Treatment Planning of High Dose-Rate Brachytherapy - Mathematical Modelling and Optimization

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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 dessa. I denna avhandling studeras högdosrat brachyterapi (HDR BT), vilket är en form av strålbehandling som till exempel används vid behandling av prostatacancer och gynekologisk cancer. Vid brachyterapibehandling används ihåliga nålar eller applikatorer för att placera en millimeterstor strålkälla 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, i alla riktningar. Genom att välja lämpliga tider för dröjpositionerna kan dosfördelningen formas efter patientens anatomi. Utöver HDR BT studeras också den nya tekniken intensitetsmodulerad brachyterapi (IMBT) vilket är en variation på HDR BT där skärmning används för att minska strålningen i vissa riktningar vilket gör det möjligt att forma dosfördelningen bättre.

Planeringen av en behandling med HDR BT omfattar hur många nålar som ska användas, var de ska placeras samt hur länge strålkällan ska stanna i de olika dröjpositionerna. För HDR BT kan dessa vara flera hundra stycken medan det för IMBT snarare handlar om tusentals möjliga kombinationer av dröjpositioner och inställningar av skärmarna. Planeringen resulterar i en dosplan som beskriver 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 döda alla cancerceller, samt att undvika att bestråla riskorgan eftersom det kan ge allvarliga biverkningar. Då alla målsättningarna inte samtidigt kan uppnås fullt ut så fås optimeringsproblem där flera målsättningar behöver prioriteras mot varandra. Utöver att dosplanen uppfyller kliniska behandlingsriktlinjer så är också tidsaspekten av planeringen viktig eftersom det är vanligt att den görs medan patienten är bedövad eller sövd.

Vid utvärdering av en dosplan används dos-volymmått. För en tumör anger ett dos-volymmått hur stor andel av tumören som får en stråldos som är högre än en specificerad nivå. Dos-volymmått utgör en viktig del av målen för dosplaner som tas upp i kliniska behandlingsriktlinjer och ett exempel på ett sådant mål vid behandling av prostatacancer är att 95% av prostatans volym ska få en stråldos som är minst den föreskrivna dosen. Dos-volymmått utläses ur de kliniskt betydelsefulla dos-volym histogrammen som för varje stråldosnivå anger motsvarande volym som erhåller den dosen.

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 bättre dosplaner, till exempel genom att riskorganen nås av en lägre dos men med bibehållen dos till tumören. Vidare så finns det även fördelar med en process som inte är lika personberoende och som inte kräver erfarenhet i lika stor utsträckning som manuell dosplanering i dagsläget gör. Vid IMBT är det dessutom så många frihetsgrader att manuell planering i stort sett blir omöjligt.

I avhandlingen ligger fokus på hur dos-volymmått kan användas och modelleras explicit i optimeringsmodeller, så kallade dos-volymmodeller. Detta omfattar såväl analys av egenskaper hos befintliga modeller, utvidgningar av tidigare använda modeller samt utveckling av nya optimeringsmodeller. Eftersom dos-volymmodeller modelleras som heltalsproblem, vilka är beräkningskrävande att lösa, så är det också viktigt att utveckla algoritmer som kan lösa dem tillräckligt snabbt för klinisk användning. Ett annat mål för modellutvecklingen är att kunna ta hänsyn till fler kriterier som är kliniskt relevanta men som inte ingår

i dos-volymmodeller. En sådan kategori av mått är hur dosen är fördelad rumsligt, exempelvis 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. Vidare studeras hur små fel i inställningarna av skärmningen i IMBT påverkar dosplanens kvalitet och de olika utvärderingsmått som används kliniskt. Robust optimering har använts för att säkerställa att en dosplan tas fram som är robust sett till dessa möjliga fel i hur skärmningen är placerad.

Slutligen ges en omfattande översikt över optimeringsmodeller för dosplanering av HDR BT och speciellt hur optimeringsmodellerna hanterar de motstridiga målsättningarna.

ABSTRACT

Cancer is a widespread class of diseases that each year affects millions of people. It is mostly treated with chemotherapy, surgery, radiation therapy, or combinations thereof. High dose-rate (HDR) brachytherapy (BT) is one modality of radiation therapy, which is used to treat for example prostate cancer and gynecologic cancer. In BT, catheters (i.e., hollow needles) or applicators are used to place a single, small, but highly radioactive source of ionizing radiation close to or within a tumour, at dwell positions. An emerging technique for HDR BT treatment is intensity modulated brachytherapy (IMBT), in which static or dynamic shields are used to further shape the dose distribution, by hindering the radiation in certain directions.

The topic of this thesis is the application of mathematical optimization to model and solve the treatment planning problem. The treatment planning includes decisions on catheter placement, that is, how many catheters to use and where to place them, as well as decisions for dwell times. Our focus is on the latter decisions. The primary treatment goals are to give the tumour a sufficiently high radiation dose while limiting the dose to the surrounding healthy organs, to avoid severe side effects. Because these aims are typically in conflict, optimization models of the treatment planning problem are inherently multi-objective. Compared to manual treatment planning, there are several advantages of using mathematical optimization for treatment planning. First, the optimization of treatment plans requires less time, compared to the time-consuming manual planning. Secondly, treatment plan quality can be improved by using optimization models and algorithms. Finally, with the use of sophisticated optimization models and algorithms the requirements of experience and skill level for the planners are lower. The use of optimization for treatment planning of IMBT is especially important because the degrees of freedom are too many for manual planning.

The contributions of this thesis include the study of properties of treatment planning models, suggestions for extensions and improvements of proposed models, and the development of new optimization models that take clinically relevant, but uncustomary aspects, into account in the treatment planning. A common theme is the modelling of constraints on dosimetric indices, each of which is a restriction on the portion of a volume that receives at least a specified dose, or on the lowest dose that is received by a portion of a volume. Modelling dosimetric indices explicitly yields mixed-integer programs which are computationally demanding to solve. We have therefore investigated approximations of dosimetric indices, for example using smooth non-linear functions or convex functions. Contributions of this thesis are also a literature review of proposed treatment planning models for HDR BT, including mathematical analyses and comparisons of models, and a study of treatment planning for IMBT, which shows how robust optimization can be used to mitigate the risks from rotational errors in the shield placement.

Acknowledgments

There are many people who played important roles in this thesis and the long process leading to the completion of it.

Both my supervisors Torbjörn and Åsa CT have helped me more than what can be expected, or even hoped for. It's thanks to them that this thesis finally is finished. Looking at my PhD studies in hindsight, they seem to consist of a series of well-planned challenges for which I've needed to improve some skill to tackle. Torbjörn was my first teacher in optimization, and we have been working together ever since; through advanced optimization courses, via Schemagi to these PhD studies. Åsa has enlightened me on the field of brachytherapy and she has been a great source of creative ideas and cooperations. I have much enjoyed working in this team during these years.

Åsa H was both one of my first and last teachers during my studies at LiU, and it was her work that laid the foundation to this thesis. Mikael introduced me to research when supervising my bachelor's thesis and gave me my first insights into doctoral studies.

During the last year I've collaborating with Gabriel, Majd, Marc, and Shirin from McGill University, Montreal. I would like to thank them all for their invaluable help, but especially Shirin for welcoming me to her group.

Working with patient data has been a new challenge for me. Frida has been very helpful in explaining brachytherapy from a clinical perspective and also in helping me understand and work with patient data.

Within the world of optimization, I'm grateful to my colleagues at the department. Nisse and Elina I have enjoyed knowing for a long time by now. The group of PhD students have enriched these years, thanks to Emil, Roghayeh, William, Uledi, Biressaw, Ando, Elias, Jonas, Johan and Pontus, and the other ones, for all fun activities and discussions. I would also like to thank my colleagues at MAI, the ones I've met on SOAF activities, and other friends and acquaintances at LiU.

A summer tradition has been to struggle with the last pieces of a paper, and right after submission head out with Simon and Camilla for some adventure, typically involving mountains and running. Those adventures and times of relief have kept me going during the most intense periods. The activities and sessions with IK Akele have been an appreciated source of joy and dis-

traction. Further, I would like to thank KPS as well as Frida and Anton for sharing many fun experiences during these years.

My parents have given me great support and always encouraged me in whatever activity I've been involved in. For that I'm deeply grateful.

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Contents

Abstract	iii
Acknowledgments	viii
Contents	ix
List of Figures	xi
List of Tables	xiii
1 Introduction	1
1.1 Outline	1
1.2 Contributions	2
1.3 Presentations	4
2 Background	7
2.1 Brachytherapy	8
2.2 Clinical treatment evaluation	11
3 Dose planning	17
3.1 Multi-objectivity	18
3.2 Why use optimization?	19
4 Mathematical models for dose planning	21
4.1 Linear penalty models	21
4.2 Dose-volume models	24
4.3 Mean-tail-dose models	25
5 Contributions of our research	31
5.1 Relationships between models	32
5.2 A modelling extension using mean-tail-dose	34
5.3 A new optimization model for spatiality	36
5.4 Review and analysis of mathematical models	39
5.5 Robust optimization of intensity modulated brachytherapy . . .	40

6 Future research	43
Bibliography	45
Paper A	57
Paper B	71
Paper C	85
Paper D	107
Paper E	149

List of Figures

2.1	Ultrasound contours of structures	10
2.2	Target definitions	10
2.3	Clinical workflow	11
2.4	Differential DVH	13
2.5	Cumulative DVH	13
3.1	Example of dose planning	18
4.1	Linear penalties	24
4.2	Differential DVH	26
5.1	Heaviside approximation	38

List of Tables

4.1	Common notations	22
4.2	Notation used for the dose-volume model	25
4.3	Notation used in the mean-tail-dose model	27

Introduction

The topic of this thesis is the use of mathematical optimization for treatment planning of high dose-rate brachytherapy. Brachytherapy is a modality of radiation therapy in which the radiation source is placed within the body. The aim with the treatment is to irradiate a tumour with a dose that is high enough while keeping the dose to healthy tissue and organs (organs at risk, OARs) low enough to avoid severe complications.

For modern external beam treatment techniques, such as intensity modulated radiation therapy and volumetric modulated 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 manageable but mathematical optimization is a growing field of research and the clinical usage of treatment planning models and algorithms is increasing. Furthermore, the emerging technique of intensity modulated brachytherapy will likely be dependent on the use of mathematical optimization for treatment planning.

1.1 Outline

This thesis is divided into two parts, being a thesis summary followed by the articles included in the thesis. The thesis is organized as follows.

In the first part, Chapter 2 introduces radiation therapy, brachytherapy, and the relevant concepts for treatment planning. The presentation does not assume any background in radiation therapy. Treatment plan evaluation and measures for treatment plan quality are introduced in Chapter 2.2. The role of optimization in treatment planning, and properties of the planning problem are discussed in Chapter 3, and in Chapter 4 several models for treatment

planning are presented. Chapter 5 describes the contributions from the papers of this thesis, and topics for future research are suggested in Chapter 6. Chapters 2–6 are partly based on the material in the licentiate thesis [1]. In the second part, five papers are appended, in form of published articles A–C and manuscripts D–E.

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

Existing dose-volume models do not take the dose to the coldest volume of the tumour into account. This is a weakness of these models since research indicates that underdosage to only a small portion of the treated volume can have an adverse 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 - A mathematical optimization model for spatial adjustments of dose distributions in high dose-rate brachytherapy

Proposes a new optimization model that adjusts a tentative dose plan to also take its spatial properties into account, with the aim to reduce dose heterogeneities in the tumour. While improving spatial properties, aggregate dose-volume criteria from clinical treatment guidelines are also respected and maintained in the adjustment step.

Paper D - Optimization in treatment planning of high dose-rate brachytherapy – Review and analysis of mathematical models

This is a literature review of the broad range of mathematical models that has been proposed for treatment planning of high dose-rate brachytherapy, with emphasis on mathematical analyses and comparisons of treatment planning models.

Paper E - Mitigating the Effects from Rotational Uncertainty in Intensity Modulated Brachytherapy with Robust Optimization

We propose a robust optimization model for treatment planning of intensity modulated brachytherapy. The uncertainty considered is the rotational angle of the shields, and scenarios are generated which corresponds to systematic errors in the rotational angles.

Publication status

Paper A has been published as Morén B., Larsson T., Carlsson Tedgren Å. (2018) “Mathematical optimization of high dose-rate brachytherapy – Derivation of a linear penalty model from a dose-volume model”. *Physics in Medicine & Biology*, volume 63, number 6, 065011.

Paper B has been published as Morén B., Larsson T., Carlsson Tedgren Å. (2019) “An extended dose-volume model in high dose-rate brachytherapy – Using mean-tail-dose to reduce tumour underdosage”. *Medical Physics*, volume 46, issue 6, pages 2556–2566.

Paper C has been published as Morén B., Larsson T., Carlsson Tedgren Å. (2019) “A mathematical optimization model for spatial adjustments of dose distributions in high dose-rate brachytherapy”. *Physics in Medicine & Biology*, volume 64, number 22, 225012.

Paper D is submitted and revised (2020). It is the full paper based on an already accepted review article proposal.

Paper E is a manuscript.

Other peer-reviewed publications

Morén B., Larsson T., Carlsson Tedgren Å. (2018) “Preventing hot spots in high dose-rate brachytherapy”. In: Kliewer N., Ehmke J., Borndörfer R. (eds) *Operations Research Proceedings 2017. Operations Research Proceedings (GOR (Gesellschaft für Operations Research e.V.))*. Springer, Cham. This is the precursor to Paper C.

Contributions by co-authors

In all papers I have been responsible for implementation of the mathematical models, computational experiments, and analyses, as well as writing. The idea for Paper B is from myself, and also the preparations for Paper D, which is developed from my licentiate thesis. All papers are co-authored with my supervisors Torbjörn Larsson and Åsa Carlsson Tedgren. The focus of Torbjörn Larsson has been mathematical optimization and the focus of Åsa Carlsson Tedgren on aspects related to radiation therapy and clinical practice. Paper E

is co-authored also with Majd Antaki, Gabriel Famulari, Marc Morcos, and Shirin A. Enger, from McGill University, Montreal, Canada. In addition to planning and discussing the study, their focuses have been on intensity modulated brachytherapy and the treatment planning system used in the paper.

1.3 Presentations

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

MBM2017, 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.

ISMP2018, International Symposium on Mathematical Programming Bordeaux, France, July 2018. I presented Paper B.

ICCR2019, The International Conference on the Use of Computers in Radiation Therapy Montreal, Canada, June 2019. I presented Paper C as a poster.

SOAK2019 Nyköping, Sweden, October 2019. 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 treatment planning.

Licentiate Seminar Linköping, March 2019. I defended my Licentiate thesis.

Karolinska University Hospital, Radiotherapy Physics and Engineering, Stockholm, Sweden, December 2019. I presented paper C.

Background

Common modalities for cancer treatment are surgery, radiation therapy, and chemotherapy, and combinations thereof. Examples of radiation therapy modalities are brachytherapy (BT), which is studied in this thesis, and external beam radiation therapy (EBRT), to which intensity modulated radiotherapy (IMRT) belongs. A brief overview of BT is given in Section 2.1 with the purpose of providing enough background for the mathematical models for treatment planning discussed in Chapters 4 and 5. High dose-rate (HDR) BT is a modality which is commonly used to treat for example prostate cancer [2]. Strong arguments of why HDR BT should be used for prostate cancer is provided in [3]. Lower risk of death was seen in prostate cancer patients treated with EBRT in combination with HDR BT, as compared to only EBRT [4]. Furthermore, prostate cancer is the most studied cancer diagnose in mathematical optimization studies for treatment planning, and we apply our methods to prostate cancer in Papers B, C, and E. In this presentation, examples and illustrations are given for prostate cancer. However, from a perspective of treatment planning and mathematical modelling, there is much in common between different treatment sites. The methods developed here could, with some adaptations, be used also for, for example, gynecological, head and neck, and breast cancer.

Our research

Treatment planning in BT is the process of planning the delivery of a treatment to a specific patient, by using information about the patient's anatomy. Treatment planning consists of several steps and decisions. The following (non-exhaustive) list contains the key components in treatment planning.

- Selection of treatment modality or combinations thereof

- Selection of modality for acquiring medical images
- Choice of fractionation schedule
- Choice of treatment protocol, including for example prescription dose for the target
- Calculations of dose-rate contributions
- Catheter placement, including which applicator to use, in case of intracavitary BT treatments, and how many needles to use (if any) and where to place them
- Decisions of dwell times

While all these decisions are important for the treatment, the focus in our research is the last two, as those are the ones to which mathematical optimization primarily has been applied. In this thesis the expression “dose planning” will be used for the decisions on catheter placements and dwell times, and the expression “dose plan” refers to the result. Furthermore, “dose distribution” refers to the 3D distribution of doses.

2.1 Brachytherapy

The purpose of this section is to introduce the basic concepts of brachytherapy to readers who are not familiar with medical physics, and to explain the two previously mentioned types of decisions, catheter placement and dwell times.

Brachytherapy is a modality for internal irradiation, in contrast to EBRT which uses radiation sources outside the body to irradiate the tumour. The three types of BT are high dose-rate, low dose-rate, and pulse dose-rate, but in this thesis we only consider high dose-rate BT.

In HDR BT, a small, sealed radiation source is placed close to or within a tumour, with catheters or needles in the case of interstitial BT (e.g. prostate cancer), or with anatomy shaped applicators, possibly in combination with needles, in the case of intracavitary BT (e.g. gynecologic cancer). In this thesis, catheters, needles, and applicators are all referred to as catheters, because from the perspective of mathematical modelling, they require similar decisions.

Each catheter is discretised into a number of dwell positions. In each position the radiation source can dwell for a certain time, irradiating the surrounding tissue with a known and pre-calculated dose per second. The absorbed dose is measured in Gray (Gy). The radiation dose from each dwell position is delivered very locally, since the dose decreases fast, in the order of the squared distance from the dwell position [5].

Intensity modulated BT (IMBT) is a variant of HDR BT in which dynamic or static shields are used to further modulate the doses. The shielding material

is of a high atomic number (high-Z); the material can for example be platinum or tungsten [6]. IMBT is a delivery technique which is not yet used in clinical practice. Studies have shown that IMBT allows for a reduction, compared to conventional HDR BT, in doses to OARs while target coverage remains the same; for an example of this, see [7], in which it was shown that the dose to urethra could be reduced by 13%. The radiation source in HDR BT is most commonly of the isotope ^{192}Ir . For IMBT, the isotope ^{169}Yb is also considered, because it has lower photon energy and a less amount of shielding material is thus needed to reduce the intensity of the radiation. The latter allows the delivery of IMBT with shields inside the thin interstitial needles.

Clinical process

The treatment is planned individually with respect to the specific anatomy of each patient. A preparatory step for the dose planning is to acquire images of the tumour and nearby OARs, that is, the structures of interest. Examples of image modalities used for BT are ultrasound, computed tomography and magnetic resonance imaging; see [8] for an overview of available imaging modalities.

Figure 2.1 illustrates how a two-dimensional cross section of the structures of interest related to prostate cancer are delineated on an ultrasound image. The largest contoured volume, the green contour, is the target (the prostate, which should be irradiated, including a margin). The urethra is delineated with a red contour within the prostate. Further, the rectum is the brown contour 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. Dwell positions can be seen as small yellow squares. The prescription dose is 10 Gy and regions with high doses can be seen surrounding dwell positions.

The medical images are used to manually contour and define the structures of interest, which include both the target (tumour, tumours, or other regions of interest, such as a cavity after surgery which is treated adjuvantly due to suspected microscopic spread) and OARs in the proximity. There are several interrelated volume definitions regarding the tumour [9]. First, the gross tumour volume (GTV) contains the region where the tumour has been identified. Secondly, the clinical target volume (CTV) contains the GTV as well as an extra margin based on clinical experience and suspected microscopic spread. Thirdly, the planning target volume (PTV) contains the CTV and possibly 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 our presentation, PTV will generally be used to denote the target. Smaller CTV margins are in general needed in BT (and hence smaller PTVs), as compared to EBRT, because the organ motion is less problematic as the radiation sources move together with the irradiated target.

2. BACKGROUND

Figure 2.1: A 2D section through a 3D dose distribution for prostate cancer on an ultrasound image. The structures of interest are delineated: the prostate (large red contour, green contour adds a margin), the urethra (red contour, in the middle of the prostate) and the rectum (brown contour, below the prostate). The radiation doses are shown in colours, where red indicates a high dose while blue indicates a lower dose, as shown on the scale in the top left corner.

Figure 2.2: The relations between the various volume definitions for the target.

Dose planning

The clinical process around the dose planning is rigorous [10]. First, the dose plan is prepared by a dosimetrist or a physicist. Secondly, the dose plan is reviewed and approved by the treating oncologist. Finally, a second physicist conducts an independent review and quality control.

For prostate cancer treatment, the catheters are inserted invasively, which requires the patient to be anaesthetised (spinal or general). As the dose planning commonly is carried out during the treatment, when the patient is anaesthetised, the time needed for planning is of importance, and should be kept short. An illustration of the clinical process for HDR BT for prostate cancer is shown in Figure 2.3.

Figure 2.3: Illustration of the clinical workflow for prostate cancer. 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.

The dose planning has traditionally been conducted with forward planning, which is a manual iterative process where the dwell times are adjusted until the treatment goals are achieved, and the planner is satisfied. This can be time-consuming, with observed planning times of more than 30 minutes [11], or in the range 20–35 minutes [12]. Forward planning is generally performed in a treatment planning system (TPS), with graphical support and other tools available.

The alternative method for dose planning is inverse planning. Here, the starting point is instead the goals of the treatment and a dose plan that achieves these goals (at least approximately) is generated. Because of the computational complexity, the use of optimization models and algorithms are fundamental for obtaining dose plans by inverse planning.

2.2 Clinical treatment evaluation

We have discussed the decisions of the dose planning problem, which are the catheter placement, how many catheters to use and where to place them, and the dwell times. When these decisions have been made, the resulting dose distribution can be calculated. Two relevant questions are now (i) how to evaluate the result, and (ii) which properties of a dose distribution are supported in the clinical treatment guidelines? In a mathematical optimization

context these questions correspond to how to formulate the objective function (or functions) and constraints in a dose planning model?

This section is organised as follows. First, the concept of dose points is introduced, and then we present and discuss several concepts that are used to evaluate dose plans. This section is based on the presentations in the licentiate thesis [1] and Paper D.

Dose points and dose calculation

The structures of interest are discretised into dose points, with each dose point corresponding to a small volume, such as a cube with sides of 1–3 mm. Clinical treatment guidelines of HDR BT for prostate cancer [10] suggests that the number of dose points should be at least 5 000 for each structure. The correlation between the number of dose points and the uncertainty in evaluation criteria is studied in [13]. For each target and OAR they suggest 32 000 and 256 000 dose points, respectively.

To calculate the dose at any dose point in the patient anatomy, the dose-rate contribution per second from each dwell position is needed. The calculations of the dose-rate contributions are today generally based on the AAPM TG43 formalism [5, 14, 15], by which the composition of the patient is approximated by water. This approximation is considered good enough for most applications using the common HDR BT isotope ^{192}Ir . The water approximation is less accurate for the isotope ^{169}Yb , since it has a lower photon energy. For IMBT applications, where high-Z shields are present within the applicators, model-based dose calculations [16] are used, taking the source model, the patient geometry and the shields into account [6].

The dose at any dose point can be calculated by summing the dose contributions from all dwell positions, which is the dwell time in seconds multiplied by the dose-rate contribution. Finally, the dose is scaled with respect to the strength of the radiation source, which depends on its daily air kerma strength [14], which decays according to the half-life of the isotope.

Dose-volume histogram

In a dose-volume histogram (DVH), portions of a structure are plotted against dose levels. The DVH is a convenient way to visualise the dose distribution, and it is routinely used in clinical dose planning. DVHs can be presented in a differential or cumulative version. The differential shows, for each dose level, the portion that receives (within an interval) that dose (in Gy), while the cumulative shows, for each dose level, the portion that receives at least that dose; see Figures 2.4 and 2.5 for examples of differential and cumulative DVHs, respectively. In this presentation, the term DVH refers to the more commonly used cumulative DVH (unless otherwise specified).

To compare different DVHs, values at specific points on the curves are of interest; such values are referred to as dosimetric indices (DIs), for which there are two formulations. These are referred to as volume-at-dose, denoted V_x^s , or dose-at-volume, denoted D_y^s , respectively. The same notation as in Paper D is used here, where x is a dose level, s is a structure, either PTV or part of the PTV, or an OAR, and y is a portion or a volume (commonly in cubic centimetres, cc) of structure s . The DI V_x^s is the portion of the structure that receives at least the specified dose level x , while the DI D_y^s is the lowest dose in either the portion or the volume, of size y , that receives the highest dose. If no structure is specified for a DI, it refers the PTV. For comparison of DIs which are calculated on different systems, it is important to be aware of that actual values depend on factors such as image slice thickness and the TPS implementation of volume interpolation, see [17].

Figure 2.4: Example of a differential DVH.

Figure 2.5: Example of a cumulative DVH.

Dose homogeneity and conformity

Conformity measures are used to quantify how well the prescription dose conforms to the target. Homogeneity measures instead quantify how homogeneous the dose is within the target. The notation here is the same as in Paper D.

A homogeneity measure that uses two specified points on the DVH is the dose homogeneity index (DHI) [18], which is defined as

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

where 100 and 150 are percentages of the prescription dose. The DHI takes a value in the range zero to one; the value one is considered ideal, and corresponds to all dose points receiving a dose between the prescription dose and 150% of the prescription dose.

A proposed conformity measure is the conformation number (CN) [19]. In addition to the dose to the PTV, the portions of the OARs that receive doses above the prescription dose are also considered. This measure is defined as

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

where PTV_{ref} corresponds to V_{100}^{PTV} but is expressed as a volume instead of as a portion, and Tot_{ref} is the total volume of the structures of interest (with both PTV and OAR included) which receives at least the prescription dose.

An extension of the CN is the conformal index (COIN) [20], which has an extra OAR-specific component. The conformal index is calculated as

$$COIN = V_{100}^{PTV} \cdot \frac{PTV_{ref}}{Tot_{ref}} \cdot \prod_{s \in S_O} (1 - V_{100}^s), \quad (2.3)$$

where S_O is the set of OARs. Both CN and COIN take a value between zero and one, with one being the best possible value in both measures; for both measures, this corresponds to the whole PTV receiving the prescription dose and no portion of any OAR receiving a higher dose than the prescription dose.

Reviews of conformity and homogeneity measures can be found in [21] and [22].

Radiobiological concepts

The previously introduced evaluation criteria, DIs and homogeneity and conformity measures, are based solely on the physical doses. Another principle for dose plan evaluation is based on radiobiological models, giving criteria meant to explicitly quantify the radiobiological treatment effect of a dose distribution. The tumour control probability (TCP) is formulated to be an estimate

of the probability of local tumour control, that is, that there are no surviving cancer cells in the tumour.

The following is an example of the calculation of a TCP, as given in [23],

$$TCP(t) = \left[1 - \frac{(S(t)e^{(b-d)t})}{\left(1 + bS(t)e^{(b-d)t} \int_0^t \frac{dt'}{S(t')e^{(b-d)t'}}\right)} \right]^n, \quad (2.4)$$

where t is a time, T is the duration of the treatment, $S(t)$ is the probability for a cell surviving until time t , n is the initial number of tumour cells, while b and d are birth and death rates for cells, respectively. As can be seen in equation (2.4) there are several parameters that must be estimated. The use of TCP and radiobiological models is discussed in [24].

For an OAR the corresponding radiobiological index is the normal tissue complication probability (NTCP), which estimates the risk for complications; see [25] for a summary of how NTCP is modelled and used. The measure p^+ [26] can be seen as a combination of TCP and NTCP, and it estimates the probability of tumour control without any severe OAR complications.

Another proposed radiobiological measure is the equivalent uniform dose (EUD) [27]. The single EUD value is the homogeneous dose which would give the same treatment effects on a tumour as the evaluated inhomogeneous dose distribution. Hence, it can be used to compare the radiobiological treatment effect from different dose distributions. The EUD has been extended to the generalized EUD (gEUD) [28], which can be used also for OARs. One way to define the gEUD is given in [29] as

$$gEUD = \left(\frac{1}{n} \sum_{i=1}^n Dose_i^a \right)^{1/a}, \quad (2.5)$$

where n is the number of dose points in the structure considered, $Dose_i$ is the dose at dose point i , and a is a parameter for radiosensitivity, which depends on the considered structure. The gEUD is easier to calculate than TCP and NTCP, and has fewer parameters, in equation (2.5) only one, but it is supposed to capture all structure specific characteristics.

Clinical treatment guidelines

There are established guidelines which are specific for different treatment sites. Guidelines for HDR BT prostate cancer treatment [10, 30, 31] include planning aims for the PTV and OARs, expressed in terms of DIs. For example, the DI V_{100} should be at least 90% with the additional recommendation to aim for 95% [10]. The guidelines [31] also recommend reporting a homogeneity measure which is equivalent to the DHI, see equation (2.1).

There are established clinical BT treatment guidelines also for other treatment sites and cancer diagnoses; see for example the guidelines for vaginal

2. BACKGROUND

cancer [32], cervical cancer [33], head and neck cancer [34], and breast cancer [35].

Dose planning

In this chapter we discuss dose planning from the point of view of mathematical optimization. The dose planning problem is here defined as either the decisions of both catheter placement and dwell times, or only the decisions on dwell times. The catheter placement problem includes how many catheters to use and where to place them. In dose planning models, the decisions on where to place the catheters are typically modelled with binary variables for the available positions, while the dwell times are modelled as continuous non-negative variables.

A general multi-objective problem formulation for the full dose planning problem, including both catheter placement and dwell times, is as follows

$$\min f_p(D), \quad \forall p, \quad (3.1)$$

$$g_r(D) \leq 0, \quad \forall r, \quad (3.2)$$

$$t_j \leq M z_k, \quad j \in C^k, \forall k, \quad (3.3)$$

$$\sum_k z_k \leq N, \quad (3.4)$$

$$D_i = \sum_j d_{ij} t_j, \quad \forall i, \quad (3.5)$$

$$z_k \in \{0, 1\}, \quad \forall k, \quad (3.6)$$

$$t_j \geq 0, \quad \forall j, \quad (3.7)$$

where $f_p(D)$ denotes an objective function p , D is the vector of doses D_i , each of which is the dose at dose point i , and functions g_r denote constraints, one for each r , in which the doses D are evaluated. Further, the variable t_j is the dwell time at position j , d_{ij} is the dose-rate contribution from a dwell position j to a dose point i , C^k is all dwell positions in catheter k , N is the maximal

number of catheters allowed, and the binary variable z_k is one if catheter k is inserted, and zero otherwise.

Constraints (3.3) ensure that only dwell positions in inserted catheters are active (non-zero), and the constraint (3.4) ensures that the number of catheters does not exceed the maximal possible number. For the dose planning models proposed in the literature it is common that the catheter placement is not considered, that is, the catheter variables z_k are fixed a priori to either zero or one. This is the case for all models introduced in Chapters 4 and 5.

To explain the construction of the dose planning model we use a simplified example in Figure 3.1. It represents a case of prostate cancer, but only in two dimensions. There is one binary variable for each catheter, and it is linked to the dwell time variables; the dwell times in a catheter can be non-zero only if the binary catheter variable is equal to one. Generally, both the objectives (3.1) and constraints (3.2) are based on an evaluation of the doses at the defined dose points in a structure. The objective functions and constraints can be based on criteria from the clinical treatment guidelines, approximations thereof, or other properties which are considered beneficial; such examples are given in Section 2.2.

Figure 3.1: A simplified example of a 2D slice and the relevant concepts for dose planning. The large ellipse depicts the tumour and the smaller grey circle in the middle depict an OAR. The two pairs of vertical lines are the two possible catheters, and the grey dots are the possible dwell positions with dwell time variables. The small dots are the dose points, at which the doses are calculated and evaluated.

3.1 Multi-objectivity

Equations (3.1)–(3.7) state a generic problem formulation, with variables for which catheters to use and for the dwell times. When the catheter variables are fixed, it is still a multi-objective formulation because there are multiple aims for the target (or targets) to which we want to give a radiation dose that

is high enough, and for the OARs to which we want to avoid or limit the dose. Furthermore, some of these aims are typically in conflict.

In practice, the multi-objective aspect of the dose planning problem is commonly handled either by considering a weighted sum of the objective functions or by considering all but one of the objectives as constraints, keeping only a single objective in the objective function. All the models presented in Chapter 4, and in Papers A, B, C, and E are single-objective models. There are several truly multi-objective approaches in the literature, see Paper D for an overview of such.

In single-objective models the dose planning results in a single dose plan and, hence if the planner is not satisfied, trade-offs and priorities are handled by changing weights for the objectives or parameters in the objectives or constraints. True multi-objective approaches however result in a number of solutions which the planner can choose from. The necessary trade-offs between conflicting aims can thus be made clear. Both the tasks of solving single-objective models repeatedly (if necessary) and navigating a number of solutions from a multi-objective approach can be time consuming.

The dose planning problem is approached quite differently in the proposed models in the literature, with different types of criteria included and different types of models. Nevertheless, dose plans which are clinically acceptable can be obtained from various approaches, possibly including parameter tuning.

3.2 Why use optimization?

There are important advantages with the use of mathematical optimization for dose planning. First, it is possible to save time in the treatment planning process. This is especially important when the patient is under some form of anaesthesia during the dose planning. Optimization methods for dose planning have been reported to only take a few seconds, see for example [11, 36], and most approaches do not require more than a few minutes to find acceptable dose plans. Secondly, several studies have shown improvements in dose plan quality compared to manual planning; see [11, 36, 37, 38, 39, 40] for prostate cancer examples. Furthermore, the use of mathematical optimization also reduces the dependence of personnel skills and experience on treatment outcome.

The emerging treatment modality IMBT puts additional demands on mathematical optimization approaches because of the additional degrees of freedom introduced by the shields. These additional degrees of freedom clearly also make manual planning of IMBT much harder than of conventional HDR BT.

Mathematical models for dose planning

In this chapter we introduce three well-studied models for dose planning. These are used or further studied in Papers A, B, C, and E. The model formulations and illustrations are based on the licentiate thesis [1] and the literature review Paper D, which is further discussed in Chapter 5.

Table 4.1 introduces the notations in common for the models. A subscript or superscript O refer to an OAR, and T refers to the PTV, which here is a single volume as is typically the case for prostate cancer. (The presented optimization models can easily be generalised to the case with several PTVs.) The set S contains all structures of interest, including both the PTV and OARs. The mathematical models use pre-calculated dose-rate contributions, denoted d_{ij} , where i is a dose point and j is a dwell position.

4.1 Linear penalty models

An optimization model for dose planning which is commonly used in clinical practice is simply based on penalties to the dose points whose doses are outside specified intervals. There is no penalty when the dose is within the specified interval, and outside this interval the penalty increases linearly. The objective function is to minimise the total sum of penalties. Such a model is referred to as the linear penalty model (LPM). A tailored meta-heuristic method for solving the LPM, for HDR BT, called inverse planning simulated annealing (IPSA), was proposed in [41]. (See e.g. [42] for a description of simulated annealing.) The LPM was in [43] formulated and solved as a linear program (LP), which made it possible to find and prove a globally optimal solution.

Table 4.1: Indices, sets, parameters and variables in common for the optimization models; the notations are taken from [1].

Indices	
i	Index for a dose point
j	Index for a dwell position
s	Index for a structure
Sets	
S	Set of structures, including PTV and OARs
S_O	Set of OARs, including an artificial structure of healthy tissue, $S_O \subset S$
P_s	Set of dose points in structure $s \in S$
P	Set of all dose points, $P = \cup_{s \in S} P_s$
P_T	Set of dose points in the PTV
J	Set of dwell positions
Parameters	
d_{ij}	Dose-rate contribution from dwell position $j \in J$ to dose point $i \in P$
L^s	Prescription dose or a lower dose bound for structure $s \in S$
U^s	Upper dose bound for structure $s \in S$
M^s	Maximum allowed dose for structure $s \in S$
w_s^l	Non-negative penalty for dose being too low in structure $s \in S$
w_s^u	Non-negative penalty for dose being too high in structure $s \in S$
Variables	
$Dose_i$	Dose at dose point $i \in P$
t_j	Dwell time for dwell position $j \in J$
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 $i \in P_s$, $s \in S$

Another linear penalty model has been proposed [44], in which the maximum deviation from the specified dose intervals is minimised.

Table 4.1 introduces the notation used for the LPM.

By definition, $x_i^l = \max\{L^s - \sum_{j \in J} d_{ij} t_j, 0\}$ and $x_i^u = \max\{\sum_{j \in J} d_{ij} t_j - U^s, 0\}$ shall hold. In the LPM, these relations are modelled with linear constraints. The LPM is mathematically formulated as follows.

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

subject to

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

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

$$x_i^l \geq 0 \quad i \in P_s, s \in S \quad (4.1d)$$

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

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

Constraints (4.1b) and (4.1d), together with the minimisation in the objective function ensure that $x_i^l = \max\{L^s - \sum_{j \in J} d_{ij} t_j, 0\}$ holds in an optimal solution. Constraints (4.1c) and (4.1e) works similarly, but for the upper dose bound penalty variable.

In the LPM there are no constraints that define feasibility from a clinical point of view. Hence, each choice of non-negative dwell times, t_j , $j \in J$, corresponds to a feasible solution in the model. Because the penalty parameters have no direct clinical interpretation and the clinical evaluation criteria are not included explicitly in the model, tuning of the penalty parameters is generally needed to obtain clinically acceptable dose plans. Thus, although computing times for solving the model are short, the overall process of dose planning can be time consuming.

The objective function value of the LPM has no clinical meaning in itself, and to evaluate solutions, criteria from the clinical treatment guidelines, such as the dosimetric indices, are used. Furthermore, it has been observed that dose plans can have equal LPM objective function values but differ in DIs, or vice versa. Such an example can be found in [45], in which two similar plans differed with a factor of 12 in terms of LPM objective value. This was also observed in [43] where solutions obtained with IPSA were compared with solutions obtained from the LPM. Although the LPM objective function value was improved significantly, this was not reflected by the DIs.

Dose plans obtained from the LPM have also been analysed with respect to other properties. Dwell times obtained from the LPM were in [46] compared to dwell times from manual dose plans and found to be less homogeneous. The inhomogeneous dwell times were further studied in [47], and shown to be an inherent property of the model.

A convex piecewise linear penalty model was proposed in [47], to obtain dose plans with more homogeneous dwell times. The piecewise linear penalty

model was shown to produce dose plans with more homogeneous dwell times, compared to the LPM [47].

The LPM can also be extended with quadratic penalty terms. Quadratic penalty models are common in conventional HDR BT studies [48, 49] as well as in IMBT studies [50, 51]. Examples of a linear penalty function, a convex piecewise linear penalty function, and a piecewise quadratic penalty function can be seen in Figure 4.1.

Figure 4.1: The solid line is a linear penalty function for one dose point. The dotted line is a piecewise linear penalty function, here with six segments (including the horizontal segment). The dashed function is a piecewise quadratic penalty function.

4.2 Dose-volume models

In dose planning with the LPM, dosimetric indices are only considered afterwards, as they are used to decide whether a dose plan is good enough or not. A more direct approach is to explicitly model DIs in the optimization model; we refer to this approach as a dose-volume model (DVM). The first optimization model for HDR BT which included an explicit DI constraint was proposed and studied in [52]. This model extended an LPM with one DI constraint, for an OAR. See [45, 53, 54], and Paper B for more examples of proposed DVMs.

The concept of DIs can be found in other fields of research. In finance the counterpart is called value-at-risk (VaR) [55], and a similar construction is also used in the field of chance constraints [56].

Tables 4.1 and 4.2 introduce the notation used for the DVM. The following mixed-integer programming (MIP) DVM model is adapted from [53] and [54], and uses the same notation as in [1] and Paper D.

Table 4.2: Notation used for the dose-volume model.

Parameters	
τ^s	Portion of a structure, here used for OAR $s \in S_O$
Variables	
y_i	Binary indicator variable for PTV dose points, $i \in P_T$, that takes the value one if the dose is at least L^T , and zero otherwise
v_i^s	Binary indicator variable for OAR dose points, $i \in P_s$, $s \in S_O$, that takes the value one if the dose is at most U^s , and zero otherwise

$$\max \frac{1}{|P_T|} \sum_{i \in P_T} y_i \quad (4.2a)$$

subject to

$$\sum_{j \in J} d_{ij} t_j \geq L^T y_i \quad i \in P_T \quad (4.2b)$$

$$\sum_{j \in J} d_{ij} t_j \leq M^s - (M^s - U^s) v_i^s \quad i \in P_s, s \in S_O \quad (4.2c)$$

$$\sum_{i \in P_s} v_i^s \geq \tau^s |P_s| \quad s \in S_O \quad (4.2d)$$

$$y_i \in \{0, 1\} \quad i \in P_T \quad (4.2e)$$

$$v_i^s \in \{0, 1\} \quad i \in P_s, s \in S_O \quad (4.2f)$$

$$t_j \geq 0 \quad j \in J \quad (4.2g)$$

The notation $|P_s|$ is used for the number of dose points in structure s . The objective is to maximise V_{100} , which corresponds to maximising the number of PTV dose points at which the dose is high enough, expressed via the binary indicator variable y_i . Constraints (4.2b) ensure that each y_i takes the correct value, that is, one if the dose is not below the prescription dose L^T and zero otherwise. The combination of constraints (4.2d) and (4.2c) ensures that the constraints on DIs for OARs are satisfied. Constraints (4.2c), belong to a type of constraints which are commonly referred to as “Big-M” constraints. These constraints impose a strict upper bound, M^s , on the dose at each dose point. The value of M^s can be set to a clinically relevant value, if available, or otherwise to a value which is large enough to not cut away any feasible solution.

4.3 Mean-tail-dose models

The conditional value-at-risk (CVaR) is a financial risk measure which has been used also in radiation therapy. In finance, CVaR is the mean value of

a set of worst outcomes; an example of its use is to limit the mean outcome of the worst 5% of the outcomes. The concept of CVaR has gained much attention since Rockafellar and Uryasev [57] showed that it can be formulated using a linear model. Apart from in radiation therapy, CVaR has been used in a wide range of applications, see [58] for a review. To focus on its use in radiation therapy, we refer to it as mean-tail-dose (MTD). This measure can be used for the mean dose to a portion of a structure of either the lowest or the highest doses. The former is referred to as $LCVaR_\alpha^s$, and the latter is referred to as $UCVaR_\beta^s$, where s is a structure, and α and β are portions of the structure.

Figure 4.2 shows the differential DVH and how it is related to the $LCVaR_\alpha^s$ and $UCVaR_\beta^s$ measures. The value of $LCVaR_\alpha^s$ corresponds to the grey area. It is calculated as

$$LCVaR_\alpha^s = \frac{1}{\alpha|P_s|} \sum_{i \in P_s: Dose_i \leq D_{1-\alpha}^s} Dose_i. \quad (4.3)$$

The value of $UCVaR_\beta^s$ corresponds to the black area. It is calculated as

$$UCVaR_\beta^s = \frac{1}{\beta|P_s|} \sum_{i \in P_s: Dose_i \geq D_\beta^s} Dose_i. \quad (4.4)$$

In a linear programming form $LCVaR_\alpha^s$ can be maximised or lower bounded, and $UCVaR_\beta^s$ can be minimised or upper bounded.

Figure 4.2: Example of a differential DVH. The mean dose in the grey area is the $LCVaR_\alpha^s$ value and the mean dose in the black area is the $UCVaR_\beta^s$ value.

Romeijn *et al.* [59] were the first to propose a dose planning model with MTD constraints for IMRT. An optimization model for HDR BT with MTD constraints was proposed in [60], but has later also been included in optimization models in Paper B and [61]. The following model with MTD constraints is adapted from [60]. The objective is to minimise an approximation of DHI, see equation (2.1). The notation is given in Tables 4.1 and 4.3.

Table 4.3: Notation used in the mean-tail-dose model.

Parameters	
α^s	A portion of structure $s \in S$
β^s	A portion of 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 $UCVaR_{\beta^s}^s$, $s \in S$
γ	Parameter to ensure the denominator is positive
Variables	
$\bar{\zeta}^s$	Auxiliary variable
$\underline{\zeta}^s$	Auxiliary variable
$\bar{\xi}_i^s$	Auxiliary variable which is used to capture the maximum of two expressions
$\underline{\xi}_i^s$	Auxiliary variable which is used to capture the maximum of two expressions
x_i^u	Auxiliary variable which is used to capture the dose above 150% of the prescription dose, at dose point $i \in P_T$.
x_i^l	Auxiliary variable which is used to capture the dose below the prescription dose, at dose point $i \in P_T$.

$$\min \frac{\sum_{i \in P_T} x_i^u}{|P_T| \gamma - \sum_{i \in P_T} x_i^l} \quad (4.5a)$$

subject to

$$\bar{\zeta}^s + \frac{1}{\beta^s |P_T|} \sum_{i \in P_T} \bar{\xi}_i^s \leq U_{\beta^s}^s \quad s \in S \quad (4.5b)$$

$$\zeta^s - \frac{1}{\alpha^s |P_T|} \sum_{i \in P_T} \xi_i^s \geq L_{\alpha^s}^s \quad s \in S \quad (4.5c)$$

$$\bar{\xi}_i^s \geq \sum_{j \in J} d_{ij} t_j - \bar{\zeta}^s \quad i \in P_s, s \in S \quad (4.5d)$$

$$\xi_i^s \geq \zeta^s - \sum_{j \in J} d_{ij} t_j \quad i \in P_s, s \in S \quad (4.5e)$$

$$x_i^u \geq \sum_{j \in J} d_{ij} t_j - 1.5 L^T \quad i \in P_T \quad (4.5f)$$

$$x_i^l \geq L^T - \sum_{j \in J} d_{ij} t_j \quad i \in P_T \quad (4.5g)$$

$$\bar{\xi}_i^s \geq 0 \quad i \in P_s, s \in S \quad (4.5h)$$

$$\xi_i^s \geq 0 \quad i \in P_s, s \in S \quad (4.5i)$$

$$x_i^u \geq 0 \quad i \in P_T \quad (4.5j)$$

$$x_i^l \geq 0 \quad i \in P_T \quad (4.5k)$$

$$t_j \geq 0 \quad j \in J \quad (4.5l)$$

This formulation is a fractional linear program, which can be reformulated and solved as a linear program; the details of this reformulation can be found in [60]. The variables x_i^u and x_i^l , for a dose point, correspond to the dose above 150% of the prescription dose, and the dose below the prescription dose, respectively. Both of these are zero if the dose is between the prescription dose and 150% of the prescription dose. The parameter γ is used to ensure that the denominator is positive. Constraints (4.5f) and (4.5j) are used to linearise $x_i^u = \max\{\sum_{j \in J} d_{ij} t_j - 1.5 L^T, 0\}$, while (4.5g) and (4.5k) are used to linearise $x_i^l = \max\{L^T - \sum_{j \in J} d_{ij} t_j, 0\}$.

Constraints (4.5b), (4.5d) and (4.5h) are used to express the $UCVaR_{\beta^s}^s$ with linear expressions; the derivation is presented by Rockafellar and Uryasev [62]. The auxiliary variable $\bar{\zeta}^s$ corresponds to $D_{\beta^s}^s$ in equation (4.4). Constraints (4.5d) and (4.5h), and auxiliary variable $\bar{\zeta}^s$, are used for the expression $\bar{\xi}^s = \max\{\sum_{j \in J} d_{ij} t_j - \bar{\zeta}^s, 0\}$. The formulation of $LCVaR_{\alpha^s}^s$ with constraints (4.5c), (4.5e) and (4.5i) is similar to the formulation of $UCVaR_{\beta^s}^s$.

A goal with the use of MTD measures is to achieve better approximations of the DIs than what is obtained from the LPM, while still using a linear model, contrary to the DVM formulation. However, although the MTD is related to the clinically used concept of DIs, it only approximates the criteria

included in the clinical treatment guidelines. Therefore, parameter tuning might be necessary to obtain clinically acceptable dose plans.

Contributions of our research

The common theme of the contributions from our research is the analyses and development of mathematical optimization models for dose planning; the sections are summarised in the following list.

- Section 5.1 describes a study on mathematical relationships between two commonly studied models, the LPM and the DVM.
- Section 5.2 describes an extension of the well-studied dose-volume model, with the purpose of providing a remedy to the inherent weakness that it does not consider cold volumes in the PTV.
- Section 5.3 describes a proposed optimization model that improves the spatial properties of dose distributions. Its purpose is to adjust a tentative dose plan to make it more spatially homogeneous, in order to reduce the prevalence of hot spots and cold spots.
- Section 5.4 describes a literature review of mathematical models for dose planning. In addition to introducing the wide range of proposed optimization models, properties of and relationships between these models are discussed and analysed.
- Section 5.5 describes a robust optimization model for IMBT dose planning. Rotational uncertainty of the shields is considered and the aim is to ensure a high dose plan quality for plausible scenarios.

One starting point in this research is to study the use of dosimetric indices in the modelling of the dose planning problem. The main motive for this is

their importance in the clinical treatment guidelines and the fact that dose plan evaluation is largely based on the DVH and the DIs. It is therefore natural to include DIs in the modelling explicitly instead of the ad hoc criteria widely used in clinically used optimization models. Models including DI constraints in different ways are presented in Papers A, B, and C. In Paper A the LP-relaxation is considered, in Paper B we study both the full MIP version and the convex approximation mean-tail-dose, and in Paper C we use a sigmoid approximation.

In Papers B and C we use data for ten patients that have been treated for prostate cancer. The imaging modality for these patients is ultrasound, and we use information about their anatomical structures, with the PTV, the CTV, 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. Dose points are distributed separately for the optimization models and for the evaluation of the dose plans. The number of dose points for optimization is in the range 4369–7939 and distributed according to [63], while the number of dose points for evaluation is in the range 51974–134509 and distributed uniformly with a volume of 1 mm^3 per dose point. The number of catheters varies between 14 and 20, and the number of dwell positions between 190 and 352.

In Paper E we use patient data for six patients, previously treated for prostate cancer, three patients from each of two clinics. Ultrasound was used for the imaging and we used the same information as described above.

5.1 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 are seemingly very different, we reveal and formulate precise mathematical relationships between the two models. Properties of the LPM have been studied by analysing solutions [46, 64] and by deriving the maximal possible number of active dwell positions [47]. The correlation between objective values in the LPM and DI values has been studied empirically in [45] and [64] and found to be weak. This observation is one motive to study mathematical relationships between the LPM and the DVM, thus complementing the earlier empirical studies with mathematical relationships.

The notation DVM^{LP} is used for the LP relaxation of the DVM presented in Section 4.2 and the linear penalty model is a special case of the formulation in Section 4.1, here given by expressions (5.1a)–(5.1g).

$$\min w_T^l \sum_{i \in P_T} x_i^l + \sum_{s \in S_O} w_s^u \sum_{i \in P_s} x_i^u \quad (5.1a)$$

subject to

$$\sum_{j \in J} d_{ij} t_j \geq L^T - x_i^l, \quad i \in P_T \quad (5.1b)$$

$$\sum_{j \in J} d_{ij} t_j \leq U^s + x_i^u, \quad i \in P_s, s \in S_O \quad (5.1c)$$

$$x_i^u \leq M^s, \quad i \in P_s, s \in S_O \quad (5.1d)$$

$$x_i^l \geq 0, \quad i \in P_T \quad (5.1e)$$

$$x_i^u \geq 0, \quad i \in P_s, s \in S_O \quad (5.1f)$$

$$t_j \geq 0, \quad j \in J \quad (5.1g)$$

The differences to the formulation in Section 4.1 are that the penalty functions are here only one-sided, that is, for each PTV dose point there is a penalty if the dose is too low and for each dose point in the OARs there is a penalty if the dose is too high, and there is an upper bound for the dose at dose points in OARs. The presented results can however easily be extended to the case with two-sided penalty functions. In this section LPM refers to the model given by expressions (5.1a)–(5.1g).

The main results of Paper A are Theorems 1 and 2. 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 optimal also in the LPM. The second theorem instead considers an instance of the LPM and an instance of the DVM^{LP} , with specified parameter values. Similar conclusions can be drawn for these models, that is, that the two instances have the same objective value and any optimal solution to the DVM^{LP} is optimal also in the LPM.

Theorem 1 *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 (4.2d). 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 optimal also in LPM, and*
2. *the optimal objective value in LPM equals that of DVM^{LP} .*

Theorem 2 *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 optimal also 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 of these theorems is that the LPM is in a certain 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. [65]) this result indicates 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 objective values with DIs from [45] and [64].

Furthermore, we also present precise mathematical relationships between a piecewise linear penalty model and a dose-volume model with several targets on DIs for each structure. These mathematical relationships have the same form as Theorems 1 and 2.

5.2 A modelling extension using mean-tail-dose

The dose-volume models in the literature include dosimetric index V_{100} (see the model in Section 4.2), but no consideration is given to the coldest portion of the PTV, that is, the volume which receives a dose that is lower than the prescription dose. There are therefore no incentives in the optimization model to increase the dose at an underdosed PTV dose point unless the dose reaches the prescription dose. In other words, two dose plans can have the same objective function value, that is, the same value of V_{100} , while still differing much 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. The impact from such cold volumes on the treatment effect, in terms of TCP, is analysed in [66]. The 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. 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 aims for V_{100} 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. In order to improve the DVM 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, that is, $LCVaR_1^{PTV}$. The complete model is given by formulation (5.2), and consists of constraints from the DVM presented in Section 4.2 and constraints from the mean-tail-dose model presented in Section 4.3.

$$\begin{aligned}
 & \max \quad w_1 \left(\frac{1}{|P_T|} \sum_{i \in P_T} y_i \right) + w_2 \left(\zeta^T - \frac{1}{0.01|P_T|} \sum_{i \in P_T} \xi_i^T \right) \\
 & \text{subject to} \\
 & \sum_{j \in J} d_{ij} t_j \geq L^T y_i, \quad i \in P_T \\
 & \sum_{j \in J} d_{ij} t_j \leq M^s - (M^s - U^s) v_i^s, \quad i \in P_s, s \in S_O \\
 & \sum_{i \in P_s} v_i^s \geq \tau^s |P_s|, \quad s \in S_O \\
 & \xi_i^T \geq \zeta^T - \sum_{j \in J} d_{ij} t_j, \quad i \in P_T \\
 & \xi_i^T \geq 0, \quad i \in P_T \\
 & y_i \in \{0, 1\}, \quad i \in P_T \\
 & v_i^s \in \{0, 1\}, \quad i \in P_s, s \in S_O \\
 & t_j \geq 0, \quad j \in J
 \end{aligned} \tag{5.2}$$

Objective function coefficients w_1 and w_2 are non-negative penalty parameters giving a priority between the terms V_{100} and $LCVaR_1^{PTV}$.

Because the adverse treatment effect from small cold volumes of the PTV [66], 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. With weights $(w_1, w_2) = (1, 1)$, the model is denoted the dose-volume mean-tail-dose model (DV-MTDM), and with weights $(w_1, w_2) = (0, 1)$ it is denoted the mean-tail-dose model (MTDM).

We compare results from model DV-MTDM with results from the standard DVM (formulation (5.2) with weights $(w_1, w_2) = (1, 0)$). The solver Gurobi [67] is used to solve all MIPs, with a time limit of two hours for benchmarking purposes.

It is found 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 (5.2) with weights $(w_1, w_2) = (0, 1)$ and are able to find proven optimal integer solutions for all ten patient instances; these solutions give upper bounds on the $LCVaR_1^{PTV}$ values which are attainable. The $LCVaR_1^{PTV}$ value from model DV-MTDM is very close to this upper bound, on average within 0.2%. In case it is clinically motivated to increase the $LCVaR_1^{PTV}$ value significantly, this is therefore not possible by solving the DV-MTDM to optimality; instead the constraints of the model must be relaxed, allowing a higher dose to OARs.

Furthermore, at all computing times, the model DV-MTDM gives better results than model DVM. The improvement is 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.

5.3 A new optimization model for spatiality

The evaluation criteria included in the clinical treatment guidelines, such as the DIs, only consider the dose distribution on an aggregated level, while criteria for how it is distributed spatially are not explicitly defined. Furthermore, there are not much research on optimization models which include spatial properties. An example in IMRT is found in [68]. To the best of our knowledge there are no such examples in HDR BT. In clinical practice the spatial properties are considered to be of importance, but to our knowledge, the effects on treatment outcome have not been studied much.

Although spatial properties are not explicit included in clinical treatment guidelines, such as [31], we have seen in clinical practice that a dose plan is manually adjusted if the dose distribution is too heterogeneous. This is done for example if it contains hot spots, which are contiguous volumes that receives a dose that is very high, for example above 200% of the prescription dose. The aim with this adjustment is to make the dose distribution more homogeneous, while at the same time keeping aggregate dose properties on acceptable levels. This process is both complex and time consuming to perform manually.

Motivated by this observation, our approach in Paper C is to replace the adjustment step with the solution of a mathematical optimization model. This model takes a tentative dose plan as input and adjusts it to improve the spatial properties, making the dose plan more homogeneous by reducing the prevalence of both hot spots and cold spots.

Furthermore, a scenario which we consider to be important is when the placement of one or several catheters fails, either because the catheter could not be inserted at the planned location at all, or because the catheter did not end up exactly where it was planned. These situations may cause the dose plan to be more heterogeneous, with large hot and cold spots. The purpose of our model is to mitigate these effects.

We have performed computational experiments with the proposed model on the patient data set previously introduced. Because there are no established evaluation criteria for the spatial properties of a 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 both receive 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 with too high (or too low) doses, and this penalty is higher the shorter the distance between the two points is.

The general formulation of the optimization model is:

$$z^* = \min_{t \in \mathcal{X}} w \sum_{i,j \in P_T: i \neq j} \frac{f(D_i(t))f(D_j(t))}{h(i,j)} + (1-w) \sum_{i,j \in P_T: i \neq j} \frac{g(D_i(t))g(D_j(t))}{h(i,j)}, \quad (5.3)$$

where w is a penalty parameter to prioritise between the hot spot and cold spot term, D_i is the dose at dose point i , evaluated for the dwell time vector t , and $\mathcal{X}$ is the feasible set, which is defined by constraints that take the aggregated dose properties into account. The functions f and g give penalties for high doses and low doses, respectively, and the function $h(i, j)$ is a measure of distance between the dose points i and j .

To evaluate our model, we specify the model components. The feasible set $\mathcal{X}$ is based on constraints on DIs, as presented in Section 4.2, and the distance function h is the squared Euclidean distance. The function f is implemented as either

$$f(D_i) = \max(0, (D_i - b))^2, \quad (5.4)$$

or

$$f(D_i) = H(D_i - b), \quad (5.5)$$

where the parameter b can be for example 200% of the prescription dose, and the function H is the Heaviside step function. The function g is formulated correspondingly, but instead giving penalties for too low doses.

These formulations contain binary variables, both from the constraints on DIs (the set $\mathcal{X}$) and from the function given in equation (5.5). When trying to solve the resulting MIP models we found these formulations to be completely intractable and with no solution progress being made at all. We therefore approximate the Heaviside step function with smooth sigmoid function,

$$H(D_i - b) = 0.5(1 + \tanh(\beta(D_i - b))), \quad (5.6)$$

where β is a parameter used to control the steepness. See Figure 5.1 for an illustration. This approximation is used also in the DI constraints; this approximation has earlier been used in for example the HDR BT studies [11] and [69]. The reformulation yields a non-linear model that is solved with the Matlab [70] solver `fmincon`, and we find solutions within computing times of a few minutes, which would be acceptable in clinical practice.

Figure 5.1: The Heaviside step function (the solid line) and the smooth non-linear sigmoid approximation (the dashed line).

Our optimization model is meant to be used for adjusting a tentative starting plan, and we have tried four types of tentative plans. These are (i) clinically used dose plans obtained with manual planning, (ii) optimized dose plans obtained from the LPM, after parameter tuning with the aim of finding dose plans with acceptable DIs, (iii) optimized dose plans obtained from the DVM, and (iv) optimized dose plans obtained from a version of the DVM in which V_{100} is maximised but the doses at dose points which receive a too low dose are minimised. The first two are used to cover the two most common methods for clinical dose planning. The purpose of the last model is to evaluate our proposed model on heterogeneous plans, and test its capability.

The parameter values used in the constraints on DIs in the adjustment step were obtained either from the tentative plans, but slightly relaxed to allow for small changes in the DI values, or from values from clinical treatment guidelines.

Our approach has similarities with the spatial model for IMRT [68] as both models take a tentative dose plan as input and improve it. The approaches however differ in two respects. First, we include the DIs as explicit constraints, and secondly, we handle the heterogeneities dynamically. In [68] there are constraints that adjust the dose at specified dose points. 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.

Compared to the clinically used dose plans, the adjustment step increased the dose to the coldest parts of the PTV, but also increased V_{100} significantly. This came at a cost of a slightly higher dose to the urethra, although the dose was still below the clinical limits.

For the three types of optimized tentative plans, and using equal weights for hot and cold spot terms, we saw improvements in terms of objective function values for both parts. For other objective weight combinations there was

a clear trade-off between improved values of the hot and cold terms in the objective function.

We also studied the size of the largest contiguous volumes in which the doses are too high, and too cold, respectively. For tentative plans obtained from the LPM and the DVM, there was a significant reduction in the volume of the largest contiguous hot volume, but only a small reduction in the contiguous cold volume. This is not surprising because, to achieve high values in terms of V_{100} , there has to be more emphasis on cold dose points. Regarding aggregate evaluation criteria, we showed improvements in V_{200} , while other DIs did not change significantly.

Moreover, 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, in terms of the average dose to the hottest subvolume, we see improvements for the optimized tentative plans. For the coldest subvolume we see improvements for the tentative plans obtained from the modified DVM, but not for the LPM and the DVM. Compared to the clinically used plans, when using equal weights on the hot and cold objective terms, there are improvements of about 10% for both the hottest and coldest subvolume.

We conclude this section with a few observations. With solution times of a few minutes for the adjustment step, solutions are found fast enough to be of clinical use. Furthermore, for all four methods of obtaining the tentative plans, there is an increase in active dwell positions. The LPM has previously been observed to produce heterogeneous dose plans [46] with long maximal dwell times [47]. It can also be noted that the dose plans obtained from the DVM contain few active dwell positions. See Paper C for detailed results, tables and figures.

5.4 Review and analysis of mathematical models

Paper D is a review of mathematical models for dose planning of HDR BT. We contribute by (i) collecting and systematising the models proposed for dose planning, and (ii) analysing properties of dose planning models and relationships between them. Models for HDR BT for the time period until June 2020 are included. Our review complements the BT review [71], which covers the time period until 2010.

In Chapter 4 three types of linear dose planning models are introduced. Other types of models have also been proposed, including nonlinear models and multi-objective models. In this thesis we primarily study linear models, although a nonlinear model is proposed in Paper C and a quadratic penalty model is studied in Paper E.

Nonlinear models for HDR BT dose planning are commonly either quadratic penalty models, which are similar to the LPM but give a quadratic

penalty for each dose point at which the dose is outside a prescribed interval, or radiobiological models. Examples of the latter are models that include EUD or TCP. Quadratic penalty models, which are common in IMRT and IMBT, are typically convex, and thus considered easy to solve. Radiobiological models are generally more difficult to use, both because they generally are non-convex and because such models contain parameters which have to be estimated [24].

As the dose planning problem is inherently multi-objective, such approaches have also been proposed. Two types of multi-objective approaches are (i) single-objective models which are solved repeatedly to generate a set of solutions, and (ii) dominance-based models. A solution is non-dominated, or Pareto optimal, if no objective can be improved without worsening another. All the non-dominated plans constitute a Pareto front, which is a common way to visualise multiple solutions, and their trade-offs.

One presented analysis of model properties is the mathematical relationship between the LPM and the DVM, presented in Section 5.1 and Paper A. In the review we also present a mathematical relationship between the LPM and the MTDM. We show that starting from the LPM, it is possible to specify parameters in the MTDM such that optimal solutions to the MTDM are optimal also in the LPM. This relationship is only one-directed, in contrast to the equivalence relationship presented in Paper A.

The impact of the choice of model on the number of active dwell positions and the dwell time heterogeneity is also discussed. It has been observed that dwell times in dose plans obtained with the LPM are more heterogeneous than those from manual dose planning, and also that the longest dwell times are longer. The number of active dwell positions in dose plans obtained with the LPM was analysed mathematically in [47]. Examples of remedies, to make heterogeneous dwell times more homogeneous, are the dwell time modulation restriction [69, 72], or the piecewise-linear penalty model [47]. Dwell time homogeneity is not a property that is included in clinical treatment guidelines, but it is considered as preferable in clinical practice.

5.5 Robust optimization of intensity modulated brachytherapy

In this IMBT study we consider a prototype of a delivery system presented in [7]. The isotope ^{169}Yb is used, instead of ^{192}Ir which is commonly used in conventional HDR BT. Compared to conventional HDR BT, there are additional degrees of freedom in IMBT, because there is a separate dwell time variable for each combination of dwell position and shield angle, instead of only for each dwell position as in conventional HDR BT. See [6] for a review of IMBT approaches.

A purpose of our study is to investigate how robust IMBT dose plans are with respect to rotational errors in the shields. Furthermore, we propose a robust optimization model to mitigate the effects from rotational uncertainty. Regarding the rotational uncertainty, 10 degrees is considered a large error and an unlikely scenario. Hence, this error is considered to be the worst case; this estimate is based on the study [7]. We consider three scenarios, the nominal scenario, and two scenarios with rotational errors of 10 degrees, in opposite directions. The rotational error is modelled to be systematic, that is, the error is the same in all catheters. The reason is that all shields are rotated simultaneously, see [7].

We propose a robust linear penalty model (LPM-R) to take rotational uncertainty into account. This is based on the LPM, introduced in Section 4.1, but in LPM-R a penalty is calculated for each scenario. The objective is to minimise a weighted sum of the average penalty for the scenarios and the penalty for the scenario with the worst outcome. The model belongs to the class of robust optimization approaches known as minimax stochastic programming [73]. Furthermore, we also consider a robust quadratic penalty model (QPM-R), in which there is a linear and quadratic penalty for each dose point in each scenario. For details and the complete models, see Paper E.

We use the patient data set of six patients described in the first part of Section 5. We have compared the worst scenario for both LPM and LPM-R, based on the evaluation of the three scenarios for the obtained dwell times. For both models, the value of D_{90}^{PTV} was normalised to 10 Gy, which is the prescription dose. The dwell times obtained from the LPM-R give better results in terms of V_{100}^{PTV} and $D_{0.1cc}^{urethra}$ for all patients. Furthermore, for five out of the six patients there is for LPM-R a decrease in V_{200}^{PTV} , for all scenarios, and not only for the worst one. The number of active dwell times increases with LPM-R and there is a trend towards shorter maximum dwell times. In the figures in Paper E showing DVHs, there are larger deviations between the scenarios for the LPM than for the LPM-R, particularly for the urethra. For the full results and figures, see Paper E.

To summarise, we show that the proposed robust models, LPM-R and QPM-R, improve the results for the worst scenario, compared to the non-robust models, LPM and QPM. Furthermore, the robust dose plan evaluated for the nominal scenario is not worse, with respect to DIs, than the non-robust model evaluated for the nominal scenario. Therefore, the robust model provides a safeguard against rotational errors, and from the perspective of dose plan quality there is no drawback with the robust model. However, the safeguard comes at a cost of longer computing times, both for calculating the dose-rate contributions and for solving the robust optimization models. With proper tuning and tailored implementations, we anticipate that significant improvements in computing times can be achieved.

Future research

In this thesis summary, and especially in Paper D, we present an overview of the optimization models and algorithms for HDR BT dose planning that have been suggested in the literature. While most of them have been shown to produce dose plans which are clinically adequate, no thorough comparison between such models and algorithms has been made. Such a comparison is a highly interesting topic for future research.

Moreover, the published benchmarks and comparisons with clinical dose plans are based on clinical evaluation criteria, and not on actual treatment outcome. To take the next step in advancing the field of HDR BT, it is important to continue the research on which measures show the best correlation with treatment outcome, both regarding local tumour control and OAR complications. It may be the currently used evaluation criteria, such as the dosimetric indices, but it seems more likely that radiobiological measures is the best way forward. The ultimate goal is of course that the choices of optimization models and evaluation criteria should be evidence-based.

The development and use of IMBT puts additional requirements on optimization algorithms, because of the increase in the degrees of freedom. Any algorithmic improvements in the field of IMBT can also be beneficial for conventional HDR BT dose planning, and may open up for possibilities in for example optimization models for catheter placement.

Several studies on catheter placement have shown that it is possible to use fewer catheters than what is typically used clinically, without worsening dose plan quality in terms of dosimetric indices. However, it is plausible that fewer catheters may have a large impact on the dose heterogeneity and the spatial properties considered in Paper C. It would therefore be interesting to evaluate the effect of the number of catheters on spatial properties. A combined

model with spatial properties and catheter placement decisions would also be interesting to investigate.

Finally, there are interesting challenges on the way towards fully automated HDR BT treatment planning, that is, to automate the entire treatment plan process from acquiring medical images to the dose planning of the dwell times. Decisions here include the contouring of the relevant structures and the catheter placement. The former is an example of a step in which machine learning can be useful. In order to fully automate the complete treatment of a patient, it will also be required to tackle the combined treatment planning of all modalities, possibly including both EBRT and HDR BT, as well as the fractionation and the treatment protocol for each fraction. This is a challenge for future research, but within reach as the optimization models and algorithms become more sophisticated and mature.

Bibliography

- [1] B. Morén. “Mathematical Modelling of Dose Planning in High Dose-Rate Brachytherapy.” Licentiate Thesis. Linköping University, 2019. DOI: 10.3384/lic.diva-154966.
- [2] N. G. Zaorsky, B. J. Davis, P. L. Nguyen, T. N. Showalter, P. J. Hoskin, Y. Yoshioka, G. C. Morton, and E. M. Horwitz. “The evolution of brachytherapy for prostate cancer.” In: *Nature Reviews Urology* 14.7 (2017), pp. 415–439. DOI: 10.1038/nrurol.2017.76.
- [3] G. C. Morton and S. M. Alrashidi. “High dose rate brachytherapy in high-risk localised disease – Why do anything else?” In: *Clinical Oncology* (2020). DOI: 10.1016/j.clon.2019.11.003.
- [4] A. Pettersson, D. Alm, H. Garmo, M. Hjelm Eriksson, E. Castellanos, L. Åström, J. Kindblom, A. Widmark, A. Gunnlaugsson, I. Franck Lissbrant, P. Nilsson, and P. Stattin. “Comparative Effectiveness of Different Radical Radiotherapy Treatment Regimens for Prostate Cancer: A Population-Based Cohort Study.” In: *JNCI Cancer Spectrum* 4.2 (2020), pp. 1–8. DOI: 10.1093/jncics/pkaa006.
- [5] M. J. Rivard, B. M. Coursey, L. a. DeWerd, W. F. Hanson, M. S. Huq, G. S. Ibbott, M. G. Mitch, R. Nath, and J. F. Williamson. “Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations.” In: *Medical Physics* 31.3 (2004), pp. 633–674. DOI: 10.1118/1.1905824.
- [6] C. M. Callaghan, Q. Adams, R. T. Flynn, X. Wu, W. Xu, and Y. Kim. “Systematic review of intensity modulated brachytherapy (IMBT): Static and dynamic techniques.” In: *International Journal of Radiation Oncology Biology Physics* 105.1 (2019), pp. 206–221. DOI: 10.1016/j.ijrobp.2019.04.009.
- [7] G. Famulari, M. Duclos, and S. A. Enger. “A novel 169 Yb-based dynamic-shield intensity modulated brachytherapy delivery system for prostate cancer.” In: *Medical Physics* 47.3 (2020), pp. 859–868. DOI: 10.1002/mp.13959.

- [8] G. C. Pereira, M. Traugher, and R. F. Muzic Jr. “The role of imaging in radiation therapy planning: Past, present, and future.” In: *BioMed Research International* (2014). DOI: 10.1155/2014/231090.
- [9] International Commission on Radiation Units and Measurements. *Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50) (ICRU Report 62)*. Tech. rep. 1999. DOI: 10.1259/bjr.74.879.740294.
- [10] Y. Yamada, L. Rogers, D. J. Demanes, G. Morton, B. R. Prestidge, J. Pouliot, G. N. Cohen, M. Zaider, M. Ghilezan, and I. C. Hsu. “American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy.” In: *Brachytherapy* 11.1 (2012), pp. 20–32. DOI: 10.1016/j.brachy.2011.09.008.
- [11] C. V. Guthrie, A. L. Damato, A. N. Viswanathan, J. W. Hesser, and R. A. Cormack. “A fast multi-target inverse treatment planning strategy optimizing dosimetric measures for high-dose-rate (HDR) brachytherapy.” In: *Medical Physics* 44.9 (2017), pp. 4452–4462. DOI: 10.1002/mp.12410.
- [12] S. Pokharel, S. Rana, J. Blikensstaff, A. Sadeghi, and B. Prestidge. “Evaluation of hybrid inverse planning and optimization (hipo) algorithm for optimization in real-time, high-dose-rate (hdr) brachytherapy for prostate.” In: *Journal of Applied Clinical Medical Physics* 14.4 (2013), pp. 96–107. DOI: 10.1120/jacmp.v14i4.4198.
- [13] M. C. Meer, P. A. N. Bosman, B. R. Pieters, Y. Niatetski, N. Wieringen, T. Alderliesten, and A. Bel. “Sensitivity of dose-volume indices to computation settings in high-dose-rate prostate brachytherapy treatment plan evaluation.” In: *Journal of Applied Clinical Medical Physics* 20.4 (2019), pp. 66–74. DOI: 10.1002/acm2.12563.
- [14] R. Nath, L. L. Anderson, G. Luxton, K. a. Weaver, J. F. Williamson, and a. S. Meigooni. “Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43.” In: *Medical Physics* 22.2 (1995), pp. 209–234. DOI: 10.1118/1.597458.
- [15] J. Perez-Calatayud, F. Ballester, R. K. Das, L. A. Dewerd, G. S. Ibbott, A. S. Meigooni, Z. Ouhib, M. J. Rivard, R. S. Sloboda, and J. F. Williamson. “Dose calculation for photon-emitting brachytherapy sources with average energy higher than 50 keV: Report of the AAPM and ESTRO.” In: *Medical Physics* 39.5 (2012), pp. 2904–2929. DOI: 10.1118/1.3703892.

-
- [16] L. Beaulieu, Å. Carlsson Tedgren, J. F. Carrier, S. D. Davis, F. Mourtada, M. J. Rivard, R. M. Thomson, F. Verhaegen, T. A. Wareing, and J. F. Williamson. “Report of the Task Group 186 on model-based dose calculation methods in brachytherapy beyond the TG-43 formalism: Current status and recommendations for clinical implementation.” In: *Medical Physics* 39.10 (2012), pp. 6208–6236. DOI: 10.1118/1.4747264.
- [17] C. Kirisits, F. A. Siebert, D. Baltas, M. De Brabandere, T. P. Hellebust, D. Berger, and J. Venselaar. “Accuracy of volume and DVH parameters determined with different brachytherapy treatment planning systems.” In: *Radiotherapy and Oncology* 84.3 (2007), pp. 290–297. DOI: 10.1016/j.radonc.2007.06.010.
- [18] A. Wu, K. Ulin, and E. S. Sternick. “A dose homogeneity index for evaluating 192Ir interstitial breast implants.” In: *Medical Physics* 15.1 (1988), pp. 104–107. DOI: 10.1118/1.596152.
- [19] A. V. t. Riet, A. C. A. Mak, M. A. Moerland, L. H. Elders, and W. Van Der Zee. “A conformation number to quantify the degree of conformality in brachytherapy and external beam irradiation: Application to the prostate.” In: *International Journal of Radiation Oncology Biology Physics* 37.3 (1997), pp. 731–736. DOI: 10.1016/S0360-3016(96)00601-3.
- [20] D. Baltas, C. Kolotas, K. Geramani, R. F. Mould, G. Ioannidis, M. Kekchidi, and N. Zamboglou. “A conformal index (COIN) to evaluate implant quality and dose specification in brachytherapy.” In: *International Journal of Radiation Oncology Biology Physics* 40.2 (1998), pp. 515–524. DOI: 10.1016/S0360-3016(97)00732-3.
- [21] L. Feuvret, G. Noël, J. J. Mazeron, and P. Bey. “Conformity index: A review.” In: *International Journal of Radiation Oncology Biology Physics* 64.2 (2006), pp. 333–342. DOI: 10.1016/j.ijrobp.2005.09.028.
- [22] G. Patel, A. Mandal, S. Choudhary, R. Mishra, and R. Shende. “Plan evaluation indices: A journey of evolution.” In: *Reports of Practical Oncology & Radiotherapy* (2020). DOI: 10.1016/j.rpor.2020.03.002.
- [23] M. Zaider and G. N. Minerbo. “Tumour control probability: A formulation applicable to any temporal protocol of dose delivery.” In: *Physics in Medicine & Biology* 45.2 (1999), pp. 279–293. DOI: 10.1088/0031-9155/45/2/303.
- [24] X. Allen Li, M. Alber, J. O. Deasy, A. Jackson, K. W. Ken Jee, L. B. Marks, M. K. Martel, C. Mayo, V. Moiseenko, A. E. Nahum, A. Niemierko, V. A. Semenenko, and E. D. Yorke. “The use and QA of biologically related models for treatment planning: Short report of the TG-166 of the therapy physics committee of the AAPM.” In: *Medical Physics* 39.3 (2012), pp. 1386–1409. DOI: 10.1118/1.3685447.

- [25] L. B. Marks, E. D. Yorke, A. Jackson, R. K. Ten Haken, L. S. Constine, A. Eisbruch, S. M. Bentzen, J. Nam, and J. O. Deasy. “Use of normal tissue complication probability models in the clinic.” In: *International Journal of Radiation Oncology Biology Physics* 76.3 SUPPL. (2010), pp. 10–19. DOI: 10.1016/j.ijrobp.2009.07.1754.
- [26] A. Brahme. “Optimized radiation therapy based on radiobiological objectives.” In: *Seminars in Radiation Oncology* 9.1 (1999), pp. 35–47. DOI: 10.1016/S1053-4296(99)80053-8.
- [27] A. Niemierko. “Reporting and analyzing dose distributions: A concept of equivalent uniform dose.” In: *Medical Physics* 24.1 (1997), pp. 103–110. DOI: 10.1118/1.598063.
- [28] A. Niemierko. “A generalized concept of equivalent uniform dose (EUD).” In: *Medical Physics* 26 (1999), p. 1100.
- [29] Q. Wu, R. Mohan, A. Niemierko, and R. Schmidt-Ullrich. “Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose.” In: *International Journal of Radiation Oncology Biology Physics* 52.1 (2002), pp. 224–235. DOI: 10.1016/S0360-3016(01)02585-8.
- [30] G. Kovács, R. Pötter, T. Loch, J. Hammer, I. K. Kolkman-Deurloo, J. J. De La Rosette, and H. Bertermann. “GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localised prostate cancer.” In: *Radiotherapy and Oncology* 74.2 (2005), pp. 137–148. DOI: 10.1016/j.radonc.2004.09.004.
- [31] P. J. Hoskin, A. Colombo, A. Henry, P. Niehoff, T. Paulsen Hellebust, F. A. Siebert, and G. Kovacs. “GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update.” In: *Radiotherapy and Oncology* 107.3 (2013), pp. 325–332. DOI: 10.1016/j.radonc.2013.05.002.
- [32] S. Beriwal, D. J. Demanes, B. Erickson, E. Jones, J. F. De Los Santos, R. A. Cormack, C. Yashar, J. J. Rownd, and A. N. Viswanathan. “American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer.” In: *Brachytherapy* 11 (2012), pp. 68–75. DOI: 10.1016/j.brachy.2011.06.008.
- [33] A. N. Viswanathan, S. Beriwal, J. F. De Los Santos, D. J. Demanes, D. Gaffney, J. Hansen, E. Jones, C. Kirisits, B. Thomadsen, and B. Erickson. “American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: High-dose-rate brachytherapy.” In: *Brachytherapy* 11 (2012), pp. 47–52. DOI: 10.1016/j.brachy.2011.07.002.

-
- [34] G. Kovács, R. Martinez-Monge, A. Budrukhar, J. L. Guinot, B. Johansson, V. Strnad, J. Skowronek, A. Rovirosa, and F. A. Siebert. “GEC-ESTRO ACROP recommendations for head & neck brachytherapy in squamous cell carcinomas: 1st update – Improvement by cross sectional imaging based treatment planning and stepping source technology.” In: *Radiotherapy and Oncology* 122.2 (2017), pp. 248–254. DOI: 10.1016/j.radonc.2016.10.008.
- [35] V. Strnad, T. Major, C. Polgar, M. Lotter, J. L. Guinot, C. Gutierrez-Miguel, R. Galalae, E. Van Limbergen, B. Guix, P. Niehoff, K. Lössl, and J. M. Hannoun-Levi. “ESTRO-ACROP guideline: Interstitial multicatheter breast brachytherapy as Accelerated Partial Breast Irradiation alone or as boost – GEC-ESTRO Breast Cancer Working Group practical recommendations.” In: *Radiotherapy and Oncology* 128.3 (2018), pp. 411–420. DOI: 10.1016/j.radonc.2018.04.009.
- [36] S. Breedveld, A. B. Bennan, S. Aluwini, D. R. Schaart, I. K. K. Kolkman-Deurloo, and B. J. Heijmen. “Fast automated multi-criteria planning for HDR brachytherapy explored for prostate cancer.” In: *Physics in Medicine & Biology* 64.20 (2019). DOI: 10.1088/1361-6560/ab44ff.
- [37] G. C. Morton, R. Sankrecha, P. Halina, and A. Loblaw. “A comparison of anatomy-based inverse planning with simulated annealing and graphical optimization for high-dose-rate prostate brachytherapy.” In: *Brachytherapy* 7.1 (2008), pp. 12–16. DOI: 10.1016/j.brachy.2007.10.001.
- [38] A. M. Dinkla, R. van der Laarse, E. Kaljouw, B. R. Pieters, K. Koedooder, N. van Wieringen, and A. Bel. “A comparison of inverse optimization algorithms for HDR/PDR prostate brachytherapy treatment planning.” In: *Brachytherapy* 14.2 (2015), pp. 279–288. DOI: 10.1016/j.brachy.2014.09.006.
- [39] S. Cui, P. Després, and L. Beaulieu. “A multi-criteria optimization approach for HDR prostate brachytherapy: II. Benchmark against clinical plans.” In: *Physics in Medicine & Biology* 63.20 (2018). DOI: 10.1088/1361-6560/aae24c.
- [40] S. C. Maree, N. H. Luong, E. S. Kooreman, N. van Wieringen, A. Bel, K. A. Hinnen, H. Westerveld, B. R. Pieters, P. A. Bosman, and T. Alderliesten. “Evaluation of bi-objective treatment planning for high-dose-rate prostate brachytherapy – A retrospective observer study.” In: *Brachytherapy* 18.3 (Feb. 2019), pp. 396–403. DOI: 10.1016/j.brachy.2018.12.010.

- [41] E. Lessard and J. Pouliot. “Inverse planning anatomy-based dose optimization for HDR-brachytherapy of the prostate using fast simulated annealing algorithm and dedicated objective function.” In: *Medical Physics* 28.5 (2001), pp. 773–779. DOI: 10.1118/1.1368127.
- [42] E.-G. Talbi. *Metaheuristics: From Design to Implementation*. Hoboken, New Jersey: John Wiley & Sons., 2009. DOI: 10.1002/9780470496916.
- [43] R. Alterovitz, E. Lessard, J. Pouliot, I.-C. J. Hsu, J. F. O’Brien, and K. Goldberg. “Optimization of HDR brachytherapy dose distributions using linear programming with penalty costs.” In: *Medical Physics* 33.11 (2006), pp. 4012–4019. DOI: 10.1118/1.2349685.
- [44] G. Jozsef, O. E. Streeter, and M. A. Astrahan. “The use of linear programming in optimization of HDR implant dose distributions.” In: *Medical Physics* 30.5 (2003), pp. 751–760. DOI: 10.1118/1.1564471.
- [45] B. L. Gorissen, D. den Hertog, and A. L. Hoffmann. “Mixed integer programming improves comprehensibility and plan quality in inverse optimization of prostate HDR brachytherapy.” In: *Physics in Medicine & Biology* 58.4 (2013), pp. 1041–1057. DOI: 10.1088/0031-9155/58/4/1041.
- [46] E. Chajon, I. Dumas, M. Touleimat, N. Magné, J. Coulot, R. Verstraet, D. Lefkopoulos, and C. Haie-Meder. “Inverse planning approach for 3-D MRI-based pulse-dose rate intracavitary brachytherapy in cervix cancer.” In: *International Journal of Radiation Oncology Biology Physics* 69.3 (2007), pp. 955–961. DOI: 10.1016/j.ijrobp.2007.07.2321.
- [47] Å. Holm, T. Larsson, and Å. Carlsson Tedgren. “Impact of using linear optimization models in dose planning for HDR brachytherapy.” In: *Medical Physics* 39.2 (2012), pp. 1021–1028. DOI: 10.1118/1.3676179.
- [48] N. Milickovic, M. Lahanas, M. Papagiannopoulou, N. Zamboglou, and D. Baltas. “Multiobjective anatomy-based dose optimization for HDR-brachytherapy with constraint free deterministic algorithms.” In: *Physics in Medicine and Biology* 47.13 (2002), pp. 2263–2280. DOI: 10.1088/0031-9155/47/13/306.
- [49] H. Badry, L. Oufni, H. Ouabi, H. Iwase, and L. Afraites. “A new fast algorithm to achieve the dose uniformity around high dose rate brachytherapy stepping source using Tikhonov regularization.” In: *Australasian Physical & Engineering Sciences in Medicine* 42.3 (2019), pp. 757–769. DOI: 10.1007/s13246-019-00775-0.
- [50] M. J. Webster, S. Devic, T. Vuong, D. Yup Han, J. C. Park, D. Scanderbeg, J. Lawson, B. Song, W. Tyler Watkins, T. Pawlicki, and W. Y. Song. “Dynamic modulated brachytherapy (DMBT) for rectal cancer.” In: *Medical Physics* 40.1 (2013). DOI: 10.1118/1.4769416.

- [51] Y. Liu, R. T. Flynn, Y. Kim, and X. Wu. “Asymmetric dose-volume optimization with smoothness control for rotating-shield brachytherapy.” In: *Medical Physics* 41.11 (2014), p. 111709. DOI: 10.1118/1.4897617.
- [52] J. Beliën, J. Colpaert, L. De Boeck, and E. Demeulemeester. “A hybrid simulated annealing linear programming approach for treatment planning in HDR brachytherapy with dose volume constraints.” In: *Proceedings of the 35th International Conference on Operational Research Applied to Health Services (ORAHS)*. 2009.
- [53] T. Siau, A. Cunha, A. Atamtürk, I.-C. Hsu, J. Pouliot, and K. Goldberg. “IPIP: A new approach to inverse planning for HDR brachytherapy by directly optimizing dosimetric indices.” In: *Medical Physics* 38.7 (2011), pp. 4045–4051. DOI: 10.1118/1.3598437.
- [54] T. M. Deist and B. L. Gorissen. “High-dose-rate prostate brachytherapy inverse planning on dose-volume criteria by simulated annealing.” In: *Physics in Medicine & Biology* 61.3 (2016), pp. 1155–1170. DOI: 10.1088/0031-9155/61/3/1155.
- [55] D. Duffie and J. Pan. “An overview of value at risk.” In: *The Journal of Derivatives* 4.3 (1997), pp. 7–49. DOI: 10.1088/0031-9155/61/3/1155.
- [56] S. Ahmed and W. Xie. “Relaxations and approximations of chance constraints under finite distributions.” In: *Mathematical Programming* 170.1 (2018), pp. 43–65. DOI: 10.1007/s10107-018-1295-z.
- [57] R. T. Rockafellar and S. Uryasev. “Optimization of conditional value-at-risk.” In: *Journal of Risk* 2 (2000), pp. 21–41. DOI: 10.2307/1165345.
- [58] C. Filippi, G. Guastaroba, and M. Speranza. “Conditional value-at-risk beyond finance: a survey.” In: *International Transactions in Operational Research* 27.3 (2020), pp. 1277–1319. DOI: 10.1111/itor.12726.
- [59] H. E. Romeijn, R. K. Ahuja, J. F. Dempsey, A. Kumar, and J. G. Li. “A novel linear programming approach to fluence map optimization for intensity modulated radiation therapy treatment planning.” In: *Physics in Medicine & Biology* 48.21 (2003), pp. 3521–3542. DOI: 10.1088/0031-9155/48/21/005.
- [60] Å. Holm, T. Larsson, and Å. Carlsson Tedgren. “A linear programming model for optimizing HDR brachytherapy dose distributions with respect to mean dose in the DVH-tail.” In: *Medical Physics* 40.8 (2013), p. 081705. DOI: 10.1118/1.4812677.
- [61] V. W. Wu, M. A. Epelman, K. S. Pasupathy, M. Y. Sir, and C. L. Deufel. “A new optimization algorithm for HDR brachytherapy that improves DVH-based planning: Truncated Conditional Value-at-Risk (TCVaR).” In: *Biomedical Physics & Engineering Express* (2020). DOI: 10.1088/2057-1976/abb4bc.

- [62] R. T. Rockafellar and S. Uryasev. “Conditional value-at-risk for general loss distributions.” In: *Journal of Banking and Finance* 26.7 (2002), pp. 1443–1471. DOI: 10.1016/S0378-4266(02)00271-6.
- [63] M. Lahanas, D. Baltas, S. Giannouli, N. Milickovic, and N. Zamboglou. “Generation of uniformly distributed dose points for anatomy-based three-dimensional dose optimization methods in brachytherapy.” In: *Medical Physics* 27.5 (2000), pp. 1034–1046. DOI: 10.1118/1.598970.
- [64] Å. Holm, T. Larsson, and Å. Carlsson Tedgren. “On the correlation between DVH parameters and linear penalties in optimization of HDR prostate brachytherapy dose plans.” In: *Mathematical Optimization of HDR Brachytherapy*. Linköping: PhD Thesis, Linköping University, 2013.
- [65] P. Bonami, A. Lodi, A. Tramontani, and S. Wiese. “On mathematical programming with indicator constraints.” In: *Mathematical Programming* 151 (2015), pp. 191–223. DOI: 10.1007/s10107-015-0891-4.
- [66] W. A. Tomé and J. F. Fowler. “On cold spots in tumor subvolumes.” In: *Medical Physics* 29.2002 (2002), pp. 1590–1598. DOI: 10.1118/1.1485060.
- [67] Gurobi Optimization LLC. *Gurobi Optimizer Reference Manual*. 2018.
- [68] P. Süß, M. Bortz, K.-H. Küfer, and C. Thieke. “The critical spot eraser - A method to interactively control the correction of local hot and cold spots in IMRT planning.” In: *Physics in Medicine & Biology* 58.6 (2013), pp. 1855–1867. DOI: 10.1088/0031-9155/58/6/1855.
- [69] A. Karabis, P. Belotti, and D. Baltas. “Optimization of catheter position and dwell time in prostate HDR brachytherapy using HIPO and linear programming.” In: *IFMBE Proceedings* 25.1 (2009), pp. 612–615. DOI: https://doi.org/10.1007/978-3-642-03474-9_172.
- [70] The Mathworks Inc. *MATLAB version 9.3.0.713579 (R2017b)*. Natick, Massachusetts, United States, 2017.
- [71] L. De Boeck, J. Beliën, and W. Egyed. “Dose optimization in high-dose-rate brachytherapy: A literature review of quantitative models from 1990 to 2010.” In: *Operations Research for Health Care* 3.2 (2014), pp. 80–90. DOI: 10.1016/j.orhc.2013.12.004.
- [72] M. Balvert, B. L. Gorissen, D. den Hertog, and A. L. Hoffmann. “Dwell time modulation restrictions do not necessarily improve treatment plan quality for prostate HDR brachytherapy.” In: *Physics in Medicine & Biology* 60.2 (2015), pp. 537–548. DOI: 10.1088/0031-9155/60/2/537.

- [73] J. Unkelbach, M. Alber, M. Bangert, R. Bokrantz, T. C. Chan, J. O. Deasy, A. Fredriksson, B. L. Gorissen, M. Van Herk, W. Liu, H. Mahmoudzadeh, O. Nohadani, J. V. Siebers, M. Witte, and H. Xu. “Robust radiotherapy planning.” In: *Physics in Medicine & Biology* 63.22 (2018). DOI: 10.1088/1361-6560/aae659.

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