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IMRT Beam Angle Optimization using Tabu Search

Otimização Angular com Pesquisa Tabu em IMRT

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IMRT Beam Angle Optimization using Tabu Search

Dissertation submitted to the University of Aveiro in partial fulfillment of the requirements for the degree in Master on Mathematics and Applications, with the scientific supervision of Dr. Jorge Manuel Sá Esteves, Assistant Professor at the Department of Mathematics of the University of Aveiro, Dr. Joana Maria Pina Cabral Matos Dias, Assistant Professor at the Faculty of Economics of the University of Coimbra and Dr. Humberto José da Silva Pereira Rocha, researcher at the Portuguese Institute for Systems Engineering and Computers at Coimbra.

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keywords Radiation Therapy, IMRT, Optimization, Bilevel Programming, Tabu Search, Algorithm.

abstract The number of cancer patients continues to grow worldwide and the World Health Organization has even considered cancer as one of the main threats to human health and development. Depending on the location and specificities of the tumor, there are many treatments that can be used, including surgery, chemotherapy, immunotherapy and radiation therapy. Intensity Modulated Radiation Therapy (IMRT) is one of the most advanced radiation therapy modalities, and optimization can have a key role in the quality of the treatment delivered. In IMRT, the radiation beam can be thought of as being composed by several small beams, through the use of a multileaf collimator, allowing radiation intensity to be modulated. This complex optimization problem can be divided in three related subproblems that can be solved sequentially. For each patient, the angles from which the radiation will be delivered have to be determined (geometric problem — beam angle optimization). Then, for each of these angles, the radiation intensity map is calculated (fluence or intensity optimization). Finally, it is necessary to determine the behavior of the multileaf collimator that guarantees that the desired radiation intensities are, indeed, delivered (realization problem). In each of these optimization problems, the quality of the treatment delivered depends on the models and algorithms used. In this work the attention will be focused in beam angle optimization, a problem known to be highly non–convex, with many local minima and with an objective function that is time expensive to calculate, which, respectively, means that algorithms that are gradient–based or that require many objective function evaluations will not be adequate. Metaheuristics can be the right tool to tackle this problem, since they are capable of escaping local minima and are known to be able to calculate good solutions for complex problems. In this work, an application of Tabu Search to beam angle optimization is described. Computational results considering ten clinical cases of head–and–neck cancer patients are presented, showing that Tabu Search is capable of improving the equidistant solution usually used in clinical practice.

palavras–chave Radioterapia, IMRT, Otimização, Programação *Bilevel*, Pesquisa Tabu, Algoritmo.

resumo O número de pacientes com cancro continua a crescer no mundo e a Organização Mundial da Saúde considerou mesmo esta como uma das principais ameaças para a saúde e o desenvolvimento humano. Dependendo da localização e das especificidades do tumor, existem muitos tratamentos que podem ser usados, incluindo cirurgia, quimioterapia, imunoterapia e radioterapia. A Radioterapia de Intensidade Modulada (IMRT — *Intensity Modulated Radiation Therapy*) é uma das modalidades mais avançadas de radioterapia, onde a otimização pode ter um papel importante no que diz respeito à qualidade do tratamento aplicado. Em IMRT, o feixe de radiação pode ser visto como se fosse constituído por vários pequenos feixes, pelo uso de um colimador multifolhas, que permite que a intensidade seja modulada. Este complexo problema de otimização pode ser dividido em três subproblemas, que estão relacionados entre si e que podem ser resolvidos sequencialmente. Para cada paciente, os ângulos de onde a radiação irá ocorrer têm de ser determinados (problema geométrico — otimização angular). Depois, para cada um desses ângulos, o mapa de intensidades (ou fluências) tem de ser calculado (problema das intensidades — otimização das fluências). Finalmente, é necessário determinar o comportamento do colimador multifolhas, de forma a garantir que as intensidades são, de facto, atribuídas (problema de realização). Em cada um destes problemas de otimização, a qualidade do tratamento atribuído depende dos modelos e algoritmos usados. Neste trabalho, a nossa atenção estará particularmente focada na otimização angular, um problema conhecido por ser altamente não–convexo, com muitos mínimos locais e com uma função objetivo que requer muito tempo de computação para ser calculada. Tal significa, respetivamente, que os algoritmos que sejam baseados no cálculo de gradientes ou que requeiram muitas avaliações da função objetivo podem não ser adequados. Assim, os procedimentos metaheurísticos podem ser uma boa alternativa para abordar este problema, visto que são capazes de escapar de mínimos locais e são conhecidos por conseguirem calcular boas soluções em problemas complexos. Neste trabalho será descrita uma aplicação para Pesquisa Tabu. Serão ainda apresentados os testes computacionais realizados, considerando dez casos clínicos de pacientes previamente tratados por radioterapia, pretendendo–se mostrar que a Pesquisa Tabu é capaz de melhorar os resultados obtidos através da solução equidistante, cujo uso é comum na prática clínica.

"Truth is ever to be found in the simplicity, and not in the multiplicity and confusion of things."

– Sir Isaac Newton (1643-1727)

Contents

Abbreviations

min	Minimize
s.t.	Subject to
3D–CRT	Three–dimensional conformal radiation therapy
BAO	Beam angle optimization
BP	Bilevel programming
CERR	Computational environment for radiotherapy research
CNTR	Critical normal tissue ring
CT	Computed tomography
CTV	Clinical target volume
DC	Decomposition cardinality
DNA	Deoxyribonucleic acid
DT	Decomposition time
DVC	Dose–volume constraint
DVH	Dose–volume histograms
FMD	Fluence map delivery
FMO	Fluence map optimization
Gy	Gray
GTV	Gross target volume
IMRT	Intensity modulated radiation therapy
Linac	Linear accelerator
MLC	Multileaf collimator

MOLP	Multiobjective linear programming
MONP	Multiobjective nonlinear programming
MOP	Multiobjective programming
NT	Normal tissue
OAR	Organ at risk
OR	Operations research
PTV	Planning target volume
TPS	Treatment planning systems

List of symbols

D	Matrix dose
D_{NT}	Dose in the NT
D_{OAR}	Dose in the OAR
D_{PTV}	Dose in the PTV
D_T	Total dose
LB_{PTV}	Lower bound for the dose in the PTV
M	Upper bound for the beamlet weight
N_b	Total number of beamlets
N_v	Total number of voxels
N_S	Total number of voxels in a given structure
N_{vNT}	Number of voxels in the NT
N_{vOAR}	Number of voxels in the OAR
N_{vPTV}	Number of voxels in the PTV
UB_{NT}	Upper bound for the dose in the NT
UB_{OAR}	Upper bound for the dose in the OAR
UB_{PTV}	Upper bound for the dose in the PTV
TG_{PTV}	Target goal prescribed for the PTV
w_j	Weight of the beamlet j
Θ	Set of all beam angles
θ	Solution
$N(\theta)$	Neighborhood of θ

$TabuList$	Tabu list
$\overline{N}(\theta)$	Admissible subset of $N(\theta)$
θ^*	Best–known solution
$f(\theta^*)$	Evaluation of the best–known solution

Chapter 1

Introduction

1.1 Motivation

According to the World Cancer Research Fund International[1] there were an estimated 14.1 million cancer cases around the world in 2012 and it is expected that by 2035 this number increases to 24 million. Despite some recent research achievements, the number of cancer patients continues to grow worldwide and it is nowadays one of the biggest problems in the health area. Prevention is still the best alternative, but there are also different treatments that can be used, depending on the type and stage of the cancer, namely surgery, chemotherapy, immunotherapy and radiation therapy. It is expected that about 50% of the cancer patients will be treated with radiation therapy at some stage of the oncology treatment. Thus, the improvement of the quality in radiation therapy treatments have a major role in the fight against cancer. In our work, we will focus on radiation therapy, particularly in Intensity Modulated Radiation Therapy (IMRT). This treatment modality, where optimization can have a key role in order to guarantee the quality of the treatment delivered to the patient, allows the radiation beam to be modulated, increasing the precision of the treatment and allowing a better sparing of healthy cells.

The development of new treatment technologies and machines allows the achievement of better results in the treatments. For the last decades, optimization in radiation therapy has followed the evolution of radiation therapy technology, with significant contributions to the quality of the treatments delivered and has become a vast, complex, interesting and challenging research field. Given the current technological capabilities associated with the distinct radiation therapy modalities, it is possible to deliver complex treatment plans. In order to take advantage of the modern technology it is important and necessary to automate the process in clinical practice. Operations research (OR) has a key role in the improvement of the quality of the treatments. The optimization problems that arise in this context can be addressed by different perspectives, according to the objectives at hand, such as shortening the treatment time, delivering more radiation to the tumor or delivering less radiation to the sensitive organs surrounding the tumor.

[1] *http://www.wcrf.org/cancer_statistics/world_cancer_statistics.php* (Last access June 30, 2014)

Our motivation, based on the work that has been done and in the existing literature, is to try new approaches for radiation therapy treatment planning optimization. We will focus our attention in the Beam Angle Optimization (BAO), choosing the best radiation directions for a radiation therapy treatment, in order to irradiate the target volume (tumor), while minimizing the effects of radiation on healthy cells. The BAO is an important problem in radiation therapy, yet to be solved satisfactorily. Most of the time, in clinical practice, beam directions are selected manually or are optimized with the use of gradient methods that, starting from an initial beam direction, are usually unable to escape from local minima.

1.2 Framework and Objectives

The objective of the present work is to contribute to an improvement of the quality of the radiation treatments delivered to patients, by applying mathematical models and optimization algorithms to determine which radiation beam directions to use for each patient. One of the main steps to produce a treatment plan in IMRT is related to the definition of the set of angles, or beam directions, that will be used to deliver the radiation (BAO). This is a complex optimization problem, highly non–convex and with many local minima, which, in clinical practice, is tackled by trial an error procedures that terminate when a treatment plan that complies with the medical prescription is achieved. In the present work, we consider an inverse planning approach for radiation therapy: given the medical prescription, calculate in an automated way a specific treatment planning in order to achieve the best possible treatment complying with the medical prescription and that is the best possible. Our goal is to develop and implement an efficient and robust procedure that, systematically and in the limited period of time available in clinical practice to elaborate a treatment plan for each patient (usually just a few hours), produces better results than the ones currently obtained.

Due to the complexity involved, it is usual to consider heuristics and metaheuristics approaches in order to tackle this problem. Also, one must define a model in which a given function, for each patient, will evaluate the distinct solutions of the set of angles referred previously. According to the objective at hand, one can consider different approaches, including: linear, nonlinear, mixed integer or multiobjective models. In this dissertation, the advantages and disadvantages of each model will be exposed. Due to the fact that in radiation therapy, for each patient, one must consider different structures and tissues, delimited *a priori* by the oncologist, one can formulate the problem in many distinct ways, namely choosing how a given model will evaluate each solution and which structures will be considered for each objective. Our purpose is also to try new approaches to this problem, like bilevel programming, in order to perceive which formulations lead to better results and also delineate the best directions to continue the research. For all the models and formulations considered, we will use a Tabu Search (TS) algorithm to produce good quality solutions.

As far as we know, the application of TS to BAO has not been experimented before.

Modeling this problem as a bilevel programming model is also a new approach that has not been considered before in the literature, as far as the authors know.

1.3 Context

This research work was developed under a research project funded by FEDER funds through *Programa Operacional Factores de Competitividade* — COMPETE and by national funds through FCT — *Fundação para a Ciência e a Tecnologia*, under project PTDC/EIA–CCO/121450/2010 (FCOMP–01–0124–FEDER–020533). This research project has joined together researchers from the Portuguese Institute for Systems Engineering and Computers at Coimbra (INESCC — *Instituto de Engenharia de Sistemas e Computadores de Coimbra* [2]) and the Portuguese Institute of Oncology at Coimbra (IPOFG — *Instituto Português de Oncologia de Coimbra Francisco Gentil* [3]), with different scientific backgrounds (mathematics, operations research, medical physics), trying to tackle the difficult BAO problem for IMRT. A protocol between INESCC and the Department of Mathematics of the University of Aveiro has also made this work possible.

1.4 Organization of the dissertation

An introduction to radiation therapy will be presented in chapter 2. Here, our purpose will be to familiarize the reader with the most important concepts, common procedures in clinical practice and terminology associated to this treatment. In this chapter we will also focus our attention in IMRT, exploring the main aspects of this radiation therapy modality. Then, in chapter 3, we will review the main literature regarding optimization in radiation therapy treatment planning.

In chapter 4, the Tabu Search procedure will be introduced, highlighting some relevant concepts, namely the neighborhood structure and the tabu lists that have to be defined in order to implement this metaheuristic. In this chapter we will also present the models that will be used to address this problem. Then, in chapter 5 we will describe the computational tests performed and present and analyze all the computational results obtained.

Finally, in chapter 6 we will present the main conclusions of our work and, facing the results obtained, highlight which could be done in the future in order to tackle this optimization problem with distinct approaches.

[2] *http://www.uc.pt/en/org/inescc* (Last access June 30, 2014)
[3] *http://www.croc.min–saude.pt/* (Last access June 30, 2014)

Chapter 2

Radiation therapy

2.1 Introduction

It is estimated that more than 33000 new cases of cancer appear and 20000 patients die everyday around the world. It is expected that one in three persons will have an oncology problem sometime during their lifetime [48]. Despite this worrying context, in the last decades, the 5–year relative survival rate for all cancers diagnosed has been increasing.

In simple terms, cancer can be defined as the changing of a healthy functioning cell into one that continues to divide and reproduce itself beyond the expected and normal need of the tissue or body. Cancerous cells can continue to grow into and beyond tissue boundaries, which can affect the well–functioning of the organs and, ultimately, can have lethal consequences to the patient [36]. Depending on the type and stage of the cancer, there can be different approaches in order to fight this disease, namely surgery, radiation therapy, chemotherapy and immunotherapy, among others. Often, a combination of the referred approaches is used in order to improve the quality of the treatments. In the present work our focus will be on radiation therapy treatments.

In radiation therapy one can use rays with different wavelengths but the most common are the X–rays. The X–rays were discovered in 1896 by Wilhelm Röntgen and, just a few weeks after, Emil Grubbé became the first person in the world to use radiation in order to treat cancer [67]. Initially, radiation therapy was applied to patients in a single massive dose of radiation, with severe side effects. Then, in 1922 it was proven that by fractioning the treatment in several sessions, the result was just as effective but with fewer side effects. Meanwhile, engineers built more powerful X–rays equipments, capable of delivering high–energy beams, which improved the quality of the treatments. Also, the objectives of radiation therapy changed since it was firstly used. While, in the early days, it was basically applied as a palliative treatment, as the advantages of radiation therapy became clear, this treatment was also and continues to be applied in order to shrink the tumor before surgery, as a measure of reducing the risk of a cancer coming back after surgery, as stand–alone curative treatment and as a complement of chemotherapy treatments [67]. Although the terms “radiation therapy” and “optimization” can be linked

before, the first linear programming model was used to assist the design of radiation therapy models in 1968 [48].

Radiation therapy became a florescent multidisciplinary field of research with an increasing importance. The objective of this oncology treatment is to find the best way to deliver a given dose of radiation to the cancerous region in order to sterilize the tumor, while minimizing the damages and consequences of radiation on the surrounding area, that can include healthy organs and other tissues [48]. The ionizing radiation will damage the deoxyribonucleic acid (DNA) of cells and the advantage of radiation therapy is precisely the fact that once cancerous cells are damaged by radiation, they have more difficulties in reproducing themselves, unlike healthy tissue cells, that can more easily recover [24]. Thus, the idea behind radiation therapy is to deliver enough radiation to the cancerous tissues, usually referred to as target volume, in order to damage their cells, while sparing the healthy cells in the surrounding tissues, so they are able to recover. Usually, the difference between the tolerable dose of radiation of the healthy cells and the tumor is referred to as a *therapeutic advantage*, related to the fact that cancerous cells lack a well–functioning repair mechanism, that exists on healthy cells [36].

One can compare the radiation therapy treatment sequence to a chain constituted by several links [48], such that each link represent a given step in the process, as shown in Figure 2.1. Considering this example, in order to guarantee the quality of the treatments in radiation therapy one must avoid the existence of weakest links.

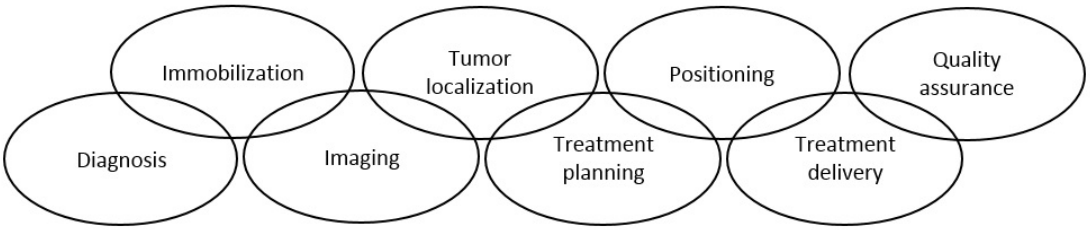

Figure 2.1: Radiation therapy treatment sequence [48].

Usually, when cancer is diagnosed on a patient, and if radiation therapy is viable or appropriate, the next step is related to the immobilization of the patient on a couch, where medical imaging techniques, such as computed tomography (CT), position emission tomography (PET) and magnetic resonance imaging (MRI) will be important in order to locate the tumor [13]. After the three–dimensional (3D) delimitation of the structures considered (tumor, organs and tissue near the tumor), the oncologist will establish a medical prescription. The next step is related with the treatment planning, where OR can have a key role in order to improve the quality of the treatments. Then, with the patient positioned on a couch, the treatment will be delivered. It is very important that the patient remains immobilized during the treatment and in exactly the same position he was when the CT scans were performed, because any small movement, even those that are created by breathing, can influence the quality of the treatment. The last step in the radiation therapy treatment sequence is related to the quality assurance of the process. In the last

decades, the development of new treatment machines increased the accuracy and control over the radiation that is delivered and improves the quality of the treatments.

The first step in any radiation therapy treatment planning is to be able to identify and delineate all structures that are of interest and that are going to be irradiated during treatment. This is done considering available medical images of the patient. After the imaging procedures, and according to the patient's 3D images, the physician will usually delimit the following structures [48]:

Gross target volume (GTV)
Represents the macroscopic volume of the tumor;

Clinical target volume (CTV)
Represents the GTV plus a marginal volume, considering a possible microscopic spread of the tumor;

Planning target volume (PTV)
Represents the CTV plus a marginal volume, considering possible inaccuracies or variations (as the organs' (or patients') movements);

Organ at risk (OAR)
Represents the sensitive organ in the neighborhood of the tumor that need to be spared;

Normal tissue (NT)
Represents the healthy tissue in the neighborhood of the tumor and the OAR.

In some cases, one can consider another structure in the neighborhood of the PTV, called critical normal tissue ring (CNTR), that should receive more radiation than NT further from the PTV [48]. The objective in considering this structure is to prevent the possible microscopic spread and avoid future complications. For a given patient, the delimitation of some structures is represented in Figure 2.2.

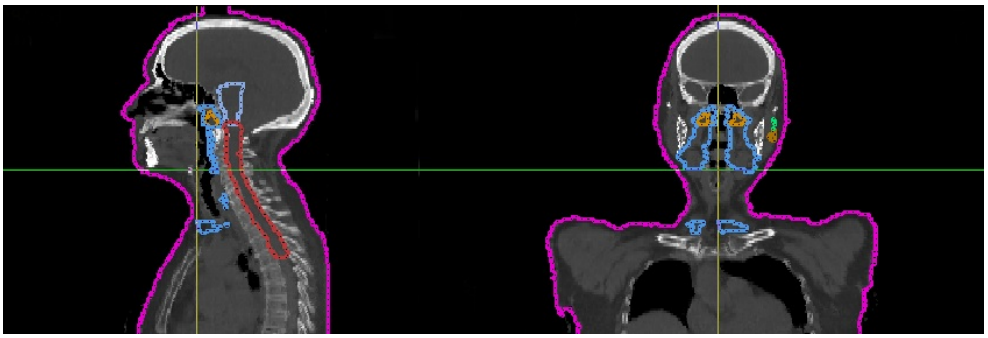

Figure 2.2: Structures delimited for a given treatment (**PTV1**, **PTV2**, **Spinal cord**, **Parotid**, **Brainstem** and **Body**), visualized in software CERR.

Usually, in clinical practice, one can consider the PTV structures for designing the treatment plans but, depending on the specificities of the tumor and its location, one can also consider other structures to irradiate. In most situations, and due to the possible irregular spread of the tumor, one can consider more than one PTV to irradiate during the treatment. Relatively to the OARs and considering how the possible damages induced by the radiation can influence the performance of the organ, one can consider two types of OARs [48]:

Modular or parallel organs
: Organs, like the parotid, that are capable of functioning even though a small part of the tissue is damaged;

Chain organs
: Organs, like the spinal cord, that are unable to function if any part of the organ is destroyed by the radiation.

Radiation therapy is a local treatment, which intends to act directly on the tumor. The radiation can be delivered mostly in two ways: brachytherapy or teletherapy. Brachytherapy can be defined as an *internal* treatment, in which radioactive substances are inserted in the body of the patient, within the tumor, by minimally invasive or non–invasive surgical procedures. The optimal arrangement of those substances, and the doses they deliver to surrounding tissues, leads also to interesting and challenging optimization problems. In our work we will focus on teletherapy, that is an *external* procedure, in which radiation is delivered from outside the body and the target is the tumor [13].

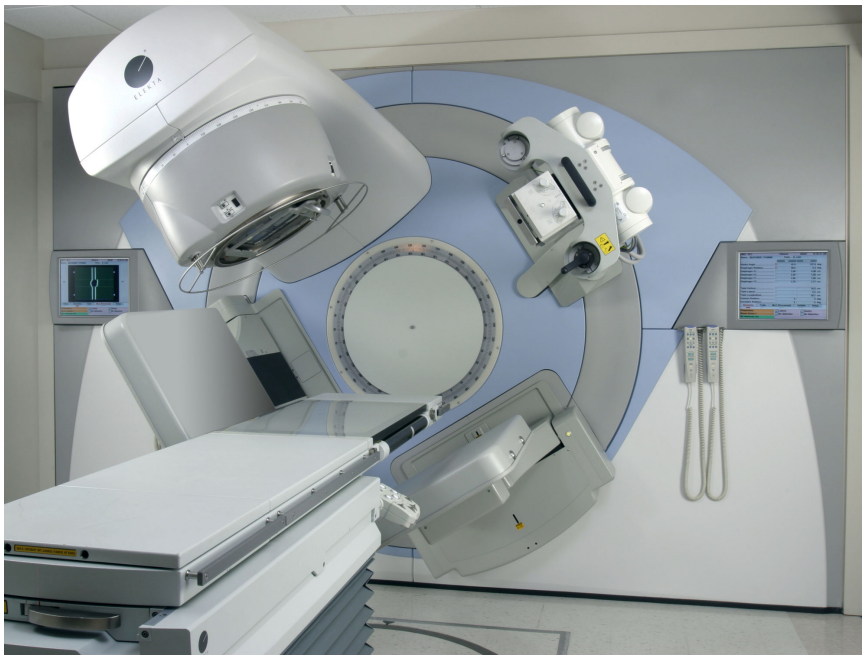

Figure 2.3: Linear accelerator and robotized positioning couch [70].

According to the diagnose and localization of the tumor, there are different radiation therapy treatments that can be applied and the equipments associated are also distinct. The most commons equipments are Cobalt–60, used in Gamma Knife radiosurgery, and linear accelerators (linac), like the one presented in Figure 2.3, used in teletherapy [48]. These linacs are photon beam machines, that deliver high–energy X–rays to the patient. There are also other equipments, like neutron beam and proton beam machines, which are the most recent, but are not yet widely spread in radiation therapy treatment institutes and facilities.

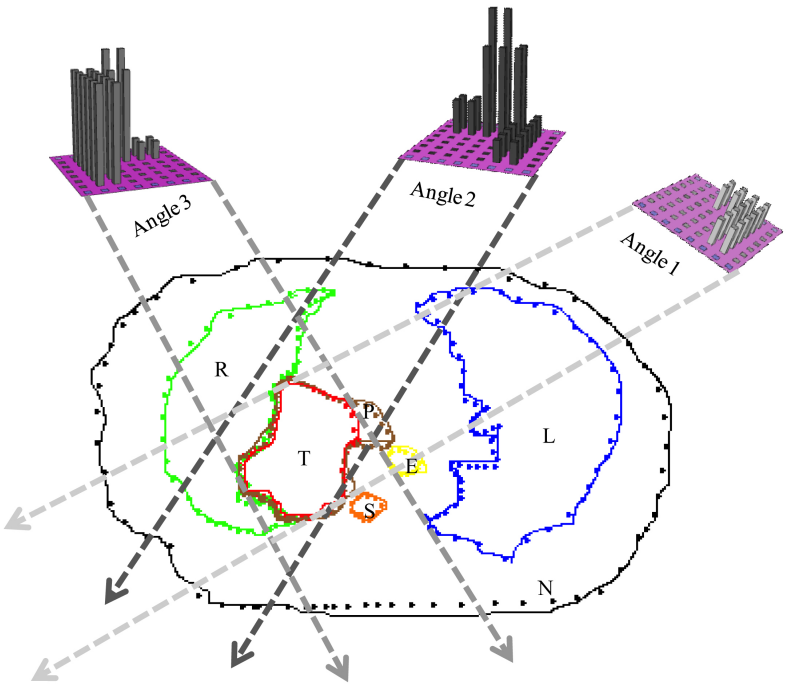

Figure 2.4: Conformal radiation therapy, using three angles with distinct intensities, where the target volume is represented by the structure T [69].

In teletherapy, one can also consider two different types of radiation therapy treatments: conformal or conventional. In both types the dose is irradiated and transmitted to the target by high–energy radiation beams. In conventional radiation therapy the beams are large enough to treat all areas in the target volume whereas in conformal radiation therapy the objective is to obtain a high conformity between the target volume and the doses absorbed by the different tissues [48]. Conformal radiation therapy has a tendency to produce better results, since it is possible to conform the radiation to the size and volume of the target regions. One can consider different techniques in conformal radiation therapy. The most common are three–dimensional conformal radiation therapy (3D–CRT) and IMRT. In both these techniques the beams of radiation used in treatment are shaped to match the target volume, focusing on the tumor while trying to spare the surrounding healthy tissues. In IMRT, the conformity is also obtained by using small beams, each targeting a small area.

A simple representation of a conformal radiation therapy treatment is shown in Figure 2.4, where radiation is delivered from three different angles and each beam direction has a distinct intensity map. One must note that the radiation intensities (or fluences) in angle 1 have the same value for all small beams. This is an example of 3D–CRT. On the other hand, in angles 2 and 3 one can observe that the fluences of the small beams have distinct values. This is an example of IMRT, which will be addressed in the next section.

One can consider two types of angles in radiation therapy: coplanar and non–coplanar. The difference between them is that coplanar angles stay in the rotation plane of the linac gantry around the patient. In clinical practice, coplanar angles are the most commonly used. Thus, non–coplanar angles will not be considered in our work. For most treatments, these angles are defined *a priori* according to the experience of the planner in similar cases. Normally, a geometric point within the tumor, called isocenter, is considered as a reference point to be strategically intersected by the radiation beam. Usually, the isocenter represents the center of mass of the tumor. The isocenter is also at the intersection of the rotation axis of the linac gantry with the central axis of the linac [48].

In radiation therapy, the dose deposition is linear, *i.e.*, the amount of radiation delivered is proportional to the irradiation time. The total dose of radiation received by the patient during the treatment is the sum of the radiation doses delivered from each beam direction. The radiation dose, usually also referred as dose absorbed, is defined as the amount of energy absorbed by the tissues per unit of mass. The radiation dose is typically expressed in Gray (Gy), such that one Gy is equal to one Joule (J) of energy deposited in one kilogram (kg) of matter ($1Gy = 1J/kg$) [36].

Typically, and according to the different types of cancer, the treatment is divided in several daily sessions, administered five days each week, for five up to eight weeks. This distribution tends to produce better results, instead of using few larger doses, with greater protection of the healthy tissues and organs in the neighborhood of the tumor [24]. For instance, considering a medical prescription of 60 Gy, the treatment could be delivered in 2 Gy daily fractions over 30 days. Considering the structures represented in Figure 2.2, one can establish a treatment plan such that the desired doses of radiation are specified in Table 2.1, that can be interpreted as the radiation treatment medical prescription.

Table 2.1: Doses used in the implementation for the structures considered in Figure 2.2.

Structures	**PTV1**	**PTV2**	**Parotid**	**Spinal cord**	**Brainstem**	**Body**
Prescribed dose	70 Gy	59.4 Gy	-	-	-	-
Mean dose	-	-	26 Gy	-	-	-
Maximum dose	-	-	-	45 Gy	54 Gy	80 Gy

The assessment of the dose irradiated to each tissue can be done by resorting to lines that indicate a constant value of radiation, called isodoses. These lines are defined as a percentage of the prescribed doses and each isodose line represents the percentage of radiation dose, according to the prescribed doses. [48]. The isodoses are important tools in order to evaluate the quality of the treatment.

There are many tools that can be used in order to evaluate the quality of the treatment, and this variety of aspects can change from patient to patient. Typically, dose–volume histograms (DVHs) are used in order to perceive the amount of radiation received by each structure. In a ideal situation, the curve of the DVH would be at 100% for the entire volume of the tumor and then it would drop immediately to zero, which indicates that the target is treated according to the prescription. Regarding OARs, ideally, the curves of the different OARs would drop instantly to zero, assuring that no vital organ receives any radiation, as represented in Figure 2.5 [48].

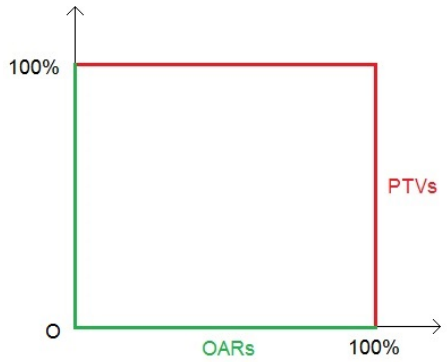

Figure 2.5: Ideal cumulative DVH.

In clinical practice, these ideal situations are not attainable. Thus, our goal is to minimize the side effects of the treatment, delivering enough radiation to the tumor while minimizing the effects on the surrounding tissues. For instance, concerning the DVH of the target volume, one of the objectives is to avoid the existence of long "tails" near the zero value. A cumulative DVH is represented in Figure 2.6, where each curve is related to a different structure or tissue.

The isodose graphic representation is also a relevant indicator and there are others parameters that can complement this analysis, such as [48]:

Coverage
: Represents the ratio between the PTV enclosed by the isodose surface prescribed and the total PTV volume;

Conformity
: Represents the ratio between the volume inside the isodose surface prescribed and the volume of the PTV inside that isodose surface;

Homogeneity
: Represents the ratio between the maximum and minimum dose received by PTV.

Another relevant analysis is related with the existence of cold (under radiated) and hot (over radiated) spots. A coldspot in a PTV can derail the treatment; a hotspot in a OAR can be deadly to the organ's functioning, specially in "chain" organs.

Due to the complexity of this problem, the planning treatment is usually done by trial and error procedures: the planner tries a given treatment plan and a treatment planning system software calculates the expected absorbed doses. If these doses are acceptable, considering the medical prescription, then the procedure stops. Otherwise, the treatment plan is changed and the process is repeated. This is called forward radiation therapy treatment planning. In our work we are interested in inverse planning radiation therapy, in which the optimal planning treatment is automatically determined given a medical prescription. Thus, inverse radiation therapy treatment planning consists in, given a prescribed treatment, compute algorithmically a specific set of parameters (beams and fluences) in order to achieve the objective at hand, *i.e.*, fulfill the prescribed doses and restrictions of the treatment [49]. This method allows the achievement of better results, on highly complex treatment planning problems, where OR has a key role in the improvement of the treatments.

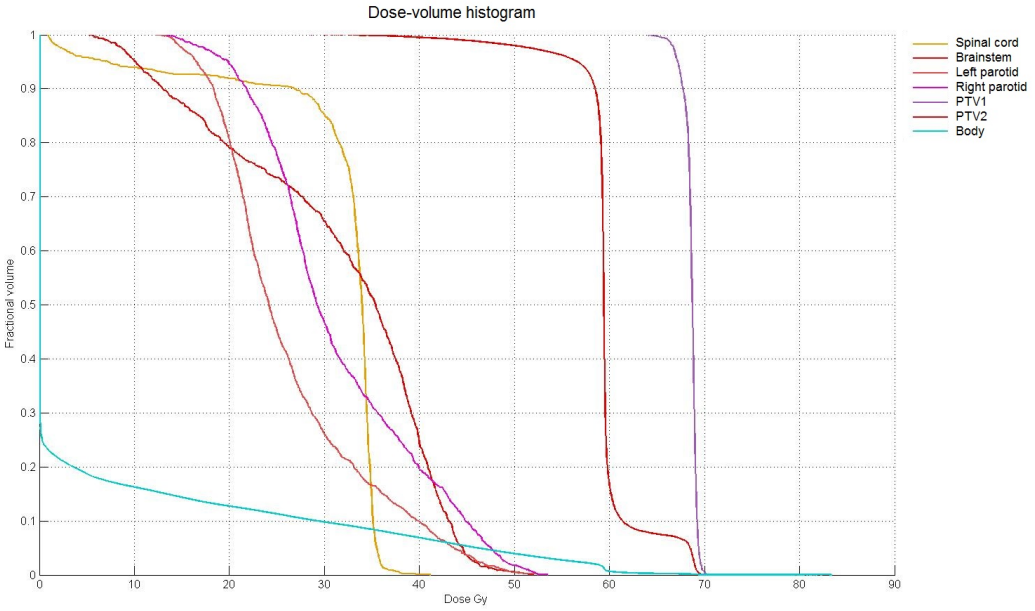

Figure 2.6: Cumulative DVH in a treatment.

There are many ways to face this optimization problem, such as aiming at delivering less radiation to OARs, increasing the radiation to the tumor or shortening the radiation time [36]. Different approaches to the problem will lead to different optimization models. The objective is to optimize the entire process, that may involve modeling, analyzing and solving deterministic, stochastic, linear, nonlinear, integer and global optimization problems. This increases the complexity of the problem and creates a vast source of new OR problems to be tackled.

In order to construct an optimal fluence map to each patient, it is necessary to evaluate the dose distribution. To do this, one must specify how radiation is deposited in the

patient. It can be accomplished by different forms, models and softwares. In our work, we will use the program MATLAB®[1], with the software CERR (Computational Environment for Radiotherapy Research[2]). This software is basically a platform for developing and sharing research results in radiation therapy treatment planning, which, among other features, returns the evaluation of a given objective function for a given selected set of beam directions and allows the access to the dose distribution matrices. An illustration of the structures visualized in CERR, with the CT information of a given patient, is represented in Figure 2.7.

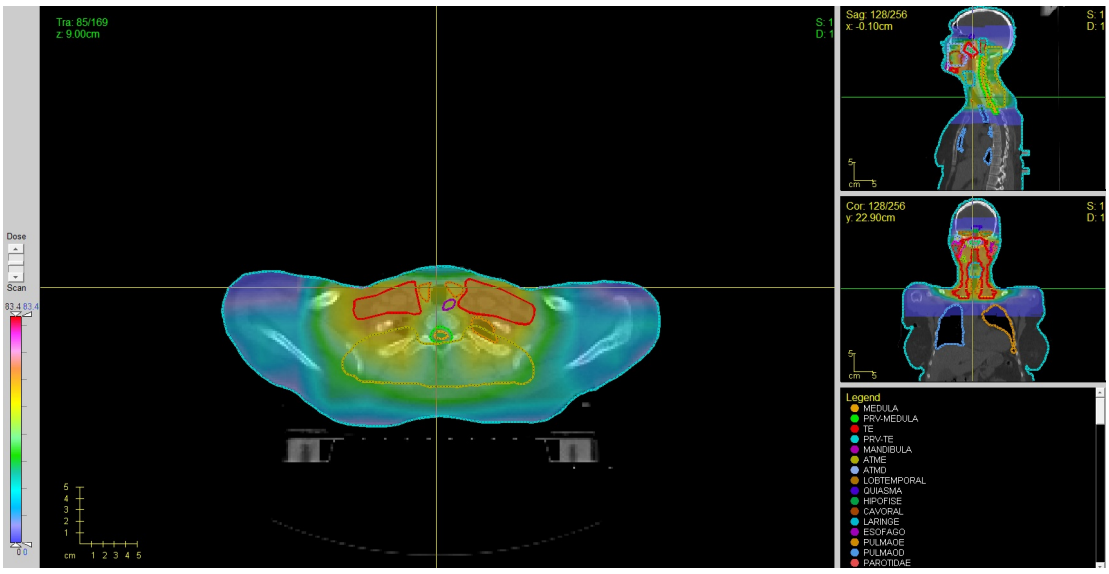

Figure 2.7: Illustration of the structures visualized in CERR.

2.2 IMRT

Some authors defend that IMRT is the most important development in radiation therapy since CT imaging was introduced in treatment planning [13]. IMRT is an advanced radiation therapy modality, where radiation is modulated by a multileaf collimator (MLC) device, clamped on a gantry that can rotate along a central axis which, combined with the rotation of the couch, allows the entire set of feasible angles to be used in the treatment. A MLC is constituted by several leaves with independent movements, which, by blocking part of the beam during a certain period of time, originate small beams, called beamlets, each with a given intensity or fluence. One must note that these beamlets do not exist physically; they are originated by the movement of the leaves.

A MLC can operate on dynamic collimation, where the leaves are always moving during the radiation treatment, or in multiple static collimation, a "step and shoot" mode, where

[1] *http://www.mathworks.com/products/matlab/* (Last access June 30, 2014)
[2] *http://www.cerr.info/about.php* (Last access June 30, 2014)

the leaves can be opened with a defined aperture and for a given period of radiation time, which creates a specific fluence or intensity [49]. This will generate a discrete set of fluence maps. Here, we will focus on multiple static collimation. A common MLC is represented in Figure 2.8.

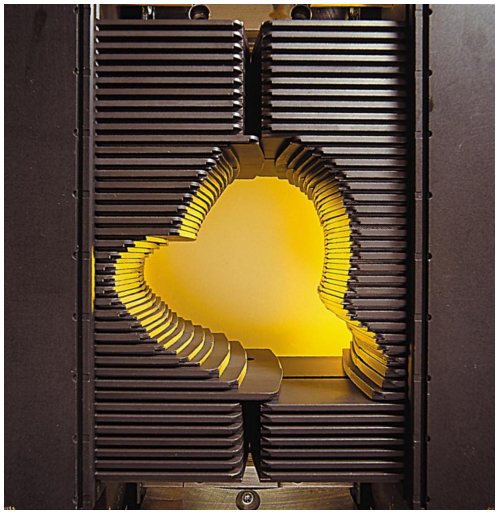

Figure 2.8: Multileaf collimator [68].

Considering that, for instance, the face of the beam is a square with 10×10 cm , then, the MLC, by the movement of the leaves, enables the conversion of the beam into a grid of beamlets (*e.g.* 3 mm), as represented in Figure 2.9, considering a MLC device with nine pairs of leaves and a given fluence map.

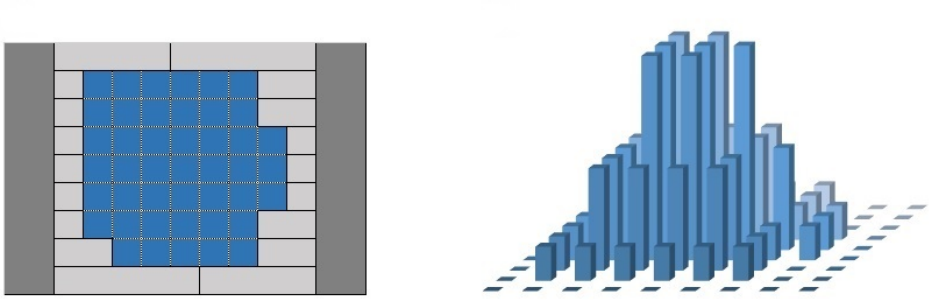

Figure 2.9: Illustration of a MLC device with nine pairs of leaves and the hypothetical correspondent beamlet fluence map (9×9).

For all the structures mentioned before, and in order to calculate the total dose absorbed by the tissues, one must determine the weighted sum of the dose irradiated by every beamlet, delivered from each angle. All the points of the body that receive a certain dose of radiation are called dose–points and each dose–point is represented by a volume element, in a form of a cube, called voxel [48]. It is assumed that the dose radiation is the same

throughout each voxel. So, in order to calculate the total dose of radiation received by the tissues, one must determine the sum of the doses received by each voxel, from every beamlet, from each angle [13].

In IMRT, we can modulate the radiation intensities across the beams and this allows the achievement of a higher conformity between the areas that need to be irradiated and the ones that need to be spared, especially for tumors with complex non–convex shapes and in difficult anatomical situations, *e.g.*, for head–and–neck tumors. One of the seminal papers regarding IMRT dates back to 1982 and it all started with the question: "Which is the desired lateral dose (intensity) profile in the incident beam that produces a desired... absorbed dose distribution in the body after one complete rotation?", by Brahme *et al.* ([14]).

Basically, we can divide the IMRT treatment planning problem in three related phases. First of all we need to calculate or define the minimum number of angles, and their values, from which the irradiation will occur (geometric problem). Normally, and depending on the diagnose and localization of the tumor, one can consider from three up to nine coplanar angles to irradiate. Then, for each of these angles, we need to calculate the fluence maps (fluence or intensity problem) and finally we need to determine the behavior the MLC in the treatment (realization problem), such that the objective is to find a suitable way to deliver the fluence maps produced by the beam angle and fluence map optimizations [13]. These distinct subproblems and the related optimization procedures will be explored in the next chapter.

Chapter 3

Optimization in IMRT

For the last decades, optimization in radiation therapy, namely in IMRT, followed the development of new treatment technologies and have had a key role guaranteeing the quality of radiation therapy treatments, which intrinsically depends on how well the following related subproblems are tackled.

Regardless of the model used to solve the IMRT optimization problem, its complexity will always be one of the main obstacles to overcome. One of the strategies that can be used in order to reduce the computing time is sampling, considering the aggregation of voxels. NT, for instance, has more voxels than any other structure and, when compared with other vital structures, is not so important in the final result of the treatment. It is possible to have a more coarse discretization by aggregating several voxels into a single one. Further work related to this problem can be developed, in order to speed up the process [13].

Typically, in most of the existing commercial softwares (TPS — treatment planning systems), the treatment planning is initiated when the planner defines the set of beam angles to be used in the treatment. In clinical practice and in the lack of better options, the planner usually considers using of a set of equidistant beam angles. Most treatment planning systems ask the user to define weights associated with the structures to be considered. So, in a second phase, the planner needs to tune the weights in order to accomplish DVH control on the PTVs and OARs. If the expected results obtained are in accordance to the medical prescription, the procedure stops. If not, new angles or different weights are tested and the procedure is repeated. Sometimes, different maximum or mean doses are also tested, but always within trial and error procedures. These human loops are time consuming [13]. In order to improve the quality of the treatment, these mechanisms should be automated. In order to automate, at least at some level, the IMRT planning process, we need to chose a model and a computational algorithm to solve the optimization problem, providing a treatment plan in a limited period of time. One of the purposes of our work is to try new approaches to the IMRT treatment problem, based on the cumulative experience of the research team and the existent literature.

3.1 Beam angle optimization

In radiation therapy, the BAO is a geometric problem where the purpose is to find the minimum number of angles and their directions, from which the irradiation will occur, that satisfies the treatment objectives [48]. In most cases, and depending on the localization of the tumor, the number of angles is defined *a priori* by the treatment planner, according to the experience in similar treatments. Thus, the BAO problem may consist in finding the best directions to irradiate the PTVs, while sparing the OARs and the NT around the tumor.

The importance of the BAO problem is related to two facts: first, the selection of adequate beam directions is decisive in order to improve the quality of the treatment. Second, it is time consuming changing the beam directions during the treatment [48]. Short treatments are desirable because the chances of any fortuitous movement by the patient increases with the duration of the sessions. In many radiation therapy facilities, the selection of the beams is still defined by trial and error procedures. Other radiation therapy facilities ignore this optimization problem and, for each treatment, this selection is defined *a priori*, given the experience in similar cases. For each set of angles, one must determine the fluence. This process is time expensive and it is based mostly in empirical knowledge. Also, it does not offer any guarantees of producing optimal or near–optimal results.

Let us assume the existence of n coplanar beams, such that $(\theta_1, \ldots, \theta_n) \in \Theta^n$, where Θ is the set of all beam angles, that can be selected from the circle around the CT–slice containing the isocenter. Basically, our objective is to select the best subset of beams from Θ^n that suits our purpose, *i.e.*, find the best directions to irradiate the PTVs and spare the OARs and NT. In order to simplify the optimization problem, usually, the continuous interval of possible gantry angles $[0°, 360°[$ is discretized in equally space directions [13]. One must note that irradiation from the angle 0° is equivalent to irradiation from the angle 360°. The obvious discretization is to consider the integer values $(0°, 1°, 2°, \ldots, 359°)$. For example, in this case and if we want to choose seven distinct angles in a certain treatment, we will have $C_7^{360} = 146622043719720$ possibilities, which shows the cardinal of the feasible solutions set of the optimization problem.

In clinical practice it is assumed that angles that differ by less than 5° can be considered as equivalents. So, instead of using the referred discretization it is usual to use others, such as $(0°, 5°, 10°, \ldots, 355°)$, which, in the same example, will reduce the number of combinations to $C_7^{72} = 1473109704$. One can even reduce the number of candidates to 36, by considering 10° apart, and the number of possibilities are reduced to $C_7^{36} = 8347680$. Even so, considering only 36 candidates and a very simple linear objective function, it will take about one minute to evaluate a given set of angles on a regular digital computer, which means that more than 15 years are required to find the optimal solution by an enumeration procedure, which is obviously impracticable in clinical practice.

There are procedures and techniques, based on heuristics and metaheuristics, that can reduce the computational time required to solve the problem. In optimization, heuristics can be seen as a family of approximative optimization techniques that provide "acceptable"

solutions in a reasonable period of time for solving hard and complex problems. Unlike exact optimization algorithms, heuristics do not guarantee the optimality of the solutions obtained and we do not know how close these solutions are from the optimal ones [58]. These approximative algorithms can be divided into two classes: specific heuristics and metaheuristics. Specific heuristics are problem related, *i.e.*, they are designed and implemented to solve a particular problem whereas metaheuristics can be adapted to solve any optimization problem. Usually, metaheuristics reduce the effective size of the search space and explore that space efficiently by using a guiding strategy [58].

One can use random search techniques to tackle the BAO problem, namely simulated annealing ([22, 26, 56]), genetic algorithms ([56, 26]) and particle swarm optimization ([43]). Although these techniques can, theoretically, escape local minima, globally optimal or even clinically better solutions are generally obtained with a large number of objective function evaluations [50]. Aleman *et al.* ([2]) propose a response surface approach to beam orientation optimization, considering non–coplanar angles. Ehrgott *et al.* ([26]) presented a mathematical framework that merges distinct approaches found in the literature. Schreibmann *et al.* ([52]) propose a multiobjective evolutionary optimization of the number of beams, their orientations and weights for IMRT. Rocha *et al.* ([50]) proposed a selection of the treatment beam directions using radial basis functions within a pattern search methods framework. Other authors proposed other approaches, including gradient searches ([19]), set cover ([42]) and maximal geometric separation of treatment beams ([20]).

Another technique used in radiation therapy treatment planning is the beam's eye view. The concept is inspired by the bird's eye view, where the gantry position can be seen as the bird's eye and the PTV is the object being viewed. The objective is to calculate the best views, which represents the beam's angles, such that the volume seen in the PTV is bigger. This procedure will result in a set of the best candidates to be used in the treatment plan. There are also other approaches, based on the beam's eye view concept, like the use of scores associated to each beam ([47]), a mathematical framework that congregates different methods ([25]), the effects of diverse approximations of the anatomical dose on the beam selection, mixed integer programming (MIP) approach for the simultaneously resolution of the geometric and intensity problems ([41]). Whatever the approach, this will always be a complex optimization problem to solve, despite the recent increasing computational abilities, mainly due to the time restrictions in the planning process and clinical practice.

In the BAO problem there are many details that can influence the final result of the treatment. For instance, beams in opposed positions have a tendency to produce hotspots, *i.e.*, points where the dose received exceeds the upper bound value for the tissue, according to the prescription. Thus, beam angles θ and $\theta \pm 180^\circ$ should not be selected in the same treatment. Also, and because, as stated before, small variations of the beam angles tend to produce similar clinical results, if the angle θ is selected then the angles in the interval $[\theta \pm 180^\circ - \delta, \theta \pm 180^\circ + \delta]$ should not be selected [48]. Usually, and depending on the type and location of the tumor, one can consider $\delta = 5^\circ$.

As stated before, the geometric and intensity problems are related and should not be solved individually. For instance, we need to use an objective function, related to the fluence map optimization problem, to evaluate the selected beams angles in order to find

the best set. Thus, a formulation of the BAO problem is

$$\begin{array}{ll} \min & f(\theta_1, \ldots, \theta_n) \\ s.t. & (\theta_1, \ldots, \theta_n) \in \Theta^n \end{array} \tag{3.1}$$

where Θ is the set of all beam angles and f represents the objective function of the fluence map optimization problem that evaluates the given set of beam angles, $(\theta_1, \ldots, \theta_n)$ [48]. One of the biggest issues in solving this problem is associated with the fact that the referred objective function can have numerous local optima, which hampers the achievement of a good global solution, specially when using classic methods of searching. In our work, we considered combinatorial optimization to tackle the BAO problem. In the next section we will address the fluence map optimization problem.

3.2 Fluence map optimization

After fixing the set of beam angles, the next step in IMRT is solving the fluence map optimization (FMO) problem and, basically, this procedure will then define a radiation plan to be delivered. In the FMO problem, the objective is to calculate the optimal beamlet weights (intensities) for the given set of beam angles. As stated before, each considered structure that will receive radiation in the treatment is discretized into volume elements, called voxels. In order to solve the FMO problem one must calculate the total dose of radiation received by each voxel on each structure, considering the contribution of each beamlet from each beam. Usually, this information is represented in a form of a matrix dose D, using the beamlet weights and indexing each voxel to the rows of D and each beamlet to the columns of D [24].

Let us assume that N_v represents the total number of voxels and N_b represents the total number of beamlets. Considering n the fixed number of angles, or beam directions, from the BAO problem and Θ the set of all possible angles, such that $(\theta_1, \ldots, \theta_n) \in \Theta^n$ represents the set of beam directions chosen to deliver the radiation, then, using a superposition principle, the total dose received by the voxel i is given by

$$\sum_{j=1}^{N_b} D_{ij} w_j, \tag{3.2}$$

where w_j represents the weight of the beamlet j [48]. This approach reveals the complexity of the optimization problem, with thousands of variables (beamlets) and hundreds of thousands of constraints.

According to the prescription given by the physician for the treatment, one can consider certain restrictions or constraints related with the different tissues and structures. Consider the following notation:

- D_T — Total dose;
- TG_{PTV} — Target goal prescription for the PTV;

- D_{PTV} — Dose in the PTV;
- UB_{PTV} — Upper bound for the dose in the PTV;
- LB_{PTV} — Lower bound for the dose in the PTV;
- D_{OAR} — Dose in the OAR;
- UB_{OAR} — Upper bound for the dose in the OAR;
- D_{NT} — Dose in the NT;
- UB_{NT} — Upper bound for the dose in the NT;
- M — Upper bound for the beamlet weight.

The definition of a set of constraints is very important in order to deliver a viable treatment that can simultaneously destroy the cancerous cells in the PTVs structures and minimize the effects of radiation in the NT and OARs structures. Then, according to (3.2), a simple formulation of this problem can be stated as

$$\begin{array}{lll} \min_w & f(D_T) & \\ \text{s.t.} & D_T & = \sum_{i=1}^{N_v} \sum_{j=1}^{N_b} D_{ij} w_j \\ & LB_{PTV} & \leq D_{PTV} \leq UB_{PTV} \\ & D_{OAR} & \leq UB_{OAR} \\ & D_{NT} & \leq UB_{NT} \\ & 0 & \leq w_j \leq M \end{array} \tag{3.3}$$

where $j = 1, \ldots, N_b$ [48].

The first linear programming model of optimization on radiation therapy was used in 1968 and since then many have been the improvements on the area [7]. This interaction between medical physics and OR has become more significant in the last decade and it brought undoubted benefits to the treatments, improving the quality of the process and increasing the average life expectancy of the patients.

There can be many different approaches to solve this problem, such as: linear models, nonlinear models, mixed integer models and multiobjective models [24]. The advantages and disadvantages of these models will be explored in the next subsections.

3.2.1 Linear programming models

In the FMO problem, different objective functions $f(D_T)$ lead to different models. One can also add other constraints and use variations of objective functions, according to the prescription and the purposes of the treatment, *e.g.*, in order to choose the adequate objective function, our purpose could be to [48]:

- minimize the average/maximum dose or deviation from upper bounds on the dose delivered to the OARs and NT;
- maximize the average/minimum dose delivered to the PTVs;
- minimize average/maximum deviation from the prescribed dose to the PTVs.

And the constraints could be:

- lower and/or upper bounds on the PTVs dose;
- upper bounds on the dose to the OARs and/or NT;
- nonnegative and upper bound for the beam intensity;
- upper bounds on the ratio between the maximum beamlet intensity and the average beamlet intensity;
- upper bounds on the mean dose to OARs.

The dose deposited by radiation is linear and linear programming (LP) models were the first to be used to tackle this optimization problem. Their advantages are related to the fact that they are fast and easy to implement [26]. For a certain treatment, and given a medical prescription with the upper and lower bounds for the structures, the basic formulation of the objective function in a LP model is

$$f(D_T) = \|D_{PTV} - TG_{PTV}\|_1 + \|(D_{OAR} - UB_{OAR})_+\|_1 + \|(D_{NT} - UB_{NT})_+\|_1, \quad (3.4)$$

where $(.)_+ = \text{maximum}\{0, .\}$ and $\|.\|_1$ represents the L_1 norm[1]. This model allows the penalization of the absolute value of deviation between the doses prescribed and planned, in each voxel on each structure [48]. One can also add weight factors, α_{PTV}, α_{OAR} and α_{NT}, tuned by the treatment planner, such that the formulation is

$$f(D_T) = \alpha_{PTV}\|D_{PTV} - TG_{PTV}\|_1 + \alpha_{OAR}\|(D_{OAR} - UB_{OAR})_+\|_1 + \alpha_{NT}\|(D_{NT} - UB_{NT})_+\|_1. \quad (3.5)$$

The choice of these weight factors can be arbitrary, in trial and error procedures, according to the experience of the treatment planner in similar cases [48]. These weights do not have a clinical meaning. One can also use the weighted average dose deviation on each structure, such that the function objective is

$$f(D_T) = \alpha_{PTV}\frac{\|D_{PTV} - TG_{PTV}\|_1}{N_{vPTV}} + \alpha_{OAR}\frac{\|(D_{OAR} - UB_{OAR})_+\|_1}{N_{vOAR}} + \alpha_{NT}\frac{\|(D_{NT} - UB_{NT})_+\|_1}{N_{vNT}}, \quad (3.6)$$

[1] The L_1 norm can be easily represented in a linear programming model.

where N_{vPTV}, N_{vOAR} and N_{vNT} represents the number of voxels, respectively, in the PTV, OARs and NT structures, such that the total number of voxels is given by $N_v = N_{vPTV} + N_{vOAR} + N_{vNT}$ [48].

One of the disadvantages in the use of LP models is the fact that these methods generate optimal solutions that are boundary points of the admissible region, which leads to treatment plans where the upper and lower bounds are often attained. The immediate consequence of this fact is that the OARs will receive the maximum dose allowable and/or the PTVs receive the lowest allowable dose. The achievement of feasible solutions is hampered by the tightness of the constraints. In order to overcome this drawback, one can add elastic constraints to the formulation, such that the formulation can be stated as

$$\begin{aligned} \min \quad & \lambda l^\top \alpha + {u_{OAR}}^\top \beta + {u_{NT}}^\top \gamma \\ \text{s.t.} \quad & LB_{PTV} - L\alpha \leq D_{PTV} \leq UB_{PTV}, \\ & D_{OAR} \leq UB_{OAR} + U_{OAR}\beta, \\ & D_{NT} \leq UB_{NT} + U_{NT}\gamma, \\ & 0 \leq L\alpha \leq LB_{PTV}, \\ & -UB_{OAR} \leq U_{OAR}\beta, \\ & 0 \leq U_{NT}\gamma, \\ & 0 \leq w \leq M, \end{aligned} \tag{3.7}$$

where vectors α, β and γ define the bounds of the constraints $LB_{PTV} - L\alpha \leq D_{PTV} \leq UB_{PTV}$, $D_{OAR} \leq UB_{OAR} + U_{OAR}\beta$, and $D_{NT} \leq UB_{NT} + U_{NT}\gamma$ [36]. The matrices L, U_{OAR}, and U_{NT} will define the elasticity and l, u_{OAR} and u_{NT} represent the corresponding weight factors in the objective function, respectively. The scalar λ defines the importance of tumor uniformity. Even when the medical prescription leads to an unfeasible problem, this elastic LP model provides the closest solution to the unfeasible prescription [48].

3.2.2 Mixed integer programming models

Mixed integer programming (MIP) is another viable approach to model this problem. This model can be seen as an extension of the linear model (3.3), with the introduction of binary variables $\psi_\sigma \in \{0, 1\}, \forall \sigma \in \Theta$, which will define if angle σ is selected or not for the treatment. One of the advantages of this model is the possible setting of an upper bound on the number of angles used in the radiation. A formulation of a MIP model can

be stated as [48]:

$$\begin{array}{lll} \min_{w,\psi} & f(D_T) & \\ \text{s.t.} & D_T & = \sum_{i=1}^{N_v} \sum_{j=1}^{N_b} D_{ij} w_j \\ & LB_{PTV} & \leq D_{PTV} \leq UB_{PTV}, \\ & D_{OAR} & \leq UB_{OAR}, \\ & D_{NT} & \leq UB_{NT}, \\ & \sum\limits_{\sigma \in \Theta} \psi_\sigma & \leq n, \\ & 0 & \leq w_j \leq M\psi_\sigma, \forall \sigma \in \Theta, \quad j = 1, \ldots, N_b. \end{array} \tag{3.8}$$

The introduction of binary variables is also associated with the use of dose–volume constraints (DVCs), allowing the definition of the voxels that receive a dose lower or higher than the threshold in each structure. Thus, the constraints used in LP models are substituted by DVCs. For instance, considering a treatment plan where the lung is an OAR, instead of specifying the upper bound dose of 20 Gy delivered to the organ, the planner could specify that no more than 35% of the lung volume can exceed the prescribed dose. The use of DVCs allows the representation of the information by dose–volume histograms (DVHs), which can simplify the interpretation of the quality of the treatment [48].

Considering ${y_i}^{S^+}$ and ${y_i}^{S^-}$ as the binary variables associated to a voxel $i \in S$, where S is a given structure, such that

$${y_i}^{S^+} = \begin{cases} 1, & \text{if the dose received by voxel } i \text{ in structure } S \text{ exceeds } UB_S, \\ 0, & \text{otherwise,} \end{cases}$$

$${y_i}^{S^-} = \begin{cases} 1, & \text{if the dose received by voxel } i \text{ in structure } S \text{ is lower than } LB_S, \\ 0, & \text{otherwise,} \end{cases}$$

then, for instance, the upper bound in OAR

$$D_i w \leq UB_{OAR}, \forall i \in OAR$$

can be substituted by the DVCs

$$D_i w \leq (1 + y_i^{OAR^+} F_{OAR}^+) UB_{OAR}, \forall i \in OAR$$

$$\sum_{i \in OAR} {y_i}^{OAR^+} \leq P_{OAR} N_{vPTV}$$

where F is the maximum overdose allowed and P is the maximum percentage of points that can receive a dose above the UB_{OAR}. Thus, these DVCs impose that no more than $P\%$ volume of the OARs can exceed $F\%$ of the UB_{OAR} [48]. The main advantage in the use of DVCs is the increased flexibility of the constraints, avoiding feasibility problems. Similar formulations can be applied to the PTV and NT, converting the LP constraints

into DVCs. One can add another constraint in order to guarantee that at most n angles are selected. The formulation of a MIP model can be [48]:

$$\begin{array}{lll}
\min_w & f(D_T) & \\
\text{s.t.} & D_T & = \sum_{i=1}^{N_v}\sum_{j=1}^{N_b} D_{ij}w_j \\
& (1-y_i^{PTV^-}F_{PTV}^-)LB_{PTV} & \leq D_i w, \forall i \in PTV, \\
& D_i w & \leq (1+y_i^{PTV^+}F_{PTV}^+)UB_{PTV}, \forall i \in PTV, \\
& \sum\limits_{i\in PTV} y_i^{PTV^-} & \leq P_{PTV}^- N_{vPTV}, \\
& \sum\limits_{i\in PTV} y_i^{PTV^+} & \leq P_{PTV}^+ N_{vPTV}, \\
& D_i w & \leq (1+y_i^{OAR^+}F_{OAR}^+)UB_{OAR}, \forall i \in OAR, \\
& \sum\limits_{i\in OAR} y_i^{OAR} & \leq P_{OAR} N_{vPTV}, \\
& D_i w & \leq (1+y_i^{NT^+}F_{NT}^+)UB_{NT}, \forall i \in NT, \\
& \sum\limits_{i\in NT} y_i^{NT} & \leq P_{NT} N_{vNT}, \\
& 0 & \leq w_j \leq M, \forall \sigma \in \Theta, j = 1,\ldots,N_b
\end{array} \tag{3.9}$$

In the objective function $f(D_T)$, according to the purposes of the treatment, one can use the LP or the nonlinear objective functions that will be described in the next section. The immediate advantage of this approach, when compared with (3.3), is related to the useful definition of an upper bound for the number of angles to deliver the radiation.

3.2.3 Nonlinear programming models

One of the most common nonlinear model is the quadratic programming model. The formulation of a quadratic objective function, considering the existence of weight factors (α_{PTV},α_{OAR} and α_{NT}), is

$$\begin{aligned} f(D_T) = \alpha_{PTV}\|D_{PTV} - TG_{PTV}\|_2^2 + \alpha_{OAR}\|(D_{OAR} - UB_{OAR})_+\|_2^2 + \\ \alpha_{NT}\|(D_{NT} - UB_{NT})_+\|_2^2. \end{aligned} \tag{3.10}$$

The quadratic model (3.10) penalizes the sum of squares of the deviations [48]. One of the main advantages in the use of nonlinear models, when compared to the similar LP models, is the fact that nonlinear models are able to penalize bigger deviations, which suits our purposes.

Instead of considering the Euclidian norm, L_2, one can use the L_∞ norm, which penalizes respectively the coldspots in the PTVs and the hotspots in the OAR and NT [48]:

$$\begin{aligned} f(D_T) = \alpha_{PTV}\|D_{PTV} - TG_{PTV}\|_\infty + \alpha_{OAR}\|(D_{OAR} - UB_{OAR})_+\|_\infty + \\ \alpha_{NT}\|(D_{NT} - UB_{NT})_+\|_\infty \end{aligned} \tag{3.11}$$

Also, one can use variations of both linear and nonlinear models in different structures, and considering the weighted average deviation dose on each structure, such that

$$f(D_T) = \alpha_{PTV}\frac{\|D_{PTV} - TG_{PTV}\|_p}{N_{vPTV}} + \alpha_{OAR}\frac{\|(D_{OAR} - UB_{OAR})_+\|_p}{N_{vOAR}} +$$

$$\alpha_{NT}\frac{\|(D_{NT}-UB_{NT})_+\|_p}{N_{vNT}}, \tag{3.12}$$

where $p=1,2,\infty$. Depending on the objectives at hand, one can use different norms on distinct structures, in the same objective function [26].

The objective of the treatment could be to penalize in different ways the cold and hot spots in the PTVs, such that

$$\begin{aligned} f(D_T) = \alpha^+_{PTV}\|(D_{PTV}-UB_{PTV})_+\|_\infty + \alpha^-_{PTV}\|(LB_{PTV}-D_{PTV})_+\|_\infty + \\ \alpha_{OAR}\frac{\|(D_{OAR}-UB_{OAR})_+\|_p}{N_{vOAR}} + \alpha_{NT}\frac{\|(D_{NT}-UB_{NT})_+\|_p}{N_{vNT}} \end{aligned} \tag{3.13}$$

or

$$\begin{aligned} f(D_T) = \alpha^+_{PTV}\|(D_{PTV}-UB_{PTV})_+\|_\infty + \alpha^-_{PTV}\|(LB_{PTV}-D_{PTV})_+\|_\infty + \\ \alpha_{OAR}\frac{\|(D_{OAR}-UB_{OAR})_+\|_p}{N_{vOAR}} + \alpha_{NT}\frac{\|(D_{NT}-UB_{NT})_+\|_p}{N_{vNT}} \end{aligned} \tag{3.14}$$

where $\alpha^+_{\{.\}}$ and $\alpha^-_{\{.\}}$ represent respectively the upper and lower weights for the different structures at hand.

If the objective is to have low maximum dose violation on the PTVs, while controlling the average dose deviation on the OARs and NT [48], then one can use the model

$$\begin{aligned} f(D_T) = \alpha_{PTV}\|D_{PTV}-TG_{PTV}\|_\infty + \alpha_{OAR}\frac{\|(D_{OAR}-UB_{OAR})_+\|_1}{N_{vOAR}} + \\ \alpha_{NT}\frac{\|(D_{NT}-UB_{NT})_+\|_1}{N_{vNT}}. \end{aligned} \tag{3.15}$$

One can also apply asymmetric quadratic penalty functions, like the one presented by Aleman *et al.* ([3]), which penalizes each voxel according to the square difference of the amount of dose desired or allowed for the voxel. This formulation only have linear non–negativity constraints on the intensity values and can be stated as:

$$\begin{aligned} \min_{w} \quad & \sum_{i=1}^{N_v}\frac{1}{v_S}\left[\underline{\lambda}_i\left(T_i-\sum_{j=1}^{N_b}D_{ij}w_j\right)^2_+ + \overline{\lambda}_i\left(\sum_{j=1}^{N_b}D_{ij}w_j-T_i\right)^2_+\right] \\ s.t. \quad & w_j\geq 0,\ j=1,\ldots,N_b, \end{aligned} \tag{3.16}$$

where T_i is the desired dose for voxel i, $\underline{\lambda}_i$ and $\overline{\lambda}_i$ are the penalty weights of underdose and overdose of the voxel i and $(\cdot)_+=\max\{0,\cdot\}$. This formulation allows that each voxel is weighted by the same factor, assigned to the structure that contains the voxel and divided by the total number of voxels in the referred structure (v_S).

All the models addressed previously ignore the biological aspect in this optimization problem. This is a controversial issue among the experts in the area but there are several approaches that add radiobiological meaning to the objective function. The concept behind

this approach is to define the tumor control probability (TCP) and normal tissue complication probability (NTCP) through mathematical formulas and the purpose is to maximize the TCP, while minimizing or controlling the NTCP [26]. Basically, TCP measures the response of the tumor to irradiation, indicating the number of clonogen cells that remain in the target, and NTCP is associated with the dose distribution on a critical structure. The main difficulty in the use of this model is the accuracy of the mathematical formulas that simulate what will happen with the patient. Some of these formulas for TCP and NTCP are Poisson–based, such as:

$$TCP = \prod_{i=1}^{N_{vPTV}} exp\left[-\frac{\Omega}{N_{vPTV}} exp(-rd_i)\right],$$

$$NTCP = 1 - \prod_{k=1}^{K}(1 - P^k),$$

$$P^k = \left(1 - \prod_{i \in OAR_k} [1 - (P(d_i))^s]^{\frac{v_i}{\sum_{i \in OAR_k} v_i}}\right)^{\frac{1}{s}},$$

where r is the radiosensitivity of the cancerous cells, *i.e.*, cells that are capable of producing a colony of similar cell types (tumor clonogens), Ω is the total number of clonogens in the tumor, d_i is the dose in the i^{th} voxel, K is the number of OAR and s represents the relative seriality of tissue organization [48]. The homogeneous dose can be stated as

$$P(d_i) = 2^{-exp\left(eg\left(1-\frac{d_i}{D_{50}}\right)\right)},$$

where D_{50} is the dose of 50% response, g is the normalized dose–response gradient and e is the Neper number. Many other models can be used on TCP and NTCP, according to different objectives, such as the maximization of the uncomplicated tumor control probability, given by

$$P_+ = TCP(1 - NTCP),$$

where TCP and NTCP are assumed to be independent [48].

Equivalent uniform dose (EUD), initially based on the TCP model, is another interesting measure. The EUD is the dose that, when administered uniformly to a certain structure, produces the equivalent clinical and biological result as a non–uniform dose. The main advantage in the use of EUD is the simplicity in the interpretation and analysis of the dose distributions. EUD can also be defined as a "mean dose" and stated as

$$EUD = \left(\frac{1}{v_S}\sum_{i=1}^{v_S} {d_i}^a\right)^{\frac{1}{a}},$$

where v_S is the total number of voxels in a given structure S (PTVs, OARs or NT) and a is a weight that varies with the type of structure and indicates the radiation tissue response to the treatment [26].

Another issue related to this problem is the definition of certain criteria that evaluate the quality of the treatment. One of the approaches could be the so called separable convex voxel–based criteria, in which the idea is to use a heuristic method that evaluates the dose received by each voxel in a certain structure through a convex function. Considering the average measure deposited in all voxels, the model can be expressed for a structure that is separable in the doses to each voxel, such as

$$F(\vec{d}) = \frac{1}{N_v} \sum_{i=1}^{N_v} f_i(d_i),$$

where f_i is a convex function. Commonly, the expression used for the PTVs is

$$f_i(d_i) = c_i |d_i - \delta_i|^{a_i},$$

and

$$f_i(d_i) = c_i \times max\{0, d_i - \delta_i|\}^{a_i}$$

is the expression used for the OARs, where δ_i is a dose threshold and a_i and c_i are parameters that are related respectively to the shape and scale for the convex function, considering the voxel i in the structure [26].

3.2.4 Multiobjective programming models

IMRT treatment planning can also be considered from a multiobjective point of view, since we want to simultaneously deliver radiation to the PTVs in order to destroy the cancerous cells, while minimizing the effects in the surrounding tissues, which can be considered as conflicting objectives. This means that, instead of looking for a single optimal solution, we can think of calculating clinical efficient solutions (nondominated or Pareto–optimal). This can be done *a priori*, *a posteriori* or in an interactive procedure [48].

In a multiobjective programming (MOP) problem, solutions of interest are nondominated solutions. A nondominated solution in the objective space is equivalent to an efficient solution in the decision space, such that an efficient solution can be defined as a solution for which an improvement in a given objective leads to a worse result in, at least, one of the other objectives.

There are distinct forms to approach MOP models. For instance, one can turn it into a single objective problem by using a specific set of weight factors for each objective considered. Thus, both linear and nonlinear models can be considered scalarizations of a MOP model. As stated before, these weights do not have a clinical meaning and one cannot predict how the changing of the weights will influence the optimal solution [25]. Also, one can consider *a posteriori* methods, in which an optimization procedure induces the discovery of the whole nondominated set or a representative subset of the nondominated

set can be conceived. The analysis of the nondominated set can help in understanding the compromises that exist between different objectives.

MOP models can also be linear or nonlinear. For instance, the objectives in a multiobjective nonlinear programming (MONP) can be defined in terms of $F = (f_{PTV}, f_{OAR}, f_{NT})$, such that [26]:

$$f_{PTV} = \frac{1}{N_{vPTV}} \|D_{PTV} - TG_{PTV}\|_2^2,$$

$$f_{NT} = \frac{1}{N_{vNT}} \|D_{NT}\|_2^2, \tag{3.17}$$

$$f_{OAR} = \frac{1}{N_{vOAR}} \|(D_{OAR} - UB_{OAR})_+\|_2^2,$$

where f_{PTV} is the average squared deviation to the prescribed dose to the PTVs, f_{NT} is the average squared dose to the normal tissue and f_{OAR} represents the average squared overdose to the OARs [40].

Considering a linear approach, the FMO problem can be reformulated and the multiobjective linear programming (MOLP) model can be stated as

$$\begin{array}{lll} \min & F = (f_{PTV}, f_{OAR}, f_{NT}) & \\ \text{s.t.} & D_{PTV} & \geqq LB_{PTV}(1 - f_{PTV}) \\ & D_{OAR} & \leqq UB_{OAR}(1 + f_{OAR}) \\ & D_{NT} & \leqq UB_{NT}(1 + f_{NT}) \\ & f_{PTV}, f_{OAR}, f_{NT} & \leqq 0 \end{array} \tag{3.18}$$

where f_{PTV} represents the maximal deviation from the LB_{PTV}, f_{OAR} is the maximal deviation from the UB_{OAR} and f_{NT} is the maximal deviation from the UB_{NT} [35].

In the literature, one can find different approaches, techniques and algorithms for MOP problems ([9, 18, 60]). For instance, one can use dose–volume objectives, that can produce better results with convex approximation than conventional formulations using dose–volume constraints ([34]). Most of the papers addressing MOP models use some weighted sum method, which could be inefficient due to the fact that the computational time required to solve the problem is proportional to the number of weight factors. In a MOP approach, several different nondominated solutions will have to be calculated, and this will have an important impact in computational times. If we have a set of nondominated solutions, it is still necessary to choose one single solution that will correspond to the treatment delivered to the patient. This is another difficult problem to solve [24]. However, MOP approaches can illustrate the compromises that exist between different objectives. They can allow a more informed decision making process.

3.3 Fluence map delivery

After the resolution of the BAO and FMO problems, one must yet solve another optimization problem: the fluence map delivery (FMD), in which the objective is to find the

most efficient way for the MLC to deliver the optimized fluences previously calculated. However, and due to physical limitations of the device, this transposition is not direct and this is also a challenging optimization problem. This section is mostly based on the paper *On the Optimization of Radiation Therapy Planning*, by Rocha *et al.* ([48]).

There are many models and techniques that can be used in the FMD problem, also called realization problem, presented by many authors ([1, 8, 17, 45, 51, 54, 59, 66]). The beamlet fluences are discretized into a range of values, *e.g.*, 0 to 10, used to construct the apertures and intensities corresponding to the fluence maps previously calculated. As stated before, one will consider multiple static collimation, where the leaves can be opened with a defined aperture and for a given period of radiation time, which creates a specific fluence or intensity.

Let us consider that a fluence map can be expressed by a matrix $m \times n$ of beamlet weights, where each value represents the intensity imputed to each beamlet, considering m leaf pairs and $n+1$ positions. Then, for instance, considering a matrix 9×9, the fluence map can be expressed as

$$D = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 & 1 & 1 & 1 & 0 & 0 \\ 0 & 1 & 3 & 3 & 3 & 3 & 1 & 0 & 0 \\ 0 & 1 & 3 & 6 & 6 & 3 & 1 & 1 & 0 \\ 0 & 1 & 3 & 6 & 6 & 6 & 3 & 1 & 0 \\ 0 & 1 & 3 & 6 & 6 & 3 & 1 & 1 & 0 \\ 0 & 1 & 1 & 3 & 3 & 3 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{3.19}$$

which can be represented graphically, as shown in Figure 3.1.

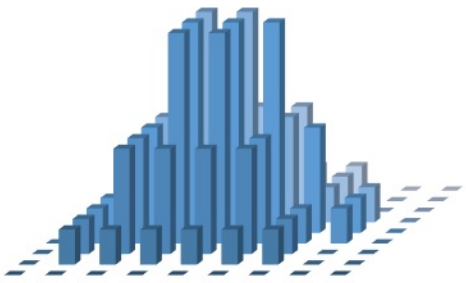

Figure 3.1: Fluence map of the matrix in (3.19).

The MLC device produces the same radiation intensity in all beamlets that are on. Since each beamlet could have a different weight attached, in order to deliver the fluence map expressed in (3.19), one must achieve beamlet variation. This can be accomplished by

modifying the beam aperture and superimposing the equivalent number of segments [48]. Thus, this optimization problem corresponds to the definition of the leaf positions, and related apertures, which is equivalent to establish the decomposition of W into K shape matrices B^k with binary digits, such that

$$W = \sum_{k=1}^{K} \mu_k B^k, \tag{3.20}$$

where μ_k is the intensity value, *i.e.*, the exposure time for each aperture, and B^k represents binary matrices, where the values 0 and 1 represent if the radiation is respectively blocked or not [48]. Note that, in this example, the MLC have eighteen leaves (two for each row), when, in fact, modern collimators have much more leaves. These leaves will move across the rows, allowing radiation to be delivered to the target while sparing the surrounding tissues.

Due to physical constraints of the MLC, there are many solutions to (3.20) that are not feasible because there cannot be any intermission between exposed beamlets in the same row. For instance, on one hand,

$$0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0$$

or

$$1 \quad 1 \quad 1 \quad 1 \quad 1 \quad 1 \quad 1 \quad 1 \quad 1$$

or

$$0 \quad 0 \quad 1 \quad 1 \quad 1 \quad 1 \quad 1 \quad 0 \quad 0$$

are examples of feasible rows. On the other hand,

$$0 \quad 0 \quad 1 \quad 1 \quad \mathbf{0} \quad \mathbf{0} \quad 1 \quad 1 \quad 0$$

is an example of an unfeasible row, due to the existence of two zeros in the middle of a nonzero sequence. It is physically impossible for the MLC device to block those two beamlets. In clinical practice, the existence of unfeasible rows on a fluence map delivery could seriously jeopardize the treatment, due to the fact that the existence of untreated cancerous areas, even tiny, or the over exposition of healthy tissues, could, in the future, trigger other cancer complications [48].

For each fluence map there may exist more than one decomposition matrix. For instance, considering the matrix (3.19), a possible decomposition is

$$\begin{pmatrix} 0&0&0&0&0&0&0&0&0\\ 0&1&1&1&1&1&1&0&0\\ 0&1&3&3&3&3&1&0&0\\ 0&1&3&6&6&3&1&1&0\\ 0&1&3&6&6&6&3&1&0\\ 0&1&3&6&6&3&1&1&0\\ 0&1&1&3&3&3&1&0&0\\ 0&0&1&1&1&1&1&0&0\\ 0&0&0&0&0&0&0&0&0 \end{pmatrix} = \begin{pmatrix} 0&0&0&0&0&0&0&0&0\\ 0&1&1&1&1&1&1&0&0\\ 0&1&1&1&1&1&1&0&0\\ 0&1&1&1&1&1&1&1&0\\ 0&1&1&1&1&1&1&1&0\\ 0&1&1&1&1&1&1&1&0\\ 0&1&1&1&1&1&1&0&0\\ 0&0&1&1&1&1&1&0&0\\ 0&0&0&0&0&0&0&0&0 \end{pmatrix} +$$

$$2 \times \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} + 3 \times \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{3.21}$$

where the overlaying radiation fields results in different MLC segments, which corresponds to the superimposition of the apertures represented in the Figure 3.2.

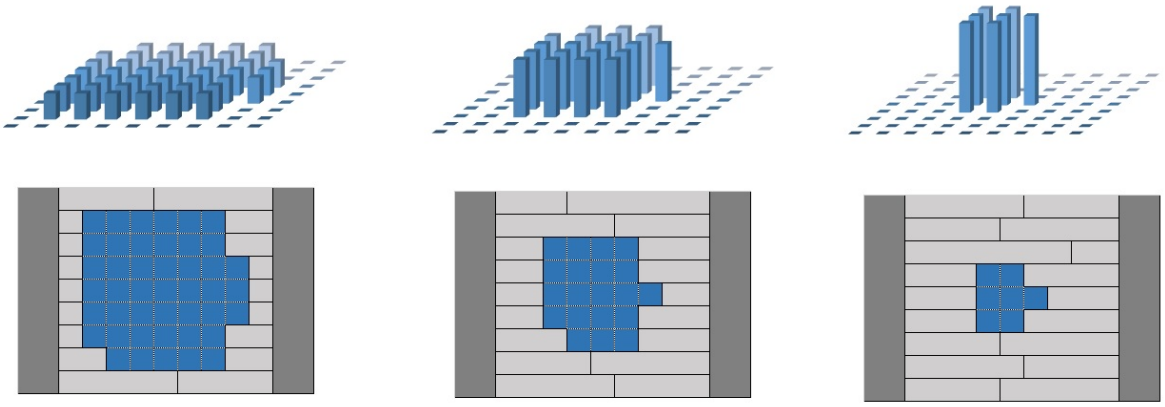

Figure 3.2: Sequence of intensities and apertures (MLC) of the decomposition of the fluence map of the Figure 3.1.

Although the resolution of this problem seems less complex, when compared with the BAO and FMO problems, in fact, there are also several issues that can increase its complexity, related with common objectives at hand, namely the minimization of the sum of the matrix weights, $\sum_{k=1}^{K} \mu_k$, by reducing the exposure time, and the minimization of the number of apertures, K, by reducing the number of times the beam is turned off during the treatment. This decomposition, based on the referred issues and objectives, may cause combinatorial and optimization problems, that can be divided in two types [36]:

Decomposition time (DT)
Represents the time a patient is exposed to radiation;

Decomposition cardinality (DC)
Represents the number of segments in the decomposition.

One can also aggregate both these problems, minimizing some weighted sum of decom-

position time and cardinality, such that the objective functions could be stated as

$$\sum_{k=1}^{K} \mu_k + \lambda K,$$

where $\lambda \in \mathbb{R}^+$. In the decomposition (3.21) one can consider three segments, *i.e.*, $K = 3$. Also, $\sum_{k=1}^{K} \mu_k = 6$, which is in fact the DT optimal.

The resolution of these two problems have different complexities. While the DT problem can be easily solved, and in fact its solution is found first, the DC problem could consume a large computational time, and it is typically solved with heuristic methods. Considering a certain set of decompositions with optimal DT, a formulation of the DC problem could be stated as

$$\begin{array}{ll} \min & K \\ \text{s.t.} & W = \sum_{k=1}^{K} \mu_k B^k, \\ & \sum_{k=1}^{K} \mu_k \quad \text{is minimal}, \\ & \mu_k \in \mathbb{N} \end{array} \tag{3.22}$$

where each output (μ, B) is an admissible segmentation pair. In the literature, there are many algorithms and techniques that can be used to solve the DT and DC problems ([27, 29, 48, 66]). None of the existing heuristics proved to be the best, so this is yet an interesting field of research. One of the techniques, called sweep, is to move the leaves always from one side to another, *e.g.*, left to right.

In certain cases, and due to physical constraints of the MLC device, a delivery plan for a given optimal fluence map may not be viable or executable. Thus, in those conditions, one can optimize the apertures and intensities, instead of the FMD problem after the FMO problem. One can also consider approaches where both problems are solved simultaneously, by integrating intensity optimization and delivery, many times solved by perform column generation procedures. In fact, there are also some authors that argue that the three problems in IMRT (BAO, FMO and FMD) should be tackled concomitantly. Due to other limitations, like leaf perturbation of adjacent beamlet intensities, the fluence map delivery could be slightly different from the optimal fluence map [37], related with "Perturbation Analysis", which represents also another field of research in this complex optimization problem.

Chapter 4

A Tabu Search approach to BAO

4.1 Tabu search

4.1.1 An introduction

Solving an optimization problem can be very complex, difficult and time consuming. Depending on the specificities of the problem, classical methods that aim at calculating the optimal solution can often take too long or be too expensive in terms of computation (memory usage, for instance). The main advantage of these so called exact optimization algorithms is the fact that they either calculate the optimal solution or, when this is not possible due to time or resources limitations, they are able to estimate how far is the current solution from the optimal one. In order to overcome these limitations, one can use heuristics or metaheuristics procedures. The objective of these techniques is to find a feasible solution, considered good enough given the circumstances, in a reasonable period of time [30]. Metaheuristics are considered as general optimization algorithms that can be easily applied to a wide range of problems, and are many times inspired by nature–based behaviors, as simulated annealing ([10]) and genetic algorithms ([44]). In this work we will focus on Tabu Search (TS). The choice of this metaheuristic is justified by the fact that it has proven to be able to find high quality solutions for complex problems and it is possible to control the number of objective function evaluations needed. As we are working with a computationally expensive objective function, this is an important feature (metaheuristics based on populations of solutions would not be advisable unless some surrogate models are used). See, for instance, ([21]). One of the main issues in complex combinatorial optimization problems is the possible existence of many local minima. Solving these problems using classical methods, like derivative–based methods, can be inappropriate, since they would easily get trapped into one of the many local minima. Using a metaheuristic, like TS, can have many benefits, directing the iterative search in a good direction and allowing the process to be influenced by other aspects beyond chance or the value of the objective function, according to the problem at hand [39].

Although some ideas behind TS can be traced back to 1960s, it is accepted that TS was firstly proposed in 1986 by F. Glover ([31]) and developed, among other contributions, by

the same author in 1989 ([32]) and 1990 ([33]). These articles represent the basis of TS and define the principles of this optimization procedure. Although TS was not well understood at the beginning, as other authors began to use this technique in different and complex optimization problems, the potential of TS became evident. The basic idea behind TS is to control a random walk in the space of feasible solutions of the optimization problem. TS can be defined as a local search procedure that uses memory, in the form of a tabu list, in order to control the random walk in the space of feasible solutions, guaranteeing that there are no cycles. Basically, TS begins with any solution to the problem (that becomes the current solution). It then searches the neighborhood of the current solution looking for a better one. To prevent the algorithm from cycling, a tabu list is maintained, that is nothing more than a list of forbidden search movements. The current solution is updated according to some criteria. The procedure continues until some termination criterion is met. In the next section we will describe in detail the most relevant concepts and components of TS.

4.1.2 Introductory concepts

Neighborhood

Let us assume that, and without loss of generality, a given combinatorial optimization problem can be formulated such as:

$$\min_{\theta \in \Theta} \quad f(\theta), \tag{4.1}$$

where θ is a feasible solution, $f(\theta)$ represents the objective function and Θ represents the entire discrete set of feasible solutions. Thus, we can define $N(\theta) \subset \Theta$ as the subset of the neighboring solutions of θ, according to a given criterion. Depending on the specificities of the optimization problem, and from a practical point of view, instead of considering the set $N(\theta)$, one can also consider the set of modifications or moves which can be induced on θ [30].

The set of solutions in the neighborhood of θ, $N(\theta)$, can be defined as the set of feasible solutions obtained by applying a move m to θ, such that $m \in M$, where M represents the set of all possible moves. This application can be formulated as $\theta \oplus m$ and one can define $N(\theta) = \{\theta' = \theta \oplus m, m \in M\}$ [30]. The choice of the search space and the neighborhood structure, according to the specificities of the optimization problem, is one of the most critical steps in the design of any TS procedure. For instance, let us assume that, for a given optimization problem, $\theta = \{1, 2, 3, 4\}$ is a feasible solution. One can define a structure of moves characterized by the modification of two elements in this permutation. This structure is represented in the Figure 4.1. One must note that not always, for a given problem, it is possible to construct a similar structure of permutations or even consider permutations in the set of solutions.

In TS, starting from a given solution, on one hand one must use a mechanism of evaluation of the solutions in the neighborhood and, on the other hand, one can also use *a*

priori knowledge regarding the given problem, in order to avoid that the procedure could get trapped in bad regions of the solution space [30].

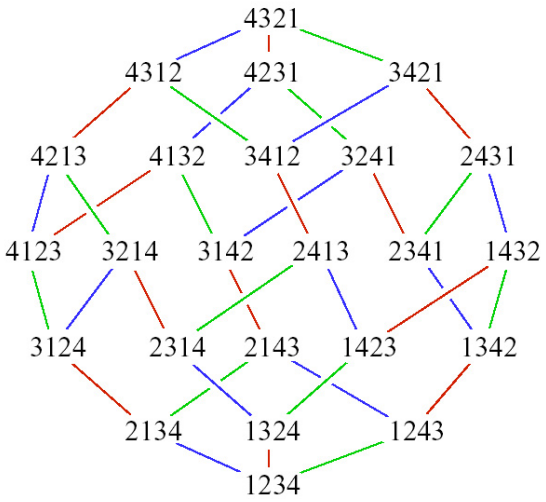

Figure 4.1: Possible permutations or moves, considering a given solution $\theta = \{1, 2, 3, 4\}$ [71]

Evaluation of the neighbor solutions

After defining the neighborhood set $N(\theta)$, one must evaluate the solutions $\theta \in N(\theta)$, using for instance, an objective function f. Thus, the purpose is to find the best or suitable solution $\theta^* \in N(\theta)$, such that the criterion could be $f(\theta^*) \leq f(\theta), \forall\theta \in N(\theta)$. This procedure is typical of local search optimization techniques and the main drawback is the possibility of the procedure being trapped in local minima, which may be far from a global minimum. In order to overcome this issue, TS allows the use of solutions that do not represent improvements to the objective function value. One can also consider other mechanisms in order to evaluate the neighborhood. For instance, one can define the finite difference $\Delta(\theta, m) = f(\theta \oplus m) - f(\theta)$. This expression could be considered equivalent to a numerical evaluation of the gradient, by means of a function defined by an algebraic expression in continuous optimization [30]. Considering a neighborhood based on moves and supposing that a move m' was applied, in the earlier iteration, to the solution θ, it could be possible to evaluate $\Delta(\theta \oplus m', m)$ for the current iteration as a function of $\Delta(\theta, m)$. In some optimization problems, these calculations can be very complex or even inappropriate. The calculation of $\Delta(\theta, m)$ cannot be accomplished by any eligible move and one must define the evaluation in other terms, using for instance the true value of $f(\theta)$ for a limited number of solutions [39].

One must note that, and depending on the dimension and specificities of the neighborhood, local search methods, including TS, do not necessarily evaluate all the solutions of $N(\theta)$. Moreover, one of the objectives in TS is to make a "smart" search, in order to

find the best or better solution from $N(\theta)$. It is common in TS to reduce the number of solutions in $N(\theta)$ to be considered at each iteration. Another approach that could diminish the dimension of $N(\theta)$, if the neighborhood is defined by a static set M of moves, is to consider partitions of M as subsets [23]. At each iteration only one subset will be evaluated. This approach can have some benefits, as the reduction of the computational time, but also could have some drawbacks, as a bad influence on the quality of the set of solutions produced.

Tabu lists

The tabu list is the feature that mainly distinguishes TS from other local search procedures. One of the main issues with these optimization techniques is related to the fact that the existence of non–improving moves increases the risk of cycling on a local minimum, *i.e.*, the search method will visit the same solution from time to time, what could lead to unsatisfactory results. In order to overcome this issue, TS uses memory to forbid moves which will lead to recently visited solutions. Thus, those forbidden moves are said to be tabus for the TS algorithms and a list of tabu movements is called a tabu list [39]. These tabu conditions are related to the set of moves M applicable for a solution.

In order to implement a tabu list in a TS algorithm one of the main concerns is associated with the dimension of the tabu list. Typically, and depending on the dimension and complexity of the optimization problem, the tabu list must have a modest size, in order to avoid being too restrictive, and should have *connectivity*, *i.e.*, from any solution one can reach an optimal solution. One also assumes that, initially, these tabu lists have the characteristic of *reversibility*, *i.e.*, when a move m is applied to a solution θ, there exists a move m^{-1} such that $(\theta \oplus m) \oplus m^{-1} = \theta$. Considering that it makes no sense to produce the move m^{-1} immediately after the move m, one can add limitations on the forward moves [30]. Thus, the idea is to avoid visiting the solutions θ and $\theta \oplus m$ repeatedly. If θ is already the local optimum, regarding a neighborhood $N(\theta)$, then θ will always be the best neighbor. By using this technique, prohibiting some moves during a given number of iterations can prevent cycles [23].

The tabu movements are stored in a *short–term memory*, the tabu list, and only a fixed and fractional part of information is recorded, depending on the specificities of the optimization problem. If all solutions were recorded, which would increase the size of the tabu list, then the process could require more storage space and one would need more computational time in each iteration, by checking if a certain move is or is not prohibited. Typically, efficient TS algorithms are based on the recording of the last few movements induced on the current solution and prohibiting reverse movements. On the other hand, tabu lists could also be based on certain specificities of the solutions, or moves, themselves [30].

When the number of tabu moves is too small, the algorithm will tend to visit the same solutions repeatedly. As the length of the list increases, the probability of visiting good solutions could also increase, due to the fact that the algorithm has a decreasing tendency to be confined to a small number of solutions. However, if the tabu list is too large,

according to the characteristics of the optimization problem, the probability of finding good solutions will also decrease, due to the lack of available moves. In this situation, the optimization process will be mainly directed by the allowed moves, instead of the objective or evaluation function [39]. One must note that in a single TS process, multiple tabu lists can be applied simultaneously. Another interesting use of tabu lists is related to the fact that this technique can be applied in order to move the search away from previously visited regions of the space search, allowing the exploration to be more extensive.

Usually, tabu moves are recorded in circular lists of fixed length. When a given tabu list is full, *i.e.*, the number of elements in the list corresponds to the length defined *a priori*, and another move must be considered tabu, the idea is to replace the "oldest" element in the list by the new one. One can also use another criterion or evaluation in order to choose the move to be replaced. Instead of using a fixed length for the tabu list, and because not always in these circumstances the cycling is prevented, one can also use a list with varied length during the search [30].

Aspiration criteria

Despite the fact that tabu lists are crucial to TS procedures, they can be too restrictive. Even when there is no risk of cycling, they can prohibit good solutions and lead to the stagnation of the process. Thus, and in order to avoid those situations, one can implement in the algorithm devices that will cancel the tabu status in some moves. These techniques are defined as *aspiration criteria* and the tabu status is said to be *aspired* [30]. The obvious aspiration criterion, used in most of the TS procedures, consists in allowing a given move if it represents a solution with a better evaluation than the current best–known solution, even if it has the tabu status. One can use another aspiration criteria, depending on the circumstances of the optimization problem. Aspiration can be seen as a *long–term memory* as it forces a given move never taken over many iterations. Typically, and when the risk of cycling can be controlled, the influence of tabu lists could be reduced or even disregarded [23].

Intensification and diversification

Facing the existence of regions with promising good results, one can orientate the TS procedures by using different techniques. One of the approaches, related to intensification search, could be to go back to the best solution found so far and then reduce the length of the tabu list, decreasing the number of iterations. Depending on the characteristics of the optimization problem, one can also divide the problem into subproblems, such that the combination of the partial solutions can lead to the optimal solution. *Long–term memory* can also be used in order to perform an intensification of the search. The idea behind this approach is to characterize each solution or move by a set of components, such that the components that represent good moves or solutions are memorized. In the intensification phase, the solutions or moves will be evaluated according to a given quantification of good components [30].

One of the issues of TS procedures, and depending on the specificities of the optimization problem, is the possibility of the existence of large regions that remain unexplored. In order to overcome this contingency, one may have to diversify the search. Perhaps the easiest way to perform diversity in a TS procedure is to consider several random restarts of the process. Another common approach is to penalize frequently performed moves or solutions that are often visited, by ensuring that the penalty is appropriated to escape from the current region, using a modified objective function for a certain number of iterations. When the optimization problems have constraints associated, one can relax these constraints and penalize their violation. These techniques can speedup the process of search into promising regions. In this diversification phase, it is possible that the solutions visited are not feasible, due to the relaxation of the constraints. In order to obtain feasible solutions one could increase the penalty for the violation of the constraints [30].

Termination criteria

Theoretically, a given TS procedure can go on forever. In practice, the search must end at some point and one must fix, *a priori*, a given stopping criterion. The most common is to define a fixed number of iterations or a fixed amount of computational time. Another common criterion is to fix a given number of iterations without any improvement in the objective function value and one can also use a threshold value according to the objective at hand. In complex optimization problems, TS procedures can be divided in several phases and one can use distinct criteria to stop each phase [39].

One must note that, in TS, one cannot speak about convergence. At each iteration, the solution could change and there are not any guarantees that by using this method one can find the global optimum. However, the application of TS in many complex optimization problems has produced interesting results, specially when other techniques or procedures failed or were unable of producing results considered good enough, according to the specificities and constraints of the problem.

Basic template for TS

According to the concepts referred previously, one can define a basic template for TS. Considering the optimization problem (4.1), where the objective is to minimize the function $f(\theta)$, and using the notation:

- Θ — Set of solutions
- θ — Current solution
- $N(\theta)$ — Neighborhood of θ
- $TabuList$ — Tabu list
- $\overline{N}(\theta)$ — Admissible subset of $N(\theta)$ (non–tabu or allowed by aspiration)

- θ^* — Best–known solution
- $f(\theta^*)$ — Evaluation of the best–known solution

one can describe the basic and generic template for a TS procedure [30]:

Initialization
Set $\theta^* \leftarrow \theta$, $f(\theta^*) \leftarrow f(\theta)$ and $TabuList \leftarrow \varnothing$

Search
While a termination criterion is not satisfied do
i) select $\theta \in \text{argmin}[f(\theta')]$, such that $\theta' \in \overline{N}(\theta)$,
ii) if $f(\theta) < f(\theta^*)$ then set $\theta^* \leftarrow \theta$ and $f(\theta^*) \leftarrow f(\theta)$,
iii) record tabu the current move in $TabuList$, deleting the oldest entry if necessary,
endwhile.

Regarding the basic template described previously, one must note that, given the optimization problem at hand, the TS algorithm can visit just some of the neighbor solutions $N(\theta)$, according to a given criteria. Also, depending on the characteristics of the problem, the current move, such that $f(\theta) < f(\theta^*)$, could not be added to the tabu list.

4.2 Tabu search for BAO

In this section we will describe in detail the TS implementation used to tackle the BAO problem. There are several features of the algorithm that have to be defined. One of the most important is the neighborhood structure that is going to be considered. It is also important to define the tabu list, and the way it is used and updated.

4.2.1 Neighborhood structure

A solution to the BAO is a set of n angles, each belonging to the interval $[0°, 360°[$. Considering a discretization $(0°, 1°, 2°, \ldots, 359°)$ of the referred interval in equally spaced directions, two solutions are considered neighbors if and only if they have at most k different angles.

Definition 1 *Consider θ an admissible solution to BAO. A solution θ' belongs to the k-neighborhood of θ if and only if θ and θ' have at most k different angles.*

In clinical practice it is considered that angles that differ by less than 5° are equivalents, because they are expected to produce similar results in terms of treatment. Based on this, we will consider that two angles are different only if they differ by more than 5°. Considering the time it takes to evaluate a given solution, and the number of solutions in a given neighborhood, it is clinically unviable to evaluate all of them and choose the best

one. This is why we have to randomly choose s neighbor solutions in each iteration of the algorithm.

The solutions that are visited are randomly generated by randomly choosing k angles that are also randomly perturbed using a uniform distribution within a given interval. We can refer to the z^{th} angle as being the angle in the z^{th} position and denote it as $angle(z)$, such that $z = 1, \ldots, n$. If a certain $angle(z)$ in a given solution is randomly chosen to be perturbed, then the algorithm will prohibit that angles in the range $([angle(z) - 5°, angle(z) + 5°])$ could be selected to belong to the next solution.

4.2.2 Tabu list

The tabu list summarizes the forbidden moves for each iteration of the algorithm implemented. In our neighborhood structure, a solution θ' will be a *k–neighbor* of θ if and only if θ' and θ differ by at most *k–angles*. A move is characterized by at most *k–random* perturbations, one for each of the k angles that will be changed. Thus, the tabu list will not store "moves" but will record the angles that were changed and the direction of the change (whether the angle was increased or decreased). A move will then originate up to k new records in the tabu list.

As angles that differ by less than 5° are considered equivalent, instead of storing the angle that was perturbed, the algorithm will store an interval that considers the angle ±5°. When a new neighbor solution is randomly being generated, for each angle that is randomly chosen to be perturbed, the tabu list is searched to see if the perturbation to be considered is allowed or not. If the angle to be perturbed belongs to one of the intervals stored in the tabu list and the direction of the change is the same, then the perturbation is considered forbidden and another angle is randomly chosen. To illustrate this situation, consider a solution with three angles $(1°, 80°, 220°)$. Imagine that angle 80° was chosen to be perturbed and that the random generated perturbation is +20°. This means that the following information will be stored in the tabu list: $[80° - 5°, 80° + 5°]$, "increase". If, in a posterior iteration, an angle belonging to the interval $[80° - 5°, 80° + 5°]$ was chosen to be increased, this would be considered as forbidden.

The tabu list implemented in our algorithm is reinitialized when a solution with a better evaluation than the current best–known solution is found and also when all the moves available are tabus, prohibiting the generation of new solutions. The size of the tabu list was defined as the double of the number of angles considered *a priori*. When the tabu list is full, and another move is considered tabu by the algorithm, the list is then initialized and the new move is added.

4.2.3 Aspiration criterion

Due to the fact that each solution is computationally expensive to evaluate, since it requires the fluence maps and radiation doses to be calculated, we choose to visit only solutions that are generated by allowed moves only. In this respect, we are not considering any aspiration criteria. Nevertheless, we have an elective move strategy, since the current

solution becomes the new solution for the next iteration only if it improves the objective function value.

4.2.4 Termination criterion

In order to terminate our algorithm we used a fixed number of iterations. This is mainly justified by the fact that it is crucial to have an upper limit to the number of objective function evaluations. When the procedure terminates, we will have the best solution found θ^*, that corresponds to a set of angles, the respective evaluation $f(\theta^*)$ and the fluence maps to be used in the treatment.

4.2.5 Global View

Algorithm 1 describes the TS implementation for BAO. In step 7 of the algorithm, the current solution is perturbed by randomly choosing an angle and changing this angle according to a uniform distribution over a defined interval. This interval considers the adjacent angles in the current solution. Considering that all angles are in ascending order, and all belong to $[0°, 360°[$, then the interval is defined as follows:

1. $[angle(1) + 10° - 360°, angle(2) - 10°]$, if $angle(z)$ to be perturbed is the first one $(z = 1)$;
2. $[angle(n-1) + 10°, angle(1) - 10° + 360°]$, if $angle(z)$ to be perturbed is the last one $(z = n)$;
3. $[angle(z-1) + 10°, angle(z+1) - 10°]$, in all other cases.

The *TabuList* will store perturbation p, as explained in section 4.2.2. The information that is stored considers whether the change was to increase or decrease the angle, and an interval of values that are considered equivalent to the angle that was changed ($[angle(z) - 5°, angle(z) + 5°]$). In this way, if in a posterior iteration we try to change the current solution by increasing/decreasing an angle belonging to the stored interval, this move will be considered forbidden.

$X_{new} \oplus m$ represents the change in solution X_{new}, by applying perturbation p, where p is characterized by the $angle(z)$ that is changed plus the width and the sign of the change. A move will be a sequence of at most k perturbations. For $k = 3$, for instance, it can be interpreted as $X_{new} \oplus m = (((X_{new} \oplus p) \oplus p) \oplus p)$.

Algorithm 1 TS applied to BAO.

Require: n — number of angles; k — number of angles to be changed in each iteration; s — number of solutions to be visited in each iteration; $maxiter$ — maximum number of iterations; X_{init} — initial solution (in our particular case $X_{init} = X_{equi}$).

Ensure: X_{best} — best solution known so far.

$X_1 \leftarrow X_{init}$; $TabuList \leftarrow \varnothing$; $X_{best} \leftarrow X_1$; $best \leftarrow f(X_{best})$; $iter \leftarrow 1$
while $(iter \leq maxiter)$ **do**
  $X_{best\_neighbor} \leftarrow X_{iter}$; $best\_neighbor \leftarrow f(X_{iter})$; $X_{new} \leftarrow X_{iter}$
  for $i = 1$ to s
  $j \leftarrow 1$
  while $(j \leq k)$ **do**
    Randomly select an $angle(z)$ and change this angle randomly using a uniform distribution over a defined interval (perturbation p)
    $change \leftarrow false$
    if $p \notin TabuList$ **then**
      $TabuList \leftarrow TabuList \cup \{p\}$
      $change = true$
      $X_{new} \leftarrow X_{new} \oplus p$
    end if
    if not $change$ **then**
      if $size(TabuList) \geq 2n$ **then**
        $TabuList \leftarrow \varnothing$
      end if
    else $j \leftarrow j + 1$
    end if
  end while
  if $f(X_{new}) < best\_neighbor$ **then**
    $X_{best\_neighbor} \leftarrow X_{new}$; $best\_neighbor \leftarrow f(X_{new})$
  end if
  end for
  if $f(X_{best\_neighbor}) < best$ **then**
    $X_{best} \leftarrow X_{best\_neighbor}$; $best \leftarrow best\_neighbor$; $X_{iter} \leftarrow X_{best}$
  end if
  $iter \leftarrow iter + 1$
end while

4.3 Models and formulations

We have chosen to apply TS considering two different modeling approaches: one model well known from the literature and a new approach considering a bilevel programming model. This latter approach will be described in section 4.3.1. The model already known from the literature is based on model (3.16):

$$\min_{w} \quad \sum_{i=1}^{N_v} \frac{1}{v_S} \left[\underline{\lambda}_i \left(T_i - \sum_{j=1}^{N_b} D_{ij} w_j \right)_+^2 + \overline{\lambda}_i \left(\sum_{j=1}^{N_b} D_{ij} w_j - T_i \right)_+^2 \right]$$

$$s.t. \qquad w_j \geq 0, \; j = 1, \ldots, N_b.$$

4.3.1 Bilevel programming

The motivation for using a bilevel programming (BP) model comes from the fact that we can interpret this as a problem where two different decision makers (OARs and PTVs) will have to make decisions that are interconnected, but each one of them will have different and conflicting objectives. Moreover, as there are two distinct but interconnected decisions that have to be made (beam angles and fluence intensities), we can think of this problem as having different decision makers controlling different decision variables. We can thus model this as a bilevel problem: in the upper level, beam angles are determined by one decision–maker (OARs or PTVs); in the lower level fluence intensities are optimized considering the angles fixed and determined by the upper level. Two different possibilities can arise:

- The decision maker in the upper level is the OARs. They will want to choose the angles that protect OARs the most. Nevertheless, the fluence intensities will then be calculated by the PTVs, that will want to receive as much radiation as possible;
- We could also think of having PTVs as decision makers in the upper level, choosing the angles that are most suited to irradiate them, and then having OARs choosing the intensities, that protect them the most.

In many real world situations, decisions are taken in a hierarchical way, such that the decisions that are made at upper levels of the hierarchy are mandatory to lower bounds, but the decisions made in lower levels influence the results obtained in upper levels. This hierarchical structure can be found in distinct areas, such as biology, transportation, game theory, environment, chemical engineering, network design, ecology, mechanics, taxation, classification theory, economics, databases, management, planning and optimal design [63].

Basic formulation

In optimization, a BP problem has a hierarchical structure with two distinct levels, in which the upper level is influenced by the lower level, *i.e.*, the subset of the variables

that is the solution of the lower level will be used in the evaluation of the upper level. Mathematically, a BP problem consists in finding the solution for the upper level problem:

$$\begin{aligned} \min_{x,y} \quad & F(x,y) \\ \text{s.t.} \quad & G(x,y) \leq 0, \end{aligned} \tag{4.2}$$

where y, for each value of x, is the solution of the lower level problem

$$\begin{aligned} \min_{x,y} \quad & f(x,y) \\ \text{s.t.} \quad & g(x,y) \leq 0, \end{aligned} \tag{4.3}$$

where $x \in \mathbb{R}^m$, $y \in \mathbb{R}^n$, $F : \mathbb{R}^{m+n} \to \mathbb{R}$, $f : \mathbb{R}^{m+n} \to \mathbb{R}$, $G : \mathbb{R}^{m+n} \to \mathbb{R}^p$ and $g : \mathbb{R}^{m+n} \to \mathbb{R}^q$[63]. The formulations (4.2) and (4.3) can be aggregated in a unique formulation, such that the BP model can be defined as

$$\begin{aligned} \min_{x \in X,\ y} \quad & F(x,y) \\ \text{s.t.} \quad & G(x,y) \leq 0 \\ & \\ & \min_{y} \quad f(x,y) \\ & \text{s.t.} \quad g(x,y) \leq 0, \end{aligned} \tag{4.4}$$

where $X \subseteq \mathbb{R}^m$[15]. According to (4.4), $F(x,y)$ and $f(x,y)$ are respectively the upper and lower levels objective functions and $G(x,y)$ and $g(x,y)$ are respectively the upper and lower levels constraints. One must notice that all the variables can be involved in both levels but each level controls different decision variables.

A common terminology used in a BP problem associates the term "leader" to the upper level and term "followers" to the lower level. This terminology was firstly related with the resolution of the problem of Stackelberg [15], an economic problem from the game theory. Let us consider an economic planning problem that evolves the relationship and interaction between two distinct agents that represent each referred level: the leader (a collective representation of some of the individuals) and the followers (the remaining individuals). In the formulation of this problem, the leader issues directives, according to his optimal strategy and in order to anticipate the reactions of the followers. In mathematical terms, the leader chooses a strategy $x \in X$, such that $X \subseteq \mathbb{R}^m$, and each follower i has a corresponding strategy set $Y_i(x) \subseteq \mathbb{R}^{n_i}$ [15].

Bilevel programming applied to IMRT

The objective function of the upper level can consider the irradiation of the PTVs (when the PTVs are the leaders), the irradiation of the OARs (when the OARs are the leaders), or have a more global view of the problem and consider both the irradiation of the OARs and PTVs. This latter approach can be interpreted as considering that the upper level cannot be totally selfish and has to incorporate in his decision the impact on the other

decision maker. After some random initial tests, we choose to perform the computational tests in a BP model that considers all the structures in the upper level and the OARs in the lower level. A basic formulation of this model is:

$$\min_{\theta} \quad \sum_{i \in S} \left[\underline{\lambda}_i \left(T_i - \sum_{j=1}^{N_b} D_{ij} w_j(\theta) \right)_+^2 + \overline{\lambda}_i \left(\sum_{j=1}^{N_b} D_{ij} w_j(\theta) - T_i \right)_+^2 \right]$$

$$\begin{aligned} s.t. \quad & \\ & \theta = (\theta_1, \ldots, \theta_n) \in \Theta^n \\ & \min_{w} \quad \sum_{i \in OAR} \left[\underline{\lambda}_i \left(T_i - \sum_{j=1}^{N_b} D_{ij} w_j \right)_+^2 + \overline{\lambda}_i \left(\sum_{j=1}^{N_b} D_{ij} w_j - T_i \right)_+^2 \right] \\ & s.t. \quad w_j \geq 0, \; j = 1, \ldots, N_b. \end{aligned} \tag{4.5}$$

where S represents the set of all structures considered.

Chapter 5

Computational tests and results

5.1 Computational tests

The formulations, models and algorithms presented in chapter 4 were tested using a set of 10 head–and–neck tumor patients already treated at the Portuguese Institute of Oncology at Coimbra. For each patient, the distinct structures considered in the treatment, the prescribed doses and the respective weights (models (3.16) and (4.5)) are represented in Table 5.1.

Table 5.1: Structures, doses and weights for the set of ten head–and–neck tumor patients.

Structures	**Mean dose**	**Maximum dose**	**Prescribed dose**	**Upper weights** ($\overline{\lambda}_i$)	**Lower weights** ($\underline{\lambda}_i$)
PTV1	-	-	70 Gy	4	4
PTV2	-	-	59.4 Gy	4	4
Left parotid	26 Gy	-	-	2	0
Right parotid	26 Gy	-	-	2	0
Spinal cord	-	45 Gy	-	2	0
Brainstem	-	54 Gy	-	2	0
Body	-	80 Gy	-	1	0

Although the shape and localization of the tumors are distinct, for all the patients the treatment planning considered two different types of cancerous structures, PTV1 and PTV2, each to be treated with a different dose of radiation. Yet, for some patients, the treatment planning also considered sub–structures in each referred PTV, to be treated with the same dose of radiation. The distinction between the mean and maximum doses in OARs is related to the organs specificity, namely being parallel or chain organs.

For each patient and each version of the TS algorithm, five runs were considered due to the random nature of the algorithm. The neighborhood structure considered was *1–neighborhood* ($k = 1$) and the algorithm only visited one solution in each iteration ($s = 1$).

The termination criterion used in our algorithm was the number of iterations (200). The algorithm was implemented in the program MATLAB® (version 7.12.0 R2011a). Software CERR was used in order to facilitate the visualization and analysis of the patients treatment planning data, and also for calculation of dosimetric data input for treatment plan optimization research. In CERR (version 4.4), we used the traditional dose computation available from the IMRTP module. The tests were performed on a 2.40 GHz Intel Core i7-3635QM CPU PC with 16.0 GB RAM.

5.2 Computational results

The analysis of the computational results of the tests performed for each patient will be based on a comparison between the use of an equidistant set of beam directions, commonly used in clinical practice to tackle the BAO problem, and the solution calculated by the TS algorithm.

Tables 5.2 and 5.3 depict the computational results obtained considering five executions of the TS procedure ($f_{TS\_i}, i = 1, \ldots, 5$). The improvement was calculated considering the relation between the mean objective function value (f_{TS_Mean}) in the five executions, using the TS procedure, and the objective function value using the equidistant set of angles (f_{equi}).

Table 5.2: Computational results applying the algorithm 1 and using the BP model (4.5).

Patient	f_{equi}	TS procedure						Improve. (%)
		f_{TS_1}	f_{TS_2}	f_{TS_3}	f_{TS_4}	f_{TS_5}	f_{TS_Mean}	
1	210.99	204.13	209.86	209.12	212.33	207.44	208.58	1.14%
2	78.31	79.16	79.60	77.67	82.18	81.61	80.04	−2.21%
3	134.20	141.70	142.74	143.93	150.04	150.99	145.88	−8.70%
4	169.11	194.07	189.28	179.44	188.75	180.20	186.35	−10.19%
5	338.45	382.95	313.46	363.60	368.95	366.30	359.05	−6.09%
6	277.69	296.91	333.18	277.78	293.47	307.56	301.78	−8.68%
7	39.48	46.97	39.59	47.70	40.69	48.50	44.69	−13.20%
8	177.04	173.52	185.85	173.28	174.49	194.81	180.39	−1.89%
9	135.70	153.37	197.70	152.43	190.79	155.09	169.88	−25.19%
10	195.98	202.59	212.36	223.15	207.88	210.90	211.38	−7.86 %

Table 5.2 shows the results obtained when the BP model was used. Although for some of the five executions performed for each patient, using the TS procedure, the algorithms returned a value of the objective function value lower than the objective function value using a set of equidistant angles, the results are in general not good. Our objective was to find a model that systematically produces better results than using the equidistant set of beam angles in the BAO problem. These results can be explained by an incorrect choice of the structures related to each level. Moreover, it is possible that the TS procedure is

inappropriate to solve this BP model. Although the results fell short of expectations, the concept behind the BP model makes sense and it could be worthy to try new approaches, using perhaps other procedures than the TS to tackle the BAO problem.

Table 5.3 shows the results obtained when using model (3.16). For all the executions of the algorithm implemented in each patient, the TS procedure produced better solutions when compared to the results obtained by the use of an equidistant set of beam directions. Also, this model lead to the achievement of better results than the ones produced by the BP model for all the computational tests performed.

Table 5.3: Computational results applying the algorithm 1 and using the model (3.16).

Patient	f_{equi}	TS procedure						Improve. (%)
		f_{TS_1}	f_{TS_2}	f_{TS_3}	f_{TS_4}	f_{TS_5}	f_{TS_Mean}	
1	210.99	200.80	199.80	201.86	199.0	199.92	200.28	5.07%
2	78.31	74.62	74.27	74.21	75.03	73.97	74.42	4.97%
3	134.20	130.63	127.89	128.80	129.12	128.10	128.91	3.94%
4	169.11	161.35	159.33	162.92	161.70	161.14	161.29	4.63%
5	338.45	304.36	308.47	306.94	306.55	304.79	306.22	9.52%
6	277.69	257.67	254.32	259.90	259.26	256.83	257.60	7.24%
7	39.48	38.65	38.81	35.64	37.61	38.65	37.87	4.07%
8	177.04	163.86	158.97	168.48	164.24	163.36	163.78	7.49%
9	135.70	122.86	122.30	121.58	120.46	122.18	121.88	10.19%
10	195.98	193.98	193.84	193.13	193.93	194.11	193.80	1.11 %

According to the tests performed, considering all patients, the use of the TS procedure in the global model (3.16) represented an improvement that varies from 1.12% up to 10.18%, when compared to the use of an equidistant set of angles. In general, and for the tests performed, this implementation represented an average improvement of about 6%. In head–and–neck cases, for instance, this improvement may lead to better parotid gland sparing. The parotid, which has bilateral structure, is the major salivary gland and secretes saliva to the oral cavity. The bad functioning of this gland affects negatively the quality of life of the patients, namely in the feeding process.

Besides the evaluation of the objective function of the model (3.16), there are also other different metrics that can be used in order to perceive the quality of the treatments. Table 5.4 depicts, for each patient, the computational results regarding targets coverage, considering the best (TS_{best}) and worst (TS_{worst}) executions from the TS procedure, as also the evaluation using the equidistant set of angles (*equi*). For both PTVs, Table 5.4 shows the volume of the referred structures that receive 95% of the prescribed dose. Typically, in clinical practice, this threshold of the PTV volume is required. The existence of coldspots can be perceived when less than 93% of the PTV volume receives the prescribed dose and the occurrence of hotspots can be noticed by the percentage of the PTV volume that receives more than 110% of the prescribed dose. Globally, one can verify that the use of the TS procedure enables the achievement of treatment plans, namely for the TS_{best}, with

slightly better target coverage, when compared to the ones obtained using an equidistant set of angles.

Table 5.4: Target coverage obtained by treatment plans applying the algorithm 1 and using the model (3.16).

Patient	Target coverage	TS_{best}	TS_{worst}	*equi*
1	PTV1 at 95 % volume	65.93 Gy	65.70 Gy	66.28 Gy
	PTV1 % > 93% of Rx (%)	97.34	97.41	97.09
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	57.53 Gy	57.30 Gy	57.93 Gy
	PTV2 % > 93% of Rx (%)	97.12	97.34	96.43
	PTV2 % > 110% of Rx (%)	28.78	28.69	28.96
2	PTV1 at 95 % volume	66.23 Gy	67.10 Gy	67.30 Gy
	PTV1 % > 93% of Rx (%)	99.53	99.39	99.53
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	54.53 Gy	55.90 Gy	55.90 Gy
	PTV2 % > 93% of Rx (%)	96.08	95.88	95.69
	PTV2 % > 110% of Rx (%)	5.89	6.05	6.27
3	PTV1 at 95 % volume	66.33 Gy	65.70 Gy	65.50 Gy
	PTV1 % > 93% of Rx (%)	97.70	97.44	96.34
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	56.63 Gy	56.90 Gy	55.70 Gy
	PTV2 % > 93% of Rx (%)	97.21	96.81	95.45
	PTV2 % > 110% of Rx (%)	25.74	25.78	25.80
4	PTV1 at 95 % volume	65.35 Gy	66.58 Gy	65.19 Gy
	PTV1 % > 93% of Rx (%)	95.50	94.90	94.53
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	55.50 Gy	53.83 Gy	55.50 Gy
	PTV2 % > 93% of Rx (%)	95.43	95.05	95.37
	PTV2 % > 110% of Rx (%)	19.49	19.72	19.88
5	PTV1 at 95 % volume	67.13 Gy	67.13 Gy	67.18 Gy
	PTV1 % > 93% of Rx (%)	98.87	98.79	99.78
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	56.93 Gy	56.93 Gy	56.63 Gy
	PTV2 % > 93% of Rx (%)	95.01	94.80	94.39
	PTV2 % > 110% of Rx (%)	12.44	12.54	12.70
6	PTV1 at 95 % volume	66.13 Gy	64.90 Gy	65.88 Gy
	PTV1 % > 93% of Rx (%)	94.68	94.66	93.86
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	58.01 Gy	57.27 Gy	58.07 Gy

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Table 5.4 – *Continued from previous page*

Patient	Target coverage	TS_{best}	TS_{worst}	*equi*
	PTV2 % > 93% of Rx (%)	97.92	97.73	97.44
	PTV2 % > 110% of Rx (%)	22.87	23.09	22.78
7	PTV1 at 95 % volume	68.58 Gy	67.10 Gy	68.33 Gy
	PTV1 % > 93% of Rx (%)	99.42	98.99	99.32
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	67.83 Gy	67.10 Gy	66.68 Gy
	PTV2 % > 93% of Rx (%)	98.09	98.07	97.95
	PTV2 % > 110% of Rx (%)	4.51	4.72	4.61
8	PTV1 at 95 % volume	67.50 Gy	66.70 Gy	67.10 Gy
	PTV1 % > 93% of Rx (%)	99.15	98.16	98.46
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	56.72 Gy	56.43 Gy	56.24 Gy
	PTV2 % > 93% of Rx (%)	97.11	96.67	96.46
	PTV2 % > 110% of Rx (%)	12.01	12.21	12.37
9	PTV1 at 95 % volume	66.70 Gy	66.70 Gy	66.50 Gy
	PTV1 % > 93% of Rx (%)	99.13	99.31	98.62
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	57.70 Gy	57.50 Gy	57.50 Gy
	PTV2 % > 93% of Rx (%)	98.12	97.72	97.75
	PTV2 % > 110% of Rx (%)	13.07	13.19	13.12
10	PTV1 at 95 % volume	65.90 Gy	65.90 Gy	66.30 Gy
	PTV1 % > 93% of Rx (%)	96.86	97.17	97.79
	PTV1 % > 110% of Rx (%)	0.00	0.00	0.00
	PTV2 at 95 % volume	57.30 Gy	57.30 Gy	57.10 Gy
	PTV2 % > 93% of Rx (%)	97.55	97.43	97.18
	PTV2 % > 110% of Rx (%)	17.50	17.78	17.97

Table 5.5 shows the results regarding the OARs sparing. For most of the treatment plans, the maximum dose requirements are fulfilled for the spinal cord and the brainsteam. Only for patients 2 and 8 these thresholds are slightly exceeded, whatever the approach considered (*TS or equi*). In order to overcome this issue, the treatment planner could have to change the treatment plan, namely the penalty weights associated with the referred structures, and repeat the process until the medical prescription is fulfilled. Also, globally, the TS procedure enables treatment plans with an improvement of about 5% concerning the parotid's mean dose, considering the comparison between the approaches TS_{best} and *equi*. Thus, the results displayed in Table 5.5 confirm the benefits of using the TS procedure in order to tackle the BAO problem.

Table 5.5: OARs sparing obtained by treatment plans applying the algorithm 1 and using the model (3.16).

Patient	OAR	Mean Dose (Gy)			Max Dose (Gy)		
		TS_{best}	TS_{worst}	*equi*	TS_{best}	TS_{worst}	*equi*
1	Spinal cord	–	–	–	39.39	38.79	42.10
	Brainstem	–	–	–	51.03	51.86	51.45
	Left parotid	22.89	24.99	26.50	–	–	–
	Right parotid	23.29	25.36	25.81	–	–	–
2	Spinal cord	–	–	–	47.58	48.60	48.99
	Brainstem	–	–	–	55.11	55.67	55.36
	Left parotid	25.89	26.02	26.97	–	–	–
	Right parotid	26.07	26.02	27.84	–	–	–
3	Spinal cord	–	–	–	40.82	38.87	42.97
	Brainstem	–	–	–	44.44	41.78	43.87
	Left parotid	26.72	25.89	25.70	–	–	–
	Right parotid	24.68	25.78	26.27	–	–	–
4	Spinal cord	–	–	–	39.85	42.76	41.66
	Brainstem	–	–	–	48.08	48.35	51.26
	Left parotid	26.93	26.82	28.14	–	–	–
	Right parotid	28.44	27.86	28.87	–	–	–
5	Spinal cord	–	–	–	39.11	40.00	38.70
	Brainstem	–	–	–	51.18	51.59	50.35
	Left parotid	24.90	23.79	23.69	–	–	–
	Right parotid	29.28	29.80	28.97	–	–	–
6	Spinal cord	–	–	–	41.19	40.54	41.19
	Brainstem	–	–	–	53.27	53.13	53.93
	Left parotid	22.46	24.14	24.35	–	–	–
	Right parotid	20.93	23.06	23.73	–	–	–
7	Spinal cord	–	–	–	40.13	39.44	43.20
	Brainstem	–	–	–	51.26	51.81	52.03
	Left parotid	23.18	26.09	27.44	–	–	–
	Right parotid	28.25	26.15	27.49	–	–	–
8	Spinal cord	–	–	–	38.13	38.60	39.36
	Brainstem	–	–	–	55.20	53.06	54.77
	Left parotid	25.41	26.35	25.48	–	–	–
	Right parotid	26.27	26.45	26.48	–	–	–
9	Spinal cord	–	–	–	40.70	42.02	41.62
	Brainstem	–	–	–	51.81	49.87	47.97
	Left parotid	24.82	23.31	26.23	–	–	–
	Right parotid	20.94	23.09	25.67	–	–	–

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Table 5.5 – *Continued from previous page*

Patient	OAR	Mean Dose (Gy)			Max Dose (Gy)		
		TS_{best}	TS_{worst}	*equi*	TS_{best}	TS_{worst}	*equi*
10	Spinal cord	–	–	–	40.48	40.45	38.81
	Brainstem	–	–	–	50.03	49.72	51.70
	Left parotid	25.14	24.99	26.42	–	–	–
	Right parotid	25.94	25.62	25.89	–	–	–

Figures 5.1 and 5.2 show the results, over all ten patients, for the dose received by PTVs. The line represents the minimum dose desired, so we would like all values to be above these lines. We can conclude that TS solutions are better for most patients. Figures 5.3 to 5.6 consider OARs. In these figures, we would like all values to be under the depicted lines, that represent the upper bound allowed for each of the structures. The bounds are satisfied for most patients regarding brainstem and spinal cord. Parotid's sparing is much more difficult due to the relative position of the PTVs regarding to these OARs. It is also possible to observe that, for most patients, parotid's sparing is improved by using TS calculated solutions.

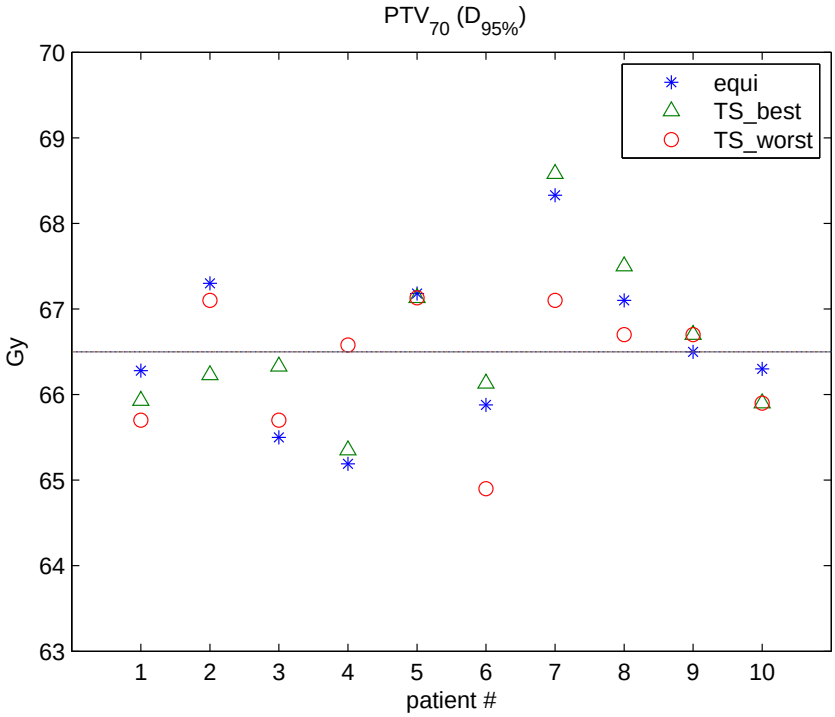

Figure 5.1: Dose plot for the PTV1, considering the information on Table 5.4.

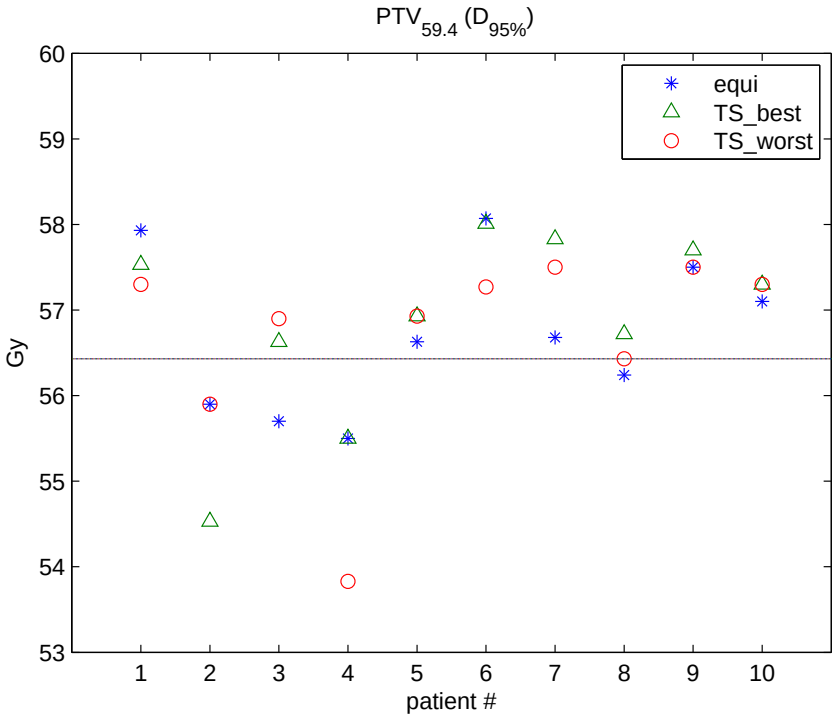

Figure 5.2: Dose plot for the PTV2, considering the information on Table 5.4.

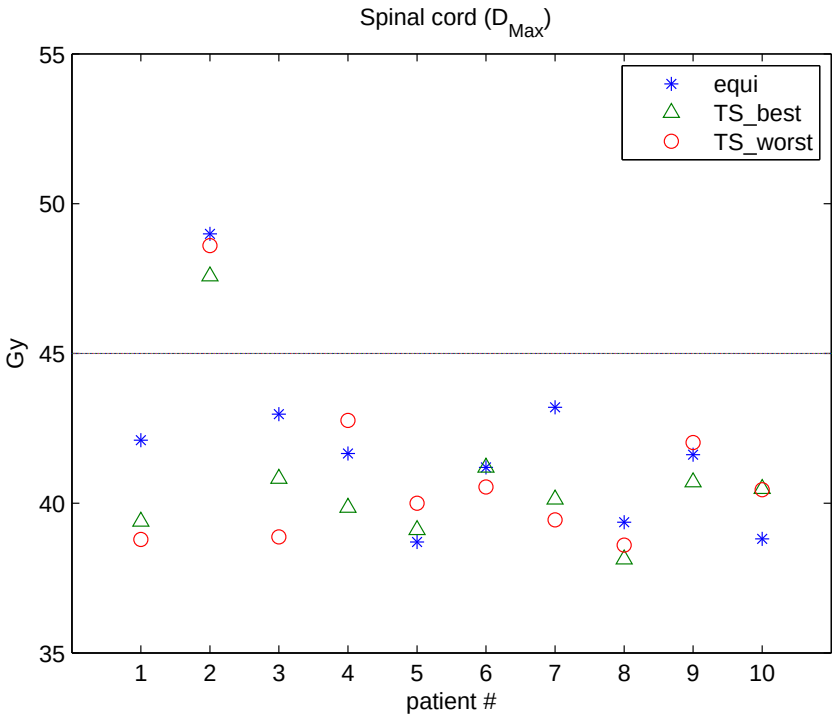

Figure 5.3: Dose plot for the spinal cord, considering the information on Table 5.5.

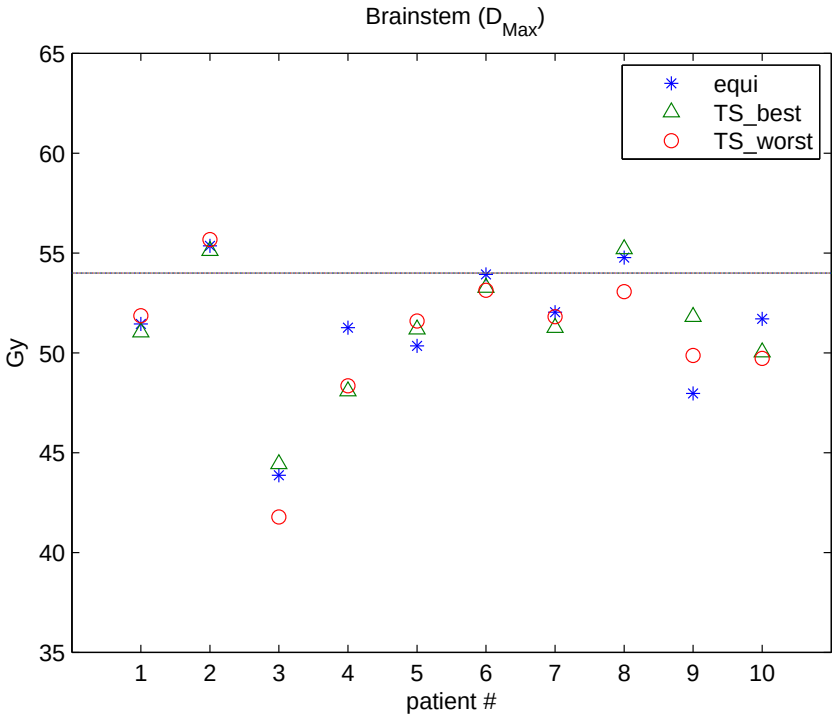

Figure 5.4: Dose plot for the brainstem, considering the information on Table 5.5.

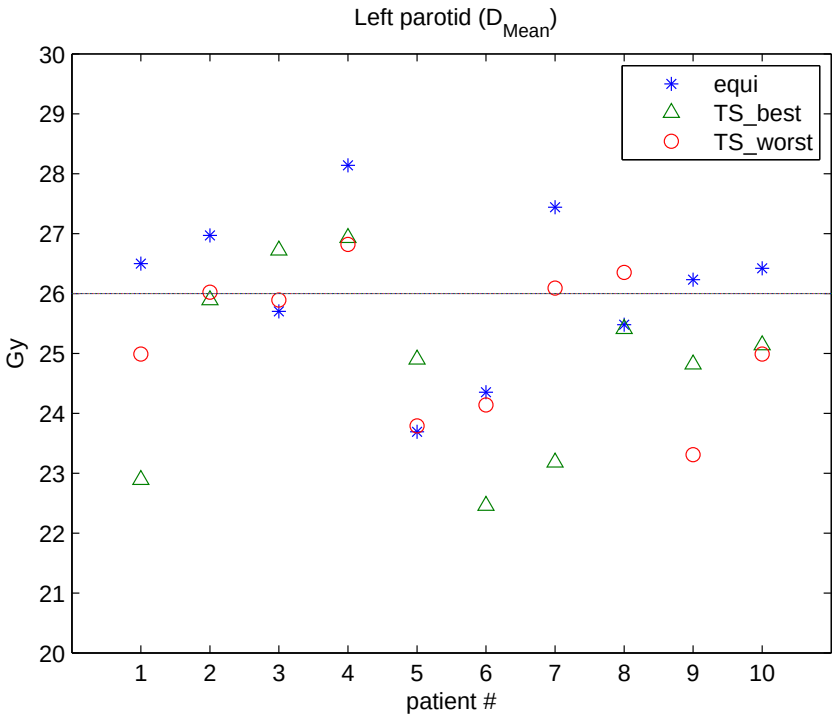

Figure 5.5: Dose plot for the left parotid, considering the information on Table 5.5.

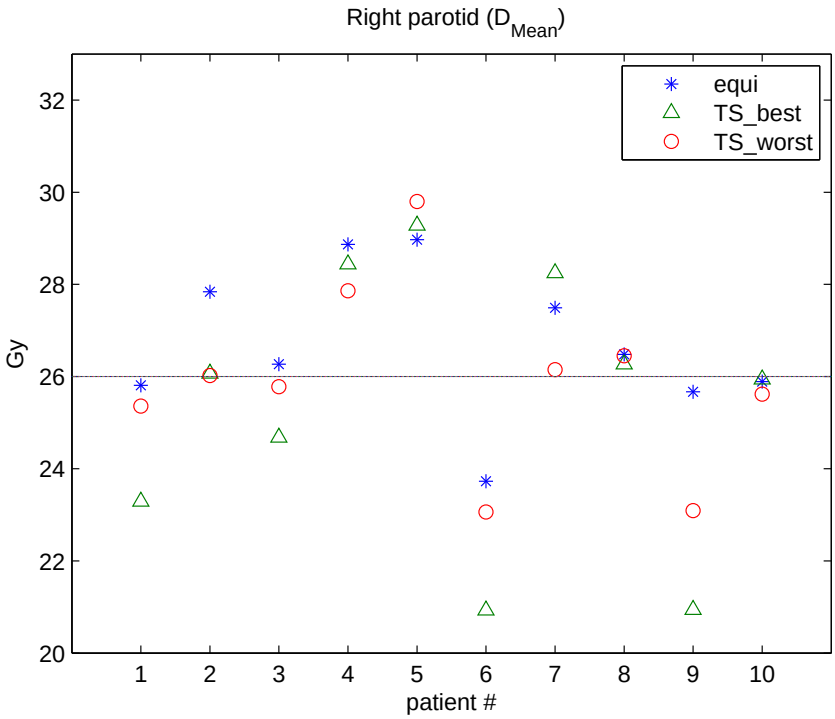

Figure 5.6: Dose plot for the right parotid, considering the information on Table 5.5.

Chapter 6

Conclusions

6.1 Synthesis

OR applied to radiation therapy is a vast, complex and challenging multidisciplinary area. IMRT can be considered an example where the conjugate work of physicists, mathematicians and computer scientists can produce a major impact on medicine, namely in the daily clinical practice in radiation therapy. Each improvement leads to better treatment plans, increasing the quality of the process and affecting positively the life of the patients. In IMRT, the BAO represents a continuous global highly non–convex optimization problem. In clinical practice, given the complexity involved and the need to find a good solution in a limited period of time, it is common to use the set of equidistant angles to tackle the problem. Any improvement, namely in terms of the total dose of radiation received by the patient, could have an impact on the quality of the treatment, with better organ sparing and target coverage, which benefits the quality of life of the patients.

Globally, the tests performed using the TS procedure allowed the achievement of better results, with a global and average improvement of the objetive function value of about 6%, when compared to the use of an equidistant set of angles in the BAO problem, commonly used in clinical practice. According to the tests performed, one can consider that this technique produced consistent results and its implementation in clinical practice can improve the quality of the treatments, namely in the parotid sparing, and, therefore, the quality of life of the patients. The BP model results are in general not good but the idea behind the model makes sense. So, other optimization strategies should be applied.

As far as the authors know, the TS approach to BAO as also the IMRT modeling with the BP model are original and have not yet been considered in the literature. Thus this dissertation contains original scientific work.

6.2 Future work

Optimization applied to IMRT is an active and challenging area of research and development, where each improvement could have the potential to increase the quality of the

treatments and lead to further relevant clinical improvements, with the reduction of side effects of radiation and better tumor control, which leads to the increase of the quality of life of the patients.

Although our implementation of the BP model in IMRT, according to the computational tests performed, did not produce good results, this fact do not derail the possibility that the implementation of this model in a different radiation therapy treatment modality could produce good results, namely in 3D–CRT. Our tests showed that the TS procedure, implemented in a global optimization model, represents a good option in order to tackle the BAO problem. In our work, we will continue to address this problem with the TS procedure, trying different parameters' settings and different definitions of tabu lists. One of the possible approaches considers changing the neighborhood settings. This modification can diversify the search and guide the algorithm into promising and unexplored regions of solutions. One can also change the size of the tabu list, implement other restrictions and change the termination criterion, considering always the limited period of time in which this optimization problem should be solved. One can also consider forbidden the solutions that have angles in opposed positions.

In future work, the TS procedure can also be applied with distinct objective functions, in another model among those presented in this dissertation (linear, nonlinear, mixed integer or multiobjective models) according to the objectives at hand.

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