line with empirical observations of weak correlation of the LPM with DIs from [39] and [51].

Furthermore, we also present precise mathematical relationships between a piecewise linear penalty model (introduced in Section 3.5.2) and a dose-volume model with several targets on dosimetric indices for each structure. These mathematical relationships have the same form as Theorems 2 and 3.

4.4 A modelling extension using mean-tail-dose

The dose-volume models in the literature include V_{100}^{PTV} (see the model in Section 3.6), but no consideration is given to the coldest portion of the PTV (the volume which receives a dose that is lower than the prescription dose). Therefore there are no incentives in the optimization model to increase the dose to underdosed PTV dose points unless the resulting dose exceeds the prescription dose. In other words, two dose plans can have the same objective function value, in terms of V_{100}^{PTV} , while still differ to a large extent in the dose to the coldest PTV volumes.

The natural question then is how the treatment effect is affected by underdosage to parts of the PTV. This question is studied in [105], in which the impact on the treatment effect, in terms of TCP, from such cold volumes is analysed. Results show that a significant underdosage, even to as small volumes as 1% of the PTV, has a large adverse impact on the TCP value (see Section 3.8). It is concluded that specifying a prescription dose for a portion of the PTV (such as 95%) is not enough to obtain a certain treatment effect. In addition to targets on V_{100}^{PTV} it is also necessary to ensure that the dose to the coldest part of the PTV is high enough.

These two observations, that DVMs do not consider the dose to the coldest volumes and the adverse treatment effect from such cold volumes, are the starting points of Paper B. To improve the dose-volume model we propose an extended formulation that also takes the dose to the coldest volume into account. This is achieved by adding an objective component which is the mean dose to the coldest 1% of the PTV ($LCVaR_1^{PTV}$). The complete model is given by formulation (4.2).

$$\begin{aligned}
\max \quad & w_1 \left(\frac{1}{|P_T|} \sum_{i \in P_T} y_i \right) + w_2 \left(\zeta^\alpha - \frac{1}{0.01 |P_T|} \sum_{i \in P_T} \eta_i \right) \\
\text{subject to} \quad & \\
& \sum_{j \in J} d_{ij} t_j \geq L^T y_i, & i \in P_T \\
& \sum_{j \in J} d_{ij} t_j \leq U^s + M^s (1 - v_i^s), & i \in P_s, s \in S_O \\
& \sum_{i \in P_s} v_i^s \geq \tau^s |S_O|, & s \in S_O \\
& \eta_i \geq \zeta^\alpha - \sum_{j \in J} d_{ij} t_j, & i \in P_T \\
& \eta_i \geq 0, & i \in P_T \\
& y_i \in \{0, 1\}, & i \in P_T \\
& v_i^s \in \{0, 1\}, & i \in P_s, s \in S_O \\
& t_j \geq 0, & j \in J
\end{aligned} \tag{4.2}$$

Objective function parameters w_1 and w_2 are non-negative penalty parameters giving a priority between the terms V_{100}^{PTV} and $LCVaR_1^{PTV}$. The formulation (4.2) consists of constraints from the DVM presented in Section 3.6 and constraints from the mean-tail-dose model presented in Section 3.7.

Because the adverse treatment effect is seen even when the cold volume is as small as 1% of the PTV [105], the LCVaR portion is set to 1%. Regarding the weights (w_1, w_2) , the results are insensitive to the specific values. As long as both values are positive, the resulting dose plans are similar. This model, with weights $(w_1, w_2) = (1, 1)$, is denoted the dose-volume mean-tail-dose model (DV-MTDM).

We compare results from model DV-MTDM with results from the standard DVM (formulation (4.2) with weights $(w_1, w_2) = (1, 0)$). The solver Gurobi (Gurobi Optimization, Inc., Houston, USA), version 7.0.1 [41], is used to solve all MIPs, with a time limit of 2 hours for benchmarking purposes.

We find that model DV-MTDM increases the value of $LCVaR_1^{PTV}$ by on average 5% (over the ten patients) compared to model DVM, while the dose plans are comparable in other aspects. We also solve formulation (4.2) with weights $(w_1, w_2) = (0, 1)$ and are able to find a proven optimal integer solution, for each of the ten instances, which gives an upper bound on the $LCVaR_1^{PTV}$ value which is attainable. The $LCVaR_1^{PTV}$ value from model DV-MTDM is very close to this upper bound, on average within 0.2%. Therefore, to be able to increase the $LCVaR_1^{PTV}$ value significantly, it is not enough to solve the DV-MTDM to optimality, and instead it is necessary to relax the constraints of the model, allowing a higher dose to OAR.

Furthermore, for all computing times, the model DV-MTDM gives better results than model DVM. The improvement was largest for clinically relevant computing times, up to 15 minutes. We also observe that computing times for model DV-MTDM are much more stable and predictable, with near-optimal solutions found within minutes, which is important for clinical purposes. This is also the case when we vary the random seed in Gurobi. Detailed results and illustrations are found in Paper B.

4.5 A new optimization model for spatiality

The criteria that are included in the clinical treatment guidelines, such as the dosimetric indices, only consider the dose on an aggregated level. How the doses are distributed spatially is not taken into account at all. We mentioned briefly in Section 3.11 that there are not much research on optimization models which include spatial aspects. In clinical practice the dose heterogeneity is considered to be of importance but nor here have the effects been studied much.

Although not an explicit part of clinical treatment guidelines, such as [52], we have seen in clinical practice that a dose plan is manually adjusted if

dose distribution is too heterogeneous, for example if it contains hot spots, which are contiguous volumes that receives a dose that is very high. The aim with this adjustment is to make the dose distribution more homogeneous, by removing hot spots, while at the same time keep aggregate dose criteria on acceptable levels. This process is both hard and time consuming to perform manually.

Motivated by this observation, our approach in Paper C is to formulate this (manual) adjustment step as a mathematical optimization model. It takes a given dose plan as input and adjusts the plan to improve the spatial aspects, making the dose plan more homogeneous by reducing the prevalence of hot spots. Furthermore, a scenario which we consider to be important is when the placement of one or several catheters fail, either because the catheter could not be inserted in the planned location or the catheter did not end up exactly where it was planned. The effect on the dose plan can be a more heterogeneous dose distribution with large hot spots.

We have proposed an optimization model for the adjustment step, to make the dose in the PTV more homogeneous by removing hot spots, and also performed computational experiments on the dataset presented in Section 4.2. Because there are no established evaluation criteria for the spatial dose distribution we have built our model on two assumptions;

1. the number of dose points that receives a dose that is too high (or too low) should be minimised, and
2. if two dose points receives a dose that is too high (or too low), it is better the farther apart they are.

Based on these assumptions, there is a penalty for each pair of dose points if the dose is too high (or too low) in both, and this penalty is higher the smaller the distance between the two points is.

The general formulation of the optimization model is given as follows:

$$z^* = \min_{t \in \mathcal{X}} \sum_{i,j \in P_T: i \neq j} \frac{f(Dose_i(t))f(Dose_j(t))}{h(i,j)}, \quad (4.3)$$

where $Dose_i$ is the dose received at dose point i and $\mathcal{X}$ is the feasible set, consisting of constraints that take the aggregated dose into account. The objective function penalises pairs of dose points in which the doses are too high. The function f gives a penalty for high doses, and the function $h(i,j)$ is a distance measure between the dose points i and j .

To test our model we specify the model components. The feasible set $\mathcal{X}$ is based on constraints on dosimetric indices, as presented in Section 3.6, and the distance function h is the squared euclidean distance. The function f is implemented as follows, either

$$f(Dose_i) = \max(0, (Dose_i - b)^2), \quad (4.4)$$

or

$$f(Dose_i) = H(Dose_i - b), \quad (4.5)$$

where the parameter b is a dose bound, such as 200% of the prescription dose, and the function H is the Heaviside step function.

These formulations contain binary variables, both from the constraints on dosimetric indices (the set $\mathcal{X}$) and from the functions given in the equation (4.5). When trying to solve the models we found these formulations to be completely intractable and with no solution progress being made at all. Therefore, we approximate the Heaviside step functions with smooth functions,

$$H(Dose_i - b) = 0.5(1 + \tanh(\beta(Dose_i - b))), \quad (4.6)$$

where β is a parameter used to control the steepness. See Figure 3.2 for an illustration. This approximation is also used for dosimetric index constraints. The reformulation yields a non-linear model that is solved with the Matlab ((The MathWorks, Inc., Natick, Massachusetts, USA) R2017b [104]) solver `fmincon`, and we find solutions within a clinically acceptable computing time, of minutes. The approximation was also used in [44] and in [53].

Our optimization model is meant to be used for adjusting a given starting plan. The dose plans that we have used as starting plans are constructed with the LPM, including parameter tuning, with the purpose of having dose plans with acceptable dosimetric indices but also with a dose distribution that were heterogeneous. The LPM was chosen as it is the clinically most used optimization model and as it has been observed to produce heterogeneous dose plans [20] with long maximum dwell times [50]. Furthermore, it is not uncommon that LPM dose plan are adjusted manually. For parameter values used in the constraints on dosimetric indices we used values from the given starting plans.

Our approach has similarities with the spatial model [101] described in Section 3.11 as both models take a given dose plan as input and improve it. However, two of the differences are that we include the dosimetric indices as explicit constraints and that we handle the heterogeneities dynamically. In [101] there are constraints that adjusts the dose in specified dose points while we rather formulate the heterogeneity in the objective function, trying to improve it in a dynamic way, if possible, without deteriorating the aggregate criteria too much, as they are considered to be the primary goals.

To evaluate the spatial effects on the dose distribution we define subvolumes. These are small contiguous volumes of the PTV containing two adjacent dwell positions and nearby dose points. Studying the worst such subvolumes, both in terms of the portion that receives a radiation dose of at least 200% of the prescription dose and in terms of mean dose, we see improvements in the adjusted dose plan compared to the starting plan. We also show results of a decrease (improvement) in V_{200}^{PTV} and an increase in

the number of active dwell positions. These observations indicate that the proposed optimization model improves the dose distribution in terms of heterogeneity. Furthermore, with solution times of a few minutes, solutions to the optimization model can be found fast enough to be of clinical use.

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Papers

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PAPER

B. Morén, T. Larsson, and Å. Carlsson Tedgren. “Mathematical optimization of high dose-rate brachytherapy - derivation of a linear penalty model from a dose-volume model”. In: *Physics in Medicine & Biology* 63.6 (2018)

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