INTEGRATING DELIVERY ISSUES IN INTENSITY-MODULATED RADIATION THERAPY TREATMENT PLAN OPTIMIZATION

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY UNIVERSITY OF FLORIDA 2011
To my parents
ACKNOWLEDGMENTS

I would like to express my deepest and everlasting gratitude to my mentor and academic father Edwin Romeijn. His wisdom, dedication, and rigorous thinking have proved invaluable over the course of my doctoral studies. I am deeply indebted to him for the efforts he put into developing my academic and research skills. His mentorship extended far beyond the duties of an advisor to genuine support in all aspects of my graduate career.

I owe a great debt of gratitude to my doctoral committee member Joseph Geunes for his valuable support and advice at different stages of my doctoral studies. His calm critical thinking has never ceased to inspire me. I am also deeply thankful to him for his tremendous help and support during my graduate career at the University of Florida.

I would like to express my deepest gratitude to Jatinder Palta for introducing me to the clinical environment and its challenges at the University of Florida Proton Therapy Institute. I was very fortunate to have him as my doctoral committee member and to use his insightful comments and suggestions in my research. I am also very thankful to him for his advice and interest in my academic and professional success.

I am extremely grateful to my doctoral committee member Cole Smith, a great researcher and a great person with a sense of humor that would always cheer me up. I have benefited considerably from his consultation and insights. I am also very thankful to him for being such a great graduate coordinator and for the constant effort he puts into it.

This dissertation has been made possible through the help and support of my senior colleague Chunhua Men. I am very grateful to her for the prompt technical support and assistance. She introduced me to the University of Florida Optimized Radiation Therapy (UFORT) treatment planning system and shared her implementation experiences and coding skills with me.
I would also like to thank my officemates, and in particular, Behnam and Soheil. I greatly enjoyed their companionship and benefited from the research discussions I had with them over the past few years. I would also like to thank other fellow students and visiting scholars: Alexey, Ashwin, Clay, Dmytro, Donatella, Kelly, May, Petros, Sibel, Somar, and Vera with whom I shared countless memorable moments. My thanks go to Soroush and Fei for their great companionship and help during my stay in Ann Arbor.

I am forever thankful to my family. I attribute all my achievements in life to my parents, Zahra and Ghasem, for their unconditional love, support, and encouragement. I dedicate this dissertation to them for having dedicated their lives to provide me with every opportunity that they never had. Finally, I am deeply grateful to Laila with whom I have shared my passions in this journey. Her love, compassion, and support have greatly helped me through difficult times.
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INTEGRATING DELIVERY ISSUES IN INTENSITY-MODULATED RADIATION THERAPY TREATMENT PLAN OPTIMIZATION

By

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August 2011

Chair: H. Edwin Romeijn
Major: Industrial and Systems Engineering

My Ph.D. dissertation focuses on model and algorithm development to enhance several aspects of an IMRT treatment plan. In particular, it addresses two major clinical issues encountered in treatment delivery, which are efficiency and accuracy. The beam-on-time, as a measure of the delivery efficiency, is incorporated into the IMRT treatment planning problem using a Direct Aperture Optimization approach. This allows for taking the efficiency factor into consideration when designing a treatment plan. Moreover, we have proposed robust and efficient models and solution approaches to account for the dosimetric inaccuracies caused during the treatment delivery. More specifically, we have considered two sources of inaccuracy which may compromise the treatment outcome; (1) the tongue-and-groove effect and (2) the organ motion. To account for the tongue-and-groove effect, we have developed robust models and efficient solution methods to obtain clinically-attractive treatment plans regardless of the exact effect of this source of inaccuracy. Furthermore, to incorporate the uncertainty caused by the organ motion into the IMRT treatment planning problem, we have proposed an entirely new modeling framework as well as solution approaches to obtain high-quality treatment plans while taking the variation of the treatment outcome into account.
CHAPTER 1
INTRODUCTION

According to the American Cancer Society (American Cancer Society, 2010), each year around 1.5 million new patients are diagnosed with cancer in the United States. External radiation therapy is one of the most commonly used treatment modalities for cancer benefiting more than 25% of cancerous patients. In this treatment modality beams of radiation are used to eradicate the disease by damaging the DNA in the cell nuclei. In particular, regions that are diagnosed to contain the disease and its possible spread (the so-called targets) are irradiated. However, the radiation beam kills both cancerous and normal cells along its path in the patient's body. Thereby, the radiation treatment must be carefully planned so that a clinically-prescribed radiation dose is delivered to targets while sparing normal cells in nearby organs and tissues (the so-called critical structures) to the greatest extent possible. Therefore, multiple beams from several directions are used so that their intersection provides a high dose to targets. On the contrary, regions covered by a single beam or only a few beams receive much lower radiation doses allowing for sparing the functionality of the critical structures.

Patients receive radiation therapy using a clinical radiation-delivery device called linear accelerator which can rotate around the patient. Technological advancements have led to the rapid development and widespread clinical implementation of a radiation delivery technique known as Intensity-Modulated Radiation Therapy (IMRT). In IMRT, the head of the linear accelerator is equipped with a Multileaf Collimator (MLC) system, consisting of rows of leaf pairs, which allows for dynamically shaping the radiation beam by blocking part of it. Each configuration of the MLC leaves is called an aperture. With the help of an MLC, apertures with a wide variety of complex shapes can be formed.

In IMRT, each orientation of the accelerator head defines a rectangular beam, each of which is conceptually discretized into a collection of beamlets which have individually adjustable intensities. In particular, the collection of all beamlet intensities form the
intensity profile or fluence map. In order to evaluate the radiation dose delivered to the patient, relevant structures (targets and critical structures) are conceptually discretized into a set of cubes, the so-called voxels. The dose deposited in each individual voxel is then calculated to determine the dose distribution. IMRT allows for delivering a highly conformal dose distribution which adequately covers the targets while sparing the critical structures surrounding them.

An IMRT treatment plan for an individual patient consists of a collection of apertures along with their associated intensities to be delivered by the MLC. The quality of an IMRT treatment plan is evaluated by considering the corresponding dose distribution. In particular, in clinical practice a collection of treatment plan evaluation criteria, which are all functions of the dose distribution, are used to measure the treatment quality. The goal in IMRT treatment planning is then to find a high-quality treatment plan with respect to the treatment plan evaluation criteria. For that purpose, IMRT treatment planning problem has been traditionally decomposed into several subproblems which are solved sequentially. The major subproblems are (1) determining the number and orientation of the radiation beams, (2) determining the fluence map for each radiation beam, and (3) decomposing the fluence maps into a collection of deliverable apertures. More specifically, beam orientation optimization (BOO) is the problem of selecting the best subset of beam angles to be used in the treatment plan, among the set of all possible beam angles. Furthermore, given the optimal set of beam directions, the fluence map optimization (FMO) is concerned with finding the optimal fluence maps for those beam directions. Finally, given the optimal fluence map for each beam direction, the leaf sequencing (LS) is the problem of decomposing each fluence map into a collection of deliverable apertures with their corresponding intensities. A more recent approach to IMRT treatment planning is aperture modulation, the so-called Direct Aperture Optimization (DAO). Given a set of beam directions to be used in the treatment plan, DAO integrates the FMO and LS problems and directly solves for the apertures shapes
and intensities. In order to adequately model many important characteristics of an IMRT treatment plan, knowledge of the shape and intensity of the apertures employed in the treatment plan is required. In contrast with the traditional sequential approach to IMRT treatment planning, DAO allows for explicitly incorporating these aspects into the treatment-plan optimization stage. In this work we have exploited this property of the DAO framework to account for several clinical considerations related to the treatment delivery in the treatment planning problem.

Leaves in commercial MLCs have a tongue-and-groove architecture to help reduce the interleaf radiation leakage (Figure 1-1). However, the exposed leaf tongues on the boundary of the delivered apertures may undesirably block or scatter part of the radiation potentially causing underdosing of the targets, this effect is known as the tongue-and-groove effect. It has been shown that the tongue-and-groove effect can be clinically significant causing deviation from the planned dose distribution as large as 10–15%. On the other hand, due to the small size of the leaf tongues, it is difficult for beamlet-based dose calculation algorithms to account for the tongue-and-groove effect. In Chapter 2 we developed a robust DAO approach to IMRT treatment planning which accounts for the dosimetric inaccuracies caused by the tongue-and-groove effect. In particular, we obtained lower and upper bounds on the dose distribution delivered to the patient. We then formulated the IMRT treatment planning problem as a robust DAO problem and developed an efficient solution approach using the column generation technique. Our robust DAO approach obtains treatment plans which are clinically attractive regardless of the exact effect of the MLC tongue-and-groove architecture. This chapter appeared in *Medical Physics* (Salari et al., 2011).

Beam-on-time is the amount of time that the linear accelerator is delivering radiation to the patient. It is a very important measure of the delivery efficiency since treatment plans with very long beam-on-times may cause biological complications to the patient. Moreover, since the patient is required to be immobilized during the radiation treatment,
a long beam-on-time causes inconvenience to the patient. Finally, time efficiency is a key factor considered by all radiation therapy facilities, impacting the patient throughput as well as costs. Hence, it is desirable to avoid treatment plans with long beam-on-times. On the other hand, if the beam-on-time is too short then the treatment outcome maybe poor particularly for tumors with complex anatomy. Therefore, there is a trade-off between the beam-on-time and the treatment plan quality. Beam-on-time can be explicitly expressed in terms of the aperture intensities. Thus, using a DAO framework in Chapter 3 we develop and test a new solution approach to IMRT treatment planning which incorporates the beam-on-time as a measure of the delivery efficiency into the treatment-plan optimization stage. More specifically, we formulated the DAO problem as a bi-criteria optimization problem and developed an exact solution method to characterize the corresponding Pareto-efficient frontier. The proposed approach can provide clinicians with the trade-off information for each patient case so that they can design a clinically-attractive and at the same time efficient treatment plan. This chapter has been accepted for publication in *INFORMS Journal on Computing* (Salari and Romeijn, 2011).
The majority of IMRT treatment plans are delivered as a sequence of daily treatments (often called fractions). Organ motion during a treatment fraction, the so-called intrafraction motion, is a major source of uncertainty in the patient geometry that can potentially compromise the quality of the IMRT treatment plan. In current practice, the organ motion is accounted for by considering a safety margin around the relevant structures. However, this approach leads to the toxicity of critical structures surrounding the tumor. Alternatively, the intrafraction-motion uncertainty can be incorporated into the treatment-plan optimization stage. This is a challenging problem due to the dynamic nature of IMRT treatment plans. In Chapter 4 we propose a stochastic DAO model to incorporate the intrafraction motion into the IMRT treatment plan optimization. In particular, we model the intrafraction motion as a stochastic process, and formulate a binary quadratic programming problem using the DAO framework to obtain high-quality treatment plans while taking the expected variation in the delivered dose distribution into account. We develop a solution approach to solve the relaxed problem using the column generation technique. Considering a Markov chain as the stochastic process under consideration, we then develop a branch-and-price algorithm to solve the discrete model. The proposed DAO model allows for studying the dosimetric effect of the intrafraction motion and, in particular, its interplay with the movements of the MLC leaves. Furthermore, using this model we can quantify the advantage of starting the treatment when the patient geometry is in a particular state as opposed to starting the treatment in an arbitrary state.
2.1 Introductory Remarks

Intensity-modulated radiation therapy (IMRT) treatment planning is concerned with the design of a treatment plan for individual cancer patients. Such a treatment plan consists of a collection of apertures to be formed by a multileaf collimator system (MLC) along with associated intensities. Leaves in most commercial MLCs have a tongue-and-groove design that helps reduce interleaf leakage. However, the exposed leaf stepped sides (tongues) may undesirably block or scatter part of the radiation resulting in underdosing of targets. It has been clinically indicated that the tongue-and-groove effect may cause underdosing as large as 10–25% (Chui et al., 1994; Deng et al., 2001; Galvin et al., 1993; Mohan, 1995; Luan et al., 2006; Siochi, 2009; Sykes and Williams, 1998; Wang et al., 1996). On the other hand, accurately estimating the dosimetric effects of the tongue-and-groove architecture is a difficult task, especially with the commonly used beamlet-based dose models. The goal of this study is to develop, implement, and test a robust method that takes dosimetric inaccuracies with respect to the MLC architecture into account explicitly. We will achieve this by employing upper and lower bounds on the dose distribution delivered to the patient, and tailoring the optimization model to find a treatment plan that is clinically attractive with respect to these bounds (i.e., one that is of high-quality regardless of the exact effect of the MLC tongues). By testing our approach on ten clinical cases of head-and-neck cancer we show that our approach is successful, in the sense that tight dose distribution bounds can be achieved even under coarse and easily obtainable bounds on the dosimetric effects. In contrast, a treatment plan optimization approach that does not take the dosimetric inaccuracies into account yields dose distribution bounds that are loose, making it hard to accurately assess the treatment plan quality.
IMRT treatment plan optimization is traditionally performed in two sequential stages; (1) fluence map optimization (FMO) and (2) leaf sequencing (LS). In particular, each orientation of the accelerator head defines a rectangular beam, each of which is conceptually discretized into a set of beamlets. The FMO problem then involves determining the optimal intensities for all beamlets. Given the optimal fluence map, the LS problem decomposes the fluence map for each beam into a manageable set of deliverable apertures. Both the FMO problem and the LS problem have been extensively studied in the literature; for modeling and solution approaches to FMO we refer to the review papers by Shepard et al. (1999) and Romeijn and Dempsey (2008). More specifically, Lee et al. (2000, 2003) studied mixed integer programming approaches; Hamacher and Küfer (2002) and Küfer et al. (2003) proposed a multi-criteria approach to the problem; and Romeijn et al. (2003, 2006) developed convex programming models.

Formally, the LS problem is to determine a set of deliverable apertures for delivering a fluence map that is optimal with respect to, typically, beam-on time, number of apertures used, or total treatment time. If the objective is to minimize beam-on time and any row-convex aperture is deliverable the LS problem is efficiently solvable (Ahuja and Hamacher, 2005; Bortfeld et al., 1994; Kamath et al., 2003; Siochi, 1999). In addition, Baatar et al. (2005), Boland et al. (2004), Kamath et al. (2004a), Dai and Hu (1999), and Siochi (1999) studied the problem under additional MLC hardware constraints. In contrast, as Baatar et al. (2005) showed, the problem of decomposing a fluence map into the minimum number of apertures is NP-hard. This has led to the development of a large number of heuristics for solving this problem, such as Baatar et al. (2005), Dai and Zhu (2001), Siochi (1999), and Xia and Verhey (1998). Additionally, Engel (2005), Kalinowski (2005b,a), and Lim and Choi (2006) developed heuristics to minimize the number of apertures while constraining the total beam-on time to be minimal. Finally, Taşkın et al. (2010b) proposed an integer programming approach to minimize the total treatment time. The tongue-and-groove effect has been widely addressed in literature.
in the LS stage. In particular, LS algorithms are divided into two categories; dynamic and static delivery; in dynamic delivery, the radiation is on when the MLC leaves are in motion, whereas in static delivery, also called the step-and-shoot, radiation is off when the leaves are in motion and it is turned on once the leaves are repositioned. Van Santvoort and Heijmen (1996) and Webb et al. (1997) have proposed LS algorithms which reduce the tongue-and-groove effect for dynamic delivery, and Que et al. (2004) and Kamath et al. (2004b) have incorporated the tongue-and-groove effect in the LS problem for the static delivery. Finally, Kamath et al. (2004c) compared different LS algorithms for static delivery with respect to the tongue-and-groove effect as well as the total treatment time.

A major issue with the traditional two-stage method is that the dose delivered to a patient not only depends on the fluence maps but also on the actual shape of the apertures used. To address this issue, an integrated approach to the FMO and LS problems, usually referred to as aperture modulation or Direct Aperture Optimization (DAO) has been proposed. DAO explicitly solves for aperture shapes and intensities rather than beamlet intensities (Shepard et al., 2002; Bednarz et al., 2002; Preciado-Walters et al., 2006; Romeijn et al., 2005; Men et al., 2007). In contrast with the traditional method, DAO explicitly incorporates the shape of the apertures while optimizing for the aperture intensities.

In general, treatment plans obtained with DAO use much fewer apertures (in fact, this is considered to be one of the attractive side effects of DAO since it reduces treatment times and beam-on-times). Therefore, one could argue that the tongue-and-groove error is more significant when using DAO since much fewer apertures are used. However, the smaller number of apertures also implies that DAO fluence maps tend to be much smoother than ones obtained with traditional two-stage approaches, and smoother fluence maps can be expected to suffer less from the most severe inaccuracies caused by the tongue-and-groove effect, namely those close to the
isocenter (rather than the boundary). In general, it is difficult to assess a priori which of these effects is larger. As Earl et al. (2006) say: “If the tongue-and-groove effect is not accounted for in the planning, an underestimation of the absolute dose is observed for DAO IMRT plans. The magnitude of the underestimation is dependent upon the aperture shapes.” This suggests that the treatment plan optimization model should make the corresponding determination and find a fluence map and corresponding collection of apertures that yield a high-quality treatment plan despite the tongue-and-groove architecture of the MLC. In this study, we address this by developing, implementing, and testing a robust DAO model that explicitly takes into account the tongue-and-groove effect and the corresponding inaccuracies of the dose calculation.

2.2 Robust DAO Model

We are assuming that a patient is irradiated from several predetermined beam directions. Each of these beams is discretized into a grid of beamlets, and the collection of all beamlets is denoted by $N$. Furthermore, $K$ represents the set of all deliverable apertures. Each aperture consists of a number of exposed beamlets, so we denote the set of beamlets in aperture $k \in K$ by $A_k \subseteq N$. In order to evaluate the dose distribution delivered to the patient, the patient geometry is discretized into a set $V$ of so-called voxels. The dose delivered to voxel $j \in V$ by aperture $k \in K$ at unit intensity is the so-called aperture dose deposition coefficient denoted by $D_{kj}$. We associate a decision variable $z_j$ with each voxel $j \in V$ representing the dose received by voxel $j \in V$. Moreover, we let decision variable $y_k$ represent the intensity of aperture $k \in K$. Voxel doses can then be expressed as a linear function of the aperture intensities through the dose deposition coefficients as follows:

$$z_j = \sum_{k \in K} D_{kj} y_k \quad j \in V.$$
2.2.1 Bounds on the Aperture Dose Deposition Coefficients

Typically, the aperture dose deposition coefficients are expressed implicitly in terms of the beamlet dose deposition coefficients $D_{ij}$, the dose delivered to voxel $j \in V$ by beamlet $i \in N$ at unit intensity:

$$D_{kj} = \sum_{i \in A_k} D_{ij} \quad k \in K, j \in V. \quad (2–1)$$

This expression only provides an approximation to the aperture dose deposition coefficients (Bjärngard and Siddon, 1982; Clarkson, 1941; Men et al., 2007; Sanz, 2000). In this study, we will focus on the fact that Equation (2–1) ignores the presence of the tongue-and-groove architecture of the leaves. In particular, beamlets on the boundary of aperture $k \in K$ that expose a tongue are partially blocked; Figure 2-1 illustrates this issue. This will cause inaccuracies in evaluating the dose distribution $z_j, j \in V$ when using the aperture dose deposition coefficients in Equation (2–1). In fact, the right-hand side of Equation (2–1) is an upper bound on $D_{kj}$ since it effectively assumes that no leaf tongue is present; in the remainder, we will denote this upper bound by

$$\overline{D}_{kj} = \sum_{i \in A_k} D_{ij}.$$

Thus, the realized dose distribution will be smaller than one that is planned based on the approximation in Equation (2–1), potentially causing underdosing of target voxels.

![Figure 2-1. Shaded beamlets on the boundary of the aperture are partially blocked by the exposed leaf tongues.](image-url)
To be able to measure the effect of the leaf tongue, let $D_{ij}^\delta$ denote the dose delivered to voxel $j \in V$ by beamlet $i \in N$ at unit intensity from which a strip of width $\delta$ is removed. (Clearly, $D_{ij}^0 = D_{ij}$ and $D_{ij}^\delta < D_{ij}^{\delta'}$ if $\delta > \delta'$.) We then define

$$D_{kj}^{\delta} \equiv \sum_{i \in A_k \setminus \partial_k} D_{ij} + \sum_{i \in \partial_k} D_{ij}^\delta \quad j \in V, k \in K$$

where $\partial_k \subseteq A_k$ is the set of beamlets in aperture $k$ that expose a tongue. Now if the leaf tongue has width $\delta$, then

$$D_{kj} = D_{kj}^{\delta} \quad k \in K, j \in V.$$  

However, since the width of the leaf tongue is typically on the order of 0.5 mm (Boyer et al., 2001), it is difficult for commonly used approximate dose models to accurately account for its effect on the beamlet dose deposition coefficients. Our approach will therefore be to obtain a lower bound for these coefficients by overestimating the width of the tongue to allow for an accurate estimation of $D_{ij}^{\delta}$. Clearly, when $\delta$ is chosen to be larger than the width of the tongue, $D_{kj}^{\delta}$ provides a lower bound on $D_{kj}$ since it effectively assumes that the leaf tongue is larger (and therefore blocks more dose) than the physical leaf tongue. For convenience, we will in the remainder denote the matrices of aperture dose deposition coefficients as well as their lower and upper bounds by $D$, $D^{\delta}$, and $\overline{D}$.

### 2.2.2 Treatment Plan Evaluation Criteria

Now suppose a collection of treatment plan evaluation criteria, say $L$, has been identified to measure the treatment plan quality and are expressed as functions of the dose distribution: $G_\ell : \mathbb{R}^{|V|} \rightarrow \mathbb{R}$ for $\ell \in L$. Without loss of generality we assume that smaller values are preferred to larger values. For convenience, we also assume that all criteria are convex. This is the case for many criteria proposed in the literature, such as voxel-based penalties, Equivalent Uniform Dose, tail means or Conditional Value-at-Risk, etc. In addition, it has been shown that in a multi-criteria
framework where the relative weights of the different criteria are varied, many others can equivalently be replaced by convex ones; e.g.: Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) (Romeijn et al., 2004). Moreover, we assume that the set $L$ can be partitioned into two subsets $L = \underline{L} \cup \overline{L}$, where criteria that deal with effects of underdosing correspond to $\ell \in \underline{L}$ while criteria that deal with overdosing correspond to $\ell \in \overline{L}$. This is usually easy to do, especially if each of the criteria is a function of the dose distribution in a specific structure only. Finally, we make the mild assumption that each of the criteria is monotone in each voxel dose. In particular, if $z, z'$ are two dose distributions such that $z \preceq z'$ then $G_\ell(z) \leq G_\ell(z')$ for all $\ell \in \underline{L}$ and $G_\ell(z) \geq G_\ell(z')$ for all $\ell \in \overline{L}$. In other words, uniformly increasing the dose distribution cannot deteriorate an underdosing criterion or improve an overdosing criterion.

### 2.2.3 Robust DAO Formulation

We next propose to use a robust DAO approach to treatment planning that identifies a high-quality treatment plan for all values of the aperture dose deposition coefficients within the bounds derived in Section 2.2.1 (Ben-Tal and Nemirovski, 1998, 2002). This is an optimization problem formulated in terms of all deliverable apertures and their associated intensities:

$$\text{minimize} \quad \max_{D^\delta \leq D \leq D^\Delta} \sum_{\ell \in L} \gamma_\ell G_\ell \left( \sum_{k \in K} D_{k}y_{k} \right)$$

subject to

$$y_{k} \geq 0 \quad k \in K$$

where the values $\gamma_\ell (\ell \in L)$ are the (nonnegative) weights associated with the criteria and $D_{k} = (D_{kj}; j \in V)$ is the vector of aperture dose deposition coefficients for aperture $k \in K$. The objective function therefore measures the worst-case weighted sum of all criteria over all aperture dose deposition coefficients within the specified bounds. (In
principle, upper bounds on any or all of the convex criteria functions $G_\ell (\ell \in L)$ could be accommodated as well; however, for ease of exposition we will not explicitly incorporate this model extension.)

The objective function of (R) has a mathematically inconvenient and cumbersome form. In the remainder of this section we will therefore propose two reformulations of this model as tractable convex optimization problems. The first is a reformulation that uses the mathematical properties of the treatment plan evaluation criteria to derive a conservative bound on the objective function. The second one is equivalent to (R), but applies only if the treatment plan evaluation criteria are convex voxel-based penalty functions. Both reformulations rely on new decision variables $z_j$ and $\bar{z}_j$ that represent a lower and upper bound on the dose received by voxel $j \in V$, respectively:

$$z_j = \sum_{k \in K} D_{kj} y_k$$  \hspace{1cm} j \in V \hspace{1cm} (2–2)$$

$$\bar{z}_j = \sum_{k \in K} \overline{D}_{kj} y_k$$ \hspace{1cm} j \in V. \hspace{1cm} (2–3)$$

In other words, Equations (2–2) and (2–3) provide lower and upper bounds on the dose distribution.

2.2.3.1 Reformulation 1

The first reformulation is based on the following intuitive and appealing argument. First, recall that $z$ and $\bar{z}$ are a lower and upper bound on the delivered dose distribution, respectively. Then suppose we let the objective function measure the treatment plan quality conservatively: any treatment plan evaluation criterion concerned with underdosing is evaluated at the lower bound of the delivered dose distribution, while any treatment plan evaluation criterion concerned with overdosing is evaluated at the upper bound of the delivered dose distribution. This then leads to the following DAO model:

$$\text{minimize} \sum_{\ell \in \mathcal{L}} \gamma_\ell G_\ell (z) + \sum_{\ell \in \mathcal{T}} \gamma_\ell G_\ell (\bar{z})$$
subject to \((\mathcal{P}_c)\)

\[
\begin{align*}
   z_j &= \sum_{k \in K} D_{kj} y_k & j \in V \\
   \bar{z}_j &= \sum_{k \in K} \overline{D}_{kj} y_k & j \in V \\
   y_k &\geq 0 & k \in K.
\end{align*}
\]  

\((2–4)\)

\((2–5)\)

\((2–6)\)

It is easy to see that the objective function satisfies

\[
\max_{\overline{D} \leq D \leq D^\ell} \sum_{\ell \in \mathcal{L}} \gamma_\ell G_\ell \left( \sum_{k \in K} D_{k,j} y_k \right) \leq \sum_{\ell \in \mathcal{L}} \gamma_\ell \max_{\overline{D} \leq D \leq D^\ell} G_\ell \left( \sum_{k \in K} D_{k,j} y_k \right).
\]  

\((2–7)\)

Since for each \(\ell \in \mathcal{L}\) the function \(G_\ell\) is nonincreasing we have

\[
\max_{\overline{D} \leq D \leq D^\ell} G_\ell \left( \sum_{k \in K} D_{k,j} y_k \right) = G_\ell \left( \sum_{k \in K} \overline{D}_{k,j} y_k \right)
\]

while for each \(\ell \in \mathcal{L}\) the function \(G_\ell\) is nondecreasing we have

\[
\max_{\overline{D} \leq D \leq D^\ell} G_\ell \left( \sum_{k \in K} D_{k,j} y_k \right) = G_\ell \left( \sum_{k \in K} D_{k,j} y_k \right).
\]

This implies that the objective function of \((\mathcal{P}_c)\) is an upper bound on that of \((\mathcal{R})\).

Therefore, this reformulation is indeed, if anything, more conservative than \((\mathcal{R})\) (i.e., it is robust against larger deviations in the dose deposition coefficients). Moreover, this optimization problem is only marginally larger than a traditional DAO model that does not account for the tongue-and-groove effect.

### 2.2.3.2 Reformulation 2

Now suppose that the treatment plan evaluation criteria are all voxel-based penalty functions. This means that the objective function of \((\mathcal{R})\), for fixed \(D\), can be written as

\[
\sum_{j \in V} F_j \left( \sum_{k \in K} D_{kj} y_k \right)
\]

where the functions \(F_j : \mathbb{R} \to \mathbb{R}\) are convex \((j \in V)\). Note that we have implicitly incorporated the criterion weights \(\gamma_\ell\) into the voxel-based penalty functions. Typically,
but not necessarily, the function $F_j$ will depend only on the structure containing the voxel $j \in V$.

Now let us evaluate, for each voxel, the penalty function at both the upper and lower bound of the voxel dose, and associate the maximum of these two penalties to this voxel. This yields the following DAO model:

$$\minimize \sum_{j \in V} \max \{ F_j(z_j), F_j(\bar{z}_j) \}$$

subject to

$$z_j = \sum_{k \in K} D_{kj} y_k \quad j \in V$$

$$\bar{z}_j = \sum_{k \in K} \bar{D}_{kj} y_k \quad j \in V$$

$$y_k \geq 0 \quad k \in K.$$

It can be shown that (P) is equivalent to (R) for voxel-based penalty objectives. More specifically, in contrast with Inequality (2–7) we can now exactly reformulate the objective function as follows:

$$\max \left\{ \sum_{j \in V} \left( \sum_{k \in K} D_{kj} y_k \right) \right\} = \sum_{j \in V} \max \left\{ F_j \left( \sum_{k \in K} D_{kj} y_k \right), F_j \left( \sum_{k \in K} \bar{D}_{kj} y_k \right) \right\}$$

where $D_j = (D_{kj}; k \in K)$ is the vector of aperture dose deposition coefficients corresponding to voxel $j \in V$ (and similarly for $\bar{D}_j$). Then for each $j \in V$ we have, due to the convexity of $F_j$ and the nonnegativity of $y_k (k \in K)$,

$$\max_{D_j \leq D \leq \bar{D}_j} F_j \left( \sum_{k \in K} D_{kj} y_k \right) = \max \left\{ F_j \left( \sum_{k \in K} D_{kj} y_k \right), F_j \left( \sum_{k \in K} \bar{D}_{kj} y_k \right) \right\}.$$ 

This implies that the objective function of (P) is equal to that of (R). Moreover, this optimization problem is of comparable size to (P*).
2.3 Solution Method

2.3.1 Column Generation Algorithm

The total number of potential apertures that needs to be included in $(P)$ (i.e., the cardinality of the set $K$) is very large. For example, for an MLC in which all possible leaf settings are allowable, a beamlet grid of $20 \times 20$ for each of 5 beams yields a total of about $2 \times 10^{46}$ deliverable apertures. Since this means that it is intractable to solve problems $(P)$ (and $(P^c)$) directly, we employ a column generation approach; in this iterative approach, we start by choosing a limited set of apertures, denoted by $\hat{K}$. We then, at each iteration, solve a restricted version of $(P)$ using only the apertures in $\hat{K}$. Given the corresponding solution, we solve an optimization subproblem that either (1) identifies one or more promising apertures that improve the current solution when added to $\hat{K}$, or (2) concludes that no such aperture exists and therefore the current solution is optimal. (This problem is often referred to as the pricing problem.) In case of (1), we add the identified apertures to $\hat{K}$ and repeat the procedure. Intuitively, the pricing problem identifies those apertures for which the improvement of the objective function per unit intensity is largest and therefore, once added to the current set of apertures, will significantly improve the treatment plan quality.

In the following we derive the mathematical form of the pricing subproblem and develop an efficient algorithm for solving this problem to optimality in case the only deliverability constraints of the MLC are the so-called row-convexity constraints. Depending on the manufacturer of the MLC, apertures can be subject to other deliverability constraints as well, and the algorithm described in Appendix B.2 can easily be extended to account for: (1) interdigitation constraints and (2) connectedness constraints.
2.3.2 Pricing Problem

2.3.2.1 Formulating the pricing problem

In this section we formulate the pricing problem of the column generation algorithm described in Section 2.3.1 and develop a solution approach to solve it. Let \( \pi_j \) and \( \pi_j \) (\( j \in V \)) and \( \rho_k \) (\( k \in K \)) be the dual multipliers associated with Constraints (2–4)–(2–6).

In order to be able to accommodate both of the two reformulations in Section 2.2.3 we will actually study a slightly more general model which, with a slight abuse of notation, allows for the treatment plan evaluation criteria to be a function of both \( z \) and \( z \): \( G_\ell(z, z) \). Since the objective function is convex and the constraints are linear, the Karush-Kuhn-Tucker (KKT) conditions (Bazaraa et al., 2006) are necessary and sufficient conditions for optimality of (P). Assuming for convenience that the objective function is differentiable they can be written as follows:

\[
\begin{align*}
Z_j &= \sum_{k \in K} D_{kj} y_k \\
\bar{z}_j &= \sum_{k \in K} \bar{D}_{kj} y_k \\
\pi_j &= \sum_{\ell \in L} \gamma_\ell \frac{dG_\ell(z, z)}{d\bar{z}_j} \\
\bar{\pi}_j &= \sum_{\ell \in L} \omega_\ell \frac{dG_\ell(z, z)}{d\bar{z}_j} \\
\rho_k &= \sum_{j \in V} D_{kj} \pi_j + \sum_{j \in V} \bar{D}_{kj} \bar{\pi}_j \\
y_k \rho_k &= 0 \\
y_k, \rho_k &\geq 0
\end{align*}
\]

(If the treatment plan evaluation criteria are convex but not everywhere differentiable we can use the generalized KKT conditions derived by Hiriart-Urruty (1978). The analysis in the remainder of this section remains essentially unchanged.) Any solution of the system above can be characterized by a vector of aperture intensities \( y \geq 0 \); this vector
then determines \( z, \bar{z}, \pi, \bar{\pi} \) and \( \rho \). Now let \( (\hat{y}; \hat{\pi}, \hat{\pi}, \hat{\rho}) \) be an optimal pair of primal and dual solutions to a restricted version of (P) in which only apertures in the set \( \hat{K} \subset K \) are considered. In other words, \( \hat{y}_k = 0 \) for \( k \in K \setminus \hat{K} \). This solution is optimal to (P) if and only if \( \hat{\rho}_k \geq 0 \) for all \( k \in K \) since in this case the set of KKT conditions for (P) will be fully satisfied. In order to check whether or not these constraints are satisfied we formulate the so-called pricing problem as follows:

\[
\text{minimize}_{k \in K} \hat{\rho}_k = \sum_{j \in V} D_{kj}^\delta \hat{\pi}_j + \sum_{j \in V} D_{kj} \hat{\pi}_j. \]

Furthermore we have

\[
\sum_{j \in V} D_{kj}^\delta \hat{\pi}_j + \sum_{j \in V} D_{kj} \hat{\pi}_j = \sum_{j \in V} \left( \sum_{i \in A_k \setminus \partial_k} D_{ij} + \sum_{i \in \partial_k} D_{ij}^\delta \right) \hat{\pi}_j + \sum_{j \in V} \left( \sum_{i \in A_k} D_{ij} \right) \hat{\pi}_j + \sum_{j \in V} \left( \sum_{i \in \partial_k} D_{ij}^\delta \hat{\pi}_j + \sum_{j \in V} D_{ij} \hat{\pi}_j \right).
\]

We can interpret the objective function of the pricing problem as follows: as we increase the intensity of a beamlet \( i \in \partial_k \), \( \sum_{j \in V} D_{ij}^\delta \hat{\pi}_j \) represents the per-unit change to the objective function value due to underdosing effects while \( \sum_{j \in V} D_{ij} \hat{\pi}_j \) represents the per-unit change in the objective function value due to overdosing effects. Similarly, for a beamlet \( i \in A_k \setminus \partial_k \), \( \sum_{j \in V} D_{ij} \hat{\pi}_j \) and \( \sum_{j \in V} D_{ij} \hat{\pi}_j \) represent the analogous per-unit changes to the objective function value, respectively.

### 2.3.2.2 Solving the pricing problem

In our pricing problem, the cost of aperture \( k \in K \), \( \hat{\rho}_k \), clearly depends on the beamlets that are exposed in the aperture (i.e., the set \( A_k \)). First note that the pricing problem decomposes by beam direction, hence, we can solve the pricing problem for each individual beam direction. Without incorporating the tongue-and-groove effect, Romeijn et al. (2005) show that the pricing problem decomposes by beamlet row, so that we can find the optimal solution to the pricing problem by independently finding an optimal pair of leaf settings for each beamlet row. However, when the tongue-and-groove
effect is taken into account the leaf settings in adjacent beamlet rows are important since these determine the set $\partial_k$. We therefore formulate and solve the pricing problem for a given beam using a modification of the network flow model that was developed in Romeijn et al. (2005) for solving the pricing problem under interdigitation constraints. In particular, consider a fixed beam with a beamlet grid of dimensions $m \times n$ (i.e., $m$ rows and $n$ columns). We then create a network where each node corresponds to a potential leaf setting in a particular beamlet row. In other words, a typical node is characterized as $(r, c_1, c_2)$, where $r$ indicates the beamlet row and $(c_1, c_2)$ represent the rightmost beamlet blocked by the left leaf and the leftmost beamlet blocked by the right leaf in row $r$ ($r = 1, \ldots, m$; $c_1 = 0, \ldots, n$; and $c_2 = 1, \ldots, n + 1$ with $c_1 < c_2$). (If $c_1 = 0$ the left leaf blocks no beamlets, and if $c_2 = n + 1$ the right leaf blocks no beamlets.) In addition, we define source node, say 0, and sink node, say $(m + 1, 0, 1)$, representing the top (“beamlet row 0”) and bottom (“beamlet row $m + 1$”) of the aperture. We then define arcs from all nodes in beamlet row $r$ to all nodes in a beamlet row $r + 1$ ($r = 0, \ldots, m$). Figure 2-2 illustrates the structure of this network for a small case of $m = 2$ rows and $n = 2$ columns.

![Network Model](image)

Figure 2-2. The network model for the pricing problem under row-convexity constraints.
Now note that there is a one-to-one correspondence between paths from the source node 0 to the sink node \((m + 1, 0, 1)\) and deliverable apertures. Without loss of generality, assume that the tongue between rows \(r\) and \(r + 1\) are part of the latter and hence partially block the former (i.e., row \(r\)). Next, we assign a cost to each arc which is defined as the cost of the exposed beamlets corresponding to the origin node of the arc. In particular, consider nodes \((r, c_1, c_2)\) and \((r + 1, c'_1, c'_2)\). Then \(c_1 + 1, \ldots, c_2 - 1\) are the exposed beamlets at row \(r\) and \(\{c_1 + 1, \ldots, c'_1\} \cup \{c'_2, \ldots, c_2 - 1\}\) are the ones among those that expose a tongue due to the leaf setting in row \(r + 1\). (Note that, if \(c_1 \geq c'_1\) the former set is empty (i.e., the left leaf of row \(r + 1\) does not expose a tongue) and similarly if \(c_2 \leq c'_2\) the latter set is empty (i.e., the right leaf of row \(r + 1\) does not expose a tongue) (Figure 2-3). Representing the beamlet in row \(r\) and column \(c\) by \((r, c)\), the cost associated with the arc from node \((r, c_1, c_2)\) to node \((r + 1, c'_1, c'_2)\) is equal to

\[
\begin{align*}
\sum_{c=c_1+1}^{c_2} \left( \sum_{j \in V} D_{(r,c),j} \hat{\pi}_j + \sum_{j \in V} D_{(r,c),j} \tilde{\pi}_j \right) &+ \sum_{c=c'_2}^{c_2-1} \left( \sum_{j \in V} D_{(r,c),j} \hat{\pi}_j + \sum_{j \in V} D_{(r,c),j} \tilde{\pi}_j \right) \\
\sum_{c=\max\{c_1, c'_1\}+1}^{\min\{c_2, c'_2\}-1} \left( \sum_{j \in V} D_{(r,c),j} \hat{\pi}_j + \sum_{j \in V} D_{(r,c),j} \tilde{\pi}_j \right)
\end{align*}
\]

(for \(r = 1, \ldots, m\)). Finally, we assign a cost of zero to the arcs from the source node 0 to the nodes corresponding to beamlet row 1. The length of any path from the source node to the sink node is then equal to the objective function value in the pricing problem of the corresponding aperture. Therefore, the optimal solution to the pricing problem can be found by solving a shortest path problem in the network described above. Since the network is acyclic, this problem can be solved in an amount of time that is proportional to the number of arcs in the network. Since it is easy to see that the total number of nodes in the network is \(O(mn^2)\) and the total number of arcs in this network is \(O(mn^4)\), the problem can be solved in \(O(mn^4)\) time (Ahuja et al., 1993).

Finally, we note that under interdigitation constraints (the left leaf of a row cannot overlap with the right leaf of an adjacent row) and connectedness constraints (the rows
in which at least one beamlet is exposed are consecutive, relevant if the left and right leaves cannot entirely block a beamlet row and backup jaws are required) the pricing problem can be solved in a very similar way and with the same running time using slight modifications of the algorithms for these cases presented in Romeijn et al. (2005).

2.4 Results

2.4.1 Patient Cases

We used a set of ten head-and-neck cases to study our model. For all cases, we designed plans using five equispaced $^{60}$Co-beams around the patient. The nominal size of each beam is $40 \times 40 \text{ cm}^2$. The beams are discretized into beamlets of size $1 \times 1 \text{ cm}^2$, yielding on the order of 1,600 beamlets. However, we reduced the number of beamlets considered in the model by defining a mask for each beam eliminating any beamlets that only have a negligible contribution to target coverage. We generated data for a voxel grid of size $4 \times 4 \times 4 \text{ mm}^3$ for all targets and critical structures. This data was used for the evaluation of all treatment plans; however, in the optimization model we used a coarser resolution of $8 \times 8 \times 8 \text{ mm}^3$ for unspecified tissue (full resolution was used for all targets and other critical structures). Table 2-1 shows the problem dimensions for the ten cases.

Each case contains two Planning Target Volumes, PTV1 and PTV2, with prescription doses of 73.8 Gy and 54 Gy, respectively. To determine the clinical quality of the treatment plans obtained by our method we employ the following clinical dose-volume histogram (DVH) criteria (from the treatment planning protocol used in the Department of Radiation Oncology at the University of Florida):
PTV1. At least 99% should receive at least 93% of the prescribed dose ($0.93 \times 73.8 = 68.6$ Gy). At least 95% should receive at least the prescribed dose (73.8 Gy). No more than 10% should receive more than 110% of the prescribed dose ($1.1 \times 73.8 = 81.2$ Gy). No more than 1% should receive more than 120% of the prescribed dose ($1.2 \times 73.8 = 88.6$ Gy).

PTV2. At least 99% should receive at least 93% of the prescribed dose ($0.93 \times 54 = 50.2$ Gy). At least 95% should receive at least the prescribed dose (54 Gy).

Salivary glands. These include left and right parotid glands (LPG/RPG) as well as left and right submandibular glands (LSG/RSG). No more than 50% of each gland should receive more than 30 Gy.

Other structures. Spinal cord (SC) should receive no more than 45 Gy. Brainstem (BS) should receive no more than 54 Gy. Unspecified tissue (UT) should receive no more than 60 Gy.

DVH constraints on additional critical structures, such as for example optic nerves and chiasm, were always easily satisfied in our experiments so we have omitted them from our results and analysis.

2.4.2 Treatment Plan Evaluation Criteria

For our proof of concept we used treatment plan evaluation criteria that consist of one-sided quadratic voxel-based penalty functions. In particular, let $T$ denote the set of

<table>
<thead>
<tr>
<th>Case</th>
<th># structures</th>
<th># beamlets</th>
<th># voxels (model)</th>
<th># voxels (full)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>813</td>
<td>17,108</td>
<td>85,017</td>
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<tr>
<td>2</td>
<td>13</td>
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<td>23,998</td>
<td>104,298</td>
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<td>36,288</td>
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<td>11</td>
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<td>195,113</td>
</tr>
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<td>15,916</td>
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<td>1,721</td>
<td>40,198</td>
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</table>
targets and $S$ the set of all structures (including targets). Moreover, let $V_s \subseteq V$ denote the set of voxels in structure $s \in S$. (For convenience we will, in the optimization model, assume that each voxel is assigned to a single structure only; the discussion below can without any problems be generalized to situations where this is not the case.) We then associate a function penalizing overdosing with the voxels in all structures, and a function penalizing underdosing with the voxels in all targets. More specifically, we let (with a slight abuse of notation) $\mathcal{L} = T \times \{-\}$ and $\mathcal{L} = S \times \{+\}$ and define

$$G_{(s,-)}(z) = \sum_{j \in V_s} F_s(z_j) \quad s \in T$$

$$G_{(s,+)}(z) = \sum_{j \in V_s} F_s(z_j) \quad s \in S$$

where

$$F_s(z_j) = \frac{1}{|V_s|} (\max\{0, T_s - z_j\})^2 \quad j \in V_s, s \in T \quad (2-8)$$

$$F_s(z_j) = \frac{1}{|V_s|} (\max\{0, z_j - T_s\})^2 \quad j \in V_s, s \in S \quad (2-9)$$

where Equation (2–8) quadratically penalizes underdosing below the underdosing threshold $T_s$ in target $s \in T$ while Equation (2–9) quadratically penalizes overdosing above the overdosing threshold $T_s$ in structure $s \in S$. In terms of the notation of Section 2.2.3.2 we have the following voxel-based penalty functions:

$$F_j(z_j) = \gamma_{(s,-)}F_s(z_j) + \gamma_{(s,+)}F_s(z_j) \quad j \in V_s; s \in T$$

$$F_j(z_j) = \gamma_{(s,+)}F_s(z_j) \quad j \in V_s; s \in S \setminus T.$$
2.4.3 Tongue-and-Groove Effect Bounds

To account for the inaccuracies caused by the tongue-and-groove effect, we provide a lower and upper bound on the realized dose distribution according to Equations (2–2) and (2–3). For that purpose, we calculated the dose deposition coefficients for the actual beamlets as well as for the reduced beamlets from which a strip of width $\delta$ was removed. In commercial MLCs the tongue-and-groove offset of the leaf can be as small as 0.5 mm (Boyer et al., 2001). We therefore generated values of $D_{ij}^{\delta}$ for $\delta \in \{0, 0.5, 1, 3, 5\}$ (where $\delta$ is measured in mm) and solved the DAO model for each of these values. Since it is hard to accurately quantify the effect of a very small value of $\delta$ we do not advocate using $\delta = 0.5$ in a clinical setting. However, we used this value to assess the importance of even small deviations from the “ideal” (i.e., without leaf tongue) dose deposition coefficients. Next, we compared the quality of the treatment plans for the coarser bounds obtained using the larger values $\delta \in \{1, 3, 5\}$ with the treatment plan obtained with the traditional model ($\delta = 0$).

2.4.4 Implementation and Results

The optimization problems of the form (P) were solved from our UFORT treatment planning system using our custom primal-dual interior point algorithm (Aleman et al., 2010). We manually tuned the model parameters (i.e., the underdosing and overdosing thresholds as well as the weights associated with the evaluation criteria) based on two of the cases. We then used this set of parameters to solve (different variants of) the problem for all ten patient cases. All the experiments were performed in MATLAB 2009b on a 2.33 GHz Intel Core 2 Duo processor with 2 GB of RAM using Windows operating system.

As mentioned earlier in this section, we use our column generation algorithm to solve the instances of (P), and at each iteration of the algorithm, we solve the pricing problem to determine if there exists any promising aperture which can improve the treatment plan. As the algorithm progresses and the number of apertures explicitly
incorporated in the model increases, the marginal benefit of additional apertures becomes clinically insignificant. Therefore, we terminate the algorithm by monitoring the clinical DVH criteria described above. More specifically, we stop the algorithm if, in the last five iterations, the range of observed DVH criterion value spans less than $\Delta$, where $\Delta = 0.2\%$ for targets and $\Delta = 2\%$ for critical structures. On the average, it takes around 3–5 minutes for the traditional DAO method and 7–9 minutes for the robust DAO method per clinical case to converge.

Table 2-2 compares the DVH criteria associated with target coverage obtained by the robust and traditional DAO methods using $\delta = 0.5$ for three clinical cases. For all cases and DVH criteria, we show both the lower and upper bound on the percent volume of a structure that receives at least the specified dose. However, due to the realistic size of the tongue width, the lower bounds are most representative of the realized delivered dose to the patient. The results therefore clearly show that treatment plans obtained by the traditional DAO model exhibit significant underdosing of PTV1 and also, to a somewhat lesser extent, of PTV2. In particular, the actual percent volume of PTV1 receiving at least the prescribed dose (73.8 Gy) in the traditional DAO model (that ignores the tongue-and-groove effect) varies from 79–92% while the corresponding values in the robust DAO model are 95–100%. This highlights the potential risk of underdosing the target when ignoring the tongue-and-groove effect during the treatment planning phase. In particular, Figure 2-4 illustrates the isodose curves on a typical CT slice for clinical case 1. More specifically, isodose lines corresponding to the lower and upper bounds on the dose distribution obtained by the traditional and robust models are separately shown in the figure. For the traditional model, the lower bound on the dose distribution yields several cold spots in PTV1. However, the lower bound obtained by the robust model has significantly fewer cold spots and yields a better target coverage.

In the remainder of this section we will focus on the robust DAO model with more conservative bounds on the dose distribution obtained with larger $\delta$ values.
Tables 2-3–2-8 compare the results of our robust DAO method that accounts for the tongue-and-groove effect with results of the traditional DAO model on ten clinical cases for $\delta = 1, 3, \text{and } 5$.

With respect to tumor coverage, the robust DAO model provides tight DVH bounds compared to the traditional DAO model. In contrast to the traditional DAO model, the robust DAO model is capable of maintaining acceptable DVH lower bounds on target coverage in the majority of the patient cases, even for large values of $\delta$. It is important to note that the width of the MLC leaf tongues is (much) smaller than the values of $\delta$ that we used in our experiments. This means that the lower bounds calculated for both models can be expected to be quite loose, especially for $\delta = 3$ or 5. This means that even in the few cases where the target coverage lower bounds fall slightly short of what is desired, the actual coverage should be clinically acceptable. This argument of course also applies to the traditional DAO model. However, for this model the lower bounds are so far away from what is clinically acceptable that we cannot conclude that the treatment plans obtained without taking tongue-and-groove effects into account are clinically acceptable. In particular, employing the robust DAO model can significantly improve the uncertainties in PTV1 and PTV2 coverage due to the tongue-and-groove effect. For example, with the robust DAO model and $\delta = 3$, the lower bound on PTV1 target coverage at the prescription dose of 73.8 Gy is at least 95% in 8 out of 10 cases, and 92% and 94% in the other two cases, respectively. For the traditional model, the corresponding lower bounds are below 10% in all cases.

With respect to structure sparing, for larger values of $\delta$ the traditional DAO model provides smaller upper bounds on the corresponding DVH criteria than the robust DAO model. This can be explained by the fact that to ensure a desirable target coverage for all aperture dose deposition coefficients in the range $D^\delta \leq D \leq \overline{D}$ (i.e., a desirable lower bound on target coverage), the robust DAO model is forced to select apertures that provide more dose to critical structures. However please note that, in the majority of the
cases, the robust DAO model satisfies the DVH criterion for a given structure whenever the traditional DAO model satisfies this criterion. Not surprisingly, the difference between the bounds obtained by the robust and traditional models decreases with the value of $\delta$.

Figure 2.5 illustrates the DVHs of the optimal treatment plans obtained by the robust and traditional DAO models for case 5 with $\delta = 3$ mm. For a given structure, the solid and dashed lines represent the upper and lower bounds on DVH values, respectively. The upper bounds correspond to an idealized dose distribution that ignores the presence of the leaf tongues, while the lower bounds indicate how much the actual delivered dose distribution may deviate from the optimized one.

Finally, we also evaluated the ability of the more conservative model ($P_c$) in providing high-quality robust treatment plans that account for the tongue-and-groove effect. As noted before, when using treatment plan evaluation criteria that are voxel-based penalty functions (as described in Section 2.4.2) we do not need to use the more conservative model but can derive an exact robust model. However, it is still interesting to compare the two approaches since the more conservative one should be used if other criteria are desired. These experiments showed that the differences between the conservative and the exact robust models in terms of DVH bounds is negligible. We illustrate the results of the two models for $\delta = 3$ in Tables 2.9 and 2.10.

2.5 Concluding Remarks

In this study, we developed a robust Direct Aperture Optimization method for IMRT treatment planning that explicitly accounts for the dosimetric inaccuracies caused by the tongue-and-groove architecture of the MLC leaves. Our approach does not rely on being able to accurately compute these dosimetric effects. Instead, we employ dose calculations that overestimate the dimensions of the leaf tongues so that commonly used dose models can be applied. Our model then aims to find a robust treatment plan that can obtain treatment plans of high clinical quality regardless of the exact consequences of the tongue-and-groove architecture. Due to the computational difficulty
of the resulting robust optimization model we propose a reformulation that provides a conservative bound on the robust model as well as an exact and tractable reformulation for the case of voxel-based penalty criteria. We investigated the performance of the robust and traditional DAO models in the presence of the tongue-and-groove effect on ten clinical head-and-neck cancer cases. The experiments validate the ability of the proposed approach in designing robust treatment plans. Although the suggested robust optimization approach is presented to account for the tongue-and-groove effect, in principle, it could be applied to any source of dosimetric inaccuracies for which a lower and upper bound on the beamlet dose deposition coefficients can be provided. Future research can extend this work by generalizing this approach to account for dosimetric inaccuracies caused by employing approximate dose calculation methods.
Figure 2-4. Isodose curves (dashed lines) for 73.8 Gy, 54 Gy, and 30 Gy on a typical CT slice corresponding to optimal treatment plans obtained for case 1.
Figure 2-5. Lower (dashed) and upper (solid) bounds on the DVHs of the optimal treatment plan obtained by the traditional and robust model for case 5 using $\delta = 3$ mm.
Table 2-2. Lower and upper bounds for target DVH criteria obtained by the new and traditional models for $\delta = 0.5$ mm (in % volume).

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Table 2-3. Lower and upper bounds for target DVH criteria obtained by the new and traditional models for $\delta = 5$ mm (in % volume).

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Table 2-4. Lower and upper bounds for critical-structure DVH criteria obtained by the new and traditional models for $\delta = 5$ mm (in % volume).

Table 2-5. Lower and upper bounds for target DVH criteria obtained by the new and traditional models for $\delta = 3$ mm (in % volume).

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Table 2-6. Lower and upper bounds for critical-structure DVH criteria obtained by the new and traditional models for $\delta = 3$ mm (in % volume).

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Table 2-7. Lower and upper bounds for target DVH criteria obtained by the new and traditional models for $\delta = 1$ mm (in % volume).

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Table 2-8. Lower and upper bounds for critical-structure DVH criteria obtained by the new and traditional models for $\delta = 1$ mm (in % volume).

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Table 2-9. Lower and upper bounds for target DVH criteria obtained by the conservative and exact robust models for $\delta = 3$ mm (in % volume).

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Table 2-10. Lower and upper bounds for critical-structure DVH criteria obtained by the conservative and exact robust models for $\delta = 3$ mm (in % volume).

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3.1 Introductory Remarks

External beam radiation therapy is a commonly used treatment modality for cancer, with over 25% of patients benefiting from this type of treatment. During radiation therapy, beams of radiation pass through the patient’s body killing both cancerous and healthy cells. Thereby, the radiation treatment must be carefully planned so that a clinically prescribed dose is delivered to cancerous cells while sparing normal cells in nearby organs and tissues to the greatest extent possible. Intensity-modulated radiation therapy (IMRT) is a delivery technique in which a multileaf collimator system (MLC) dynamically shapes the radiation beam by blocking part of the radiation (Webb, 2001; Bortfeld, 2006). In particular, each configuration of the MLC leaves is called an aperture. An IMRT treatment plan consists of a collection of apertures to be formed by the MLC along with their associated intensities. Beam-on-time is the amount of time that the linear accelerator is delivering dose to the patient, which can be expressed as the sum of all aperture intensities. Beam-on-time is an important aspect of a treatment plan. Firstly, long beam-on-times can cause inconvenience to the patient since they are required to be immobilized while receiving radiation. Furthermore, total body dose (or integral dose) and its biological complications are highly dependent on the beam-on-time (Hall and Wuu, 2003; Hall, 2006). Finally, time efficiency is a key factor considered by all radiation therapy facilities, impacting the number of patients that can be treated as well as costs. On the other hand, obtaining a clinically acceptable treatment plan, especially for tumors with complex anatomy, requires relatively long beam-on-times (Mohan et al., 2000).

The goal of this paper is to develop and test a new solution approach to IMRT treatment planning which incorporates the beam-on-time as a measure of the delivery efficiency into the treatment-plan optimization stage. This will allow for explicitly quantifying the trade-off between the beam-on-time and the quality of the treatment plan. The proposed
approach can assist clinicians in visualizing this trade-off to design effective and efficient
treatment plans.

IMRT treatment plan optimization is traditionally performed in two sequential stages:
(1) fluence map optimization (FMO) and (2) leaf sequencing (LS). In particular, the
radiation head at each beam direction defines a rectangular beam, which is conceptually
discretized into a set of small beamlets. The FMO problem then involves determining
the optimal intensities for all beamlets; for modeling and solution approaches to FMO
we refer to the review papers by Shepard et al. (1999) and Romeijn and Dempsey
(2008). Given the optimal fluence map, the LS problem decomposes the fluence
map for each beam into a set of deliverable apertures that is optimal with respect to,
typically, beam-on-time, number of apertures used, or total treatment time. Minimizing
beam-on-time in the LS problem has been extensively studied in the literature. In
particular, if any row-convex aperture is deliverable, several polynomial-time algorithms
have been proposed to solve the problem (Ahuja and Hamacher, 2005; Bortfeld et al.,
1994; Kamath et al., 2003; Siochi, 1999). In addition, Baatar et al. (2005), Boland
et al. (2004), Dai and Hu (1999), Kamath et al. (2004a), and Siochi (1999) studied
the problem under additional MLC hardware constraints. However, postponing the
beam-on-time minimization to the LS stage prevents us from studying the desired
trade-off since the treatment quality is determined by the fluence map which is fixed
at this stage. Hence, some studies have addressed the beam-on-time minimization
in the FMO stage. In particular, it has been empirically shown that decomposing
smoother fluence maps results in shorter beam-on-times (Mohan et al., 2000; Webb
et al., 1998). Based on this observation, Craft et al. (2007) use the maximum variation
in beamlet intensities at MLC rows as an approximate measure of the beam-on-time.
They then formulate the FMO problem as a multi-criteria optimization problem which
minimizes this approximate measure along with other measures of treatment plan
quality. Moreover, recently Jin et al. (2010) developed a quadratic programming model
for the FMO problem in which the total required beam-on-time is linearly constrained using the leaf trajectory matrices. However, their modeling framework is only applicable to unidirectional leaf sweeping schemes.

Aperture modulation or Direct Aperture Optimization (DAO) is a relatively new approach to IMRT treatment planning which integrates the FMO and LS problems. More formally, DAO explicitly solves for aperture shapes and intensities rather than beamlet intensities (Bednarz et al., 2002; Preciado-Walters et al., 2006; Romeijn et al., 2005). Shepard et al. (2002) and Ludlum and Xia (2008) compare IMRT treatment plans obtained using DAO and the traditional two-stage method, and show that DAO produces comparable dose conformity while significantly improving the treatment efficiency. In particular, Ludlum and Xia (2008) and Men et al. (2007) report that to achieve a similar treatment quality, the beam-on-time required by the traditional two-stage method is more than twice as long as the beam-on-time required by DAO. Additionally, a long treatment time can undesirably increase the sensitivity of the treatment outcome to dosimetric inaccuracies caused during the delivery (Shepard et al., 2002; Romeijn et al., 2005). Furthermore, fluence map decomposition during the LS stage of the traditional method requires discretization which may compromise the treatment quality as well. Finally, in order to adequately model many important characteristics of an IMRT treatment plan, knowledge of the shape and intensity of the apertures employed in that treatment plan is required. In contrast with the traditional two-stage approach, DAO allows for explicitly incorporating these aspects into the treatment-plan optimization stage. For example, Men et al. (2007) exploited this to develop a DAO approach that accounts for transmission effects (i.e., dose that is transmitted through the MLC leaves), and Salari et al. (2011) developed a robust DAO approach to account for the dosimetric inaccuracies caused by the MLC architecture known as the tongue-and-groove effect.

To account for the delivery efficiency in IMRT treatment-plan optimization stage, we employ the bi-criteria optimization approach which is widely used when a trade-off
between two criteria needs to be made. In this approach, the concept of *Pareto efficiency* is used to characterize the candidate solutions that should be considered in quantifying the trade-off. In particular, solutions with the property that improving one criterion value is not possible unless the other criterion value deteriorates are called Pareto efficient. On the contrary, solutions for which it is possible to improve one criterion value without making the other criterion value worse are called inefficient, and therefore not worth considering. For a recent and comprehensive discussion of multi-criteria optimization we refer to Ehrgott (2005). In this paper, we propose a bi-criteria DAO model to explicitly incorporate the beam-on-time as a measure of the delivery efficiency into the IMRT treatment plan optimization. Taking advantage of the structure of the problem, we develop an exact solution technique to obtain the associated set of Pareto-efficient solutions. However, some classes of treatment plan evaluation criteria may not satisfy the mathematical assumptions required by the exact method or it may be computationally prohibitive to apply the exact method to them. Therefore, an approximate solution technique is also developed which is applicable to more classes of evaluation criteria. This method sequentially employs our exact algorithm to closely approximate segments of the Pareto-efficient frontier. Finally, using the set of Pareto-efficient solutions we investigate the effect of the beam-on-time on the treatment plan quality.

The outline of the remainder of the paper is as follows. In Section 2 we formulate a convex bi-criteria model to incorporate the beam-on-time into the DAO problem. In Section 3 we use the properties of the proposed model to obtain some fundamental results which are then employed to develop an algorithmic framework to generate the Pareto-efficient frontier associated with the bi-criteria model. In Section 4 we present the computational results obtained by applying the algorithm to clinical cancer cases, and investigate the trade-off between the beam-on-time and the treatment plan quality. Finally, in Section 5 we conclude the paper and discuss future research directions.
3.2 Direct Aperture Optimization Problem

3.2.1 Introduction

In IMRT treatment planning, the patient geometry is discretized into a set $V$ of cubes (referred to as voxels), typically based on a set of CT images. This allows for evaluating the dose distribution delivered to the patient. Furthermore, let $K$ denote the set of all deliverable apertures using the particular MLC system used. We then define the aperture dose deposition coefficients, denoted by $D_{kj}$, as the dose deposited in voxel $j \in V$ by aperture $k \in K$ at unit intensity. For convenience, we let $D_k = (D_{kj}; j \in V)$ denote the vector of aperture dose deposition coefficients corresponding to aperture $k \in K$, and $D = [D_{kj}]_{|K| \times |V|}$ the matrix of aperture dose deposition coefficients. We then associate a decision variable, $z_j$, with each voxel $j \in V$ representing the dose received by that voxel. Moreover, we let decision variable $y_k$ represent the intensity of aperture $k \in K$. Voxel doses can be expressed as a linear function of the aperture intensities through the aperture dose deposition coefficients as follows:

$$z_j = \sum_{k \in K} D_{kj} y_k \quad j \in V.$$

3.2.2 Treatment Plan Evaluation Criteria

The clinician or physician typically identifies a number of treatment plan evaluation criteria to measure the treatment plan quality, indexed by $\ell \in L$. These criteria are then expressed as functions of the dose distribution: $G_\ell : \mathbb{R}^{|V|} \rightarrow \mathbb{R}$ for $\ell \in L$. Without loss of generality we assume that smaller values are preferred to larger values. For convenience, we also assume that all criteria are convex. This is the case for many criteria proposed in the literature, such as voxel-based penalties, Equivalent Uniform Dose, tail means or Conditional Value-at-Risk, etc. In addition, it has been shown that in a multi-criteria framework where the relative weights of the different criteria are varied, many others can equivalently be replaced by convex ones; for example Tumor Control
Probability (TCP) and Normal Tissue Complication Probability (NTCP) (Romeijn et al., 2004).

### 3.2.3 Formulating the DAO Problem

We take the common approach of measuring treatment plan quality as a weighted sum of treatment plan evaluation criteria, summarized using the function $G : \mathbb{R}^{|V|} \rightarrow \mathbb{R}$ of the dose distribution:

$$G(z) = \sum_{\ell \in L} \gamma_{\ell} G_{\ell}(z)$$

where $z = (z_j; j \in V)^T$ and the coefficients $\gamma_{\ell} (\ell \in L)$ are nonnegative weights reflecting the relative importance of the different criteria. We will make the following mild assumption on $G$:

**Assumption 1.** The function $G$ is continuously differentiable and strictly convex on $\mathbb{R}^{|V|}$.

For convenience, we let $\nabla G(z) = \left( \frac{\partial G(z)}{\partial z_j}; j \in V \right)^T$.

As mentioned earlier, the beam-on-time can be expressed as the sum of all aperture intensities, which we represent by the function $H : \mathbb{R}^{|K|} \rightarrow \mathbb{R}$:

$$H(y) = \sum_{k \in K} y_k$$

where $y = (y_k; k \in K)^T$. We then formulate the direct aperture optimization problem in terms of all deliverable apertures and their associated intensities as a bi-criteria optimization problem as follows:

$$\text{minimize } \{ G(z), H(y) \}$$

subject to (P)

$$z_j = \sum_{k \in K} D_{kj} y_k \quad j \in V \quad (3-1)$$

$$y_k \geq 0 \quad k \in K. \quad (3-2)$$
Here Constraints (3–1) evaluate the dose distribution while Constraints (3–2) ensure that the aperture intensities are nonnegative. It is easy to see that any nonnegative vector \( y \) uniquely determines a dose distribution \( z \). We will therefore often refer to \( y \) as the treatment plan.

We can then use the concept of Pareto-efficiency to characterize the set of treatment plans that need to be considered in quantifying the trade-off between the two criteria (i.e., \( G \) and \( H \)). In particular, consider treatment plan \( \hat{y} \) which yields dose distribution \( \hat{z} \). \( \hat{y} \) is a Pareto-efficient treatment plan if it is not dominated by any other treatment plan. More formally, if a treatment plan, say \( \bar{y} \) with dose distribution \( \bar{z} \), exists such that either \( G(\bar{z}) \leq G(\hat{z}) \) and \( H(\bar{y}) < H(\hat{y}) \), or \( G(\bar{z}) < G(\hat{z}) \) and \( H(\bar{y}) \leq H(\hat{y}) \), then \( \hat{y} \) is dominated by \( \bar{y} \) and therefore not worth considering. On the other hand, if no such treatment plan exists, then \( \hat{y} \) is a Pareto-efficient treatment plan.

The feasible region of (P) and both objectives are convex. It is well-known that under convexity of the evaluation criteria as well as the solution space, the set of Pareto-efficient solutions can be obtained by solving the following family of optimization problems:

\[
\begin{align*}
\text{minimize} & \quad G(z) + \alpha H(y) \\
\text{subject to} & \quad \sum_{k \in K} D_{kj} y_k = z_j \quad j \in V \\
& \quad y_k \geq 0 \quad k \in K
\end{align*}
\]

where \( \alpha \geq 0 \) is a nonnegative weight that can be interpreted as a penalty on beam-on-time. This method is known as the weighted-sum method (Chankong and Haimes, 1983). Hence, any optimal solution to (P(\( \alpha \))) for some \( \alpha \geq 0 \) will be a Pareto-efficient treatment plan. Note also that the Pareto-efficient frontier, consisting of Pareto-efficient pairs of values for the two objectives \( G \) and \( H \), is a surface of a convex body.
In the remainder of this paper we will propose a solution method that obtains the optimal solutions to the family of optimization problems \( (P(\alpha)) \) for \( \alpha \geq 0 \).

### 3.3 Solution Method

The primary goal of a bi-criteria optimization problem is to obtain a complete or partial description of the set of Pareto-efficient solutions. This set can then be used to quantify the trade-off between the two criteria. For the majority of the bi-criteria optimization problems it is either impossible to obtain an exact representation of the set of Pareto-efficient solutions or it is computationally prohibitive. Therefore, an alternative is to obtain an approximate description of this set. There are various methods to approximate the Pareto-efficient frontier in the literature (Ruzika and Wieck, 2005). These techniques can be classified (based on the structure of the approximation functions) into \( 0^{\text{th}} \) order (a single Pareto point) to \( 3^{\text{rd}} \) order (piecewise cubic) approximations. Among these, \( 1^{\text{st}} \) order approximations are the most popular ones where the Pareto-efficient frontier is approximated by a piecewise linear function. These techniques mainly employ weighted-sum and \( \epsilon \)-constraint methods (Chankong and Haimes, 1983; Ehrgott, 2005) in an iterative manner to generate Pareto-efficient solutions. The Pareto-efficient frontier is then approximated using the obtained Pareto-efficient solutions. In particular, non-inferior set estimation (NISE) technique was originally proposed by Cohon et al. (1979) to generate an approximate representation of the Pareto-efficient frontier for bi-criteria convex problems (Chankong and Haimes, 1983). It is a \( 1^{\text{st}} \)-order sandwich approximation which uses piecewise linear curves to construct inner and outer envelopes on the Pareto-efficient frontier. In particular, an inner envelope comes from the convex hull of a finite collection of generated Pareto-efficient points while an outer envelope is provided by the line segments that support the Pareto-efficient frontier at these points as shown in Figure 3-1.

The NISE method first generates the two end points on the Pareto frontier by minimizing each objective function individually. At this step, the initial sandwich
approximation is a triangle spanned between the two end points and the ideal point (which is obtained by intersecting the two perpendicular lines passing through the two points). Given two adjacent Pareto-efficient points, NISE then employs the weighted-sum method to generate a new Pareto-efficient point using a weight equal to the negative slope of the inner envelope between the two adjacent points. Hence, new Pareto-efficient points are generated and the envelopes are updated accordingly in an iterative manner. Finally, NISE terminates when the maximum distance between the inner and outer envelopes is within a user-specified threshold.

There are two major issues in applying the approximation techniques to our bi-criteria optimization model \((P)\). In particular, suppose that we would use the weighted-sum method to iteratively obtain Pareto-efficient solutions. Then instances of \((P(\alpha))\) for \(\alpha \geq 0\) need to be solved individually at each iteration. Regardless of the manufacturer-dependent MLC constraints, the total number of deliverable apertures that need to be considered in \((P(\alpha))\) (i.e., the cardinality of set \(K\)) is very large (Romeijn et al., 2005). Therefore, solving each instance of \((P(\alpha))\) requires employing a column generation approach; in this approach, we implicitly consider all deliverable apertures and sequentially generate them as needed (Romeijn et al., 2005; Men et al., 2007). However, employing this approach for each individual instance can be computationally very expensive. We propose an exact approach that avoids this issue by solving
instances sequentially while gathering and using the information obtained along the way. Secondly, not all trade-offs are clinically worth considering. However, there is no explicit approach to identify range of beam-on-time penalties for which the corresponding Pareto-efficient treatment plans are clinically relevant. Our approach allows to terminate the algorithm as soon as the clinically relevant part of the Pareto-efficient frontier is obtained, potentially saving a significant fraction of the computational effort.

In the remainder of this paper we develop a solution method which obtains the family of Pareto-efficient treatment plans as a function of the beam-on-time penalty $\alpha$. In particular, we will sequentially reduce the value of $\alpha$ and characterize segments of the Pareto-efficient frontier. To this end, we first show that, under mild conditions, the optimal dose distribution to $(P(\alpha))$ is unique for each $\alpha \in \mathbb{R}_+$, say $z^*(\alpha)$. Next, we derive an explicit expression for the (finite) smallest value of $\alpha$, say $\alpha_0$, for which it is optimal not to treat. In other words, for sufficiently large beam-on-time penalty $\alpha \geq \alpha_0$ we have that $z^*(\alpha) = 0$. Then, starting with $\alpha_0$, we iteratively determine intervals for $\alpha$ for which $z^*(\alpha)$ can be explicitly characterized.

### 3.3.1 Fundamental Results

In this section, we will start by deriving some results that will form the foundation of our solution method.

#### 3.3.1.1 Uniqueness

We first show the uniqueness of the optimal dose distribution for a given beam-on-time penalty. That will allow us to characterize the family of optimal dose distributions as a function of the beam-on-time penalty $\alpha$. To this end, we first let $Z \subseteq \mathbb{R}_+^{|V|}$ be the set of all deliverable dose distributions using the apertures in $K$, in other words,

$$Z = \left\{ z = D^\top y : y \in \mathbb{R}_+^{|K|} \right\}.$$

Clearly $Z$ is convex since it is a linear transformation of $\mathbb{R}_+^{|K|}$. Next, we consider the restriction to the optimization problem $(P(\alpha))$ to a fixed dose distribution $z \in Z$. Note that
the resulting optimization problem is independent of $\alpha$:

$$\text{minimize } H(y)$$

subject to

$$(Q(z))$$

$$D^\top y = z$$

$$y \geq 0.$$ 

The following theorem then shows the uniqueness of the optimal dose distribution:

**Theorem 3.1.** For each $\alpha \in \mathbb{R}_+$ the optimal dose distribution, which we will denote by $z^*(\alpha)$, is unique.

**Proof.** Let $\Phi : Z \rightarrow \mathbb{R}_+$ denote the optimal value function of $(Q(z))$ with respect to $z$, in other words,

$$\Phi(z) = \min \{ H(y) : D^\top y = z, y \geq 0 \}.$$ 

In other words, given any dose distribution $z \in Z$, the function $\Phi$ provides the minimum beam-on-time required to deliver the dose distribution $z$. The problem $(P(\alpha))$ can then equivalently be formulated as follows:

$$\text{minimize } G(z) + \alpha \Phi(z)$$

subject to

$$(\tilde{P}(\alpha))$$

$$z \in Z.$$ 

For $z \in Z$, $\Phi(z)$ is the optimal solution to a feasible linear programming problem with right-hand-side $z$, so that $\Phi$ is convex on $Z$ (Jansen et al., 1997). Since, by Assumption 1, $G$ is strictly convex, the objective function in $(\tilde{P}(\alpha))$ is strictly convex as well and consequently $(\tilde{P}(\alpha))$ has a unique optimal solution. \qed
Although the optimal dose distribution is uniquely determined by $\alpha$, in general the
treatment plan that delivers this dose distribution at minimum beam-on-time (i.e., the
optimal solution to the corresponding instance of (Q(z))) is not unique. We will next
investigate this issue further using the concept of aperture independence.

3.3.1.2 Aperture independence

The following definition characterizes a desirable property of a subset $\bar{K} \subseteq K$ of
apertures:

**Definition 1.** A set of apertures $\bar{K} \subseteq K$ is linearly independent if the associated vectors
of aperture dose deposition coefficients $D_k$, for $k \in \bar{K}$ are linearly independent.

Let $Y^*(z)$ be the set of optimal aperture intensity vectors to (Q(z)), in other words,

$$Y^*(z) = \arg \min \{ H(y) : D^T y = z, y \geq 0 \}.$$  \hfill (3–5)

In other words, $Y^*(z)$ is the set of all treatment plans that deliver $z$ with minimal
beam-on-time. The following theorem says that there always exists a treatment plan that
delivers a given dose distribution with minimal beam-on-time using a set of independent
apertures:

**Theorem 3.2.** For any $z \in Z$ there exists $y^* \in Y^*(z)$ such that the set of apertures with
positive intensities in $y^*$, is linearly independent.

**Proof.** Since $z \in Z$, the linear programming problem (Q(z)) has an optimal solution (i.e.,
$Y^*(z) \neq \emptyset$). Therefore, it also has an optimal basic feasible solution. Let $y^* \in Y^*(z)$ be
an optimal basic feasible solution to the LP. By partitioning the matrix $D^T$ into basic and
nonbasic columns ($D_B^T$, $D_N^T$) we can express $y^*$ as $(y_B^*, y_N^*) = \left( (D_B^T)^{-1} z, \mathbf{0} \right)$ (note that
the optimal basic feasible solution may be degenerate). Moreover, we partition the set of
apertures $K$ into $K = (K_B, K_N)$, accordingly. Clearly, $y_k^* > 0$ implies that $k \in K_B$. Since
the columns in $D_B^T$ are linearly independent, then by definition the apertures in $K_B$ are
independent. Consequently, the apertures with positive intensity in $y^*$ are independent
as well. \hfill $\square$
From Theorem 3.2 we conclude that, for all \( \alpha \in \mathbb{R}_+ \), the optimal dose distribution \( z^*(\alpha) \) can be delivered with minimal beam-on-time using a set of linearly independent apertures. Note that this immediately yields an upper bound on the number of apertures required to deliver any deliverable dose distribution:

**Corollary 1.** Any deliverable dose distribution can be delivered using no more than \( |V| \) apertures.

We next show how to determine the maximum beam-on-time penalty \( \alpha_0 \) that can be used as the starting point of our solution method.

**3.3.1.3 Maximum beam-on-time penalty**

Since \( (P(\alpha)) \) is a convex optimization problem with linear constraints, the KKT conditions are necessary and sufficient for optimality (Bazaraa et al., 2006). Associating dual multipliers \( \pi = (\pi_j; j \in V)^\top \) with Constraints \((3–3)\) and \( \rho = (\rho_k; k \in K)^\top \) with Constraints \((3–4)\), the KKT conditions for \((P(\alpha))\) can be expressed as follows:

\[
\begin{align*}
z_j &= \sum_{k \in K} D_{kj} y_k & j \in V \\
\pi_j &= \frac{\partial G(z)}{\partial z_j} & j \in V \\
\rho_k &= \sum_{j \in V} D_{kj} \pi_j + \alpha & k \in K \\
\rho_k y_k &= 0 & k \in K \\
y_k, \rho_k &\geq 0 & k \in K.
\end{align*}
\]

Note that Equations \((3–6)–(3–8)\) can alternatively be expressed in vector-notation as \( z = D^\top y, \pi = \nabla G(z), \) and \( \rho = D\pi + \alpha 1 \) where \( 1 \) is a column vector whose elements are all equal to 1.

Solving the system of nonlinear Equations \((3–6)–(3–10)\) yields an optimal solution to \((P(\alpha))\) for a given \( \alpha \in \mathbb{R}_+ \). In particular, any vector \( y(\alpha) \geq 0 \) (where \( 0 \) is a vector whose elements are all equal to 0) is a candidate solution to that system. This vector...
then uniquely determines \( z(\alpha) \), \( \pi(\alpha) \), and \( \rho(\alpha) \). The following theorem provides us with the smallest beam-on-time penalty, \( \alpha_0 \), beyond which the optimal solution is not to treat:

**Theorem 3.3.** For \( \alpha \geq \alpha_0 \), where

\[
\alpha_0 = -\min_{k \in K} D_k \cdot \nabla G(0)
\]

we have that \( z^*(\alpha) = 0 \).

**Proof.** Consider the candidate solution \( y^*(\alpha) = 0 \). We will identify the values of \( \alpha \) for which this solution satisfies the KKT conditions (3–6)–(3–10). Clearly, Equation (3–6) implies that \( z^*(\alpha) = 0 \). Since, by Assumption 1, \( G \) is differentiable, according to Equation (3–7) we have that \( \pi^*(\alpha) = \nabla G(0) \), and \( \pi^*(\alpha) \) is defined and finite. Moreover, according to Equation (3–8) \( \rho^*(\alpha) = D \nabla G(0) + \alpha 1 \). Since \( y^*(\alpha) = 0 \), then Equation (3–9) is satisfied. Now let \( \alpha_0 \) be as defined in the theorem, then KKT condition (3–10) and, in particular, \( \rho^*(\alpha) \geq 0 \) is satisfied whenever \( \alpha \geq \alpha_0 \). Therefore, for these values of \( \alpha \) the solution \((y^*(\alpha), z^*(\alpha), \pi^*(\alpha), \rho^*(\alpha))\) is an optimal solution to \((P(\alpha))\).

We will now turn to the problem of characterizing the family of Pareto-efficient treatment plans and study how \( z^*(\alpha) \) changes as \( \alpha \) changes.

### 3.3.1.4 Parametric optimal treatment plans

Consider a fixed value of \( \alpha \in \mathbb{R}_+ \). According to Theorem 3.1 the corresponding optimal dose distribution \( z^*(\alpha) \) is unique. Moreover, let \( \rho^*(\alpha) \) be the vector of dual multipliers in KKT conditions (3–6)–(3–10) for \((P(\alpha))\). Note that \( \rho^*(\alpha) \) is unique since \( z^*(\alpha) \) is unique. The following definition characterizes a desirable property of a subset \( K^*(\alpha) \subseteq K \) of apertures:

**Definition 2.** A set of apertures \( K^*(\alpha) \subseteq K \) is a basic set of apertures for beam-on-time penalty \( \alpha \) if and only if it is linearly independent, \( \rho^*_k(\alpha) = 0 \) for \( k \in K^*(\alpha) \), and \( z^*(\alpha) \) is deliverable using only apertures in \( K^*(\alpha) \).

Theorem 3.2 guarantees the existence of a basic set of apertures \( K^*(\alpha) \) for any \( \alpha \in \mathbb{R}_+ \). In particular, given an optimal treatment plan \( y^* \in Y^*(z^*(\alpha)) \) for which the set of
apertures with positive intensities is linearly independent, a basic set of apertures can be obtained as $K^*(\alpha) = \{ k \in K : y_k^* > 0 \}$. However, note that $K^*(\alpha)$ is not necessarily unique. Now to study the effect of reducing $\alpha$ on $z^*(\alpha)$, we formulate a family of optimization problems at beam-on-time penalty $\alpha$ using a given basic set of apertures $K^*(\alpha)$. In particular, considering only those apertures in the basic set $K^*(\alpha)$, we formulate a parametric unconstrained optimization problem as follows:

$$
\min_y G \left( \sum_{k \in K^*(\alpha)} D_k^T y_k \right) + (\alpha - \Delta \alpha) \sum_{k \in K^*(\alpha)} y_k
$$

where $\Delta \alpha$ is the changing parameter. For notational convenience, in the context of the parametric problem $(P_{\Omega}(\cdot; \alpha))$, vector $y$ will represent the restricted vector $(y_k : k \in K^*(\alpha))^T$.

We next study the optimal solutions to the parametric problem $(P_{\Omega}(\cdot; \alpha))$ as well as corresponding optimal dose distributions and treatment plans to the original problem. We first show the validity of the following lemma:

**Lemma 1.** If $A \in \mathbb{R}^{n \times n}$ is strictly positive definite and $B \in \mathbb{R}^{m \times n}$ has full row rank, then $BAB^T$ is strictly positive definite.

**Proof.** $A$ is strictly positive definite if and only if there exists $\epsilon > 0$ such that for all $u \in \mathbb{R}^n$, we have $u^T Au \geq \epsilon \| u \|^2$. Moreover, for $v \in \mathbb{R}^m$, $v^T (BAB^T) v = (v^T B) A (B^T v) = \bar{v}^T A \bar{v}$ where $\bar{v} = B^T v$. Hence, using strict positive definiteness of $A$ we have $\bar{v}^T A \bar{v} \geq \epsilon \| \bar{v} \|^2$.

Now we can rewrite $\| \bar{v} \|^2$ as

$$
\| \bar{v} \|^2 = \| B^T v \|^2 = v^T BB^T v.
$$

Since $BB^T$ is symmetric, it is well-known that the optimal solution value to the optimization problem

$$
\min_{v \neq 0} \frac{v^T BB^T v}{\| v \|^2}
$$
is the minimum eigenvalue of $BB^\top$ which is denoted by $\lambda_{\text{min}}$. Hence

$$v^\top BB^\top v \geq \lambda_{\text{min}} \|v\|^2.$$ 

Now since $B$ has a full row rank, then $BB^\top$ is positive definite and $\lambda_{\text{min}} > 0$. Hence, for all $v \in \mathbb{R}^m$ we have

$$v^\top (BAB^\top) v \geq \hat{\epsilon} \|v\|^2$$

where $\hat{\epsilon} = \epsilon \lambda_{\text{min}} > 0$. Therefore, $BAB^\top$ is strictly positive definite. \qed

The following theorem provides sufficient conditions on $G$ under which solutions to the parametric unconstrained problem $(P_U(\cdot; \alpha))$ can be characterized as continuously differentiable functions:

**Theorem 3.4.** If $G$ is twice differentiable and $\nabla^2 G$ is strictly positive definite everywhere, then optimal solutions to the family of optimization problems $(P_U(\cdot; \alpha))$ can be expressed as a unique collection of continuously differentiable functions which we denote by $y_k^*(\cdot; \alpha) : \mathbb{R} \to \mathbb{R}$ for $k \in K^*(\alpha)$.

**Proof.** For any $\Delta \alpha \in \mathbb{R}$, $(P_U(\Delta \alpha; \alpha))$ is a convex unconstrained optimization problem. The first-order optimality conditions can then be expressed as follows:

$$D_k \nabla G \left( \sum_{k' \in K^*(\alpha)} D_{k'}^\top y_{k'} \right) + \alpha = \Delta \alpha \quad k \in K^*(\alpha). \quad (3-11)$$

Any solution to this system of nonlinear equations with $|K^*(\alpha)|$ equations and unknown variables is a stationary point of $(P_U(\Delta \alpha; \alpha))$. More specifically, the Jacobian matrix of Equations (3–11) can be written as follows:

$$J(y) = \bar{D} \left( \nabla^2 G \left( \sum_{k \in K^*(\alpha)} D_k^\top y_k \right) \right) \bar{D}^\top$$

where $\bar{D}$ is a $|K^*(\alpha)| \times |V|$ submatrix of $D$ consisting of only the rows corresponding to apertures $k \in K^*(\alpha)$ (note that $J(y)$ is the Hessian of the objective function in
\( \mathcal{P}(\Delta \alpha; \alpha) \)). \( \bar{D} \) has a full row rank since apertures in \( K^*(\alpha) \) are independent. Moreover, \( \nabla^2 G \) is strictly positive definite everywhere. Hence, \( J(y) \) is strictly positive definite (Lemma 1). The Global Inverse Mapping Theorem (Ohtsuki and Watanabe, 1969; Wu and Desoer, 1972) now says that there exists a unique collection of continuously differentiable functions \( y^*_k(\cdot; \alpha) : \mathbb{R} \to \mathbb{R} \) for \( k \in K^*(\alpha) \) that satisfies Equations (3–11) as the right-hand-side (i.e., \( \Delta \alpha \)) changes in \( \mathbb{R} \). Hence, \( (y^*_k(\Delta \alpha; \alpha) : k \in K^*(\alpha))^T \) is the stationary point of \( \mathcal{P}(\Delta \alpha; \alpha) \). Finally, since the Hessian of the objective function (i.e., \( J(y) \)) is positive definite everywhere, the stationary point is the global minimum of \( \mathcal{P}(\Delta \alpha; \alpha) \).

The next theorem links the parametric unconstrained problem \( \mathcal{P}(\cdot; \alpha) \) with our original problem and shows how the optimal solution to \( \mathcal{P}(\Delta \alpha; \alpha) \) can be used to obtain the optimal solution to \( \mathcal{P}(\alpha - \Delta \alpha) \) for sufficiently small values of \( \Delta \alpha \).

**Theorem 3.5.** For sufficiently small \( \Delta \alpha \in \mathbb{R} \), the vector \( y^* \in \mathbb{R}^{|K|} \) defined by

\[
  y^*_k = \begin{cases} 
    y^*_k(\Delta \alpha; \alpha) & k \in K^*(\alpha) \\
    0 & k \in K \setminus K^*(\alpha)
  \end{cases}
\]

is optimal to \( \mathcal{P}(\alpha - \Delta \alpha) \).

**Proof.** We show that for sufficiently small \( \Delta \alpha \in \mathbb{R} \), \( y^* \) satisfies the KKT conditions (3–6)–(3–10) for \( \mathcal{P}(\alpha - \Delta \alpha) \). In particular, substituting \( y^* \) in KKT condition (3–6) yields

\[
  z^* = \sum_{k \in K} D_k y^*_k = \sum_{k \in K^*(\alpha)} D_k y^*_k(\Delta \alpha; \alpha),
\]

and substituting \( z^* \) in KKT condition (3–7) yields

\[
  \pi^* = \nabla G(z^*) = \nabla G \left( \sum_{k \in K^*(\alpha)} D_k y^*_k(\Delta \alpha; \alpha) \right).
\]
It then follows that the dual multipliers $\rho_k^*$ for $k \in K$ in Equation (3–8) are

$$\rho_k^* = D_k \pi^* + \alpha - \Delta \alpha$$

$$= D_k \nabla G \left( \sum_{k' \in K^*(\alpha)} D_{k'}^T y_{k'}^*(\Delta \alpha; \alpha) \right) + \alpha - \Delta \alpha \quad k \in K.$$

Now let us define the family of functions $\rho_k^*(\Delta \alpha; \alpha) : \mathbb{R} \rightarrow \mathbb{R}$ for $k \in K$ as follows:

$$\rho_k^*(\Delta \alpha; \alpha) \equiv D_k \nabla G \left( \sum_{k' \in K^*(\alpha)} D_{k'}^T y_{k'}^*(\Delta \alpha; \alpha) \right) + \alpha - \Delta \alpha \quad k \in K,$$

so that $\rho_k^* = \rho_k^*(\Delta \alpha; \alpha)$ for $k \in K$. The followings hold by definition:

$$\rho_k^* = 0 \quad k \in K^*(\alpha)$$

$$y_k^* = 0 \quad k \in K \setminus K^*(\alpha).$$

Hence, the KKT condition (3–9) (complementary slackness) is satisfied.

Finally, we need to ensure that $y^* \rho^* \geq 0$. In particular, we first consider the special case $\Delta \alpha = 0$, and show that at $\Delta \alpha = 0$, $y_k^*(0; \alpha) \geq 0$ for $k \in K^*(\alpha)$, and $\rho_k^*(0; \alpha) \geq 0$ for $k \in K$. Note that $K^*(\alpha)$ is a basic set of apertures. Hence, $\rho_k^*(\alpha) = 0$ for $k \in K^*(\alpha)$ and as a result

$$D_k \nabla G (z^*(\alpha)) + \alpha = 0 \quad k \in K^*(\alpha). \quad (3–12)$$

Moreover, $z^*(\alpha)$ is deliverable using only apertures in $K^*(\alpha)$. Hence, for some $y \in \mathbb{R}_{+}^{\vert K^*(\alpha) \vert}$ we have

$$z^*(\alpha) = \sum_{k \in K^*(\alpha)} D_k^T y_k.$$

Substituting the expression for $z^*(\alpha)$ in the system of Equations (3–12) yields

$$D_k \nabla G \left( \sum_{k \in K^*(\alpha)} D_k^T y_k \right) + \alpha = 0 \quad k \in K^*(\alpha)$$
which is the same as the system of Equations (3–11) when \( \Delta \alpha = 0 \), that is

\[
D_k \nabla G \left( \sum_{k \in K^*(\alpha)} D_k^T y_k^*(0; \alpha) \right) + \alpha = 0 \quad k \in K^*(\alpha)
\]

and since according to Theorem 3.4 the solution to this system is unique for a given \( \Delta \alpha \), one can conclude that \( y_k^*(0; \alpha) \geq 0 \) for \( k \in K^*(\alpha) \), and \( z^*(\alpha) = \sum_{k \in K^*(\alpha)} D_k^T y_k^*(0; \alpha) \).

Furthermore, at \( \Delta \alpha = 0 \), for aperture \( k \in K \) we have

\[
\rho_k^*(0; \alpha) = D_k \nabla G \left( \sum_{k' \in K^*(\alpha)} D_{k'}^T y_{k'}^*(0; \alpha) \right) + \alpha
\]

\[
= D_k \nabla G (z^*(\alpha)) + \alpha = \rho^*(\alpha),
\]

and since \( \rho_k^*(\alpha) \geq 0 \), then \( \rho_k^*(0; \alpha) \geq 0 \). Thus, at \( \Delta \alpha = 0 \), \( y^*, \rho^* \geq 0 \). Next, we consider the general case \( \Delta \alpha \geq 0 \). More specifically, to ensure nonnegativity of \( y_k^*(\Delta \alpha; \alpha) \) for \( k \in K^*(\alpha) \) (and consequently \( y^* \)), we enforce \( \Delta \alpha \leq \Delta \alpha_1 \) where \( \Delta \alpha_1 \) is defined as:

\[
\Delta \alpha_1 \equiv \inf \left\{ \Delta \alpha \geq 0 : \min_{k \in K^*(\alpha)} y_k^*(\Delta \alpha; \alpha) < 0 \right\}.
\]

Similarly, to ensure nonnegativity of \( \rho_k^*(\Delta \alpha; \alpha) \) for \( k \in K \) (and consequently \( \rho^* \)), we enforce \( \Delta \alpha \leq \Delta \alpha_2 \) where \( \Delta \alpha_2 \) is defined as:

\[
\Delta \alpha_2 \equiv \inf \left\{ \Delta \alpha \geq 0 : \min_{k \in K} \rho_k^*(\Delta \alpha; \alpha) < 0 \right\}.
\]

Therefore, for \( \Delta \alpha \leq \min \{ \Delta \alpha_1, \Delta \alpha_2 \} \), \( y^* \) satisfies KKT condition (3–10) (nonnegativity) as well, hence \( y^* \) is optimal to \( (P(\alpha - \Delta \alpha)) \).

Starting from a given beam-on-time penalty \( \alpha \) and for sufficiently small \( \Delta \alpha \), Theorem 3.5 uses the parametric unconstrained problem \( (P_U(\cdot; \alpha)) \) to obtain the optimal dose distribution \( z^*(\alpha - \Delta \alpha) \) as well as a treatment plan \( y^* \in Y^* (z^*(\alpha - \Delta \alpha)) \) that delivers \( z^*(\alpha - \Delta \alpha) \) with minimal beam-on-time. Therefore, at a given beam-on-time penalty \( \alpha \), one can locally characterize the Pareto-efficient frontier using Theorem 3.5. In the next section, we employ the fundamental results from this section to develop an algorithmic
framework which can be used to characterize the solutions to the family of optimization problems (P(α)).

3.3.2 Algorithmic Framework

Based on the results obtained so far, we propose an algorithmic framework to solve the family of optimization problems (P(α)) for α ≥ 0 that applies whenever the objective function G is twice differentiable and \( \nabla^2 G \) is strictly positive definite everywhere.

In particular, our algorithmic framework characterizes the optimal dose distribution \( z^*(\alpha) \) along with an optimal treatment plan, say \( y^*(\alpha) \in Y^*(z^*(\alpha)) \), as a function of beam-on-time penalty \( \alpha \in \mathbb{R}_+ \). For that purpose, it employs functions \( y_k^*(\cdot; \alpha) \) and \( \rho_k^*(\cdot; \alpha) \) defined in Section 3.3.1, which characterize the optimal intensity and the dual multiplier associated with aperture \( k \in K \) as the beam-on-time penalty changes, respectively. Recall from Theorem 3.3 that \( z^*(\alpha_0) = 0 \), hence an optimal treatment plan and a basic set of apertures for beam-on-time penalty \( \alpha_0 \) can be obtained as \( y^*(\alpha_0) = 0 \) and \( K^*(\alpha_0) = \emptyset \), respectively. Therefore, we will start with \( \alpha = \alpha_0 \) and initialize the iteration counter of the algorithm at \( m = 0 \). Then, at iteration \( m \), we perform the following steps:

1. Find

   \[
   \Delta\alpha_1 = \inf \left\{ \Delta\alpha : \Delta\alpha \geq 0 \text{ and } \min_{k \in K^*(\alpha)} y_k^*(\Delta\alpha; \alpha_m) < 0 \right\} \\
   \Delta\alpha_2 = \inf \left\{ \Delta\alpha : \Delta\alpha \geq 0 \text{ and } \min_{k \in K} \rho_k^*(\Delta\alpha; \alpha_m) < 0 \right\}
   \]

   and let \( \Delta\alpha_{\text{min}} = \min \{ \Delta\alpha_1, \Delta\alpha_2 \} \).

2. Set \( \alpha_{m+1} = \alpha_m - \Delta\alpha_{\text{min}} \). If \( \Delta\alpha_{\text{min}} = \Delta\alpha_1 \), then set

   \[
   k^* = \arg \min_{k \in K^*(\alpha_m)} y_k^*(\Delta\alpha_1; \alpha_m) \\
   K^*(\alpha_{m+1}) = K^*(\alpha_m) \setminus \{k^*\};
   \]
otherwise set
\[ k^* = \arg \min_{k \in K} \rho_k^*(\Delta \alpha_2; \alpha_m) \]
\[ K^*(\alpha_{m+1}) = K^*(\alpha_m) \cup \{k^*\}. \]

3. Set
\[ z^*(\alpha_{m+1}) = \sum_{k \in K^*(\alpha_m)} D_k^\top y_k^*(\Delta \alpha_{\text{min}}; \alpha_m) \]
\[ y_k^*(\alpha_{m+1}) = \begin{cases} y_k^* (\Delta \alpha_{\text{min}}; \alpha_m) & \text{for } k \in K^*(\alpha_m) \\ 0 & \text{for } k \in K \setminus K^*(\alpha_m). \end{cases} \]

At each iteration of the algorithm, either a current aperture is dropped from, or a new aperture is added to, the basic set of apertures \( K^*(\alpha) \). It is important to ensure that \( K^*(\alpha) \) remains a basic set of apertures as the algorithm proceeds. More specifically, we need to investigate if the linear-independence property is maintained while updating the basic set of apertures. In the following we show that any aperture whose vector of dose deposition coefficients is linearly dependent to the current basic set of apertures, cannot be chosen in Step 2 of the algorithmic framework. In particular, suppose the vector of aperture dose deposition coefficients \( D_k' \) corresponding to aperture \( k' \in K \) can be expressed as a linear combination of \( D_k \) for \( k \in K^*(\alpha) \). To show that \( k' \) cannot be chosen in Step 2 of the algorithmic framework, we show that \( \rho_{k'}^*(\Delta \alpha; \alpha) \geq 0 \) for \( \Delta \alpha \leq \alpha \).

**Theorem 3.6.** If \( D_k' \), corresponding to aperture \( k' \in K \) can be expressed as a linear combination of \( D_k \) for \( k \in K^*(\alpha) \), then \( \rho_{k'}^*(\cdot; \alpha) \) is a linear function, and \( \rho_{k'}^*(\Delta \alpha; \alpha) \geq 0 \) for \( \Delta \alpha \leq \alpha \).

**Proof.** Recall that for aperture \( k \in K \) we have
\[ \rho_k^*(\Delta \alpha; \alpha) = D_k \nabla G \left( \sum_{k' \in K^*(\alpha)} D_{k'}^\top y_{k'}^*(\Delta \alpha; \alpha) \right) + \alpha - \Delta \alpha, \]
and by definition we have
\[ \rho_k^*(\cdot; \alpha) = 0 \quad k \in K^*(\alpha). \]
Moreover, for some $\beta \in \mathbb{R}^{\mid K^*(\alpha)\mid}$ the vector of aperture dose deposition coefficients $D_{k'}$ can be expressed as:

$$D_{k'} = \sum_{k \in K^*(\alpha)} \beta_k D_k.$$

Multiplying $\rho^*_k (\Delta \alpha; \alpha) = 0$ for $k \in K^*(\alpha)$ by $\beta_k$ and summing them we get

$$\left( \sum_{k \in K^*(\alpha)} \beta_k D_k \right) \nabla G \left( \sum_{k \in K^*(\alpha)} D^T_k y^*_k (\Delta \alpha; \alpha) \right) = - \left( \sum_{k \in K^*(\alpha)} \beta_k \right) (\alpha - \Delta \alpha).$$

Hence, for aperture $k'$ we have

$$\rho^*_k (\Delta \alpha; \alpha) = D_{k'} \cdot \nabla G \left( \sum_{k \in K^*(\alpha)} D^T_k y^*_k (\Delta \alpha; \alpha) \right) + \alpha - \Delta \alpha$$

$$= \left( \sum_{k \in K^*(\alpha)} \beta_k D_k \right) \nabla G \left( \sum_{k \in K^*(\alpha)} D^T_k y^*_k (\Delta \alpha; \alpha) \right) + \alpha - \Delta \alpha$$

$$= \left( 1 - \sum_{k \in K^*(\alpha)} \beta_k \right) (\alpha - \Delta \alpha).$$

Therefore, $\rho^*_k (\cdot; \alpha)$ is a linear function with respect to $\Delta \alpha$. In particular, at $\Delta \alpha = 0$ we have

$$\rho^*_k (0; \alpha) = \left( 1 - \sum_{k \in K^*(\alpha)} \beta_k \right) \alpha$$

$$= \rho^*_k (\alpha) \geq 0,$$

as a result, $1 - \sum_{k \in K^*(\alpha)} \beta_k \geq 0$. Thus, for $\Delta \alpha \leq \alpha$ we have

$$\rho^*_k (\Delta \alpha; \alpha) \geq 0.$$

Hence, the linear-independence property of the basic set of apertures $K^*(\alpha)$ is maintained during the course of the algorithm.
Furthermore, we show that \( y^*(\alpha) \) characterized by the algorithmic framework is continuous in \( \alpha \).

**Theorem 3.7.** The family of Pareto-efficient treatment plans \( y^*(\alpha) \) generated by the general algorithmic framework is continuous in beam-on-time penalty \( \alpha \).

**Proof.** At iteration \( m \) of the algorithm, according to Theorem 4, \( y^*_k(\cdot;\alpha_m) \) for \( k \in K^*(\alpha_m) \), are continuous functions, and as a result \( y^*(\alpha) \) for \( \alpha \in (\alpha_m - \Delta\alpha_{\min}, \alpha_m) \) is continuous. Hence, to show continuity of \( y^*(\alpha) \), all we need to show is that \( y^*_{\alpha}^{*}(\alpha) \) does not change as the basic set of apertures changes from \( K^*(\alpha) \) to \( K^*(\alpha_m) \). In particular, according to Step 3 of the algorithm, we have

\[
\sum_{k \in K^*(\alpha)} D_k^T y_k^*(\alpha_m) = \sum_{k \in K^*(\alpha)} D_k^T y_k^*(\Delta\alpha_{\min};\alpha_m) = 0.
\]

Moreover, suppose \( K^*(\alpha_m) = K^*(\alpha_m) \cup \{k^*\} \), we can alternatively express \( z^*(\alpha_m) \) as

\[
z^*(\alpha_m) = \sum_{k \in K^*(\alpha_m)} D_k^T y_k^*(0;\alpha_m).
\]

Subtracting the two equations above yields

\[
D_k^T (y_k^*(0;\alpha_m) - 0) + \sum_{k \in K^*(\alpha_m)} D_k^T (y_k^*(0;\alpha_m) - y_k^*(\Delta\alpha_{\min};\alpha_m)) = 0.
\]

Since \( K^*(\alpha_m) \) is linearly independent, then \( y_k^*(0;\alpha_m) = y_k^*(\Delta\alpha_{\min};\alpha_m) \) for \( k \in K^*(\alpha_m) \) and \( y_k^*(0;\alpha_m) = 0 \). Similarly, suppose \( K^*(\alpha_m) = K^*(\alpha_m) \setminus \{k^*\} \), then

\[
D_k^T (y_k^*(\Delta\alpha_{\min};\alpha_m) - 0) + \sum_{k \in K^*(\alpha_m)} D_k^T (y_k^*(\Delta\alpha_{\min};\alpha_m) - y_k^*(0;\alpha_m)) = 0,
\]

and since \( K^*(\alpha_m) \) is linearly independent, then \( y_k^*(0;\alpha_m) = y_k^*(\Delta\alpha_{\min};\alpha_m) \) for \( k \in K^*(\alpha_m) \) and \( y_k^*(\Delta\alpha_{\min};\alpha_m) = 0 \). Therefore, \( y^*(\alpha_m) \) does not change as the
basic set of apertures changes from $K^*(\alpha_m)$ to $K^*(\alpha_{m+1})$. Thus, $y^*(\alpha)$ is continuous in $\alpha$.

This will be used in Section 3.3.3.2 to show finite convergence of the algorithm when applied to the class of convex quadratic evaluation criteria.

In Step 1 of the algorithm, we may have $\Delta \alpha_{min} = 0$. In this case, the algorithm takes a degenerate step and updates the basic set of apertures without reducing the current beam-on-time penalty. Therefore, it is possible that the algorithm goes through a sequence of degenerate iterations where the basic set of apertures is modified during each iteration without taking a positive step length. However, since there are only a finite number of basic sets of apertures for a given beam-on-time penalty, employing an appropriate anti-cycling rule will prevent the algorithm from cycling.

It is clear that, in general, Steps 1 and 2 of the algorithm can be computationally prohibitive. Moreover, the assumption of twice differentiability of $G$ may not be satisfied under some clinically relevant treatment plan evaluation criteria. Therefore, in the remainder of this section, we will first study the special case of convex quadratic evaluation criteria for which we can explicitly solve the parametric unconstrained optimization problems. Next, we will propose a method that uses our general algorithmic framework to closely approximate the Pareto-efficient frontier using a sequence of quadratic approximations to $G$. Finally, we will discuss a commonly-used objective function that is based on piecewise quadratic voxel-based penalty functions to illustrate this method.

### 3.3.3 Convex Quadratic Evaluation Criteria

A very common class of treatment plan evaluation criteria is given by the so-called voxel-based (convex) penalty functions. More specifically,

$$G(z) = \sum_{j \in V} F_j(z_j)$$
where \( F_j : \mathbb{R} \rightarrow \mathbb{R} \ (j \in V) \) are convex functions (Romeijn and Dempsey, 2008). The most elementary and clinically used penalty functions are quadratic ones, in which case \( G \) can be expressed as

\[
G(z) = \frac{1}{2} z^\top Q z + q^\top z + q_0
\]

where \( Q \in \mathbb{R}^{|V| \times |V|}, q \in \mathbb{R}^{|V|}, \) and \( q_0 \) is a scalar. Typically, \( Q \) is a diagonal matrix with strictly positive elements; however, for our discussion below it suffices to assume that \( Q \) is positive definite and symmetric.

### 3.3.3.1 Application of the algorithmic framework

To apply the algorithmic framework to this class of evaluation criteria, \( y_k^* (\cdot; \alpha) \) for \( k \in K^*(\alpha) \) need to be determined. These functions are then used to evaluate \( \Delta \alpha_1 \) and \( \Delta \alpha_2 \) in Step 1 of the algorithm. For this class of evaluation criteria, the system of Equations (3–11) in the proof of Theorem 3.4 reduces to the following linear system:

\[
D_k \left( Q \sum_{k' \in K^*(\alpha)} D_{k,k'}^\top y_{k'} + q \right) + \alpha = \Delta \alpha \quad k \in K^*(\alpha).
\]

We can then obtain analytical expressions for the optimal solutions to \((P_U (\cdot; \alpha))\) as a function of \( \Delta \alpha \):

\[
y_k^* (\Delta \alpha; \alpha) = - \left( \bar{D} Q \bar{D}^\top \right)_k^{-1} \left( \bar{D} q + (\alpha - \Delta \alpha) 1 \right) \quad k \in K^*(\alpha)
\]

(3–13)

where \( \bar{D} \) is a \(|K^*(\alpha)| \times |V| \) submatrix of \( D \) consisting of only the rows corresponding to \( k \in K^*(\alpha) \), \( 1 \) is the column vector of ones of size \( |K^*(\alpha)| \), and \( (\bar{D} Q \bar{D}^\top)^{-1} \) is the \( k \)th row of \((\bar{D} Q \bar{D}^\top)^{-1}\). Note that \( y_k^*(\cdot; \alpha) \) for \( k \in K^*(\alpha) \) are linear functions with respect to \( \Delta \alpha \).

Hence, the value of \( \Delta \alpha_1 \) in Step 1 of the algorithmic framework can be obtained using a ratio test as follows:

\[
\Delta \alpha_1 = \min_{k \in K^*(\alpha)} \frac{(\bar{D} Q \bar{D}^\top)_k^{-1} (\bar{D} q + \alpha 1)}{(\bar{D} Q \bar{D}^\top)_k^{-1} 1}. 
\]
However, determining $\Delta \alpha_2$ is somewhat more involved since we need to consider all deliverable apertures in $K$. In particular, $\rho_k^*(\cdot; \alpha)$ for $k \in K$ can be expressed as:

$$
\rho_k^*(\Delta \alpha; \alpha) = D_k \left( Q \sum_{k' \in K^\ast(\alpha)} D_{k'}^T y_{k'}(\Delta \alpha; \alpha) + q \right) + \alpha - \Delta \alpha \quad k \in K. \tag{3–14}
$$

Since $y_k^*(\cdot; \alpha)$ for $k \in K^\ast(\alpha)$ are linear functions as shown in Equation (3–13), it is easy to see that substituting them in Equation (3–14) will yield linear functions with respect to $\Delta \alpha$ as follows:

$$
\rho_k^*(\Delta \alpha; \alpha) = \left( 1 - (D_k Q \bar{D}^T) (\bar{D} Q \bar{D}^T)^{-1} 1 \right) (\alpha - \Delta \alpha) \\
+ \left( D_k - (D_k Q \bar{D}^T) (\bar{D} Q \bar{D}^T)^{-1} \bar{D} \right) q \quad k \in K. \tag{3–15}
$$

Now to obtain $\Delta \alpha_2$, let us define function $\Psi (\cdot; \alpha) : \mathbb{R} \to \mathbb{R}$ as

$$
\Psi (\Delta \alpha; \alpha) = \min_{k \in K} \rho_k^*(\Delta \alpha; \alpha).
$$

Since $\rho_k^*(\cdot; \alpha)$ for $k \in K$ are linear functions, it follows that $\Psi (\cdot; \alpha)$ is a concave piecewise linear function with respect to $\Delta \alpha$ (Figure 3-2). Moreover, since $\rho_k^*(\cdot; \alpha) = 0$ for $k \in K^\ast(\alpha)$, we have that $\Psi (\cdot; \alpha) \leq 0$, and since $\rho_k^*(0; \alpha) = \rho_k^*(\alpha)$ for $k \in K$ and $\rho_k^*(\alpha) = 0$ for $k \in K^\ast(\alpha)$, then we have that $\Psi (0; \alpha) = 0$ (proof of Theorem 3.5). Therefore, it is easy to see that $\Delta \alpha_2$ corresponds to the smallest $\Delta \alpha$ beyond which $\Psi (\cdot; \alpha)$ is negative.

![Figure 3-2. $\Psi (\cdot; \alpha)$ is a concave piecewise-linear function.](image)
The total number of potential apertures that needs to be included in \( P(\alpha) \) is typically very large. For example, if each beam direction is discretized into a beamlet grid of \( 20 \times 20 \), then an MLC which allows for all possible leaf settings yields a total of about \( 10^{45} \) apertures per beam direction. Therefore it is computationally prohibitive to derive a closed-form expression for \( \Psi(\cdot; \alpha) \). Instead, for a given \( \Delta \alpha \in \mathbb{R} \), we can evaluate \( \Psi(\Delta \alpha; \alpha) \) by formulating and solving the so-called pricing problem.

To formulate the pricing problem, we let \( B \) represent the collection of prespecified beam directions. We then let \( N_b \) be the set of beamlets in beam direction \( b \in B \) and \( N = \bigcup_{b \in B} N_b \) be the set of all beamlets. Aperture \( k \in K \) can then be expressed as the set of all exposed beamlets, say \( A_k \subseteq N \), in that aperture. Moreover, we define a beamlet dose deposition coefficient, denoted by \( D_{ij} \), as the dose deposited by beamlet \( i \in N \) in voxel \( j \in V \) at unit intensity. Aperture dose deposition coefficient \( D_{kj} \) for aperture \( k \in K \) and voxel \( j \in V \) can then be expressed as the sum of all beamlet dose deposition coefficients corresponding to the beamlets exposed in the aperture. In other words:

\[
D_{kj} = \sum_{i \in A_k} D_{ij}. 
\]  

(3–16)

Using the expression in Equation (3–16) we can express \( \rho_k^*(\Delta \alpha; \alpha) \) for \( k \in K \) in Equation (3–14) in terms of beamlet dose deposition coefficients. In particular, let us define \( \pi_j^*(\cdot; \alpha) : \mathbb{R} \rightarrow \mathbb{R} \) for \( j \in V \) as

\[
\pi_j^*(\Delta \alpha; \alpha) = Q_j \sum_{k \in K^\alpha(\alpha)} D_{k,j} y_k^*(\Delta \alpha; \alpha) + a_j, \quad j \in V
\]

where \( Q_j \) is the \( j \)th row of matrix \( Q \). Using \( \pi^*(\cdot; \alpha) = (\pi_j^*(\cdot; \alpha) : j \in V)^\top \), \( \rho_k^*(\cdot; \alpha) \) for \( k \in K \) in Equation (3–14) can be rewritten as follows:

\[
\rho_k^*(\Delta \alpha; \alpha) = D_{k,j} \pi_j^*(\Delta \alpha; \alpha) + \alpha - \Delta \alpha \\
= \sum_{i \in A_k} \left( \sum_{j \in V} D_{ij} \pi_j^*(\Delta \alpha; \alpha) \right) + \alpha - \Delta \alpha, \quad k \in K.
\]
Now since each aperture contains beamlets from a single beam only, to evaluate \( \psi(\Delta \alpha; \alpha) \) we formulate the pricing problem for each individual beam direction \( b \in B \) as:

\[
\min_{k \in K_b} \sum_{j \in A_k} \left( \sum_{j \in V} D_{ij} \pi_j^*(\Delta \alpha; \alpha) \right).
\]

where \( K_b \) is the set of all deliverable apertures in beam direction \( b \). Therefore, \( \psi(\Delta \alpha; \alpha) \) can be obtained as the minimum value among the solutions to the pricing problem for all beam directions \( b \in B \).

In order to determine \( \Delta \alpha_{\text{min}} \) in Step 1 of the algorithmic framework, we need to obtain \( \Delta \alpha_2 \) only if \( \Delta \alpha_2 \leq \Delta \alpha_1 \) since otherwise \( \Delta \alpha_{\text{min}} = \Delta \alpha_1 \). Thus, we first evaluate \( \psi(\Delta \alpha_1; \alpha) \) by solving the pricing problem for each individual beam direction \( b \in B \) at \( \Delta \alpha = \Delta \alpha_1 \). If \( \psi(\Delta \alpha_1; \alpha) = 0 \), then clearly \( \Delta \alpha_2 \geq \Delta \alpha_1 \) and \( \Delta \alpha_{\text{min}} = \Delta \alpha_1 \); otherwise \( \Delta \alpha_2 \in [0, \Delta \alpha_1] \). In that case, we can employ a binary search algorithm to obtain \( \Delta \alpha_2 \).

In particular, we start with the initial interval containing \( \Delta \alpha_2 \) (i.e., \( I_0 = [0, \Delta \alpha_1] \)). We then evaluate \( \psi(\Delta \alpha; \alpha) \) at the mid point \( \Delta \alpha = \frac{\Delta \alpha_1}{2} \); if \( \psi(\Delta \alpha; \alpha) < 0 \), then \( I_1 = [0, \frac{\Delta \alpha_1}{2}] \); otherwise, \( I_1 = [\frac{\Delta \alpha_1}{2}, \Delta \alpha_1] \). The binary search is continued until the length of the interval is within a user-specified threshold. Therefore, we can obtain \( \Delta \alpha_2 \) and the corresponding aperture using a binary search algorithm which solves the pricing problem at each iteration.

Depending on the MLC manufacturer and the particular delivery technique used, apertures can be subject to various hardware constraints. In particular, there are four common sets of hardware constraints:

(C1) **Row-convexity constraint** which requires that the exposed beamlets are consecutive at each beamlet row,

(C2) **Interdigitation constraint** which requires that, in addition to (C1), the left leaf of a row does not overlap with the right leaf of an adjacent row, and

(C3) **Connectedness constraint** which requires that, in addition to (C2), beamlet rows with at least one exposed beamlet are consecutive.
Rectangular constraint which corresponds to the use of conventional jaws, and only allows rectangular apertures to be formed.

Romeijn et al. (2005) provide polynomial-time algorithms for solving the pricing problem under (C1)–(C3). In particular, suppose that each beam direction is discretized into a beamlet grid of dimensions $m \times n$. They then show that under (C1) the pricing problem for a particular beam direction can be solved in $O(mn)$ time. For (C2) and (C3) they formulate the pricing problem as a shortest path problem on an appropriately defined network for which there is a one-to-one correspondence between paths from the source node to the sink node and deliverable apertures. Their shortest-path algorithm yields the optimal solution in $O(mn^4)$ time. Finally, Men et al. (2007) provide a solution method that solves the pricing problem under (C4) in $O(m^2n)$ time.

3.3.3.2 Finite convergence of the algorithmic framework

We argue that the general algorithmic framework terminates in finitely many steps when applied to the class of convex quadratic voxel-based penalty functions. Consider aperture $k \in K$, and let $y^*_k(\alpha)$ be the optimal intensity for this particular aperture characterized by the general algorithmic framework as a function of beam-on-time penalty $\alpha$. To show the finite convergence of the algorithm, we investigate the behavior of $y^*_k(\alpha)$ as $\alpha$ is reduced from its initial value $\alpha_0$. In particular, we know that $y^*_k(\alpha)$ is continuous in $\alpha$ (Theorem 3.7). Moreover, using a basic set of apertures at $\alpha$, the algorithm employs $y^*_k(\cdot; \alpha)$ to locally characterize $y^*_k(\alpha)$. Recall that for this particular class of evaluation criteria, $y^*_k(\cdot; \alpha)$ is a linear function with respect to $\Delta \alpha$. Moreover, for a given beam-on-time penalty $\alpha$, there are only a finite number of basic sets of apertures (i.e., $K^*(\alpha)$). In particular, an upper bound can be obtained by simply considering all linearly-independent subsets of apertures $\bar{K} \subseteq K$. Now suppose for every linearly-independent subset $\bar{K} \subseteq K$ such that $k \in \bar{K}$, we obtain $y^*_k(\cdot; \alpha_0)$ as shown in Equation (3–13), so that we obtain a collection of lines corresponding to aperture $k$. Note that this collection contains finitely many lines. At iteration $m$ of the general
algorithmic framework, as the beam-on-time penalty $\alpha$ decreases from $\alpha_m$ to $\alpha_m - \Delta \alpha$, $y^*_k(\alpha)$ moves along the line which corresponds to the basic set of apertures $K^*(\alpha_m)$ employed in that iteration. Moreover, as the algorithm proceeds from iteration $m$ to $m + 1$ and the basic set of apertures $K^*(\alpha_m)$ changes to $K^*(\alpha_{m+1})$, $y^*_k(\alpha)$ is shifted to the new line corresponding to $K^*(\alpha_{m+1})$. However, if aperture $k$ is dropped from $K^*(\alpha_{m+1})$, then $y^*_k(\alpha)$ stays at zero until aperture $k$ is again introduced to the basic set of apertures $K^*(\alpha)$, if at all. Therefore, $y^*_k(\alpha)$ follows a continuous piecewise linear path; Figure 3-3 illustrates part of a possible path.

Due to continuity of $y^*_k(\alpha)$, the break points can only occur at intersection points of the lines in the collection. Hence, there is an intersection point associated with each iteration of the algorithmic framework. Suppose the step length (i.e., $\Delta \alpha_{\text{min}}$ in Step 1 of the algorithm) is positive at each iteration, so that the algorithm takes only nondegenerate steps. In that case, we do not visit the same intersection point twice during the course of the algorithm. As a result, since there are only a finite number of intersection points, the algorithm takes finitely many steps. We have therefore shown that the following result holds:

**Theorem 3.8.** In the absence of degeneracy, the algorithmic framework terminates in finitely many steps when applied to the class of convex quadratic evaluation criteria.

It is possible that at an iteration of the algorithm, the step length vanishes (i.e., $\Delta \alpha_{\text{min}} = 0$) which will result in a degenerate iteration. In particular, suppose several lines each corresponding to a different basic set of apertures, pass through the same intersection point. In that case, the algorithm may go through a sequence of degenerate steps before identifying the basic set of apertures for which the step length is strictly positive. Using an appropriate anti-cycling rule will prevent the algorithm from cycling in such intersection points.
Figure 3-3. $y^*_k(\alpha)$ characterized by the general algorithmic framework is continuous piecewise linear.

3.3.4 Sequential Quadratic Approximation

Theorem 3.4 guarantees that the family of optimal solutions to the parametric unconstrained problem can be characterized when $G$ is twice differentiable and $\nabla^2 G$ is strictly positive definite everywhere. However, for some classes of evaluation criteria, the system of nonlinear Equations (3–11) may not yield an analytical solution, or it might be computationally prohibitive to derive the solution. In that case, functions $y^*_k(\cdot; \alpha)$ for $k \in K^*(\alpha)$ and consequently $\rho^*_k(\cdot; \alpha)$ for $k \in K$ are not available. Hence, in this section, we propose an approximate method that we refer to as **Sequential Quadratic Approximation** (SQA). This method is based on our general algorithmic framework as well as the analytical results for quadratic functions $G$ in Section 3.3.3. SQA also requires $G$ to be twice differentiable but $\nabla^2 G$ needs only to be positive definite everywhere. It is based on sequentially approximating ($P(\alpha)$) with a quadratic programming problem, where the general algorithm framework is employed to the approximation.

Suppose that, for a given $\alpha \in \mathbb{R}_+$, the optimal dose distribution $z^*(\alpha)$ (along with a treatment plan $y^* \in Y^*(z^*(\alpha))$ for which the set of positive-intensity apertures is linearly independent) is given. SQA then starts by constructing the first and second-order Taylor series expansions of $G$ around $z = z^*(\alpha)$ which are denoted by $G^L$ and $G^Q$, respectively.
respectively:

\[ G^L(z) = \nabla G(z^*(\alpha))\top (z - z^*(\alpha)) + G(z^*(\alpha)) \]

\[ G^Q(z) = \frac{1}{2} (z - z^*(\alpha))\top \nabla^2 G(z^*(\alpha)) (z - z^*(\alpha)) + \nabla G(z^*(\alpha))\top (z - z^*(\alpha)) + G(z^*(\alpha)) . \]

Replacing \( G \) in the objective function of \((P(\alpha))\) with \( G^L \) yields a linear relaxation, which we denote by \((P^L(\alpha))\); this can be used to determine lower bounds. In addition, replacing \( G \) in the objective function of \((P(\alpha))\) by \( G^Q \) yields a quadratic approximation, which we denote by \((P^Q(\alpha))\). SQA proceeds by applying the general algorithmic framework to the quadratic approximation starting with \( z^*(\alpha), y^*, \) and \( K^*(\alpha) \) (which is chosen to be the set of positive-intensity apertures in \( y^* \)).

The results in Section 3.3.3 can then be used to obtain functions \( y^*_k(\cdot; \alpha) \) for \( k \in K^*(\alpha) \) that are optimal to \((P^Q_U(\cdot; \alpha))\). It is important to note that these solutions are not necessarily optimal to \((P_U(\cdot; \alpha))\). However, evaluating the true objective function at these solutions does of course yield an upper bound on the optimal solution values to \((P_U(\cdot; \alpha))\). Moreover, due to convexity of \( G \), evaluating the objective function value of \((P^L_U(\cdot; \alpha))\) at this solutions yields a lower bound on \( G \). More importantly, evaluating the individual components of the objective function of \((P^Q_U(\cdot; \alpha))\) and \((P^L_U(\cdot; \alpha))\) yields local upper and lower bounds on the actual Pareto-efficient frontier, respectively. SQA will keep track of these upper and lower bounds as a surrogate to identify the reduction in beam-on-time penalty (i.e., \( \Delta \alpha \)) for which the approximation \((P^Q_U(\Delta \alpha; \alpha))\) deviates from \((P_U(\Delta \alpha; \alpha))\). In particular, if the difference between these bounds exceeds a user-specified threshold (say \( \delta \)) at a certain beam-on-time penalty \( \alpha' \), SQA optimizes the corresponding problem \((P(\alpha'))\). Hence, at each iteration of SQA we obtain an approximate segment of the Pareto-efficient frontier along with an exact Pareto-efficient treatment plan at \( \alpha' \).

More formally, starting with \( \alpha_0 \) and iteration counter \( m = 0 \), SQA performs the following steps at iteration \( m \):
1. Find the approximate functions $G_L$ and $G_Q$ at $z^*(\alpha_m)$.

2. Apply the steps of the general algorithmic framework to $(P_Q(\alpha))$ starting with $\alpha_m$, $z^*(\alpha_m)$, $y^*(\alpha_m)$, and $K^*(\alpha_m)$, until the lower and upper bounds on the optimal value of $(P(\alpha))$ differ by more than $\delta$.

3. Let $\alpha_{m+1}$ be the final beam-on-time penalty obtained in Step 2. Solve $(P(\alpha_{m+1}))$ starting with the initial solution provided by $(P_Q(\alpha_{m+1}))$ to obtain $z^*(\alpha_{m+1})$, $y^*(\alpha_{m+1})$, and $K^*(\alpha_{m+1})$ (for example using the column generation algorithm developed by Romeijn et al. (2005)).

3.3.5 Continuously Differentiable Convex Penalty Functions

Since there is an asymmetry in the degree of undesirability of underdosing versus overdosing in different structures, asymmetric voxel-based penalties are widely used as treatment plan evaluation criteria. Recall the general form of $G$ composed of voxel-based penalty functions in Section 3.3.3:

$$G(z) = \sum_{j \in V} F_j(z_j)$$

where $F_j : \mathbb{R} \rightarrow \mathbb{R}$ ($j \in V$) are convex functions. Often, but not necessarily, the functions $F_j$ are piecewise-quadratic and of the following form:

$$F_j(z_j) = w_j^- (\max\{0, T_j - z_j\})^2 + w_j^+ (\max\{0, z_j - T_j\})^2 \quad j \in V$$  

where $w_j^-$ and $w_j^+$ are nonnegative weights and $T_j$ is a nonnegative threshold value ($j \in V$) (Romeijn and Dempsey, 2008). In this section, we will simply assume that each $F_j$ is continuously differentiable and convex. Moreover, we assume that for all $j \in V$, if $w_j^- = 0$, then $T_j = 0$ to disallow flat spots in the corresponding penalty function.

The weighted sum of the evaluation criteria will therefore be a convex piecewise quadratic function. In particular, function $G$ is piecewise quadratic if its domain is a union of finitely many convex polyhedra, on each of which the function is given by a quadratic expression (Rockafellar and Roger, 1998). More formally, let us denote the domain of function $G$ by dom $G$, and the set of convex polyhedra forming dom $G$ by $R$. Polyhedron $r \in R$ and its interior are then denoted by $P(r)$ and int $P(r)$, respectively. $R$ has the
property that \( \text{dom } G = \bigcup_{r \in R} P^{(r)} \) and \( \text{int } P^{(r)} \cap \text{int } P^{(\hat{r})} = \emptyset \) for \( r, \hat{r} \in R \) and \( r \neq \hat{r} \). The quadratic expression for \( G \) at \( z \in P^{(r)} \) is then as follows:

\[
G(z) = \frac{1}{2} z^\top Q^{(r)} z + q^{(r)}^\top z + q_0^{(r)}.
\]

Since \( F_j \) for \( j \in V \) are continuously differentiable functions, \( G \) is continuously differentiable on \( \mathbb{R}^{|V|} \). However, \( G \) is not necessarily twice differentiable everywhere. In particular, if \( z \in \text{int } P^{(r)} \) for some \( r \in R \), then \( G \) has a unique quadratic representation on a neighborhood around \( z \) and as a result it is twice differentiable at \( z \). On the contrary, if \( z \) lies on the common boundaries of some polyhedra, (i.e., \( z \in \bigcap_{r \in \bar{R}} P^{(r)} \) where \( \bar{R} \subseteq R \)), then there are multiple quadratic representations for \( G \) at \( z \), and \( G \) is not necessarily twice differentiable at \( z \). In the following, we argue that the SQA method can still be applied to this class of evaluation criteria.

The main difficulty in employing the SQA method to convex piecewise quadratic evaluation criteria stems from the lack of twice differentiability of \( G \) on the boundary points. In particular, the second-order Taylor expansion of \( G \) is not well-defined everywhere. Suppose at iteration \( m \) of SQA, \( z^*(\alpha_m) \in \bigcap_{r \in \bar{R}} P^{(r)} \) for some \( \bar{R} \subseteq R \) (i.e., \( z^*(\alpha_m) \) is a boundary point). Then a collection of quadratic representations exist at \( z = z^*(\alpha_m) \) as follows:

\[
G(z) = \frac{1}{2} z^\top Q^{(r)} z + q^{(r)}^\top z + q_0^{(r)} \quad r \in \bar{R}.
\]

Now suppose \( G^Q \) is constructed using an arbitrary quadratic representation chosen from \( \bar{R} \). In the following, we argue that \( z^*(\alpha_m) \) is also the optimal dose distribution to \( (P^Q(\alpha_m)) \). In particular, since \( z^*(\alpha_m) \) is the optimal dose distribution to \( (P(\alpha_m)) \), then it satisfies the KKT conditions (3–6)–(3–10) for \( (P(\alpha_m)) \). Moreover, since \( G \) is differentiable at \( z^*(\alpha_m) \), then we have

\[
\nabla G(z^*(\alpha_m)) = Q^{(r)} z^*(\alpha_m) + q^{(r)} \quad r \in \bar{R}.
\]
Thus, $\nabla G^Q(z^*(\alpha_m)) = \nabla G(z^*(\alpha_m))$. As a result, $z^*(\alpha_m)$ also satisfies the KKT conditions (3–6)–(3–10) for $(P^Q(\alpha_m))$ and is optimal to $(P^Q(\alpha_m))$. Therefore, the SQA method can pick any of the quadratic representations in $\tilde{R}$ to obtain $G^Q$.

3.4 Computational Results

3.4.1 Clinical Problem Instances

We used a head-and-neck and prostate cancer case to study the performance of our model. In particular, we obtained Pareto-efficient treatment plans using five and nine equispaced $^{60}$Co-beams around the patient for the head-and-neck and prostate case, respectively. The nominal size of each beam is $40 \times 40$ cm$^2$. The beams are discretized into beamlets of size $1 \times 1$ cm$^2$. We reduced the number of beamlets considered in the model by defining a mask for each beam eliminating any beamlets that only have a negligible contribution to target coverage. Moreover, we considered a voxel grid of size $4 \times 4 \times 4$ mm$^3$ for all targets and critical structures. This was used for the evaluation of all treatment plans; however, in the optimization model we used a coarser resolution of $8 \times 8 \times 8$ mm$^3$ for unspecified tissue (full resolution was used for all targets and other critical structures). The head-and-neck case has 1,113 beamlets and 86,255 voxels where the coarser resolution reduces the number of voxels to 15,985 in the corresponding optimization model. For the prostate case, there are 1,211 beamlets and 210,307 voxels, and the optimization model contains 36,535 voxels. We then used a pencil-beam dose model with heterogeneous depth scaling to calculate the matrix of beamlet dose deposition coefficients (Fox et al., 2006).

The head-and-neck case contains two Planning Target Volumes, PTV1 and PTV2, with prescription doses of 73.8 Gy and 54 Gy, respectively. The prostate case contains only a single Planning Target Volume PTV with prescription dose of 73.8 Gy. Dose-volume histogram (DVH) is a commonly used tool in clinical practice to evaluate the quality of a treatment plan. For a given target or critical structure, this histogram specifies the fraction of its volume that receives at least a certain amount of dose. Thus,
to determine the clinical quality of the treatment plans, we employ a list of DVH criteria in the treatment planning protocol used in the Department of Radiation Oncology at the University of Florida. The criteria for head-and-neck cancer cases are as follows:

**PTV1.** At least 99% should receive at least 93% of the prescribed dose \((0.93 \times 73.8 = 68.6 \text{ Gy})\). At least 95% should receive at least the prescribed dose (73.8 Gy). No more than 10% should receive more than 110% of the prescribed dose \((1.1 \times 73.8 = 81.2 \text{ Gy})\). No more than 1% should receive more than 120% of the prescribed dose \((1.2 \times 73.8 = 88.6 \text{ Gy})\).

**PTV2.** At least 99% should receive at least 93% of the prescribed dose \((0.93 \times 54 = 50.2 \text{ Gy})\). At least 95% should receive at least the prescribed dose (54 Gy).

**Salivary glands.** These include left and right parotid glands (LPG/RPG) as well as left and right submandibular glands (LSG/RSG). No more than 50% of each gland should receive more than 30 Gy.

Moreover, the DVH criteria for prostate cancer cases are:

**PTV.** These criteria are the same as the DVH criteria for PTV1 in head-and-neck cases.

**Bladder.** No more that 15% of the bladder should receive more than 80 Gy. No more that 20% of the bladder should receive more than 75 Gy. No more that 25% of the bladder should receive more than 70 Gy. No more that 30% of the bladder should receive more than 65 Gy.

**Rectum.** No more that 15% of the rectum should receive more than 75 Gy. No more that 20% of the rectum should receive more than 70 Gy. No more that 25% of the rectum should receive more than 65 Gy. No more that 30% of the rectum should receive more than 60 Gy.

DVH criteria for additional critical structures, such as brainstem, spinal cord, skin, optic nerves and chiasm in head-and-neck cases and femoral head in prostate cases,
were always easily satisfied in our experiments so we have omitted them from our results and analysis.

Recently, the clinical feasibility of using conventional jaws rather than MLC for delivering IMRT has been investigated for several disease sites (Kim et al., 2007; Earl et al., 2007; Men et al., 2007; Mu and Xia, 2009; Taşkın et al., 2010a). In particular, it has been shown that this delivery technique, the so-called jaws-only IMRT, is capable of constructing complex dose distributions using solely rectangular apertures. These apertures can be formed using conventional jaws without the need to operate expensive MLC. Although the development of DAO has made jaws-only IMRT more practical, the average beam-on-time for this delivery technique is about twice as long as the beam-on-time required for MLC delivery (Mu and Xia, 2009). Hence, delivery efficiency is a critical factor in the successful application of this IMRT delivery technique in particular. Therefore, in our experimental results we use this delivery technique as our proof of concept.

3.4.2 Implementation and Results

We ran the SQA method on the two cases discussed above, using piecewise quadratic voxel-based penalty functions as the treatment plan evaluation criteria. We also compared the performance of the SQA method with the NISE technique (Section 3.3). All experiments were implemented and performed in MATLAB 7.9.0 (2009b) on a 2.33 GHz Intel Core 2 Duo with 2 GB of RAM under Windows XP operating system. It takes 35 and 75 minutes to approximate the Pareto-efficient frontier for the head-and-neck and prostate case, respectively. The $\delta$ parameter in Step 3 of the SQA method is set to 0.01. Note that $\delta$ determines how closely the Pareto-efficient frontier is estimated, and $\delta = 0.01$ was found to yield an appropriate estimation for both cancer cases.

Figure 3-4 illustrates the approximated Pareto-efficient frontier for both cancer cases. The Pareto-efficient frontier consists of two distinguishable parts; in the first
part, allowing for slightly larger beam-on-times improves the treatment plan quality significantly, while in the second part, relatively minor improvements in the treatment plan quality come at the expense of significant increases in the beam-on-time. The shape of the Pareto-efficient frontiers suggest that one can significantly shorten beam-on-time without compromising the treatment quality.

To investigate this further, we study the clinical quality of the Pareto-efficient treatment plans as the beam-on-time increases. In particular, we evaluate the DVH criteria for the target coverage as well as the critical-structure sparing at different Pareto-efficient treatment plans obtained by the SQA method. Figures 3-5 and 3-6 illustrate the DVH criteria associated with the head-and-neck and prostate cancer case, respectively. Initially, the target DVH criteria (i.e., the DVH criteria corresponding to PTV1 and PTV2 in the head-and-neck case and PTV in the prostate case) substantially improve as the beam-on-time increases, and beyond a certain beam-on-time they relatively converge. On the contrary, the critical-structure DVH criteria (i.e., the DVH criteria corresponding to salivary glands in the head-and-neck case and the bladder and rectum in the prostate case) initially deteriorate as the beam-on-time increases, and after an early peak, they start improving up to a certain beam-on-time value beyond which they become relatively fixed. The collection of Pareto-efficient treatment plans with beam-on-time values larger than 4.8 and 3 minutes satisfy all the DVH criteria for the head-and-neck and prostate case, respectively. Men et al. (2007) present a DAO model that does not account for the delivery efficiency. The treatment plans obtained using their model require a beam-on-time of at least 6.1 and 4.8 minutes to satisfy the DVH criteria for the head-and-neck and prostate case, respectively. However, the SQA method can achieve Pareto-efficient treatment plans with 20% shorter beam-on-time to satisfy the DVH criteria.

From the collection of Pareto-efficient treatment plans that satisfy the DVH criteria for each cancer case, Figure 3-8 illustrates and compares the DVH curves associated
with the following beam-on-time values: (1) the shortest beam-on-time for which the DVH criteria are met, (2) the beam-on-time beyond which the DVH-criteria values are relatively fixed, and (3) the longest beam-on-time. In particular, for the head-and-neck cancer case, the Pareto-efficient treatment obtained at beam-on-time of 4.8 minutes has the shortest beam-on-time in the collection. This treatment plan satisfies all the head-and-neck DVH criteria. However, by extending the beam-on-time to 9.8 minutes (where the DVH-criteria values relatively converge), an overall improvement in salivary glands sparing can be obtained. By increasing the beam-on-time from 9.8 to 14.4 minutes, we observe further improvement in the right-submandibular gland (RSG) sparing. For the prostate cancer case, the Pareto-efficient treatment plan obtained at beam-on-time of 3 minutes satisfies all the prostate DVH criteria. By allowing for a longer beam-on-time of 5.9 minutes (where the DVH-criteria values relatively converge), a significant improvement in bladder and rectum sparing can be obtained. Finally, further increases in beam-on-time to 15 minutes will result in further improvements in bladder and rectum sparing. On the contrary, once the DVH criteria are met, the DVH curves associated with targets do not change significantly in both cancer cases. This is due to the fact that the model primarily seeks to achieve a satisfactory target coverage at all values of beam-on-time (note that this can be controlled in the model by assigning a relatively larger weight to penalizing target underdosing versus critical-structure overdosing). This can also be observed in DVH-criteria values in Figures 3-5 and 3-6. More specifically, as the beam-on-time increases, the target DVH criteria are met prior to the critical-structure DVH criteria, and once a satisfactory target coverage is achieved, further increases in beam-on-time will mostly improve the critical-structure sparing.

Figure 3-9 illustrates the isodose curves corresponding to Pareto-efficient treatment plans obtained at different beam-on-time values on a CT slice for the prostate case. A Pareto-efficient treatment plan with a low beam-on-time of 0.7 minute spends the entire available beam-on-time at a single beam direction which has the largest
dose contribution to the target. By increasing the beam-on-time to 1.8 minutes, the target coverage improves significantly; however, that comes at the expense of rectum overdosing. By further increasing the beam-on-time to 3 minutes, the Pareto-efficient treatment plan satisfies all DVH criteria including the ones associated with PTV coverage and rectum sparing. Finally, by further extending the beam-on-time to 5.9 minutes, the treatment plan will achieve a better rectum sparing in the intersection region of rectum and PTV (this region is pointed by the arrow in the figure). Hence, as the beam-on-time increases, the rectum sparing improves after a satisfactory PTV coverage is achieved.

In addition to beam-on-time, the number of apertures employed in a treatment plan plays an important role in the delivery efficiency. The number of apertures used in Pareto-efficient treatment plans are shown in Figures 3-5D and 3-6D. In particular, to obtain Pareto-efficient treatment plans that satisfy the DVH criteria, 90 and 75 apertures are used for the head-and-neck and prostate cancer case at beam-on-time of 4.8 and 3 minutes, respectively. Furthermore, a positive correlation exists between the number of apertures used in the Pareto-efficient treatment plans and the corresponding beam-on-time values.

The NISE technique can be employed to approximate the Pareto-efficient frontier of (P). However, a major drawback of this technique is the large amount of computational effort required. In particular, NISE takes around 75 minutes for the head-and-neck case and around 5 hours for the prostate case to approximate the Pareto-efficient frontier using the same number of points generated by the SQA method (i.e., 38 for the head-and-neck case and 36 for the prostate case). More specifically, at each iteration of the NISE technique an instance of (P(α)) for a given $\alpha \in \mathbb{R}_+$ is solved using the column generation algorithm. Solving (P(α)) for smaller beam-on-time penalties requires relatively more computational effort. Therefore, NISE initially spends a large amount of computational effort (16–18% of the total computation time) to solve (P(α))
for $\alpha = 0$. However, since the treatment plan quality does not significantly improve beyond a certain beam-on-time, the tail of the Pareto-efficient frontier is not clinically worth considering. On the other hand, there is no explicit approach to choose a beam-on-time penalty other than $\alpha = 0$ to ensure that the clinically-relevant part of the Pareto-efficient frontier is preserved. Hence, the NISE method spends a large amount of computational effort to produce part of the Pareto-efficient frontier which is clinically not worth considering. In contrast with the NISE technique, since the SQA method sequentially obtains points on the Pareto-efficient frontier according to an increasing order of the beam-on-time, it can be terminated as soon as the desired part of the Pareto-efficient frontier is generated.

Additionally, in applying the column generation technique to instances of $(P(\alpha))$, due to the slow convergence of this method, we employ the DVH-convergence rule proposed in Men et al. (2007) as the stopping criteria. In particular, we terminate the column generation procedure when the changes in DVH criteria within the last five iterations span less than a user-specified threshold, say $\sigma$. In the head-and-neck cancer case, $\sigma = 0.025\%$ for the target coverage and $\sigma = 0.25\%$ for the glands sparing, and in the prostate case, $\sigma = 0.05\%$ for the target coverage and $\sigma = 0.5\%$ for the bladder and rectum sparing. However, terminating the column generation algorithm using the DVH-convergence rule causes inaccuracy in estimating the inner and outer envelopes on the Pareto-efficient frontier. Figure 3-10 illustrates different parts of the NISE envelopes for the head-and-neck and prostate case. In particular, for shorter beam-on-times, Pareto-efficient points obtained by the SQA method lie within the envelopes, whereas, for relatively longer beam-on-times, these points lie below the NISE outer envelope.

3.5 Conclusion and Future Research

In this paper, we incorporated the beam-on-time into the IMRT treatment-plan optimization problem by formulating a bi-criteria convex DAO model. In particular, the
proposed DAO model allows us to explicitly quantify the trade-off between the weighted sum of the evaluation criteria as a measure of the treatment plan quality and the beam-on-time as a measure of the delivery efficiency. We developed an exact solution approach to obtain the set of Pareto-efficient treatment plans. More specifically, our solution method sequentially characterizes segments of the Pareto-efficient frontier. Furthermore, we proposed an approximate method which can closely approximate the Pareto-efficient frontier. This method was applied to the class of piecewise quadratic voxel-based penalty functions, and its performance was compared to the NISE technique. Our approach spends 33–75% less computational effort depending on the case, and, in contrast to the NISE method, can be terminated as soon as the clinically-relevant part of the Pareto-efficient frontier is obtained. Using the set of Pareto-efficient treatment plans, the trade-off between the treatment plan quality and the beam-on-time was investigated for a head-and-neck and prostate cancer case. The results suggest that beyond a certain beam-on-time value, all Pareto-efficient treatment plans satisfy the DVH criteria.

An important aspect of the delivery efficiency is the number of apertures employed in the treatment plan. Future research can extend this work by quantifying the trade-off between the treatment plan quality and the number of apertures required to deliver the treatment plan.
Figure 3-4. Pareto-efficient frontier obtained for clinical cancer cases.
Figure 3-5. DVH criteria associated with target coverage and salivary glands sparing evaluated at Pareto-efficient treatment plans for the head-and-neck cancer case.
Figure 3-6. DVH criteria associated with target coverage and rectum and bladder sparing evaluated at Pareto-efficient treatment plans for the prostate case.
Figure 3-7. DVH curves associated with Pareto-efficient treatment plans at different levels of beam-on-time (BOT) (in minutes) for the head-and-neck case.
Figure 3-8. DVH curves associated with Pareto-efficient treatment plans at different levels of beam-on-time (BOT) (in minutes) for the prostate case.
Figure 3-9. Isodose curves (dashed lines) for 60 and 73.8 Gy on a typical CT slice corresponding to Pareto-efficient treatment plans for the prostate case.
Figure 3-10. Inner and outer envelopes obtained using the NISE technique. (a) and (b) head-and-neck case, (c) and (d) prostate case.
CHAPTER 4
ACCOUNTING FOR THE INTRAFACTION MOTION USING A DIRECT APERTURE OPTIMIZATION APPROACH

4.1 Introductory Remarks

The vast majority of Intensity-Modulated Radiation Therapy (IMRT) treatment plans are not delivered to a patient in a single session, but rather as a sequence of daily treatments (often called fractions) over an extended period of time (usually on the order of 4-8 weeks). This is to take advantage of the fact that healthy cells recover faster from radiation damage than cancer cells. However, this introduces several sources of uncertainty that can compromise the quality of the IMRT treatment plan. A major source of error is introduced by changes in patient geometry during the course of treatment (Langen and Jones, 2001). In particular, we distinguish between two types of motion: (1) interfraction motion which refers to changes in patient geometry that takes place between treatment fractions, caused by the fact that patients cannot be perfectly repositioned at the accelerator for each fraction, and the internal organs of the patients can move or change between fractions; and (2) intrafraction motion which refers to the motion of the patient’s body during a fraction, for example, due to breathing. The impact of organ motion on IMRT dose delivery has been clinically studied for different tumor sites and both step-and-shoot and dynamic delivery techniques (Yu et al., 1998; Huang et al., 2002; George et al., 2003; Bortfeld et al., 2004).

In current practice, these errors are usually accounted for by artificially expanding all relevant structures in the patient by some margin (Wambersie and Landberg, 1999). In particular, the volume identified to contain the disease and its possible spread is called clinical target volume (CTV). This volume is then expanded by a safety margin to form the planning target volume (PTV). To ensure the delivery of the prescribed dose to CTV, PTV is then irradiated with the prescription dose. Since in this approach a larger region is irradiated, surrounding healthy tissues are harmed. Alternatively, we can incorporate the organ motion uncertainty into the treatment plan optimization stage.
In particular, accounting for the interfraction motion essentially transforms the Fluence map optimization (FMO) problem from a deterministic into a stochastic optimization problem. Relatively recently, several researchers have proposed probabilistic (Men, 2009; Unkelbach and Oelfke, 2005; Baum et al., 2006) as well as robust optimization approaches (Chu et al., 2005; Ólafsson and Wright, 2006) to this problem. In addition, to address the intrafraction motion uncertainty, Bortfeld et al. (2002) and Unkelbach (2006) formulated the FMO problem as a stochastic optimization problem, and Chan et al. (2006) and Heath et al. (2009) have proposed robust FMO approaches.

The main difficulty with modeling the intrafraction motion is the dynamic character of IMRT treatments making the current FMO approaches inadequate. Since it is possible that the movements of the patient conspire with the motion of the multileaf collimator (MLC), the delivered dose distribution may differ significantly from the planned one (often called the interplay effect). As an extreme example, breathing motion may move the target in and out of the dynamically changing field of radiation in such a way that parts of the target are missed entirely, or severely underdosed or overdosed. Several researchers have investigated the interplay effect on the delivered dose distribution. In particular, Bortfeld et al. (2002) report that in highly-fractionated IMRT delivery (≥ 30 fractions), the interplay effect on the expected dose delivery is negligible. However, Jiang et al. (2003) and Seco et al. (2007) report that ignoring the interplay effect can cause non-negligible biological impact when a high dose rate or apertures with low number of monitor units (of the order of the motion period) are employed in the treatment plan. Therefore, to account for the intrafraction motion in the treatment plan optimization stage, we need a modeling framework that incorporates the associated uncertainty in its entirety.

The only approach that can explicitly account for intrafraction motion uncertainties is one that directly models the sequence of apertures that is delivered during a particular fraction. In other words, a rigorous approach to this problem requires the use of models
that keep track of the movements of MLC leaves during the treatment fraction. In contrast with FMO approaches, the problem of incorporating intrafraction motion using a Direct Aperture Optimization (DAO) approach has thus far not been adequately studied.

In this chapter, we account for the intrafraction motion in the treatment plan optimization stage using a DAO framework. In particular, we describe the state of the patient geometry over time using a stochastic process. Moreover, to keep track of the movement of the MLC leaves at each row, we associate a collection of binary variables to all possible leaf configurations in that row over time. Using the above modeling framework, we then formulate the treatment plan optimization problem as a stochastic binary quadratic programming problem and develop a column generation method to solve the relaxation of the model. We then use the column generation algorithm in a branch-and-bound framework to solve the discrete problem.

4.2 A Continuous-Time DAO Model

Intrafraction motion introduces uncertainty to the patient geometry. As a result, the dose deposition rates are not known with certainty anymore. To model this source of uncertainty, we assume that the organ motion can be discretized into a finite number of states, denoted by $F$, and that the patient geometry transitions between these states. We then model these transitions over time using a stochastic process, denoted by $\{\Phi(t); t \geq 0\}$, with state space $F$. Moreover, we let $p_f(t) = Pr\{\Phi(t) = f\}$ represent the probability of being in state $f \in F$ at time $t \geq 0$. Finally, we assume that for each state of the patient geometry the dose deposition rates are obtainable and fixed.

We consider a dynamic IMRT delivery in which the patient is irradiated using a set of beam directions, denoted by $B$. We assume that the gantry spends a total of $t_b$ time units at beam direction $b \in B$. We let $R_b$ denote the set of MLC rows when it is positioned at beam direction $b \in B$ and $R = \bigcup_{b \in B} R_b$ denote the set of all MLC rows. Moreover, we let $C$ denote the set of all possible leaf-pair configurations at each MLC row. To evaluate the dose deposited in the patient’s body, targets and other relevant
structures are discretized into a set $V$ of cubes (voxels). In particular, we let $V_s$ denote the set of all voxels in structure $s \in S$. We assume that $V$ and $V_s$ remain the same as the patient geometry changes. Each time the gantry is repositioned in a new beam direction, $\{\Phi(t); t \geq 0\}$ is initialized again. Therefore, the treatment at beam direction $b \in B$ takes place during a time window of $[0, t_b]$.

In the absence of MLC-manufacturer constraints (Romeijn et al., 2005), MLC leaves at each row can independently move. To keep track of the movements of the MLC leaves at row $r \in R$, we define dynamic aperture $A_r : [0, t_b] \to \{0, 1\}^{|C|}$ as follows:

$$A_{rc}(t) = \begin{cases} 
1, & \text{if configuration } c \text{ is used at row } r \text{ at time } t; \\
0, & \text{otherwise.}
\end{cases}$$

Since at each point in time only a single leaf configuration can be used, $\sum_{c \in C} A_{rc}(t) = 1 \ (t \in [0, t_b])$. $A = (A_r : r \in R)$ then shows the dynamic aperture used for each MLC row. The DAO problem involves identifying the optimal deliverable dynamic aperture for each MLC row $r \in R$.

Depending on the particular state of the patient geometry $f \in \mathcal{F}$, the dose deposition rates may change. Therefore, we let $D_{rcj}^f$ denote the rate of dose deposition in voxel $j \in V$ from MLC row $r \in R$ when the leaves are in configuration $c \in C$ and the patient geometry is in state $f \in \mathcal{F}$. Hence, the total dose received by voxel $j \in V$ from dynamic aperture $A$, can be expressed as a random variable as follows:

$$z_j = \sum_{b \in B} \sum_{r \in R_b} \int_0^{t_b} \sum_{c \in C} D_{rcj}^{\Phi(t)} A_{rc}(t) dt.$$  

(4–1)

Moreover, we let $\mathcal{E}(z_j)$ denote the expected value of the random variable $z_j \ (j \in V)$. To account for the intrafraction motion, we can then formulate the DAO problem in terms of all deliverable dynamic apertures as a binary stochastic optimization problem as follows:

$$\min \gamma_1 \sum_{j \in V} F_j(\mathcal{E}(z_j)) + \gamma_2 \sum_{j \in V_T} \mathcal{E}(F_j(z_j))$$
subject to $(\tilde{P})$

$$z_j = \sum_{b \in B} \sum_{r \in R_b} \int_0^{t_b} \sum_{c \in C} D_{rcj}^{b(t)} A_{rc}(t) dt \quad j \in V$$

(4–2)

$$\sum_{c \in C} A_{rc}(t) = 1 \quad t \in [0, t_b], r \in R_b, b \in B$$

(4–3)

$$A_{rc}(t) \in \{0, 1\} \quad t \in [0, t_b], r \in R_b, b \in B, c \in C.$$

(4–4)

where $V_T$ represents the set of all target voxels. $F_j : \mathbb{R}^{|V|} \rightarrow \mathbb{R} (j \in V)$ are convex quadratic voxel-based penalties expressed as

$$F_j(z_j) = \frac{\alpha_s}{|V_s|} (z_j - T_s)^2 \quad j \in V_s, s \in S$$

in which $\alpha_s$ and $T_s$ are the relative importance weight and the prescribed dose corresponding to structure $s \in S$, respectively. The first term in the objective function evaluates the treatment quality with respect to the expected dose distribution delivered to the patient. The second term measures the expected deviation of the dose distribution from the prescribed dose in target voxels. Hence, while evaluating the quality of a treatment plan, we consider both the quality of the expected dose distribution as well as the expected variation of the dose distribution in target voxels. Random variables defined by Equation (4–2) describe the dose distribution, and Constraints (4–3) and (4–4) ensure that $A = (A_r : r \in R)$ are deliverable dynamic apertures. $(\tilde{P})$ is an infinite programming problem with an infinite number of constraints and binary variables.

Now suppose for the stochastic process $\{\Phi(t) : t \geq 0\}$ under consideration, there are only finitely-many deliverable dynamic apertures for MLC row $r \in R$, indexed by $m \in M_r$ (for instance, in case of using a discrete-time stochastic process). We can then associate a collection of binary decision variables $y_{rm}^m \in \{0, 1\} (m \in M, r \in R)$ with dynamic apertures $m \in M_r (r \in R)$ and reformulate the DAO problem as

$$\min \gamma_1 \sum_{j \in V} F_j(\mathcal{E}(z_j)) + \gamma_2 \sum_{j \in V_T} \mathcal{E}(F_j(z_j))$$
subject to (P)

\[ z_j = \sum_{b \in B} \sum_{r \in R_b} \sum_{m \in M_r} \left( \int_0^{t_b} \sum_{c \in C} D_{rcj}^{b(t)} A_{rc}^{m}(t) \, dt \right) y_r^m \quad j \in V \] (4–5)

\[ \sum_{m \in M_r} y_r^m = 1 \quad r \in R_b, b \in B \] (4–6)

\[ y_r^m \in \{0, 1\} \quad m \in M_r, r \in R \] (4–7)

where Constraints (4–6) and (4–7) ensure that exactly one dynamic aperture is chosen for each MLC row \( r \in R \). In the next section, we show that this formulation leads to a branch-and-price algorithm in which we solve the relaxation of (P) using a column generation method.

For some classes of stochastic processes, we have to consider an uncountably-infinite number of deliverable dynamic apertures for each MLC row. In that case, it is essentially impossible to enumerate and index all dynamic apertures corresponding to each MLC row. Hence, for such stochastic processes we cannot formulate the DAO problem as (P). However, using any finite subset of dynamic apertures yields a restricted version of (\( \bar{p} \)) which can be formulated as (P). Therefore, to solve the relaxation of (\( \bar{p} \)), we use the result proved by Dantzig (1960) saying that a column generation procedure that employs the relaxation of the restricted version as the master problem, either finds the optimal solution to the full problem in finitely many iterations, or converges to the optimal solution in the limit provided that there exists a non degenerate basic solution to the master problem.

**4.3 Solution Approach**

In this section we first study KKT optimally conditions for the relaxation of (P) and discuss the results obtained for developing a column generation algorithm to solve the relaxed problem. The column generation algorithm can then be employed in a branch-and-bound framework to solve (P). In particular, we consider (1) a special case in which \( \gamma_2 = 0 \), and (2) the general case in which \( \gamma_2 > 0 \).
4.3.1 Case of $\gamma_2 = 0$

Let $(\mathcal{P})$ represent the model in which $\gamma_2 = 0$. The objective function of this model is only in terms of the expected dose distribution. Therefore, we let decision variable $z_j$ denote the total expected dose received by voxel $j \in V$. In other words:

$$z_j = \mathcal{E}(z_j) = \sum_{b \in B} \sum_{r \in R} \int_0^{t_b} \sum_{c \in C} \mathcal{E}(\mathcal{D}_{rcj}^b(t)) A_{rc}(t) dt.$$

We can then formulate $(\mathcal{P})$ in terms of $z = (z_j : j \in V)$ as follows:

$$\min \sum_{j \in V} F_j(z_j)$$

subject to

$$z_j = \sum_{b \in B} \sum_{r \in R} \sum_{m \in M_r} \left( \int_0^{t_b} \sum_{c \in C} \mathcal{E}(\mathcal{D}_{rcj}^b(t)) A_{rc}^m(t) dt \right) y_{rm}^m, \quad j \in V$$

(4–8)

$$\sum_{m \in M_r} y_{rm}^m = 1, \quad r \in R$$

(4–9)

$$y_{rm}^m \in \{0, 1\}, \quad m \in M_r, r \in R.$$  

(4–10)

Relaxing Constrains (4–10) to the following nonnegativity constraints

$$y_{rm}^m \geq 0, \quad m \in M_r, r \in R$$

(4–11)

yields a convex optimization problem with linear constraints, which we denote by $(\mathcal{P}_R)$. Hence, KKT conditions are necessary and sufficient for the optimality of $(\mathcal{P}_R)$ (Bazaraa et al., 2006). By associating dual multipliers $\pi_j (j \in V), \lambda_r (r \in R)$, and $\rho_{rm}^r (m \in M_r, r \in R)$, with Constraints (4–8), (4–9), and (4–11), respectively, we can
express the KKT conditions for \((\mathcal{P}_R)\) as follows:

\[
    z_j = \sum_{b \in B} \sum_{r \in R_b} \sum_{m \in M_r} \left( \int_0^{t_b} \sum_{c \in C} \mathcal{E} \left( D_{rcj}^m(t) \right) A_r^m(t) dt \right) y^m_r \quad j \in V \tag{4–12}
\]

\[
    \pi_j = F_j'(z_j) \quad j \in V \tag{4–13}
\]

\[
    \rho_r^m = \sum_{j \in V} \left( \int_0^{t_b} \sum_{c \in C} \mathcal{E} \left( D_{rcj}^m(t) \right) A_r^m(t) dt \right) \pi_j + \lambda_r \quad m \in M_r, r \in R \tag{4–14}
\]

\[
    \rho_r^m y^m_r = 0 \quad m \in M_r, r \in R \tag{4–15}
\]

\[
    \rho_r^m, y^m_r \geq 0 \quad m \in M_r, r \in R. \tag{4–16}
\]

Note that any solution \((\bar{y}, \bar{\lambda}, \bar{z}, \bar{\pi}, \bar{\rho})\) to the KKT conditions (4–12)–(4–16) can be characterized by \(\bar{y}\) and \(\bar{\lambda}\) only since \(\bar{y}\) determines \(\bar{z}\), \(\bar{z}\) determines \(\bar{\pi}\), and finally \(\bar{y}\) and \(\bar{\lambda}\) determines \(\bar{\rho}\). Now suppose \((\bar{y}, \bar{\lambda})\) is the optimal solution to a restricted problem obtained from \((\mathcal{P}_R)\) in which for each MLC row \(r \in R\), only a limited number of dynamic apertures \(m \in \bar{M}_r\) are considered. In other words, \(\bar{y}_r^m = 0 (m \in M_r \setminus \bar{M}_r, r \in R)\). \((\bar{y}, \bar{\lambda})\) is also optimal to the full problem \((\mathcal{P}_R)\) if and only if \(\bar{\rho}_r^m \geq 0 (m \in M_r, r \in R)\). To check for the validity of such condition we can formulate and solve an optimization problem, the so-called pricing problem, for each MLC row \(r \in R\). More specifically, given the optimal solution \((\bar{y}, \bar{\lambda})\) to the restricted problem, the pricing problem, when solved for MLC row \(r \in R\), identifies the dynamic aperture \(m^* \in M_r\) with the most negative \(\bar{\rho}_r^{m^*}\). In other words,

\[
    \bar{\rho}_r^{m^*} = \min_{m \in M_r} \sum_{j \in V} \left( \int_0^{t_b} \sum_{c \in C} \mathcal{E} \left( D_{rcj}^m(t) \right) A_r^m(t) dt \right) \bar{\pi}_j + \bar{\lambda}_r
\]

if \(\bar{\rho}_r^{m^*} \geq 0 (r \in R)\), then \((\bar{y}, \bar{\lambda})\) is optimal to the full problem. \(\bar{\rho}_r^m\), the so-called reduced gradient, shows the rate of change in the objective function of \((\mathcal{P}_R)\) as \(y^m_r\) increases from \(\bar{y}_r^m\).

### 4.3.1.1 The pricing problem

In this section we derive the pricing problem for \((\mathcal{P}_R)\). To this end, to be able to formulate \((\mathcal{P})\), we have considered only finitely-many deliverable dynamic apertures \(M_r\),
for each MLC row $r \in R$. However, in a continuous-time setting, the leaf configuration at each MLC row may change at any point in time during the treatment. Therefore, there exist an uncountably-infinite number of dynamic apertures for each MLC row. In formulating the pricing problem we need to consider all deliverable dynamic apertures. In particular, assuming that MLC leaves have an infinite speed, any $A : [0, t_b] \to \{0, 1\}^{|C|}$ that satisfies

$$\sum_{c \in C} A_{rc}(t) = 1 \quad t \in [0, t_b], r \in R$$

is a deliverable dynamic aperture. To formulate the pricing problem considering all deliverable dynamic apertures, let us define $\Delta_{rc} : [0, t_b] \to \mathbb{R}$ for MLC row $r \in R_b (b \in B)$ and configuration $c \in C$ as follows:

$$\Delta_{rc}^\pi(t) = \sum_{j \in V} \mathcal{E} \left( D_{rcj}^{\pi(t)} \right) \pi_j. \tag{4–17}$$

$\Delta_{rc}^\pi(t)$ can be explained as the average rate of change per unit time in the objective function of $(P_R)$ at time $t \in [0, t_b]$ caused by MLC row $r \in R_b (b \in B)$ when leaves at this row are in configuration $c \in C$. Using the definition in Equation (4–17), we can formulate the pricing problem for MLC row $r \in R$ as

$$\min \int_0^{t_b} \sum_{c \in C} \Delta_{rc}^\pi(t) A_{rc}(t) dt + \lambda_r$$

subject to

$$\sum_{c \in C} A_{rc}(t) = 1 \quad t \in [0, t_b]$$

$$A_{rc}(t) \in \{0, 1\} \quad c \in C, t \in [0, t_b].$$

$(\overline{G})$ is an infinite programming problem with uncountably-infinite number of binary variables and constraints. The objective function in $(\overline{G})$ measures the total change in the objective function of $(P_R)$ caused as a result of employing dynamic aperture $A_r$ at
MLC row $r \in R_b (b \in B)$ over the entire time interval $[0, t_b]$. Both sets of constraints in $(\mathcal{G})$ ensure that $A_r$ is a deliverable dynamic aperture. Note that $(\mathcal{G})$ can be decomposed over the time interval $[0, t_b]$. Hence, to solve the pricing problem, we can determine the leaf setting $c \in C$ corresponding to the most negative $\Delta_{rc}^\pi (t)$ at each point in time $t \in [0, t_b]$. More formally, the optimal solution to $(\mathcal{G})$ can be expressed as $A^*_{rc} (t) = e_c$ where $e_c$ is a unit vector with one at element $c = \text{argmin} \Delta_{rc}^\pi (t) (t \in [0, t_b])$. Therefore, using the closed-form expressions for $\Delta_{rc}^\pi (c \in C)$ we can determine the lower envelope to obtain the optimal dynamic aperture to $(\mathcal{G})$. Using the state probability distribution $p_f(t) (f \in \mathcal{F})$ we can rewrite $\Delta_{rc}^\pi$ in Equation (4–17) as follows:

$$
\Delta_{rc}^\pi (t) = \sum_{j \in V} \mathcal{E} (D_{rcj}^f (t)) \pi_j = \sum_{f \in \mathcal{F}} \left( \sum_{j \in V} D_{rcj}^f \pi_j \right) p_f(t).
$$

Since the state probability distribution $p_f(t) (f \in \mathcal{F})$ depends on the starting probability distribution (i.e., $p_f(0) (f \in \mathcal{F})$), in the following we first consider the special case in which the treatment starts when the patient geometry is in its steady state. We then establish a connection between $(\mathcal{G})$ and the traditional DAO model.

4.3.1.2 Starting the treatment in the steady state

Let us assume that for each beam direction $b \in B$ the treatment starts at $t = t_0$ rather than $t = 0$. Hence, the corresponding treatment window is $[t_0, t_0 + t_b]$. To comply with the definition of dynamic aperture given in Section 4.2, we consider decision variables of the form $A_{rc} (t - t_0) (t \in [t_0, t_0 + t_b], r \in R, c \in C)$ in the pricing problem $(\mathcal{G})$. Now suppose that the treatment starts when the patient geometry is in its steady state (i.e, $t_0 \rightarrow \infty$). Assuming that the limiting state probabilities exist for the stochastic process under consideration, denoted by $p_f (f \in \mathcal{F})$, we can write Equation (4–18) for
the steady state as
\[
\lim_{t_0 \to \infty} \Delta^\pi_{rc} (t + t_0) = \sum_{f \in F} \left( \sum_{j \in V} D^f_{rcj} \pi_j \right) \lim_{t_0 \to \infty} p_f (t + t_0)
\]
\[
= \sum_{f \in F} p_f \sum_{j \in V} D^f_{rcj} \pi_j
\]
\[
= \bar{\Delta}^\pi_{rc}
\]
which is independent of time. Hence, in case of starting the treatment in the steady state, the optimal solution to (\(G\)) can be simply obtained as
\[
A^*_rc (t - t_0) = e_c
\]
where \(c = \arg\min \bar{\Delta}^\pi_{rc} (t \in [t_0, t_0 + t_b])\). In other words, since \(\bar{\Delta}^\pi_{rc}\) is constant over the time interval \(t \in [t_0, t_0 + t_b]\), the pricing problem chooses the leaf configuration with the most negative \(\bar{\Delta}^\pi_{rc}\) for the entire treatment interval.

4.3.1.3 Static DAO model

We next establish the connection between (\(P_R\)) and the traditional static DAO model. If the treatment starts at time \(t = t_0\), then the expected dose distribution \(z_j (j \in V)\) in Equation (4–8) can be written as
\[
z_j = \sum_{b \in B} \sum_{r \in R_b} \sum_{m \in M_r} \left( \int_{t_0}^{t_0 + t_b} \sum_{c \in C} E \left( D^{\Phi(t)}_{rcj} \right) A^m_{rc} (t - t_0) dt \right) y^m_r
\]
\[
= \sum_{b \in B} \sum_{r \in R_b} \sum_{m \in M_r} \left( \int_{t_0}^{t_0 + t_b} \sum_{c \in C} E \left( D^{\Phi(t)}_{rcj} \right) A^m_{rc} (t) dt \right) y^m_r
\]
where the last expression is obtained by a variable transformation. Now suppose the treatment starts when the stochastic process is in its steady state, then
\[
z_j = \sum_{b \in B} \sum_{r \in R_b} \sum_{m \in M_r} \lim_{t_0 \to \infty} \left( \int_{t_0}^{t_0 + t_b} \sum_{c \in C} E \left( D^{\Phi(t)}_{rcj} \right) A^m_{rc} (t) dt \right) y^m_r
\]
\[
= \sum_{b \in B} \sum_{r \in R_b} \sum_{m \in M_r} \left( \int_{t_0}^{t_0 + t_b} \sum_{c \in C} \lim_{t_0 \to \infty} E \left( D^{\Phi(t)}_{rcj} \right) A^m_{rc} (t) dt \right) y^m_r
\]
where the limit and integral signs were swapped since the integrand is bounded. We then let \(\bar{D}_{rcj}\) be the average rate of dose disposition in voxel \(j \in V\) from MLC row \(r \in R\).
when leaves are in configuration $c \in C$. In other words,

$$D_{rcj} = \lim_{t \to \infty} E \left(D_{rcj}^{\Phi(t+t_0)}\right)$$

$$= \sum_{r \in F} D_{rcj}^f p_r,$$

the expected dose distribution can then be expressed as

$$z_j = \sum_{b \in B} \sum_{r \in R_b} \sum_{c \in C} D_{rcj} \left(\sum_{m \in M_r} \left(\int_0^{t_b} A_{rc}^m(t) dt\right) y_r^m\right)$$

$$= \sum_{b \in B} \sum_{r \in R_b} \sum_{c \in C} D_{rcj} \left(\sum_{m \in M_r} \xi_{rc}^m y_r^m\right)$$

where $\xi_{rc}^m$ is the amount of time out of $t_b$ time units during which leaves at row $r \in R_b (b \in B)$ have configuration $c \in C$ under dynamic aperture $m \in M_r$. Moreover, due to the definition of a dynamic aperture we have

$$\sum_{c \in C} \xi_{rc}^m = t_b \quad m \in M_r, r \in R_b, b \in B,$$

multiplying both sides by $y_r^m$ yields

$$\sum_{c \in C} \xi_{rc}^m y_r^m = t_b y_r^m \quad m \in M_r, r \in R_b, b \in B,$$

and since $\sum_{r \in M_r} y_r^m = 1$ for $r \in R$, then

$$\sum_{c \in C} \sum_{m \in M_r} \xi_{rc}^m y_r^m = t_b \quad r \in R_b, b \in B.$$

Finally, we let decision variable $x_{rc} (r \in R c \in C)$, be defined as

$$x_{rc} = \sum_{m \in M_r} \xi_{rc}^m y_r^m. \quad (4–19)$$

$x_{rc}$ shows the amount of time out of $t_b$ time units during which leaves at row $r \in R$ have configuration $c \in C$. We can then formulate the static DAO problem in terms of the new
decision variables as follows:

$$\min \sum_{j \in V} F_j(z_j)$$

subject to

$$(4-20)$$

$$z_j = \sum_{r \in R} \sum_{c \in C} D_{rc} x_{rc} \quad j \in V$$

$$(4-21)$$

$$\sum_{c \in C} x_{rc} = t_b \quad r \in R_b, b \in B$$

$$(4-22)$$

$$x_{rc} \geq 0 \quad r \in R, c \in C.$$ 

where the objective function evaluates the quality of the treatment plan based on the average dose distribution. Equation (4–20) measures the expected value of the total dose received by voxel $j \in V$, and Constraint (4–21) ensures that a total treatment time of $t_b$ time units is spent at beam direction $b \in B$.

The traditional DAO model (Romeijn et al., 2005; Men et al., 2007) is concerned with finding the optimal collection of apertures along with their associated intensives to deliver the desired dose distribution to the patient. In the absence of MLC-manufacturer constraints, the problem can be decomposed over MLC rows and formulated in terms of all leaf-configuration intensities. Given the optimal leaf-configuration intensities, we can then form the optimal collection of apertures by simply combining these leaf settings. Therefore, (ST) represents the traditional DAO formulation if we limit the treatment time at beam direction $b \in B$ to $t_b$ time units.

4.3.2 Case of $\gamma_2 > 0$

In this section we study the general form of (P). In particular, we derive the KKT conditions for the relaxed problem associated with (P) and formulate the corresponding pricing problem. Relaxing Constraints (4–7) in (P) yields the following relaxed problem:

$$\min_{j \in V} \gamma_1 \sum_{j \in V} F_j(z_j) + \gamma_2 \sum_{j \in V} E(F_j(z_j))$$
subject to \((P_R)\)

\[
z_j(y) = \sum_{b \in B} \sum_{r \in R_b} \sum_{m \in M_r} \left( \int_0^{t_b} \sum_{c \in C} \mathcal{D}_{rcj}^b(t) A_{rc}^m(t) dt \right) y_r^m \quad j \in V \tag{4–23}
\]

\[
\sum_{m \in M_r} y_r^m = 1 \quad r \in R_b, b \in B \tag{4–24}
\]

\[
y_r^m \geq 0 \quad m \in M_r, r \in R_b, b \in B. \tag{4–25}
\]

Note that \(z = (z_j : j \in V)\) is a vector of random variables and should not be considered as decision variables in \((P)\). Moreover, these random variables are functions of \(y\).

Moreover, the objective function in \((P_R)\) is convex, since it is convex for each possible realization of the stochastic process over the treatment time. Therefore, \((P_R)\) is a convex optimization problem with linear constraints. Associating dual multipliers \(\lambda_r (r \in R)\) and \(\rho_r^m (m \in M_r, r \in R)\) with Constraints \((4–24)\) and \((4–25)\), the KKT conditions for \((P_R)\) can be expressed as

\[
\rho_r^m = \gamma_1 \sum_{j \in V} \frac{\partial F_j \left( \mathcal{E} \left( z_j(y) \right) \right)}{\partial y_r^m} + \gamma_2 \sum_{j \in V_r} \frac{\partial \mathcal{E} \left( F_j \left( z_j(y) \right) \right)}{\partial y_r^m} + \lambda_r \quad m \in M_r, r \in R \tag{4–26}
\]

\[
\rho_r^m y_r^m = 0 \quad m \in M_r, r \in R \tag{4–27}
\]

\[
\rho_r^m, y_r^m \geq 0 \quad m \in M_r, r \in R. \tag{4–28}
\]

Note that similar to the KKT conditions derived for \((P_R)\), a solution to the KKT conditions above can be uniquely characterized by \(\bar{y} = (\bar{y}_r^m : m \in M_r, r \in R)\) and \(\bar{\lambda} = (\bar{\lambda}_r : r \in R)\).

Since \(\mathcal{E} \left( z_j(y) \right)\) is a deterministic function of \(y\), the first term associated with voxel \(j \in V\) in Equation \((4–26)\) can be rewritten as

\[
\frac{\partial F_j \left( \mathcal{E} \left( z_j(y) \right) \right)}{\partial y_r^m} = F_j' \left( \mathcal{E} \left( z_j(y) \right) \right) \frac{\partial \mathcal{E} \left( z_j(y) \right)}{\partial y_r^m} = F_j' \left( \mathcal{E} \left( z_j(y) \right) \right) \int_0^{t_b} \sum_{c \in C} \mathcal{E} \left( \mathcal{D}_{rcj}^b(t) \right) A_{rc}^m(t) dt. \tag{4–29}
\]
To obtain the second term in Equation (4–26), we define

\[ D_{mj} \equiv \int_{0}^{t_b} \sum_{c \in C} D_{\Phi(t)}^c A_{rc}^m(t) dt. \]

as a random variable describing the total dose received by voxel \( j \in V \) from dynamic aperture \( A_{\Phi}^m (m \in M_r) \) used at MLC row \( r \in R_b (b \in B) \). Note that \( D_{mj} \) is a continuous random variable that may assume any value in the interval

\[ \left( t_b \min_{f \in F} D_{rcj}^f, t_b \max_{f \in F} D_{rcj}^f \right). \]

Using column vector \( D_j = (D_{mj} : m \in M_r, r \in R) \) we can then rewrite \( z_j(y) \) as

\[ z_j(y) = D_j^T y. \] (4–30)

Now suppose \( \Omega_j \) is the joint probability distribution associated with \( D_j \). Using Equation (4–30), we can rewrite the second term in the objective function of \( (P_R) \) associated with voxel \( j \in V_T \) as

\[ \mathcal{E} \left( F_j \left( z_j(y) \right) \right) = \mathcal{E} \left( F_j \left( D_j^T y \right) \right) = \int_{D_j} F_j \left( D_j^T y \right) \Omega_j (D_j) dD_j \]

where \( dD_j \) is the n-dimensional volume differential. Assuming \( F_j \) and \( \Omega_j \) are continuous, we can use Leibniz integral rule (Flanders, 1973), to rewrite the second term in Equation
(4–26) associated with voxel $j \in V_T$ as follows:

$$
\frac{\partial \mathcal{E} \left( F_j \left( z_j(y) \right) \right)}{\partial y^m_r} = \frac{\partial}{\partial y^m_r} \left( \int_{D_j} F_j \left( D_j^T y \right) \Omega_j \left( D_j \right) dD_j \right) \\
= \int_{D_j} \frac{\partial}{\partial y^m_r} \left( F_j \left( D_j^T y \right) \Omega_j \left( D_j \right) \right) dD_j \\
= \int_{D_j} \frac{\partial F_j \left( D_j^T y \right)}{\partial y^m_r} \Omega_j \left( D_j \right) dD_j \\
= \int_{D_j} D_{mj} F_j^\prime \left( D_j^T y \right) \Omega_j \left( D_j \right) dD_j \\
= \mathcal{E} \left( D_{mj} F_j^\prime \left( z_j(y) \right) \right).
$$

Finally, substituting $D_{mj}$ yields

$$
\frac{\partial \mathcal{E} \left( F_j \left( z_j(y) \right) \right)}{\partial y^m_r} = \mathcal{E} \left( F_j^\prime \left( z_j(y) \right) \int_0^{t_b} \sum_{c \in C} D_{rcj}^\phi(t) A^m_{rc}(t) dt \right). \quad (4–31)
$$

In the following, we first obtain the first and second terms in Equations (4–29) and (4–31) for convex quadratic penalties, and then formulate the pricing problem. In particular, Equation (4–29) can be obtained as

$$
\frac{\partial F_j \left( \mathcal{E} \left( z_j(y) \right) \right)}{\partial y^m_r} = F_j^\prime \left( \mathcal{E} \left( z_j(y) \right) \right) \frac{\partial \mathcal{E} \left( z_j(y) \right)}{\partial y^m_r} \\
= 2 \left( \sum_{b \in B} \sum_{r \in R_b} \sum_{m' \in M_r} \left( \int_0^{t_b} \sum_{c' \in C} \mathcal{E} \left( D_{rcj}^\phi(t') \right) A^m_{r'c'}(t') dt' \right) y^{m'}_{r'} - T_j \right) \left( \int_0^{t_b} \sum_{c \in C} \mathcal{E} \left( D_{rcj}^\phi(t) \right) A^m_{rc}(t) dt \right) \\
= 2 \int_0^{t_b} \sum_{c \in C} \left( \sum_{b \in B} \sum_{r \in R_b} \sum_{m' \in M_r} \sum_{c' \in C} \int_0^{t_b'} \mathcal{E} \left( D_{rcj}^\phi(t') \right) \mathcal{E} \left( D_{rcj}^\phi(t) \right) A^m_{r'c'}(t') y^{m'}_{r'} dt' \right) A^m_{rc}(t) dt \\
- 2 T_j \int_0^{t_b} \sum_{c \in C} \mathcal{E} \left( D_{rcj}^\phi(t) \right) A^m_{rc}(t) dt. \quad (4–32)
$$
Finally, by summing over the corresponding voxels we get

\[ \Delta_{rc}(t) = \sum_{j \in V} \Delta_{r dj}(t) \]

\[ \Omega_{rc}(t) = \sum_{j \in V} \Omega_{r dj}(t). \]

Similarly, Equation (4–31) for this class of evaluation criteria can be obtained as:

\[
\frac{\partial \mathcal{E} \left( F_j(z_j(y)) \right)}{\partial y^m_{jr}} = \mathcal{E} \left( F_j(z_j(y)) \right) \int_0^{t_b} \sum_{c \in C} D_{rcj}^m(t) A_{rc}^m(t) dt
\]

\[= 2 \int_0^{t_b} \sum_{c \in C} \left( \sum_{b' \in B} \sum_{r' \in R_b} \sum_{c' \in C} \int_0^{t'} \mathcal{E} \left( D_{r'c'j}^m(t') D_{rcj}^m(t) \right) A_{r'c'}^m(t') y_{r'c'}^m dt' \right) A_{rc}^m(t) dt
\]

\[- 2 T_j \int_0^{t_b} \sum_{c \in C} E \left( D_{rcj}^m(t) \right) A_{rc}^m(t) dt. \]  

(4–33)

Now suppose \((\bar{y}, \bar{\lambda})\) is the optimal solution to the restricted version of \((P_R)\) where \(\bar{y}_r^m = 0 (m \in M_r \setminus \overline{M_r}, r \in R)\). We define:

\[ q_{rc}(t) \equiv \sum_{m \in M_r} A_{rc}^m(t) \bar{y}_r^m \]  

(4–34)

which shows if configuration \(c \in C\) is used at row \(r \in R\) at time \(t \in [0, t_b]\). Note that since \(\bar{y}\) can be a fractional solution, then \(q_{rc}(t) \in [0, 1]\). Using \(q_{rc} (r \in R, c \in C)\) we can further simplify Equations (4–32) and (4–33). For that purpose, let

\[ \Delta_{r dj}(t) = 2 \sum_{b' \in B} \sum_{r' \in R_b} \sum_{c' \in C} \left( \int_0^{t'} \mathcal{E} \left( D_{r'c'j}^m(t') D_{rcj}^m(t) \right) q_{r'c'}^m dt' \right) \]

\[\Omega_{r dj}(t) = 2 \sum_{b' \in B} \sum_{r' \in R_b} \sum_{c' \in C} \left( \int_0^{t'} \mathcal{E} \left( D_{r'c'j}^m(t') D_{rcj}^m(t) \right) q_{r'c'}^m dt' \right) \]

(4–35)

Hence,

\[ \frac{\partial F_j \left( \mathcal{E} \left( z_j(y) \right) \right)}{\partial y^m_{jr}} = \int_0^{t_b} \sum_{c \in C} \Delta_{rcj}(t) A_{rc}^m(t) dt \]

\[ \frac{\partial \mathcal{E} \left( F_j(z_j(y)) \right)}{\partial y^m_{jr}} = \int_0^{t_b} \sum_{c \in C} \Omega_{rcj}(t) A_{rc}^m(t) dt. \]

Finally, by summing over the corresponding voxels we get

\[ \Delta_{rc}(t) = \sum_{j \in V} \Delta_{r dj}(t) \]

\[ \Omega_{rc}(t) = \sum_{j \in V} \Omega_{r dj}(t). \]
Hence, similar to \((\mathcal{G})\), we can formulate the pricing problem for \((P)\) corresponding to MLC row \(r \in R\) as follows:

\[
\min \int_0^{t_b} \sum_{c \in C} (\gamma_1 \Delta_{rc}(t) + \gamma_2 \Omega_{rc}(t)) A_{rc}(t) \, dt + \lambda_r
\]

subject to \((G)\)

\[
\sum_{c \in C} A_{rc}(t) = 1 \quad t \in [0, t_b]
\]

\[
A_{rc}(t) \in \{0, 1\} \quad c \in C, t \in [0, t_b].
\]

Note that the pricing problem \((\mathcal{G})\) obtained for \((P_R)\) is a special case of \((G)\) in which \(\gamma_1 = 1\) and \(\gamma_2 = 0\). \((G)\) is also an infinite programming problem. Note that \((G)\) can also be decomposed over the treatment time \([0, t_b]\). Therefore, given \(\Omega_{rc}(t)\) and \(\Delta_{rc}(t)\), one can determine the optimal solution to \((G)\) by obtaining the lower envelope (i.e., \(\min_{c \in C} \gamma_1 \Delta_{rc}(t) + \gamma_2 \Omega_{rc}(t)\) \(t \in [0, t_b]\)). However, depending on the stochastic process under consideration, determining closed-form expressions for \(\Omega_{rc}(t)\) and \(\Delta_{rc}(t)\) may be computationally prohibitive.

We next reformulate \((G)\) to obtain a beamlet representation of the problem. For that purpose, let \(I_b\) be the set of all beamlets in beam direction \(b \in B\). We then let \(D_{ij}^f\) be the dose deposited per unit time in voxel \(j \in V\) from beamlet \(i \in I_b\) \((b \in B)\) when the patient geometry is in state \(f \in \mathcal{F}\). Moreover, we let \(I_{rc}\) denote the set of exposed beamlets when leaves are in configuration \(c \in C\) at row \(r \in R\). We can then approximate the dose deposition rates using

\[
D_{rcj}^f = \sum_{i \in I_{rc}} D_{ij}^f \quad r \in R, c \in C, j \in V,
\]

so that we can write

\[
D_{rcj}^{\Phi(t)} = \sum_{i \in I_{rc}} D_{ij}^{\Phi(t)} \quad r \in R, c \in C, j \in V
\]
and
\[ E(D_{rcj}^{\Phi(t)}) = E\left(\sum_{i \in I} D_{ij}^{\Phi(t)}\right) , \quad r \in R, c \in C, j \in V \]
\[ = \sum_{i \in I} E(D_{ij}^{\Phi(t)}) . \tag{4–39} \]

We next define beamlet-based \( \delta_{ij}(t) (i \in I, j \in V) \) and \( \omega_{ij}(t) (i \in I, j \in V) \), similar to Equations (4–35) and (4–36), as follows:
\[ \delta_{ij}(t) = 2 \sum_{b' \in B} \sum_{r' \in R} \sum_{c' \in C} \left( \int_{0}^{t'} E(D_{r'c'j}^{\Phi(t')}) E(D_{ij}^{\Phi(t)}) q_{r'c'}(t') dt' \right) - 2 T_j E(D_{ij}^{\Phi(t)}) \]  
\[ \omega_{ij}(t) = 2 \sum_{b' \in B} \sum_{r' \in R} \sum_{c' \in C} \left( \int_{0}^{t'} E(D_{r'c'j}^{\Phi(t')}) D_{ij}^{\Phi(t)} q_{r'c'}(t') dt' \right) - 2 T_j E(D_{ij}^{\Phi(t)}) . \tag{4–40} \]

\[ \Delta_{rcj}(t) = \sum_{i \in I} \delta_{ij}(t) \]
\[ \Omega_{rcj}(t) = \sum_{i \in I} \omega_{ij}(t) . \tag{4–42} \]

Finally, by defining \( \delta_i(t) = \sum_{j \in V} \delta_{ij}(t) (i \in I) \) and \( \omega_i(t) = \sum_{j \in V} \delta_{ij}(t) (i \in I) \) we have
\[ \Delta_{rc}(t) = \sum_{i \in I} \delta_i(t) \]  
\[ \Omega_{rc}(t) = \sum_{i \in I} \omega_i(t) . \tag{4–43} \]

Therefore, one can use Equations (4–42) and (4–43) to determine the lower envelope (this will be addressed in Section 4.4).

### 4.4 A Time-Discretized Stochastic DAO Model

Ideally, we would like to assume that \( \{\Phi(t) : t \geq 0\} \) is a semi-Markov process, which would allow for general probability distributions of the time spent at each state of the patient geometry. However, for reasons of tractability we consider Markov processes.
In particular, we assume that the intrafraction motion has the Markov property so that
the future states of the patient geometry, given the present state and the past states,
depend only upon the present state. Markov processes have been previously employed
to model and predict the intrafraction motion, and in particular, the respiratory motion
(Khamene et al., 2007; Mu et al., 2008; Kalet et al., 2010).

In this section we study a discrete-time model in which we assume that the state of
the patient geometry can only change at equispaced points in time. More formally, time
is discretized into time periods of length $\sigma$, indexed by $\tau \in \mathbb{Z}_+$ where $\mathbb{Z}_+ = \{0, 1, 2, \ldots\}$. We assume that the state of the patient geometry as well as the MLC leaf configurations
are fixed during each time period and can only change at the end of the period. We then
consider a discrete-time Markov chain to represent the stochastic process \( \{\Phi(t) : t \geq 0\} \)
that describes the changes in the patient geometry. In particular, we let
\[
    p_{f_1 f_2} = \Pr\{\Phi((\tau + 1)\sigma) = f_2 | \Phi(\tau \sigma) = f_1\} \quad f_1, f_2 \in \mathcal{F},
\]
\[
    p_f(\tau) = \Pr\{\Phi(\tau \sigma) = f\} \quad f \in \mathcal{F}
\]
denote the transition probability of going from state $f_1$ to $f_2$ in one time period and the
probability of being at state $f$ during time period $\tau \in \mathbb{Z}_+$, respectively. Note that $p_{f_1 f_2}$ is
independent of the time period $\tau$. Furthermore, we assume that the limiting probabilities
$p_f = \lim_{\tau \to \infty} p_f(\tau) \ (f \in \mathcal{F})$ exist. Finally, we choose treatment time $t_b$ to be a multiple of
$\sigma$, i.e., $t_b = n_b \sigma \ (b \in B)$. We then let $T_b = \{0, 1, 2, \ldots, n_b\}$ denote the collection of all time
periods spent at beam direction $b \in B$.

Now consider MLC row $r \in R_b \ (b \in B)$, since leaf configuration at this row can
only change at the end of each time period, we redefine the notion of dynamic aperture
$A_r : T_b \to \{0, 1\}^{[C]}$ for discrete-time settings as
\[
    A_{rc}(\tau) = \begin{cases} 
    1, & \text{if configuration } c \text{ is used at row } r \text{ during time period } \tau; \\
    0, & \text{otherwise.}
    \end{cases}
\]
Since during each time period only a single leaf configuration is used, we set $\sum_{c \in C} A_{rc}(\tau) = 1 (\tau \in T_b)$. Note that according to the definition above there exist only finitely many dynamic apertures. We can then rewrite random variable $z_j$ in Equation (4–1) describing the total dose received by voxel $j \in V$ as follows:

$$z_j = \sigma \sum_{b \in B} \sum_{r \in R_b} \sum_{\tau \in T_b} \sum_{c \in C} D_{rcj}^{\Phi(\tau)} A_{rc}(\tau).$$

In the remainder of this section, we reformulate our stochastic DAO model ($\tilde{\mathcal{P}}$) for the discrete-time case and study the particular column generation algorithm used to solve the relaxed problem (for notational convenience we assume $\sigma = 1$).

The discrete-time version of ($\tilde{\mathcal{P}}$) can be rewritten as

$$\min_{j \in V} \gamma_1 \sum_{j \in V} F_j (E(z_j)) + \gamma_2 \sum_{j \in V} E(F_j(z_j))$$

subject to

$$z_j = \sum_{b \in B} \sum_{r \in R_b} \sum_{\tau \in T_b} \sum_{c \in C} D_{rcj}^{\Phi(\tau)} A_{rc}(\tau),$$

$$\sum_{c \in C} A_{rc}(\tau) = 1 \quad \tau \in T_b, r \in R_b, b \in B$$

$$A_{rc}(\tau) \in \{0, 1\} \quad \tau \in T_b, r \in R_b, b \in B, c \in C.$$  \hspace{1cm} (4–46)

Since there exist only finitely many dynamic apertures of the form $A_r (r \in R)$, ($\tilde{\mathcal{P}}^D$) is a stochastic binary quadratic programming problem in finite-dimensional space. In particular, if $M_r (r \in R)$ contains all such dynamic apertures, we can then alternatively use formulation (P) to represent the full problem ($\tilde{\mathcal{P}}^D$). Hence, we can use the column generation algorithm developed for solving (P) for the time-discretized model as well. In particular, we study the pricing problem (G) for this model. We start by considering a discrete version of Equation (4–34), that is $q_{rc}(\tau) (\tau \in T_b, r \in R_b, c \in C, b \in B)$ where $A_{rc}(t)$ is substituted with $A_{rc}(t)$. We then define the discrete form of Equations (4–40)
and (4–41) (i.e., \( \delta_{ij}(\tau) \) and \( \omega_{ij}(\tau) \)) as follows:

\[
\delta_{ij}(\tau) = 2 \sum_{b' \in B} \sum_{r' \in R} \sum_{c' \in C} \sum_{\tau' \in T} \mathcal{E}\left(D_{r'c'ij}^{\Phi(\tau')}\right) \mathcal{E}\left(D_{ij}^{\Phi(\tau)}\right) q_{r'c'}(\tau') - 2Tj\mathcal{E}\left(D_{ij}^{\Phi(\tau)}\right) \tag{4–47}
\]

\[
\omega_{ij}(\tau) = 2 \sum_{b' \in B} \sum_{r' \in R} \sum_{c' \in C} \sum_{\tau' \in T} \mathcal{E}\left(D_{r'c'ij}^{\Phi(\tau')}\right) \mathcal{E}\left(D_{ij}^{\Phi(\tau)}\right) q_{r'c'}(\tau') - 2Tj\mathcal{E}\left(D_{ij}^{\Phi(\tau)}\right). \tag{4–48}
\]

Note that \( \mathcal{E}\left(D_{ij}^{\Phi(\tau)}\right) \) and \( \mathcal{E}\left(D_{r'c'ij}^{\Phi(\tau')}\right) \) are obtained by conditioning on the state of the Markov chain at time \( \tau \) and \( \tau' \), respectively, and \( \mathcal{E}\left(D_{r'c'ij}^{\Phi(\tau')}\right) \) is obtained by conditioning on the joint states at \( \tau \) and \( \tau' \). By summing over the corresponding voxels we then obtain

\[
\Delta_i(\tau) = \sum_{j \in V} \delta_{ij}(\tau) \tag{4–49}
\]

\[
\Omega_i(\tau) = \sum_{j \in V_T} \omega_{ij}(\tau). \tag{4–50}
\]

Thus, for MLC row \( r \in R_b \) \((b \in B)\) and using Equations (4–49) and (4–50) we can reformulate (G) for the discrete-time model as follows:

\[
\min \sum_{\tau \in T_b} \sum_{c \in C} \left( \sum_{i \in I_{rc}} \gamma_1 \Delta_i(\tau) + \gamma_2 \Omega_i(\tau) \right) A_{rc}(\tau) + \lambda_r
\]

subject to \((G^D)\)

\[
\sum_{c \in C} A_{rc}(\tau) = 1 \quad \tau \in T_b \tag{4–51}
\]

\[
A_{rc}(\tau) \in \{0, 1\} \quad c \in C, \tau \in T_b. \tag{4–52}
\]

\((G^D)\) is a binary optimization problem in finite-dimensional space. It is easy to see that \((G^D)\) can be decomposed over time periods \( \tau \in T_b \). Furthermore, for a given time period \( \tau \in T_b \), Equations (4–51) and (4–52) enforce that exactly one leaf configuration is chosen. Each leaf configuration \( c \in C \) can be uniquely expressed in terms of its exposed beamlets, i.e., \( I_{rc} \). In particular, let \( l_r \) represent the set of all beamlets in MLC row \( r \in R \), \( l_{rc} \in l \), can then be shown as a binary vector \( u \in \{0, 1\}^{|l_r|} \) where \( u_i \) indicates
whether beamlet \( i \in I_r \) is exposed in configuration \( c \) or not. Now suppose \( U \subseteq \{0, 1\}^{\|I_r\|} \) is the collection of all binary vectors representing a feasible leaf configuration for MLC row \( r \). \((G^D)\) then involves finding the optimal binary vector \( u \in U \) corresponding to each time period \( \tau \in T_b \). More formally, for time period \( \tau \in T_b \), the pricing problem reduces to the following unconstrained binary optimization problem:

\[
\min_{u \in U} \sum_{i \in I_r} (\gamma_1 \Delta_i(\tau) + \gamma_2 \Omega_i(\tau)) u_i,
\]

assuming any leaf configuration with consecutive beamlets is deliverable, the problem can be solved by finding a subset of consecutive beamlets in the given MLC row such that the objective value is minimal. This problem is known as the minimum subarray sum problem which can be efficiently solved in \( O(n) \) time \((\text{Bentley, 1984})\) where \( n \) is the cardinality of \( I_r \), i.e., the number of beamlets in MLC row \( r \).

### 4.5 A Branch-and-Price Algorithm

In this section we discuss some implementation details of the branch-and-price algorithm developed as a solution approach to the time-discretized model. We call this model in short the stochastic DAO model.

#### 4.5.1 Bounding

At each node of the branch-and-bound tree, we solve the relaxed problem \((P_R)\) to obtain a lower bound. For that purpose, we employ the column generation algorithm. At each iteration of the column generation algorithm, the optimal solution to the restricted master problem provides an upper bound on the optimal objective value of \((P_R)\). Moreover, a lower bound can be obtained by solving the pricing problem for each MLC row. In the following we show the validity of this lower bound.

For notational convenience, let us denote the objective function of \((P_R)\) by \( F \). Suppose \( F(\bar{y}^*) \) is the optimal objective value of the full problem (i.e., \((P_R)\)). Moreover, let \((\bar{y}, \bar{\lambda}, \bar{p})\) be the solution to the KKT conditions \((4-26)-(4-28)\) corresponding to the restricted master problem. Therefore, \( F(\bar{y}) \) is the optimal objective value of the
restricted master problem. Clearly, \( F(\bar{y}) \geq F(y^*) \). To obtain a lower bound on \( F(y^*) \), we dualize the nonnegativity constrains in \((P_R)\) as follows:

\[
\mathcal{L} (\rho) = \min \left\{ F(y) - \sum_{r \in R} \sum_{m \in M_r} \rho^m_r y^m_r : \sum_{m \in M_r} y^m_r = 1, r \in R \right\}.
\]

Using the weak duality theorem we have \( \max_{\rho \geq 0} \mathcal{L} (\rho) \leq F(y^*) \) and, in particular, \( \mathcal{L} (0) \leq F(y^*) \). Moreover by convexity of \( F \), we have

\[
\min_y \left\{ F(\bar{y}) + \nabla F(\bar{y})^\top (y - \bar{y}) : \sum_{m \in M_r} y^m_r = 1, r \in R \right\} \leq \mathcal{L} (0).
\]

Using KKT condition (4–26) we can substitute \( \nabla F(\bar{y}) \) as follows:

\[
\nabla F(\bar{y})^\top (y - \bar{y}) = \sum_{r \in R} \sum_{m \in M_r} (\bar{\rho}^m_r - \bar{\lambda}_r) (y^m_r - \bar{y}^m_r)
\]

\[
= \sum_{r \in R} \sum_{m \in M_r} \bar{\rho}^m_r y^m_r - \sum_{r \in R} \sum_{m \in M_r} \bar{\rho}^m_r \bar{y}^m_r - \sum_{r \in R} \sum_{m \in M_r} \bar{\lambda}_r y^m_r + \sum_{r \in R} \sum_{m \in M_r} \bar{\lambda}_r \bar{y}^m_r
\]

\[
= \sum_{r \in R} \sum_{m \in M_r} \bar{\rho}^m_r y^m_r
\]

where the second to last terms drop since \((\bar{y}, \bar{\rho})\) satisfy KKT condition (4–27) and \( y \) and \( \bar{y} \) both satisfy Equation (4–24). Finally, the optimization problem

\[
\min_y \left\{ F(\bar{y}) + \sum_{r \in R} \sum_{m \in M_r} \bar{\rho}^m_r y^m_r : \sum_{m \in M_r} y^m_r = 1, r \in R \right\}
\]

yields the optimal solution

\[
\hat{y}^{m'}_r = \begin{cases} 1, & m' = \arg\min_{m \in M_r} \bar{\rho}_r^m, \quad r \in R \\ 0, & \text{otherwise}. \end{cases}
\]

in which for each MLC row \( r \in R \), the dynamic aperture \( m \in M_r \) with the smallest reduced gradient \( \bar{\rho}^m_r \) is chosen. We have shown that

\[
F(\bar{y}) + \sum_{r \in R} \sum_{m \in M_r} \bar{\rho}^m_r \hat{y}^{m'}_r \leq \mathcal{L} (0) \leq F(y^*) \leq F(\bar{y}),
\]

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and as a result, the desired bound holds on the optimal objective value of the relaxed problem.

4.5.2 Branching Scheme

In order to preserve the structure of the pricing problem, we avoid branching on the decision variables $y_r^m (m \in M_r, r \in R)$. Instead, we propose to branch in the beamlet space. More specifically, let $I_b$ be the collection of all beamlets in beam direction $b \in B$. We then associate a binary decision variable $x_{ir} \in \{0, 1\}$ with beamlet $i \in I_b (b \in B)$ and period $\tau \in T_b (b \in B)$ indicating if beamlet $i$ is exposed or covered during time period $\tau$. Note that any dynamic aperture $A$ can be expressed in the form of a binary vector $x = (x_{ir} : i \in I_b, \tau \in T_b, b \in B)$. Consider the optimal solution to the relaxed problem, given by $\bar{y}_r^m (m \in M_r, r \in R)$. We can then obtain the equivalent solution in the beamlet representation as follows:

$$\bar{x}_{ir} = \sum_{m \in M_r} A_{rc}^m (\tau) \bar{y}_r^m \quad i \in I_{rc}, r \in R, c \in C, \tau \in T_b, b \in B.$$  

where $\bar{x}_{ir} \in [0, 1]$ shows the presence of beamlet $i$ during time period $\tau$. Clearly, in case of a feasible integral solution, we have that $\bar{x}_{ir} \in \{0, 1\} (i \in I_b, \tau \in T_b, b \in B)$. Hence, we propose to branch on these variables. More specifically, at each node and given the optimal solution to the relaxed problem, we first evaluate $\bar{x}_{ir} (i \in I_b, \tau \in T_b, b \in B)$, and then choose $x_{ir}$ with the highest fractional value (i.e., $|\bar{x}_{ir} - 0.5|$) to branch on.

4.5.3 Pricing Problem

At each iteration of the column generation algorithm, given the optimal solution to the restricted master problem, we solve the pricing problem for each MLC row. This yields a dynamic aperture for the corresponding MLC row. Depending on the tree node at which the relaxed problem is solved, there are several constraints enforced by the branching constraints on the pricing problem. In particular, one or several beamlets are required to be exposed (covered) during the corresponding time periods. Recall that in the absence of branching constraints and assuming no leaf motion restriction,
the pricing problem for each MLC row reduces to the minimum subarray sum problem for each time period. In other words, for each pair of MLC row and time period, the pricing problem would yield the subsequence of beamlets with the smallest cumulative reduced cost which can be efficiently determined in $O(n)$ time where $n$ is the number of beamlets in an MLC row. Now to ensure that a beamlet is covered during the associated time period, we can simply enlarge its reduced cost for that time period so that the beamlet will not be present in the optimal subsequence. Furthermore, if one or several beamlets are enforced to be exposed during the same time period, we have to ensure that the optimal subsequence contains those beamlets. More specifically, any feasible subsequence should include all the beamlets between the first and last enforced beamlets. Thus, to obtain the optimal subsequence, we first locate the first and last enforced beamlets, and then determine if we can extend the obtained subsequence from either sides by scanning the remaining beamlets which can be done in $O(n)$ time as well.

4.5.4 Initial Columns

To initialize the column generation algorithm at each node, we need to introduce a feasible solution to the relaxed problem. In particular, for each MLC row we consider a deliverable dynamic aperture that includes those beamlets which are enforced by the branching constraints to be exposed during a particular time period. This can be easily obtained by construction. Starting with this solution, the column generation algorithm is then performed to solve the relaxed problem.

4.5.5 Heuristic and Node Selection Strategy

Given the solution to the relaxed problem at each tree node, we can employ a relaxation-based heuristic to obtain an integer solution. In particular, suppose $\bar{y} = (\bar{y}_i^m : m \in M_r, r \in R)$ is the optimal solution to the relaxed problem. Using $\bar{y}$ the heuristic constructs an integer solution, say $\hat{y}$, by choosing the dynamic aperture with the largest
value for MLC row \( r \in R \) in \( \bar{y} \). In other words,

\[
\hat{y}_r^{m'} = \begin{cases} 
1, & m' = \arg\max_{m \in M_r} \bar{y}_r^m; \\
0, & \text{otherwise.}
\end{cases}
\]

Hence, the heuristic is run using the optimal solution to the relaxed problem at each node to generate an integer solution. Note that the objective value of the integer solution obtained using the heuristic is clearly an upper bound on the optimal objective value.

Since using our relaxation-based heuristic we can easily find integer solutions (which are found to be of good quality in the experiments), we chose a node-selection rule to mainly reduce the integrality gap. Therefore, we determine the order according which the nodes are selected by using the best-bound rule.

### 4.5.6 Column Management

As the column generation algorithm proceeds, a large number of columns are introduced to the master problem. However, most of these columns may not be present in the optimal solution to the relaxed problem. Therefore, a column management process is performed to discard unnecessary columns and reduce the size of the master problem. In particular, we drop those columns which have the most positive reduced gradient in the optimal solution to the restricted master problem. Therefore, at each iteration of the column generation, once the restricted master problem is solved, the number of columns in the master problem is checked. If it is beyond a user-specified threshold, then the column management process is triggered to drop as many columns as possible to bring the total number of columns back to a user-specified limit.

### 4.5.7 Early Termination and Integrality Gap

In our branch-and-price algorithm, we use the column generation technique to solve the relaxed problem at each tree node. Due to the slow convergence of this method, solving the relaxed problem to optimality may take a long time. Therefore, at each iteration of the column generation method, an optimality gap, discussed in Section 4.5.1,
is calculated and used to terminate the algorithm. In this section, we investigate the
effect of early termination of the column generation on the integrality gap.

Suppose the column generation is used to solve the relaxed problem at tree node
\( n \in N \). At iteration \( k \) of the column generation algorithm, lower and upper bounds on the
optimal objective value of the relaxed problem, denoted by \( F_{LB}^{(k)} \) and \( F_{UB}^{(k)} \), are obtained.
We then define the column generation (CG) optimality gap, denoted by \( \epsilon^{(k)} \), as follows:

\[
\epsilon^{(k)} = \frac{F_{UB}^{(k)} - F_{LB}^{(k)}}{F_{LB}^{(k)}}.
\]

Therefore, we terminate the column generation algorithm at iteration \( k \) if

\[
\epsilon^{(k)} \leq \epsilon
\]

where \( \epsilon \) is a user-specified optimality gap.

In exploring the branch-and-bound tree, the minimum optimal objective value of the
relaxed problem among all leaf nodes, the so-called best bound, usually serves as a
lower bound on the objective value of the optimal solution. However, if we terminate the
column generation algorithm prior to optimality, the exact optimal objective value of the
relaxed problem is not known anymore. Hence, in a branch-and-price setting we have to
consider a different lower bound. More specifically, let \( N_L \) denote the set of all leaf nodes
in the branch-and-bound tree. Furthermore, suppose for leaf node \( n \in N_L \), \( F_{LB}^n \) is the
final lower bound obtained on the optimal objective value of the relaxed problem using
the column generation method. We then define the best bound as

\[
F_{LB}^* = \min_{n \in N_L} F_{LB}^n.
\]

Since \( F_{LB}^* \) is a lower bound on the optimal objective value of the relaxed problem at
all leaf nodes, it is a valid lower bound on the objective value of the optimal solution
as well. Moreover, we let \( F_I^* \) be the best integer solution found while exploring the
branch-and-bound tree. Clearly, \( F_I^* \) is an upper bound on the objective value of the
optimal solution. Therefore, we define the integrality gap in our branch-and-bound tree as
\[
\delta = \frac{F^*_I - F^*_LB}{F^*_LB}.
\] (4–55)

4.6 Computational Results

For the proof of concept, we applied the stochastic DAO model and the branch-and-price algorithm to a prostate cancer case. The case contains one target and three critical structures. We obtained treatment plans using 5 equispaced $^{60}$Co beams around the patient. We used a beamlet grid of $1 \times 1$ cm$^2$. This yields 1600 beamlets per beam direction. We then reduced the number of beamlets at each beam direction by considering a beamlet mask around those beamlets which have a significant contribution to target voxels, and ignored the ones whose contribution were negligible. Moreover, we used a voxel grid of $1 \times 1 \times 1$ cm$^3$ in the target and critical structures. To reduce the number of voxels in the optimization model, we used a coarser resolution of $2 \times 2 \times 2$ cm$^3$ in the unspecified tissue. The above setting yields 13766 voxels in the cancer case from which 199 are target voxels. Moreover, there are a total of 572 beamlets and 2292 voxels in the optimization model.

We considered a treatment time of 1 minute per beam direction which was discretized into 30 time periods (2 seconds each). Moreover, we made the simplifying assumption that the MLC leaves have an infinite speed. In other words, regardless of the leaf configuration at the current time period, all leaf configurations are accessible for the next time period. To replicate the intrafraction motion, we considered a rigid body motion in which the patient geometry transitions between two states $\mathcal{F} = \{1, 2\}$. To define the second state, we perturbed the location of the patient by 5 mm in each coordinate direction. We modeled the resulting changes in the patient geometry as a Markov chain with a transition probability of $p \in \{0.9, 0.93, 0.95, 0.99\}$. For instance, if the patient...
geometry is currently at state $f = 1$, it will be at state $f = 2$ with probability $p$ during the next time period.

When solving the relaxation of (P) using the column generation method, a relatively-large amount of computational effort is required to evaluate the second term corresponding to target voxels in the objective function of (P) as well as Equation (4–41) in the pricing problem. Therefore, we estimate these terms by considering only a fraction of target voxels (5%) and then scaling the obtained results, accordingly.

To quantify the advantages of using the stochastic DAO model, we compare the results obtained from this model with the results of the static DAO model. Note that the static DAO model assumes that the treatment starts when the patient geometry is in its steady state. However, the stochastic DAO treatment plans start when the patient geometry is in a particular state. Therefore, to compare the quality of the two treatment plans we need to evaluate the quality of the static treatment plans using the objective function of (P). However, the treatment plans obtained from the static DAO model are not in the form of a dynamic aperture. In particular, there are two properties that require to be fixed. Firstly, leaf-configuration intensities in Equation (4–19) obtained from the static DAO model (ST) are fractional and need to be discretized to conform to our time discretization. Therefore, given the static DAO treatment plan, we round the intensities to the nearest multiple of the length of the time period. While rounding, we ensure that the treatment time spent at each beam direction $b \in B$ remains $t_b$ time units. Secondly, the static DAO model ignores the sequence of leaf configurations delivered at each MLC row. Thus, we generate 100 dynamic apertures from a static DAO treatment plan by randomly perturbing the sequence of configurations at each MLC row individually. We then evaluate the objective function of (P) for all 100 dynamic apertures and report the minimum and maximum values. While comparing the dynamic apertures obtained from the stochastic and static DAO models, we assume that both treatment plans start when the patient geometry is in the same state, and that the patient geometry transitions
between the two states according to a Markov chain with the same transition probability \( p \).

Tables 4-1–4-3 show the results obtained from employing our branch-and-price algorithm to the prostate cancer case as well as the results obtained from the static DAO model. In particular, Table 4-1 shows the results obtained from the stochastic DAO model for the special case of \( \gamma_2 = 0 \) and compares them with the results from the static DAO model. The first column (p) shows the transition probability of the Markov chain used to model the changes in the patient geometry. The second column (Best integer) reports the smallest objective value among the integral solutions obtained from the tree within a time limit of 3600 sec. The third column (Best bound) shows the largest lower bound on the optimal objective value obtained within a time limit of 3600 sec. The fourth column (Root) reports the lower bound obtained on the optimal objective value of the relaxation problem at the root node as well as the computational time required by the column generation algorithm at this node. The fifth column (Gap) reports the integrality gap defined in Equation (4–55). The next column (objective value) shows the minimum and maximum objective values among 100 dynamic apertures obtained from the static DAO model. Finally, the last column (Imprv.) reports the relative improvement in the objective value of (P) obtained from the stochastic DAO model (Best integer) compared to the static DAO model (min Objective value). Table 4-2 shows the same results obtained when \( \gamma_2 > 0 \). Moreover, Table 4-3 compares the best integer solution obtained from (p) using \( \gamma_2 > 0 \) with the solution obtained from the static DAO model that has the minimum objective value. In particular, the solutions are compared with respect to the first and second terms of the objective function of (P), which we call evaluation criteria I and II, respectively.

Table 4-1 shows an improvement of 13–24% in the objective value (evaluation criteria I) obtained as a result of employing (P). Table 4-2 shows an improvement of 3–14% in the objective value. Since computing the second term in the objective function
of \((P)\) is time consuming, more computational effort is required to solve the relaxed problem at each node. This is reflected in the CPU time reported for solving the root node. As a result, the branch-and-price algorithm struggles to reduce the integrality gap when \(\gamma_2 > 0\). Table 4-3 shows an improvement of 18–52% in the evaluation criteria II (i.e. expected deviation of the dose distribution from the desired one in target voxels) when using the stochastic model. However, this may come at the expense of degrading evaluation criteria I (i.e., quality of the treatment measured based on the expected dose distribution) for \(p \in \{0.9, 0.93\}\). Finally, in case of using the stochastic model, both evaluation criteria I and II tend to be smaller for a higher transition probability. This can be justified similar to the case of \(\gamma_2 = 0\).

4.7 Future Research

In this section, we discuss some ideas to extend this work as well as the challenges that need to be addressed. In particular, we first present two improvement ideas related to the discrete-time model that can improve the solution approach and broaden the scope of the model. We next explain challenges facing the development of a solution approach for the continuous-time model.

4.7.1 Discrete-Time Model

The proposed branch-and-price algorithm seems to struggle in improving the optimality gap when \(\gamma_2 > 0\). This issue, to some extent, is due to the relatively large computational effort required to solve the relaxed problem using the column generation method. As a result, fewer nodes can be explored. Considering a larger CG optimality gap \(\epsilon\) can mitigate this issue. However, that leads to a poor performance of the relaxation-based heuristic. Therefore, to allow for larger CG optimality gaps better heuristics are required to find high-quality integer solutions at each node. Furthermore, to reduce the computational effort required to solve the relaxed problem (and perhaps to obtain higher-quality treatment plans), we need to get a better approximation for the second term of the objective function in \((P)\). Currently, we approximate this term by only
considering a limited number of target voxels (5%) and scale the result accordingly, which seems to be still slow and can have a negative impact on the quality of the obtained treatment plans.

The current stochastic DAO model, and in particular, the discrete-time version, is based on the assumption that MLC leaves have an infinite speed. Hence, leaf configurations in different time periods are independent. However, in clinical settings, MLC leaf motions are restricted. In particular, the MLC leaf speed is around 2 cm/sec (1.5–2.5 cm/sec (Boyer et al., 2001)). Therefore, to have a more realistic model, this assumption needs to be relaxed. More specifically, ideally we would like to limit the set of deliverable dynamic apertures for each MLC row to the ones respecting the leaf motion restriction. Note that in the presence of leaf motion restriction, the pricing problem for each MLC row cannot be decomposed over time periods anymore since leaf configurations in consecutive time periods will be dependent. Hence, we need to develop a different solution approach that takes this dependence into account (Romeijn et al., 2005).

4.7.2 Continuous-Time Model

In the Appendix we have studied the pricing problem for the column generation algorithm developed to solve the relaxation of the continuous-time DAO model with $\gamma_2 = 0$, i.e, $(P_R^*)$. We assumed that the stochastic process under consideration is a cyclic continuous-time (CT) Markov process. In particular, we have considered three different cases based on the treatment starting time as follows: (1) the treatment starts in the steady state, (2) the treatment starts in a particular state and the CT Markov process under consideration has only two states, and (3) the treatment starts in a particular state and the CT Markov process contains multiple states. We have developed exact solution approaches to the pricing problem under (1) and (2). Moreover, for (3) we have obtained the closed-form expressions for transition probabilities when transition rates are identical. Using the transition probabilities, we then derived the closed-form expression
of $\Delta_{rc}$, and discussed how to use the lower envelope $\min_{c \in C} \Delta_{rc}(t) \ t \in [0, t_b]$ to solve the pricing problem. However, determining the lower envelope under (3) turned out to be more difficult than (1) and (2) due to the behavior of $\Delta_{rc}$. Thus, a new solution approach to obtaining the lower envelope in this case is yet to be explored.

Furthermore, in Section 4.3.2 we derived the KKT conditions for the general stochastic DAO model (i.e., when $\gamma_2 > 0$), and showed how to find the optimal solution to the pricing problem by finding the corresponding lower envelope (i.e., $\min_{c \in C} (\gamma_1 \Delta_{rc}(t) + \gamma_2 \Omega_{rc}(t)) \ (t \in [0, t_b])$). But this is only the case when closed-form expressions for $\Delta_{rc} (r \in R, c \in C)$ and $\Omega_{rc} (r \in R, c \in C)$ are both given. In the Appendix we derived the closed-form expression for $\Delta_{rc} (r \in R, c \in C)$. Therefore, we also need to obtain the closed-form expression of $\Omega_{rc}(t)$ which is yet to be studied. Moreover, similar to the special case of $\gamma_2 = 0$, we need to develop a solution method to obtain the lower envelope.

In Section 4.4 we discussed a branch-and-price algorithm for the discrete-time model that employs the column generation method developed to solve the relaxed problem at each node of the branch-and-bound tree. For the continuous-time DAO model, we would like to consider a similar branch-and-price algorithm. However, since the model is in a continuous-time setting, we cannot use the branching scheme proposed for the discrete-time version. More specifically, in the discrete-time model, we chose to branch on the fractional variables $x_{i, \tau}$ indicating whether beamlet $i \in I_b \ (b \in B)$ is exposed during time period $\tau \in T_b \ (b \in B)$ or not. However, this branching scheme causes an extremely imbalanced branch-and-bound tree when applied to a continuous setting. Therefore, defining an appropriate branching scheme which also preserves the structure of the pricing problem is extremely critical to the success of a branch-and-price algorithm for the continuous-time problem.
4.8 Concluding Remarks

In this chapter we presented a DAO approach to incorporate the intrafraction motion into the treatment-plan optimization stage. More specifically, we modeled the changes in the patient geometry using a stochastic process. To keep track of the movements of the MLC leaves at each row, we defined the notion of a dynamic aperture that shows the leaf configuration used at each point during the treatment. To measure the quality of the treatment plan associated with a dynamic aperture, we used two classes of convex quadratic voxel-based penalties. In particular, the first class measures the quality of the treatment plan based on the expected dose distribution delivered, whereas the second class measures the expected deviation of the dose distribution from the desired one in target voxels. We then formulated a stochastic binary quadratic programming problem in infinite-dimensional space. We studied a column generation method to solve the relaxation of this model. Considering a time-discretized version of the problem, we then developed a branch-and-price algorithm to solve the binary model. We quantified the advantages of using the stochastic DAO model over the traditional model using a prostate cancer case. The results suggest that the stochastic DAO model can achieve treatment plans with higher quality (measured in terms of the two classes of voxel-based penalties) particularly for larger transition probabilities. Finally, we discussed future research directions and challenges facing the development of a solution approach for the continuous-time DAO model.
Table 4-1. Results obtained from solving the stochastic DAO model for $\gamma_2 = 0$ within a time limit of 3600 sec using a CG optimality gap of $\epsilon = 3\%$ and comparing with the static DAO model.

<table>
<thead>
<tr>
<th>$p$</th>
<th>Best integer</th>
<th>Best bound</th>
<th>Root CPU time</th>
<th>Integ. gap %</th>
<th>Objective value Imprv.</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stochastic DAO</td>
</tr>
<tr>
<td></td>
<td>min</td>
<td>max</td>
<td>min</td>
<td>max</td>
<td>%</td>
</tr>
<tr>
<td>0.90</td>
<td>2196.86</td>
<td>2101.13</td>
<td>2079.46</td>
<td>164</td>
<td>4.6</td>
</tr>
<tr>
<td>0.93</td>
<td>2087.74</td>
<td>2024.59</td>
<td>2001.48</td>
<td>217</td>
<td>3.1</td>
</tr>
<tr>
<td>0.95</td>
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<td>1953.01</td>
<td>1929.00</td>
<td>164</td>
<td>4.8</td>
</tr>
<tr>
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<td>1943.15</td>
<td>1863.72</td>
<td>1839.41</td>
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<td>4.3</td>
</tr>
<tr>
<td>0.99</td>
<td>1946.20</td>
<td>1730.70</td>
<td>1697.96</td>
<td>214</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Table 4-2. Results obtained from solving the stochastic DAO model for $\gamma_2 > 0$ within a time limit of 3600 sec using a CG optimality gap of $\epsilon = 5\%$ and comparing with the static DAO model.

<table>
<thead>
<tr>
<th>$p$</th>
<th>Best integer</th>
<th>Best bound</th>
<th>Root CPU time</th>
<th>Integ. gap %</th>
<th>Objective value Imprv.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stochastic DAO</td>
</tr>
<tr>
<td></td>
<td>min</td>
<td>max</td>
<td>min</td>
<td>max</td>
<td>%</td>
</tr>
<tr>
<td>0.90</td>
<td>3202.65</td>
<td>2176.66</td>
<td>2146.94</td>
<td>740</td>
<td>47.1</td>
</tr>
<tr>
<td>0.93</td>
<td>3005.96</td>
<td>2106.46</td>
<td>2079.74</td>
<td>733</td>
<td>42.7</td>
</tr>
<tr>
<td>0.95</td>
<td>2683.46</td>
<td>2045.62</td>
<td>2019.35</td>
<td>700</td>
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</tr>
<tr>
<td>0.97</td>
<td>2514.76</td>
<td>1947.44</td>
<td>1917.28</td>
<td>599</td>
<td>29.1</td>
</tr>
<tr>
<td>0.99</td>
<td>2691.52</td>
<td>1807.90</td>
<td>1766.27</td>
<td>954</td>
<td>48.9</td>
</tr>
</tbody>
</table>

Table 4-3. Comparing the results obtained from the stochastic and static DAO models with respect to both evaluation criteria I and II.

<table>
<thead>
<tr>
<th>$p$</th>
<th>Evaluation criteria I</th>
<th>Evaluation criteria II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stochastic DAO</td>
<td>Static DAO</td>
</tr>
<tr>
<td></td>
<td>min</td>
<td>max</td>
</tr>
<tr>
<td>0.90</td>
<td>2775.66</td>
<td>2526.08</td>
</tr>
<tr>
<td>0.93</td>
<td>2599.53</td>
<td>2531.11</td>
</tr>
<tr>
<td>0.95</td>
<td>2437.24</td>
<td>2544.62</td>
</tr>
<tr>
<td>0.97</td>
<td>2307.17</td>
<td>2545.44</td>
</tr>
<tr>
<td>0.99</td>
<td>2456.28</td>
<td>2586.19</td>
</tr>
</tbody>
</table>
In this section we develop a column generation method for \( \hat{P}_R \) where \( \gamma_2 = 0 \). In particular, we study the pricing problem \( \hat{G} \) assuming that the stochastic process under consideration is a cyclic continuous-time (CT) Markov chain. Such a model is much more flexible than it initially seems since we can allow for Erlang-distributed state transition times simply by duplicating the individual states appropriately. Therefore, we define \( \{ \Phi(t); t \geq 0 \} \) as a cyclic continuous-time Markov chain with state space \( \mathcal{F} \) for which \( \lambda_f \) denotes the rate of leaving state \( f \in \mathcal{F} \). Moreover, we let

\[
p_{f_1,f_2}(t) = \Pr\{\Phi(t+s) = f_2 | \Phi(s) = f_1\}
\]

denote the transition probability from state \( f_1 \) to state \( f_2 \) after an additional \( t \) time units. Finally, we let \( p_f(t) = \Pr\{\Phi(t) = f\} \) represent the probability of being in state \( f \in \mathcal{F} \) at time \( t \geq 0 \). Depending on the treatment starting time, the state probabilities \( p_f(t) \ (f \in \mathcal{F}) \) may change. Therefore, we consider the pricing problem for three possible cases in which the treatment starts when the patient geometry is in (1) the steady state, (2) a particular state and the CT Markov process has only 2 states, and (3) a particular state and the CT Markov process has multiple states.

### A.1 Steady-State Case

We first need to obtain the limiting state probabilities. For that purpose, we can model the CT Markov chain as an alternating renewal process which is on when the patient geometry is in state \( f \), and off otherwise. Since the process is cyclic, the expected length of each renewal interval is \( \sum_{f \in \mathcal{F}} \lambda_f^{-1} \). Hence, we have

\[
\lim_{t \to \infty} p_f(t) = \frac{\lambda_f^{-1}}{\sum_{f' \in \mathcal{F}} \lambda_{f'}^{-1}}.
\]
(Ross, 2004). Using the limiting probability distribution, we can obtain Equation (4–18) for the steady state as

$$\bar{\Delta}_\text{rc} = \frac{\sum_{j \in V} \sum_{f \in F} \lambda_f^{-1} D_{rcj}^f \pi_j}{\sum_{f \in F} \lambda_f^{-1}}$$

which is independent of time. Therefore, the solution approach proposed in Section 4.3.1.2 is applicable to this case. We next study the case in which the treatment starts when the patient geometry is in a particular state.

### A.2 Binary-State Case

In this section we consider the case in which the organ motion consists of only two states \( F = \{1, 2\} \). Moreover, we assume that the patient geometry is in state \( f = 1 \) at the start of the treatment (i.e., \( p_1(0) = 1 \)). For a binary-state CT Markov chain the state probabilities \( p_f(t) (f \in F) \) can be obtained as follows (Ross, 2004):

$$p_1(t) = \frac{\lambda_2}{\lambda_1 + \lambda_2} + \frac{\lambda_1}{\lambda_1 + \lambda_2} e^{-(\lambda_1 + \lambda_2)t}$$

$$p_2(t) = \frac{\lambda_1}{\lambda_1 + \lambda_2} - \frac{\lambda_1}{\lambda_1 + \lambda_2} e^{-(\lambda_1 + \lambda_2)t}.$$

Substituting the state probabilities in Equation (4–18) yields

$$\Delta^\pi_{rc}(t) = \sum_{f \in F} \left( \sum_{j \in V} D_{rcj}^f \pi_j \right) p_f(t)$$

$$= \left( \sum_{j \in V} D_{rcj}^1 \pi_j \right) \left( \frac{\lambda_2}{\lambda_1 + \lambda_2} + \frac{\lambda_1}{\lambda_1 + \lambda_2} e^{-(\lambda_1 + \lambda_2)t} \right)$$

$$+ \left( \sum_{j \in V} D_{rcj}^2 \pi_j \right) \left( \frac{\lambda_1}{\lambda_1 + \lambda_2} - \frac{\lambda_1}{\lambda_1 + \lambda_2} e^{-(\lambda_1 + \lambda_2)t} \right)$$

$$= \frac{\lambda_2}{\lambda_1 + \lambda_2} \left( \sum_{j \in V} D_{rcj}^1 \pi_j \right) + \frac{\lambda_1}{\lambda_1 + \lambda_2} \left( \sum_{j \in V} D_{rcj}^2 \pi_j \right)$$

$$+ \left( \sum_{j \in V} D_{rcj}^1 \pi_j \right) - \left( \frac{\lambda_2}{\lambda_1 + \lambda_2} \left( \sum_{j \in V} D_{rcj}^1 \pi_j \right) + \frac{\lambda_1}{\lambda_1 + \lambda_2} \left( \sum_{j \in V} D_{rcj}^2 \pi_j \right) \right) e^{-(\lambda_1 + \lambda_2)t}.$$
Now let
\[ \bar{\Delta}_{rc}^{\pi} = \frac{\lambda_2}{\lambda_1 + \lambda_2} \left( \sum_{j \in V} D_{rcj}^{1} \pi_j \right) + \frac{\lambda_1}{\lambda_1 + \lambda_2} \left( \sum_{j \in V} D_{rcj}^{2} \pi_j \right), \]
so that we obtain
\[ \Delta_{rc}^{\pi}(t) = \bar{\Delta}_{rc}^{\pi} + \left( \left( \sum_{j \in V} D_{rcj}^{1} \pi_j \right) - \bar{\Delta}_{rc}^{\pi} \right) e^{-(\lambda_1 + \lambda_2)t}. \] (A–56)

\[ \Delta_{rc}^{\pi} \]

is a monotone function that starts from
\[ \Delta_{rc}^{\pi}(0) = \sum_{j \in V} D_{rcj}^{1} \pi_j, \]
and in the limit it becomes
\[ \lim_{t \to \infty} \Delta_{rc}^{\pi}(t) = \bar{\Delta}_{rc}^{\pi}. \]

Finally, if the treatment started when the patient geometry was in state \( f = 2 \) (rather than \( f = 1 \)), then \( \sum_{j \in V} D_{rcj}^{1} \pi_j \) in Equation (A–56) would be substituted with \( \sum_{j \in V} D_{rcj}^{2} \pi_j \).

Similar to the steady-state case, we can solve the pricing problem for MLC row \( r \in R \) by decomposing it over the time interval \([0, t_b]\). More formally, we need to determine the lower envelope (i.e., \( \min_{c \in C} \Delta_{rc}^{\pi}(t) \)) over the interval \([0, t_b]\). Since \( \Delta_{rc}^{\pi}(r \in R, c \in C) \) are all exponential functions with the same exponent, every two of them can intersect at most once. Hence, we can obtain the lower envelope by simply sweeping across the interval and identifying the intersection points. More specifically, we first determine \( c_0 = \arg\min_{c \in C} \Delta_{rc}^{\pi}(0) \). We then intersect \( \Delta_{rc}^{\pi}(t) \) with \( \Delta_{rc}^{\pi}(t) \) (\( c \in C, c \neq c_0 \)), and determine the intersection point with the smallest \( t \) value, say \( (t_1, \Delta_{rc}^{\pi}(t_1)) \) (if there is no intersection point, then \( \Delta_{rc}^{\pi} \) is clearly the lower envelope over the entire time interval). Now starting with \( (t_1, \Delta_{rc}^{\pi}(t_1)) \) we continue the above procedure iteratively to sweep across the interval \([0, t_b]\) (Figure A-1). Using the obtained lower envelope we can determine the optimal dynamic aperture \( A_r^{\pi} \) by considering the corresponding leaf configurations at each point in the time interval.
A.3 Multi-State Case

Next we consider the multi-state case in which there are several states for the patient geometry, i.e, $|F| > 2$. For this case, we first obtain the closed-form expressions for the transition probabilities. We assume that the leaving rates are all identical, and in particular, $\lambda_f = 1$ ($f \in F$) (this can also be easily generalized to the case in which all leaving rates are identical but different from one). Using the transition probabilities, we then obtain the probability distribution of being at each state $f \in F$ at time $t \geq 0$.

The transition probabilities for a CT Markov chain can be obtained using the method of integral equations (Birolini, 2007) that forms a system of equations by conditioning on the first transition as follows:

$$p_{f_1 f_1}(t) = e^{-\lambda_{f_1} t} + \sum_{f \in F, f \neq f_1} \int_0^t \lambda_{f_1} e^{-\lambda_{f_1} x} p_{ff_1}(t-x) dx$$

$$p_{f_1 f_2}(t) = \sum_{f \in F, f \neq f_1} \int_0^t \lambda_{f_1} e^{-\lambda_{f_1} x} p_{ff_2}(t-x) dx \quad f_1 \neq f_2$$

where $\lambda_{f_1 f_2}$ is the transition rate from state $f_1$ to $f_2$, and $\lambda_{f_1}$ is the rate of leaving state $f_1$.

Note that we are considering a cyclic CT Markov process, and as a result

$$\lambda_{f_1 f_1+1} = \lambda_{f_1} \quad f_1 \in F$$

$$\lambda_{f_1 f_2} = 0 \quad f_2 \neq f_1 + 1.$$
hence, the system of integral equations (A–57)–(A–58) can be further simplified in the context of our application as follows:

\[
\begin{align*}
    p_{f_1f_1}(t) &= e^{-\lambda t} + \int_0^t \lambda e^{-\lambda x} p_{f_1+1f_1}(t-x) \, dx \\
    p_{f_1f_2}(t) &= \int_0^t \lambda e^{-\lambda x} p_{f_1+1f_2}(t-x) \, dx \quad f_1 \neq f_2.
\end{align*}
\]

Using the Laplace transform we get the following recursive equations:

\[
\begin{align*}
    \tilde{p}_{f_1f_1}(s) &= \frac{1}{s + \lambda_{f_1}} + \frac{\lambda_{f_1}}{s + \lambda_{f_1}} \tilde{p}_{f_1+1f_1}(s) \\
    \tilde{p}_{f_1f_2}(s) &= \frac{\lambda_{f_1}}{s + \lambda_{f_1}} \tilde{p}_{f_1+1f_2}(s)
\end{align*}
\]

which yields the following solution:

\[
\begin{align*}
    \tilde{p}_{f_1f_1}(s) &= \frac{\prod_{f \in \mathcal{F}} (s + \lambda_f)_{f \neq f_1}}{\prod_{f \in \mathcal{F}} (s + \lambda_f) - \prod_{f \in \mathcal{F}} \lambda_f} \quad f_1 \in \mathcal{F} \quad (A–59) \\
    \tilde{p}_{f_1f_2}(s) &= \left( \prod_{f = f_1}^{f_1-1} \frac{\lambda_f}{s + \lambda_f} \right) \tilde{p}_{f_2f_2}(s) \quad f_1, f_2 \in \mathcal{F}, f_1 \neq f_2. \quad (A–60)
\end{align*}
\]

To obtain \( p_{f_1f_1}(t) \) and \( p_{f_1f_2}(t) \), we then use the Laplace inverse transform as follows:

\[
\begin{align*}
    p_{f_1f_1}(t) &= \mathcal{L}^{-1}(\tilde{p}_{f_1f_1}(s)) \quad f_1 \in \mathcal{F} \quad (A–61) \\
    p_{f_1f_2}(t) &= \mathcal{L}^{-1}(\tilde{p}_{f_1f_2}(s)) \quad f_1, f_2 \in \mathcal{F}, f_1 \neq f_2. \quad (A–62)
\end{align*}
\]

In particular, let us define the following polynomials corresponding to the numerator and denominator of \( \tilde{p}_{f_1f_1}(s) \), respectively:

\[
\begin{align*}
    R_{f_1f_1}(s) &= \prod_{f \in \mathcal{F} \setminus f_1} (s + \lambda_f) \\
    Q_{f_1f_1}(s) &= \prod_{f \in \mathcal{F}} (s + \lambda_f) - \prod_{f \in \mathcal{F}} \lambda_f,
\end{align*}
\]

we then have

\[
\tilde{p}_{f_1f_1}(s) = \frac{R_{f_1f_1}(s)}{Q_{f_1f_1}(s)} \quad f_1 \in \mathcal{F}.
\]
Now let $s_k (k \in \mathcal{F})$ be the roots of $Q_{f_1} (s)$, then the Laplace inverse transform (and the transition probabilities) can be expressed as:

$$p_{f_1} (t) = L^{-1} (\tilde{p}_{f_1} (s)) = \sum_{k=1}^{\mathcal{F}} \frac{R_{f_1} (s_k)}{Q'_{f_1} (s_k)} e^{s_k t}$$

where $Q'_{f_1} (s)$ is the derivative of $Q_{f_1} (s)$. In general, finding the closed-from expression for $s_k (k \in \mathcal{F})$ (i.e., roots of $Q_{f_1} (s)$) may not be straightforward. Hence, in the following we consider a special CT Markov chain in which $\lambda_f = 1 \ (f \in \mathcal{F})$ (this can be easily generalized to the case in which $\lambda_f \ (f \in \mathcal{F})$ are all identical and different from one).

Suppose for $f \in \mathcal{F}$, we have $\lambda_f = 1$, then

$$R_{f_1} (s) = (s + 1)^{|\mathcal{F}| - 1} \quad f_1 \in \mathcal{F}$$
$$Q_{f_1} (s) = (s + 1)^{|\mathcal{F}|} - 1 \quad f_1 \in \mathcal{F}.$$  

using a variable transformation yields

$$p_{f_1} (t) = L^{-1} \left( \frac{(s + 1)^{|\mathcal{F}| - 1}}{(s + 1)^{|\mathcal{F}|} - 1} \right) \quad f \in \mathcal{F}$$
$$= e^{-t} L^{-1} \left( \frac{s^{|\mathcal{F}| - 1}}{s^{|\mathcal{F}|} - 1} \right).$$

Therefore, we need to determine the roots of unity $s^{|\mathcal{F}|} = 1$, which can be expressed as follows:

$$s_k = \sin \left( \frac{2\pi k}{|\mathcal{F}|} \right) + i \cos \left( \frac{2\pi k}{|\mathcal{F}|} \right)$$
$$= e^{i2\pi k / |\mathcal{F}|}.$$

Substituting $s_k (k \in \mathcal{F})$ in $p_{f_1} (t)$ yields

$$p_{f_1} (t) = \frac{1}{|\mathcal{F}|} \sum_{k \in \mathcal{F}} e^{(\xi_k - 1)t} \cos (\varrho_k t)$$
where
\[
\begin{align*}
\theta_k &= \frac{2\pi k}{|F|} \\
\xi_k &= \cos(\theta_k) \\
\varrho_k &= \sin(\theta_k).
\end{align*}
\]

Similarly, using Equation (A–62) we have
\[
p_{f_1f_2}(t) = \frac{1}{|F|} \sum_{k \in F} e^{(\xi_k-1)t} \cos(\varrho_k t - (f_2 - f_1)\theta_k).
\]

Therefore, assuming the cyclic CT Markov chain starts from state \( f = 1 \) at time \( t = 0 \), the probability of being at each state \( f \in F \) at time \( t \geq 0 \) can be expressed as:
\[
p_f(t) = \frac{1}{|F|} \sum_{k \in F} e^{(\xi_k-1)t} \cos(\varrho_k t - (f-1)\theta_k).
\]

Figure A-2 illustrates \( p_f(t) (f \in F) \) for a cyclic CT Markov chain that starts from state \( f = 1 \) with \(|F| = 10\).

Therefore, starting from state \( f = 1 \) at time \( t = 0 \), the probability of being at each state \( f \in F \) is as follows:
\[
p_f(t) = \frac{1}{|F|} \sum_{k \in F} e^{(\xi_k-1)t} \cos(\varrho_k t - (f-1)\theta_k)
\]

where
\[
\begin{align*}
\theta_k &= \frac{2\pi k}{|F|} \\
\xi_k &= \cos(\theta_k) \\
\varrho_k &= \sin(\theta_k).
\end{align*}
\]

Substituting \( p_f(t) (f \in F) \) in Equation (4–18) and using the property that every linear combination of Sine or Cosine functions with the same frequency is a Cosine function with the same frequency but a different phase shift and amplitude, we can obtain the
closed-form expression for $\Delta_{rc}^\pi$ as follows:

$$ \Delta_{rc}^\pi (t) = \sum_{f \in \mathcal{F}} \left( \sum_{j \in V} D_{rcj}^f \pi_j \right) p_f(t) $$

$$ = \sum_{f \in \mathcal{F}} \left( \sum_{j \in V} D_{rcj}^f \pi_j \right) \left( \frac{1}{|\mathcal{F}|} \sum_{k \in \mathcal{F}} e^{(\xi_k-1)t} \cos (\varrho_k t - (f-1)\theta_k) \right) $$

$$ = \frac{1}{|\mathcal{F}|} \sum_{k \in \mathcal{F}} e^{(\xi_k-1)t} \left( \sum_{f \in \mathcal{F}} \left( \sum_{j \in V} D_{rcj}^f \pi_j \right) \cos (\varrho_k t - (f-1)\theta_k) \right) $$

$$ = \frac{1}{|\mathcal{F}|} \sum_{k \in \mathcal{F}} (\kappa_{rc}^\pi \cos (\varrho_k t - \Psi_k)) $$

$$ = \frac{1}{|\mathcal{F}|} \sum_{k \in \mathcal{F}} \kappa_{rc}^\pi e^{(\xi_k-1)t} \cos (\varrho_k t - \Psi_k). $$

To obtain the amplitude $\kappa_{rc}^\pi$ and phase shift $\Psi_k$ of the Cosine function corresponding to $k \in \mathcal{F}$, we can evaluate the associated sum of Cosine functions at two different values of $t$ and solve a system of two equations and two unknowns.

Similar to the binary-state case, the pricing problem can be decomposed over the time interval $t \in [0, t_b]$. Therefore, to solve the pricing problem for the multi-state case, we need to obtain the lower envelope ($\min_{c \in C} \Delta_{rc}^\pi (t)$) over the time interval. However, in contrast to the the binary-state case, in the multi-state case $\Delta_{rc}^\pi (r \in R, c \in C)$ are not necessarily monotone due to the existence of the Cosine term (Figure A-2), and as a result any pair of these functions may have several intersection points. Thus, the solution method developed for the binary-state case cannot be directly employed to the multi-state case. Further research is required to develop an efficient solution approach for the pricing problem of the multi-state case.
Figure A-2. The propagability of being at each state $p_f(t) (f \in F)$ for a cyclic CT Markov chain starting from $f = 1$ with identical transition rates.
REFERENCES


Lim, G.J., J. Choi. 2006. A two-stage integer programming approach for optimizing leaf sequence in IMRT. Tech. rep., Department of Industrial Engineering, University of Houston, Houston, Texas.


BIOGRAPHICAL SKETCH

Ehsan Salari was born in Mashhad, Iran in 1981. He holds a bachelor's degree in Industrial Engineering from Amirkabir University of Technology and a master's degree in Systems Engineering from Sharif University of Technology, Tehran, Iran. He received his Ph.D. in Industrial and Systems Engineering from the University of Florida in the Summer of 2011. He then joined the Radiation Oncology Department at Massachusetts General Hospital and Harvard Medical School as a postdoctoral research fellow. Ehsan’s research interests are in Operations Research applications to health-care systems and particularly cancer care.