Multicriteria Optimization for Radiotherapy

Multicriteria optimalisatie voor radiotherapie

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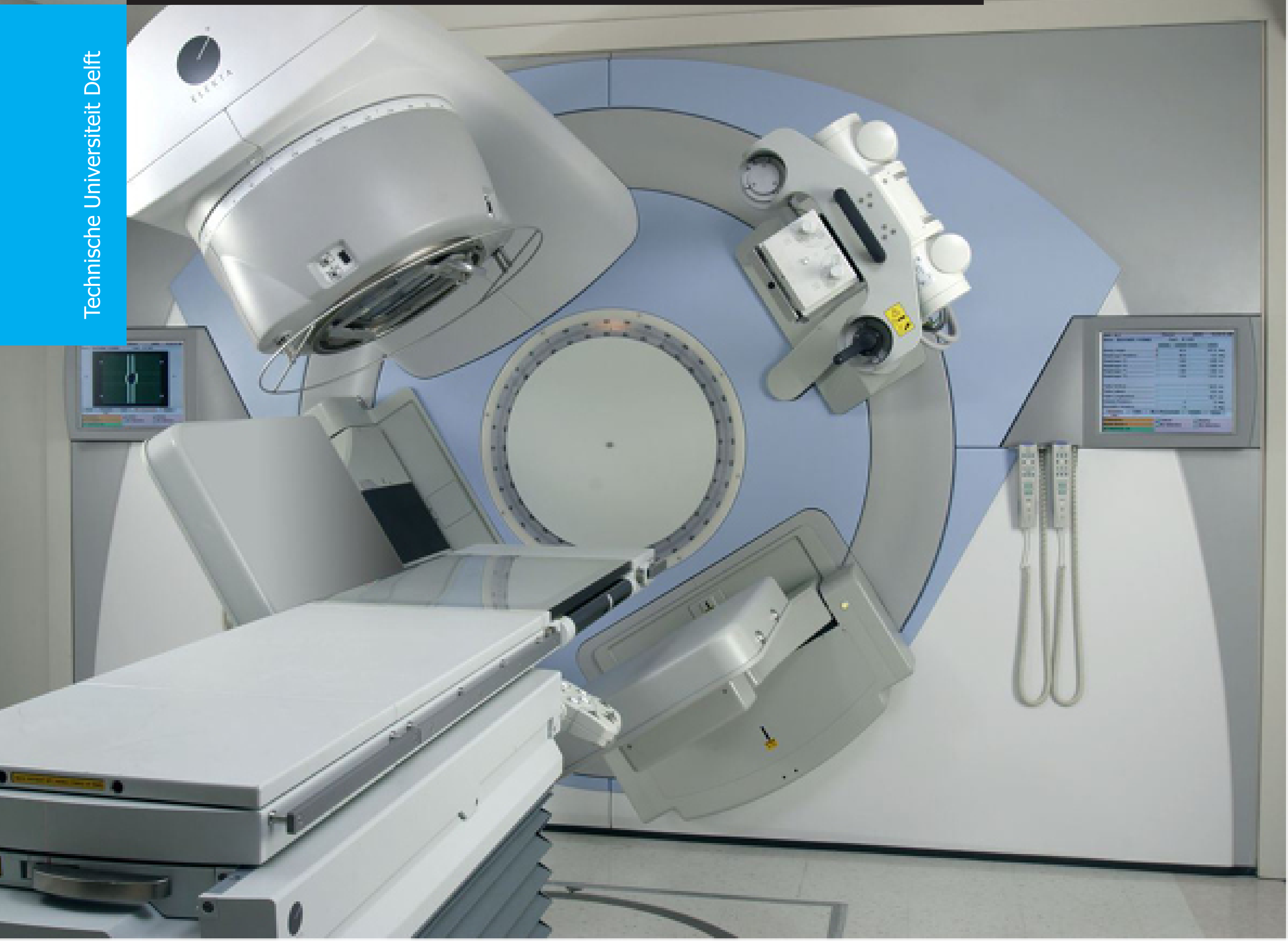

TU Delft

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Multicriteria Optimization for Radiotherapy

Multicriteria optimalisatie voor radiotherapie

by

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Summary

Radiotherapy is one of the main treatments for cancer, and a multi-disciplinary field of research, mostly involving medicine, physics and mathematics. The focus of this thesis lies in improvements for the treatment planning, which is a multi-criteria process. We have been constructing a new method to form the Pareto front for certain objectives. For a Pareto optimal plan one objective cannot be improved without worsening another objective.

The main question is with which plan the patient should be treated. To compare treatments we have developed a new method to look at other optimal solutions on the Pareto front around a given solution. This is done by quickly using of the reference point method. The main advantage is that, when a clinical isn't pleased enough with a certain objective in a given solution, it is possible the optimize that objective some more.

Preface

For my Bachelor project I had an internship at the Erasmus Medical Center in Rotterdam. The research project took place at the Daniel den Hoed Cancer Center of the Erasmus Medical Center in collaboration with the Delft Institute of Applied Mathematics of the TU Delft.

This report contains an overview of the subject radiotherapy as well as the research done during the internship and the results of this project. I would like to thank the following people. Marleen Keijzer, my supervisor from the TU Delft, for bringing me in contact with the Erasmus Medical Center and advice. Rens van Haveren and Sebastiaan Breedveld, for their help and support during the internship at the Daniel Den Hoed Cancer Center.

I learned a lot about how mathematics is applied in radiotherapy and I really enjoyed working at the Daniel den Hoed Cancer Center.

Larissa Scholte
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Contents

1
Introduction

There are different cancer treatments, such as surgery, chemotherapy and radiation therapy. Approximately half of the patients diagnosed with cancer is treated with radiation therapy. Radiation therapy is a treatment that makes use of ionizing radiation. The radiation injures or destroys cells in the area being treated by damaging their genetic material, making it impossible for these cells to continue to grow and divide.

Radiation damages both cancer cells and normal cells, although most normal cells can recover from the effects of radiation. The goal is to destroy the tumour, while saving the healthy tissues as much as possible. Hence, it is given in many fractions, allowing healthy tissue to recover between fractions.

Different mathematical problems show up in optimizing the treatment plan. For a treatment, the accelerator is rotated around the patient and the leaf placement in the multileaf collimator (MLC) is adjusted such that the beams overlap at the tumour to maximize the radiation delivered to the tumour and minimize the dose to the surroundings. So one must know the directions from which to irradiate. In addition to knowing the beam angles, one must also know the intensity of the beams at each point. Optimizing the intensity profiles is a multi-criteria problem, i.e. there are several treatment objectives which have to be taken into account.

We will focus on methods of computing the intensity of the irradiation, such that the tumour receives the prescribed dose and the healthy structures receive as little as possible. This is done by first calculating an optimal solution by the ϵ-constraint method introduced by Sebastiaan Breedveld (Breedveld, 2013).

The main focus of this thesis is to obtain a new method to generate the Pareto front near the solution derived by the ϵ-constraint method. At this moment the methods that are used to look for solutions near a given solution are very time-consuming. The goal is to derive a new method, which uses the reference point method, such that it takes less time to compute the Pareto front. The idea behind this is that we can compare different treatments plans.

In Chapter 2 we will give an overview of the subject radiotherapy. In Chapter 3 we will introduce the concept of multi-criteria optimization and present two optimization methods, namely the 2-phase ϵ-constraint method and the multiple reference point method. This latter method is the main focus of this project. In Chapter 4 we will give an example of how the multiple reference method works in two-dimensional space. Next, we will show how we used the reference point method to generate the Pareto front for two objectives (Chapter 5) and three objectives (Chapter 6). Then we will show in Chapter 7 how the method is applied on a realistic patient. Finally, Chapter 8 and Chapter 9 conclude this report.

2

Radiotherapy

Radiation therapy, or radiotherapy in short, is a medical treatment for cancer that kills tumour cells by means of ionizing radiation. The main delivery techniques are external beam therapy, where the patient is irradiated by external sources. The goal of the treatment is to destroy the tumour, while saving the healthy tissues as much as possible. The absorbed dose in surrounding tissues should thus be minimized in order to reduce damage to healthy organs.

2.0.1. Treatment

Cancer patients can be treated with radiation therapy with the intention to cure and for palliative care, where the goal is to reduce suffering caused by cancer. Radiation therapy is also commonly used as a complementary treatment for patients who undergo chemotherapy or surgery. Advantages of radiation therapy include that the treatment is non-invasive, potentially organ preserving, and that systemic side effects are generally avoided, because only a part of the body is irradiated.

Improving the treatment plans is one of the ways to achieve a small chance on complications. To avoid treatment complications as much as possible, it is important to construct a treatment plan which gives enough dose to the tumour and minimizes the dose to the surrounding healthy structures. Examples of side effects are pneunomitis when a tumour in the lung has been irradiated or reduced saliva production when the patient has a tumour in the head-and-neck area. Another risk is development of secondary cancer caused by the ionizing radiation.

Because each patient is anatomically unique, a personal treatment plan is generated. A treatment plan contains information on how the dose, and consequently the probability of physical damage from irradiation is distributed inside the patient. Prior to a treatment, a treatment plan for each patient is made by making a CT-scan of the patient. The CT-scan produces cross-sectional X-ray slices that can be processed into a three-dimensional volume image of the patient volume. The tumour, also called the target volume, and the organs-at-risk (OARs) are delineated by a physican. After this a personal treatment plan can be made. Sometimes to localize the tumour a MRI, PET or SPECT scan are required as well. In Figure 2.1 we can see an example of delineated CT-slices of the head-and-neck area in the axial (upper-left), sagittal (upper-right) and coronal (bottom-left) view.

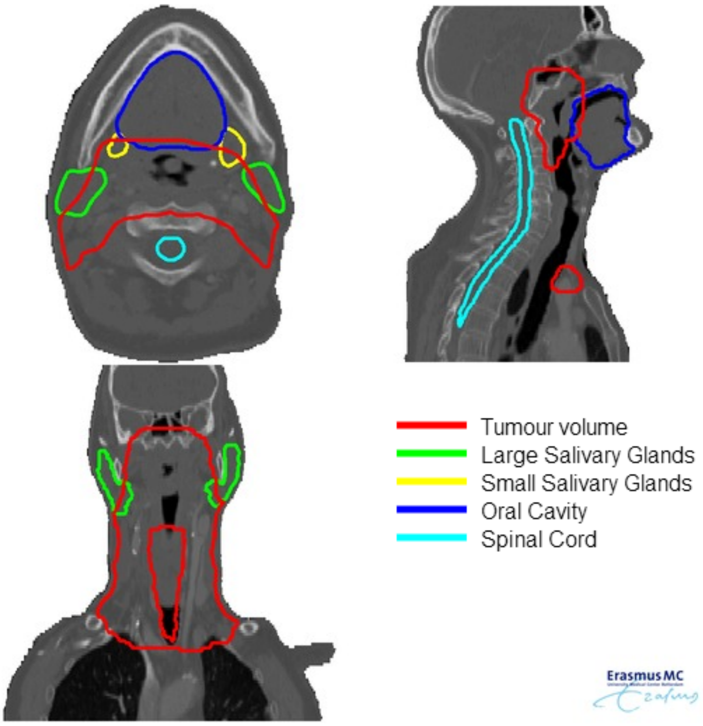

Figure 2.1: Example of a delineated CT-scan.

Ionizing radiation damages the cellular DNA and thereby stops the cell division of the radiated cells. Since healthy cells can recover faster than the tumour cells, the patient receives the radiation dose in multiple fractions, approximately 20 fractions on average. The treatment fractions are delivered with daily intervals, which is a time-scale that permits the healthy cells to recover from the effects of the irradiation.

Radiation therapy can be given by using an external radiation source: 'external beam radiation therapy' (EBRT). The most common medical device for external beam radiation therapy is a linear accelerator whose beam rotates through a gantry around the patient, emitting beams of X-rays (see Figure 2.2). The field shape is determined by a multileaf collimator (MLC) which is attached to the gantry. Its adjustable heavy-metal acts as a filter, blocking or allowing radiation through, in order to tailor the beam shape to the shape of the tumour.

Figure 2.2: Lineair accelerator whose beam can rotate

2.0.2. Treatment planning

Different mathematical problems show up in optimizing the treatment plan. During treatment the accelerator is rotated around the patient and the leaf placement in the MLC is adjusted such that the beams overlap at the tumour. So one must know the directions from which to irradiate. In addition to knowing the beam angles, one must also know the intensity of the beams at each point.

The main parameters that need to be determined during treatment planning are the number of radiation fields, their orientations, and the intensity of the beams. Optimizing the intensity profiles is a multi-criteria problem, i.e. there are several treatment objectives which have to be taken into account.

In Figure 2.3 a dose distribution for the example in Figure 2.1 inside the patient is shown. Red indicates high-dose areas (high damage) and blue low-dose (less damage). The ultimate aim is to colour only the red contour, the tumour.

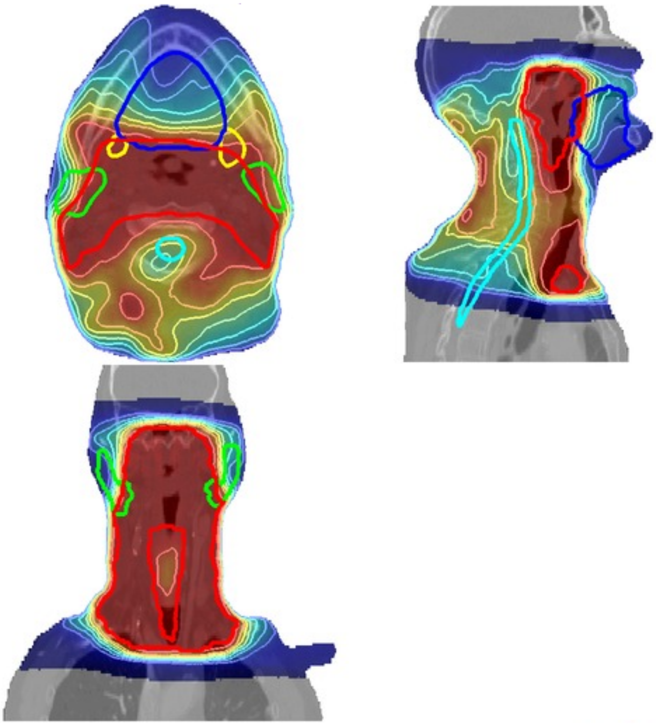

Figure 2.3: Effect of a specified dose to a patient.

The patient geometry is for optimization purposes divided into volume elements called voxels, and the beam planes are divided into surface elements called bixels. The corresponding minimization problem will be discussed in Section 3.1. The treatment planning problem is assumed to be solved only once and the optimized treatment plan is then kept identical during all treatment fractions. Beam orientation optimization and adaptive replanning are not discussed in this thesis.

3

Multicriteria optimization

3.1. Basic Concepts

A general multicriteria optimization problem consist of optimizing a set of $k \geq 2$ objective (or criterion) functions $f_1(x)$, $f_2(x)$, …, $f_k(x)$. The objectives, denoted as $f_i : \mathbb{R}^n \rightarrow \mathbb{R}$ for $i \in \{1, \dots, k\}$, are assumed to be convex. Each objective can be maximized or minimized. We assume, without loss of generality, that all are to be minimized. The most important objective is to irradiate the tumour sufficiently enough, otherwise the patient will not be cured. The other objectives involve minimizing the specified dose to the healthy tissues. The decision vector $x \in \mathbb{R}^n$ is a vector of n variables: $x = (x_1, x_2, \dots, x_n)^T$, which are the fluences in bixels. So the variables x are the parameters that determine the intensity modulation of the radiation fields.

A function $f : \mathbb{R}^n \rightarrow \mathbb{R}$ is convex if

$$f(\alpha x + (1-\alpha)y) \leq \alpha f(x) + (1-\alpha) f(y) \tag{3.1}$$

for all $x, y \in \mathbb{R}^n$ and all $0 \leq \alpha \leq 1$.

Let S denote the set of feasible solutions in the decision space $\mathbb{R}^n$. The feasible set consists of vectors satisfying the constraints imposed by the decision maker, e.g. each fluence $x_i \geq 0$. A number of $l \in \mathbb{N}$ constraints $g(x) = (g_1(x), \dots, g_l(x)) \leq 0$ has to be satisfied, so $S = \{x \in \mathbb{R}^n | g(x) \leq 0\}$. We assume that all functions g_i are convex and S is a non-empty compact set.

To each decision vector $x \in S$ one objective vector, $z = f(x) = (f_1(x), f_2(x), \dots, f_k(x))$, is assigned. Therefore, we can consider the following multicriteria problem:

$$\begin{array}{ll} \text{minimize} & \{f_1(x), f_2(x), \dots, f_k(x)\} \\ \text{subject to} & x \in S \end{array} \tag{3.2}$$

Solving a multi-objective problem results in a set of optimal solutions. All optimization functions f are defined with the dose distribution d as the argument $f(d) = f(d(x))$. Appropriate optimization functions should not only accurately model the clinical goals, but also be convex in order to be suitable for optimization. Below we will define a number of terms: Pareto optimality, the ideal objective vector, anchor points, the nadir point and the wish-list.

3.1.1. Pareto optimality

In multicriteria optimization, several conflicting functions, or objectives, have to be optimized. Since the objectives are conflicting, there is not one optimal solution, but there are multiple optimal solutions to a multi-objective optimization problem. These optimal solutions are called Pareto optimal.

In general, a decision vector $x^* \in S$ is Pareto optimal if there does not exist another vector $x \in S$ such that $f_i(x) \leq f_i(x^*)$ for all $i = 1, \dots, k$ and $f_j(x) < f_j(x^*)$ for at least one index j. The set of Pareto optimal solutions is called the Pareto set and its image in the objective space is called the Pareto Front. Further we denote the the objective vector as $z^* = f(x^*)$ (Miettinen, 1999).

So Pareto optimality is a state of outcome in which it is impossible to improve any objective without worsening at least one other objective.

3.1.2. Ideal Objective Vector

The ideal objective vector, $z^* = (z_1^*, z_2^*, \dots, z_k^*)$ denotes the array with the lower bound of all objective functions.

$$z_i^* = \min_{x \in S} \; f_i(x) \quad i \in \{1, \dots, l\} \tag{3.3}$$

In general, the ideal objective vector corresponds to a non-existent solution except when the objective functions are non conflicting.

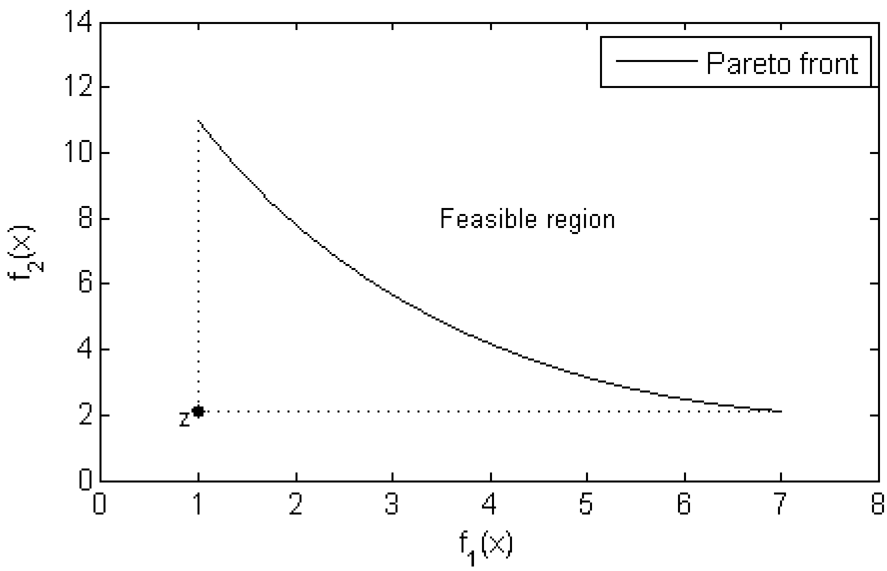

Figure 3.1: An example of a Pareto front for two objective functions and the corresponding ideal point.

3.1.3. Anchor points

An anchor point μ_i corresponds to the optimal value of the i-th objective function in the feasible space. Thus, n objective functions give n anchor points. An example for two objectives functions can be seen in Figure 3.2

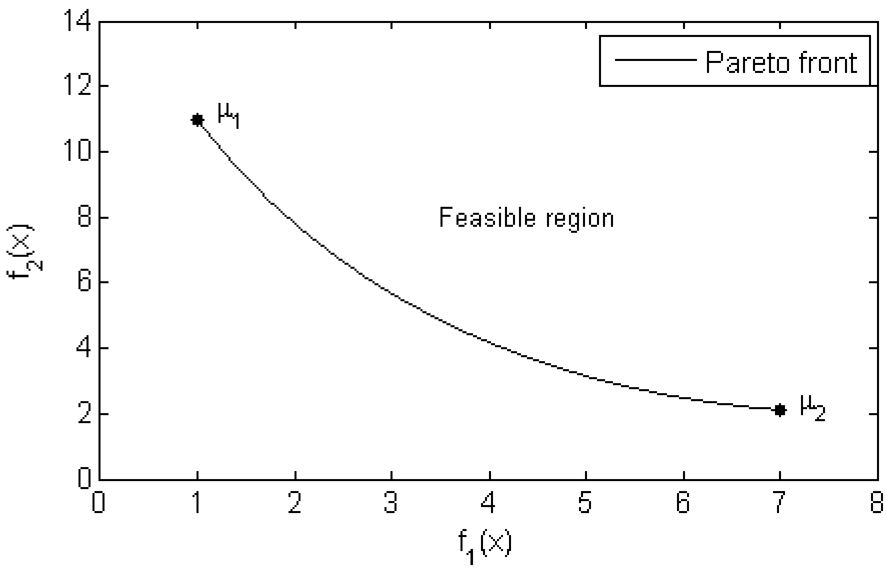

Figure 3.2: An example of a Pareto front for two objective functions with the corresponding anchor points.

3.1.4. Nadir point

The nadir point $z^{nad} = (z_1^{nad}, z_2^{nad}, \ldots, z_k^{nad})$ is the vector with the worst objective values over the Pareto set. The m-th component of the nadir objective vector z^{nad} is the constrained maximum of the following problem:

$$\begin{array}{ll} \text{maximize} & f_m(x) \\ \text{subject to} & x \in P \end{array} \tag{3.4}$$

where P is the Pareto optimal set. Unlike the ideal objective vector, z^{nad} represents the upper bound of each objective function in the Pareto-optimal set. The nadir objective vector may represent an feasible or non-feasible solution (depending on the convexity and continuity of the Pareto-optimal set). This nadir point is much more difficult to compute. The nadir point can be approximated by taking the maximal values of all objective functions obtained by their separated minimizations. An example of a nadir point can be seen in Figure 3.3.

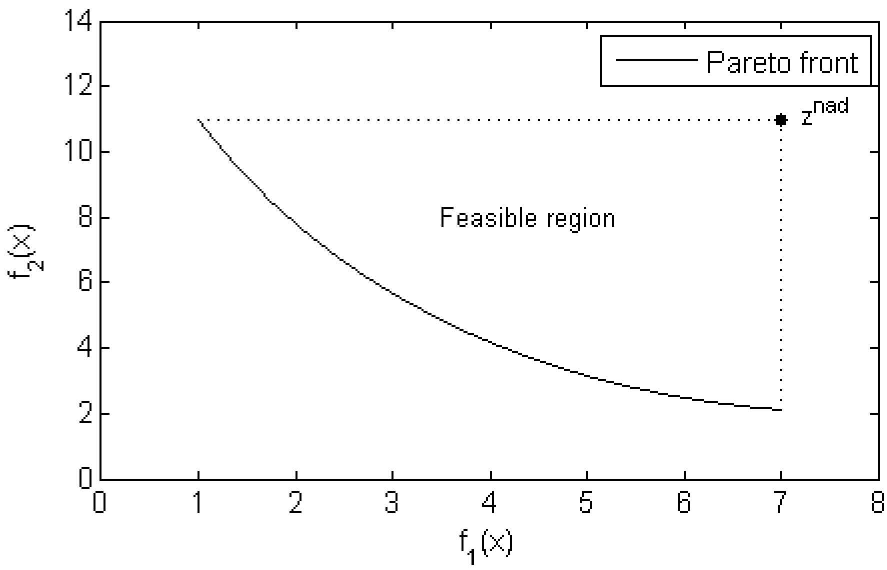

Figure 3.3: An example of a Pareto front for two objective functions with the corresponding nadir point.

3.1.5. Wish-list

The objectives and their priorities and goals are given in a prioritized list, which we call a wish-list. For k objectives, objective $f_i(x)$ has priority i and goal b_i. Furthermore, the list contains (hard) constraints $g(x)$ which are to be met at all times. An objective f_1 may be to minimize the dose in a certain organ. The goal b_i may be a certain threshold of that objective, minimize f_i below that goal is nice, but f_i has a lower priority, the other objectives are then minimized first. An example is given in Table 3.1.

Table 3.1: General wish-list.

Priority	Objective	Goal
1	$f_1(x)$	b_1
2	$f_2(x)$	b_2
	$\vdots$	
k	$f_k(x)$	b_k
	$g(x) \leq 0$	

3.2. 2-phase epsilon-constraint Method

The first optimization method used in this thesis is the 2-phase ϵ-constraint method, introduced in radiotherapy by Breedveld et al. (2007). In this method, a goal can be assigned to each objective. When it is possible to minimize the dose below a certain threshold (i.e. its goal) for one objective, it is often more desired to minimize the dose for other (lower priority) objectives first, than to directly minimize the dose for the higher priority objectives to their fullest extent. In this thesis we denote the ϵ-solution by z^ϵ.

In this method, one of the objective functions is selected to be optimized and all the other objective functions are converted into constraints by setting an upper bound to each of them. In the first iteration of the first phase, the objective with the highest priority is optimized

$$\begin{aligned} \text{minimize} \quad & f_1(x) \\ \text{subject to} \quad & g(x) \leq 0 \end{aligned} \tag{3.5}$$

This gives the result x^*, and a new bound is chosen as follows. If the goal for f_i is reached, $f_i(x_i) < b_i$, then we set $f_i(x) \leq b_i$ as a new constraint. When the goal is not reached, $f_i(x_i) \geq b_i$, we set $f_i(x) \leq \delta f_i(x_i)$ as a new constraint. δ is a slight relaxation to create some space for the subsequent optimizations, usually set to 1.03:

$$\epsilon_i = \begin{cases} b_i & f_i(x^*)\delta < b_i \\ f_i(x^*)\delta & f_i(x^*)\delta \geq b_i \end{cases} \tag{3.6}$$

And in the next optimization, f_2 is optimized while keeping f_1 constrained.

$$\begin{aligned} \text{minimize} \quad & f_2(x) \\ \text{subject to} \quad & g(x) \leq 0 \\ & f_1(x) \leq \epsilon_1 \end{aligned} \tag{3.7}$$

The 2-phase ϵ-constraint problem is of the form

$$\begin{aligned} \text{minimize} \quad & f_i(x) \\ \text{subject to} \quad & g(x) \leq 0 \\ & f_j(x) \leq \epsilon_j \;\; j \in \{1, \ldots, i-1\} \end{aligned} \tag{3.8}$$

where $i \in \{1, \ldots, k\}$

In this research project the solution obtained by the ϵ-constraint method is used as a base. We are going to look at optimal solutions around the ϵ-constraint solution and investigate whether we can relax one objective and maybe gain much on other objectives. These surrounding solutions are obtained using the reference point method, explained in next section.

3.3. Multiple Reference Point Method

The multiple reference point method can be used to approximate the Pareto front. In this research project we use the same method used by van Haveren et al. (2015).

3.3.1. The reference points

A reference point gives desirable or acceptable values for each one of the objective functions (f_i). The resulting objective vector is called a reference point and can be defined either in the feasible or in the infeasible region of the objective space. The reference points have to be chosen such that all objectives should improve for all subsequent reference points. The first reference point consists of pessimistic aspiration levels for the f_i while the last one consists of too optimistic reference levels.

The decision maker specifies $p \in \mathbb{N}$ reference points in the objective space. The reference points $r^j \in \mathbb{R}$ are denoted as $r^1, ..., r^p$, with $r^p < ... < r^2 < r^1$, such that the objectives only improve. The reference points are collected in a reference list, see Table 3.2.

Table 3.2: General reference list.

Priority	Reference Point	f_1	f_2	...	f_n
1	r^1	r_1^1	r_2^1	...	r_n^1
2	r^2	r_1^2	r_2^2	...	r_n^2
$\vdots$	$\vdots$	$\vdots$	$\vdots$		$\vdots$
p	r^p	r_1^p	r_2^p	...	r_n^p

Table 3.2 can be read as follows: r_1^1 is the goal for the first objective f_1, r_2^1 is the goal for the second objective f_2, ... , r_n^1 is the goal for the last objective f_n. With p priority levels, we get p reference points r^j, $j = 1, ...p$.

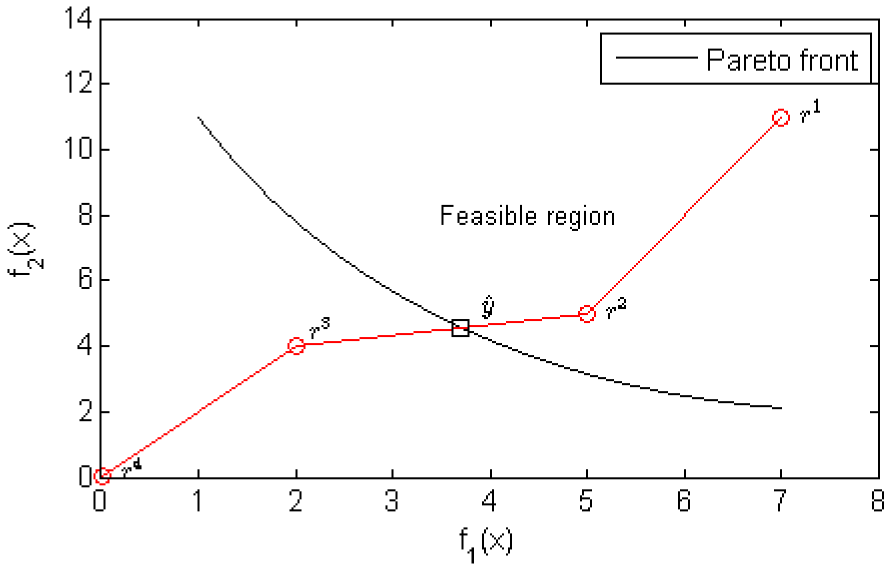

Figure 3.4: An example of a reference path for two objective functions. The circular points are the reference points and $\hat{y}$ represents the most desired point of the decision maker.

3.3.2. The partial achievement functions

In this subsection we describe how a convex optimization problem is obtained. Using the reference list a referene pad can automatically be constructed by applying linear interpolation to the reference points. This results in a path $\gamma : \mathbb{R} \to \mathbb{R}^n$, for which every value $z \in \mathbb{R}$ corresponds to a unique point on the reference path.

The entries of the strictly decreasing sequence $(v_j)_{j=1}^p \subseteq \mathbb{R}$, defined later in Section 4.1, are mapped to the reference points $\gamma(v_j) = r^j$ for all $j \in \{1, \dots, p\}$. The values in between are linearly interpolated.

The partial achievement functions s_i are given by:

$$s_i(f_i(x)) = \begin{cases} v_p + \alpha_1 w_i^p (f_i(x) - r_i^p), & f_i(x) \leq r_i^p \\ v_j + w_i^j (f_i(x) - r_i^j), & r_i^j < f_i(x) \leq r_i^{j-1}, \quad j \in \{2, \dots, p\} \\ v_1 + \alpha_2 w_i^2 (f_i(x) - r_i^1), & r_i^1 < f_i(x), \end{cases} \tag{3.9}$$

where,

$$w_i^j = \frac{v_{j-1} - v_j}{r_i^{j-1} - r_i^j}, \quad i \in \{1, \dots, n\}, \quad j \in \{2, \dots, p\}, \tag{3.10}$$

Parameters α_1 and α_2 satisfy $0 < \alpha_1 \leq 1 \leq \alpha_2$. Parameter α_1 models the increase of the satisfaction of the decision maker in case better outcomes than the last reference level r^p are generated. Parameter α_2 represents the increase of the decision makers dissatisfaction for generated outcomes worse than the first reference point r^1. Note that these parameters are irrelevant when all aspiration levels of the first reference point r^1 are feasible while all aspiration levels of the last reference point r^p are infeasible ($r_i^p \leq f_i(x) \leq r_i^1$ for all $i \in [n]$ and $x \in X$).

By choosing appropriate values for $(v_j)_{j=1}^p$, the convexity of all partial achievement functions can be guaranteed. It suffices to choose an initial pair $v_p < v_{p-1}$ and ensure that the following inequalities hold

$$v_{j-1} \geq v_j + (v_j - v_{j+1}) \max_{i \in \{1,\dots,n\}} \frac{r_i^{j-1} - r_i^j}{r_i^j - r_i^{j+1}}, \quad j \in \{2, \dots, p-1\} \tag{3.11}$$

This condition guarantees that the slopes w_i^j are monotonic, $w_i^2 \geq w_i^3 \geq \dots \geq w_i^p$, which results in convex partial achievement functions. Defining the achievement functions $a_i : \mathbb{R}^m \to \mathbb{R}$ as $a_i(x) = s_i(f_i(x))$, we can formulate the convex optimization problem with multiple reference points as follows:

$$\begin{aligned} \text{minimize} \quad & z + \sum_{i \in \{1,\dots,n\}} \rho_i a_i \\ \text{subject to} \quad & a_i \leq z, & i \in \{1, \dots, n\} \\ & v_p + \alpha_1 w_i^p (f_i(x) - r_i^p) \leq a_i, & i \in \{1, \dots, n\} \\ & v_j + w_i^j (f_i(x) - r_i^j) \leq a_i, & i \in \{1, \dots, n\},\ j \in \{2, \dots, p\} \\ & v_1 + \alpha_2 w_i^2 (f_i(x) - r_i^1) \leq a_i, & i \in \{1, \dots, n\} \\ & x \in S \end{aligned} \tag{3.12}$$

with z and a_i unbounded variables. Sensitivity parameters $\rho = (\rho_1, \dots, \rho_n) > 0$ are small positive scalars forming the regularization term, $\sum \rho_i a_i$, and are used to guarantee Pareto optimal solutions. Effectively, the scalarizing achievement function is minimized (Ogryczak & Kozlowski):

$$S(s_1(f_1(x)), \dots, s_n(f_n(x))) := \max_{i \in \{1,\dots,n\}} s_i(f_i(x)) + \sum_{i \in \{1,\dots,n\}} \rho_i s_i(f_i(x)). \tag{3.13}$$

4

Reference Point Method

4.1. The reference point method for two objectives

For an explanation of the method, we start with a test patient with two objectives. Later on we extend this to three objectives and use this as a generalization for n objectives. As an example we consider a wish-list for two objectives, namely for the average dose in the left and right parotid. In table 4.1 you can see that the objectives alternate.

Table 4.1: Wish-list for two objectives

Priority	Objective	Name	Goal
1	$f_1(x)$	Parotid Left	39
2	$f_2(x)$	Parotid Right	39
3	$f_1(x)$	Parotid Left	20
4	$f_2(x)$	Parotid Right	20
5	$f_1(x)$	Parotid Left	10
6	$f_2(x)$	Parotid Right	10
7	$f_1(x)$	Parotid Left	2
8	$f_2(x)$	Parotid Right	2

By the method explained in Section 3.3.1 we gain the reference points listed in Table 4.2.

Table 4.2: Reference list for the left parotid and right parotid.

Priority	Reference Point	f_1	f_2
1	r^1	$r_1^1 = 39$	$r_2^1 = 39$
2	r^2	$r_1^2 = 20$	$r_2^2 = 20$
3	r^3	$r_1^3 = 10$	$r_2^3 = 10$
4	r^4	$r_1^4 = 2$	$r_2^4 = 2$

We start with choosing appropriate v_j's such that the sequence $(v_j)_{j=1}^p$ is strictly decreasing and such that inequality 3.11 holds. So we take

$$v_{j-1} = v_j + (v_j - v_{j+1}) \max_{i \in \{1,\dots,n\}} \frac{r_i^{j-1} - r_i^j}{r_i^j - r_i^{j+1}} + 1, \quad j \in \{2,3\} \tag{4.1}$$

With $v_4 = 0$ and $v_3 = 1$ we can calculate the other two values v_2 and v_1:

$$v_2 = v_3 + (v_3 - v_4) \max_{i \in \{1,2\}} \frac{r_i^2 - r_i^3}{r_i^3 - r_i^4} + 1 = 1 + 1.25 + 1 = 3.25 \tag{4.2}$$

$$v_1 = v_2 + (v_2 - v_3) \max_{i\in\{1,2\}} \frac{r_i^1 - r_i^2}{r_i^2 - r_i^3} + 1 = 3.25 + (3.25 - 1) \cdot 1.9 + 1 = 8.525 \tag{4.3}$$

Now we can calculate the values for w_i^j $i \in \{1,2\}$, $j \in \{2,3,4\}$, where $w_i^j = \frac{v_{j-1}-v_j}{r_i^{j-1}-r_i^j}$: see Table 4.3 .

Table 4.3: The values for w_i^j for the given reference points for the left parotid and right parotid.

j	w_i^j
2	0.2776
3	0.2250
4	0.1250

Note that $r_1^j = r_2^j$ and $w_1^j = w_2^j$ for all $j \in \{2,3,4\}$. For these value levels with $\alpha_1 = \alpha_2 = 1$, the partial achievement functions for the two objectives ($i = 1,2$) take the following form:

$$a_i(x) = \begin{cases} 0.125(f_i(x) - 2), & f_i(x) \le 2 \\ 0.125(f_i(x) - 2), & 2 < f_i(x) \le 10 \\ 1 + 0.225(f_i(x) - 10), & 10 \le f_i(x) \le 20 \\ 3.25 + 0.2776(f_i(x) - 20), & 20 \le f_i(x) \le 39 \\ 8.525 + 0.2776(f_i(x) - 39), & 39 < f_i(x), \end{cases} \tag{4.4}$$

Also note the first two and last two equations are the same since $\alpha_1 = \alpha_2 = 1$, so we get for the partial achievement functions

$$a_1(x) = \begin{cases} 0.125(f_i(x) - 2), & f_i(x) \le 10 \\ 1 + 0.225(f_i(x) - 10), & 10 \le f_i(x) \le 20 \\ 3.25 + 0.2776(f_i(x) - 20), & f_i(x) > 20 \end{cases} \tag{4.5}$$

Next we take $\rho_1 = \rho_2 = 0$. By the method described in Section 3.3 we can solve the following optimization problem:

$$\begin{aligned} \text{minimize} \quad & z \\ \text{subject to} \quad & a_i \le z, & i \in \{1,2\} \\ & 0 + 0.1250(f_i(x) - 2) \le a_i, & i \in \{1,2\}, \\ & 1 + 0.2250(f_i(x) - 10) \le a_i, & i \in \{1,2\}, \\ & 3.25 + 0.2776(f_i(x) - 20) \le a_i, & i \in \{1,2\} \\ & x \in S. \end{aligned} \tag{4.6}$$

The $f_i(x)$'s and $x \in S$ are computed with the Erasmus iCycle program, where the solution of the multiple reference point method is given in Table 4.4.

Table 4.4: Solution in Gray of the reference point method for the left parotid (f_1) and right parotid (f_2).

$f_1(x)$	$f_2(x)$
4.0404	21.3741

5

Generate the Pareto front with the reference point method

In this chapter we are introducing a new method to generate the Pareto front. This can be done by taking different points as reference points and then solve them with the reference point method, still having the same constraints as the original problem. We are going to discuss which reference points are preferable to generate the Pareto front. The different types of reference points we are going to investigate are the zero point, the ideal point and the nadir point. For simplicity we will first discuss this method for two objectives.

5.1. Generate useful reference points

In this section we will generate a new reference point by taking the ϵ-solution and optimize with a stepsize s in the first or second objective.

Assume we obtained $z^\epsilon = (z_1^\epsilon, z_2^\epsilon)$ as the ϵ-constraint solution in the objective space. So for example, when we want to further optimize with respect to the first objective we can generate a new reference point $r^1 = (z_1^\epsilon - s, z_2^\epsilon)$. Furthermore we take for the second reference point, r^2, the zero point or the ideal point. In the case we use the nadir point instead of the zero or ideal point, the nadir point is the first reference point r^1. With this two reference points, r^1 and r^2, the multiple reference point method is applied to determine the new solution z'^1 on the Pareto front. The same procedure is applied to the new solution z'^1 and this gives an other solution z'^2. In this way we can proceed until the first reference point has reached its maximum, i.e. until the reference path has no solution on the Pareto front.

5.1.1. The reference point method using the zero point

In this section we apply the reference point method using the zero point. We are going to optimize with respect to the first objective, f_1. With zero as the second reference point, $r^2 = (0, 0)$, the reference list for the first iteration is shown in Table 5.1.

Table 5.1: Reference list for the first iteration.

Priority	Reference Point	f_1	f_2
1	r^1	$r_1^1 = z_1^\epsilon - s$	$r_2^1 = z_2^\epsilon$
2	r^2	$r_1^2 = 0$	$r_2^2 = 0$

This problem is solved with the reference point method. The solution is then notated as z'^1 and we have for the second iteration

Table 5.2: Reference list for the second iteration.

Priority	Reference Point	f_1	f_2
1	r^1	$r_1^1 = z_1'^1 - s$	$r_2^1 = z_2'^1$
2	r^2	$r_1^2 = 0$	$r_2^2 = 0$

In this way we can iterate further until we have generated n reference points in the direction of the first objective. In the same way we can optimize in the direction of the second objective. The reference points then are constructed as in Table 5.3.

Table 5.3: Reference list for the first iteration for further optimizing f_2.

Priority	Reference Point	f_1	f_2
1	r^1	$r_1^1 = z_1^\epsilon$	$r_2^1 = z_2^\epsilon$-s
2	r^2	$r_1^2 = 0$	$r_2^2 = 0$

and the same procedure as in optimizing the first objective follows.

5.1.2. The reference point method using the ideal point

In the case we make use of the ideal point, we proceed the same as in the case with the zero point. The only difference is the second reference point. In this case the second reference point equals $z*$. As an example we only give the the reference list for the first iteration, Table 5.4.

Table 5.4: Reference list for the first iteration.

Priority	Reference Point	f_1	f_2
1	r^1	$r_1^1 = z_1^\epsilon - s$	$r_2^1 = z_2^\epsilon$
2	r^2	$r_1^2 = z_1^*$	$r_2^2 = z_2^*$

5.1.3. The reference point method using the nadir point

When we apply the reference point method using the nadir point, z^{nad}, the reference point method is slightly different. In this case we use the nadir point as the first reference point, as the first priority now lies on the nadir point. The reference list for the first iteration is given in Table 5.5.

Table 5.5: Reference list for the first iteration.

Priority	Reference Point	f_1	f_2
1	r^1	$r_1^2 = z_1^{nad}$	$r_2^2 = z_2^{nad}$
2	r^2	$r_1^1 = z_1^\epsilon - s$	$r_2^1 = z_2^\epsilon$

This method has been tested on several simplified test cases, which can be seen in the following sections.

5.2. The reference point method for the left and right parotid

In this section we will generate the Pareto front for different reference points as described in the previous section. We will do this for different simplified test cases. The first test case involves the average doses in the left parotid gland (f_1) and in the right parotid gland (f_2). Radiotherapy to the salivary glands can cause side effects such as a sore, dry mouth, taste changes and teeth problems. So f_1 and f_2 have to be minimized.

5.2.1. The reference point method for the left and right parotid, using the zero point

For this test case the wish-list is as Table 4.1 and the reference points are generated as discussed in Section 5.1.1. For the average doses in the left parotid gland (f_1) and the right parotid gland (f_2) the ϵ-constraint solution is given by $(z_1^\epsilon, z_2^\epsilon) = (2.1600, 22.0153)$.

To form the Pareto front we first optimized the first objective and thereafter did the second one. With stepsize $s = 0.3$ the max iterations we could do optimizing the first objective, i.e. the right parotid, was four. There is a maximum number of iterations because it is possible to generate a line between the two reference points which does not intersect the Pareto front. We did fifteen iterations optimizing the second objective, i.e. the left parotid. The results can be seen in Figure 5.1. Notice that the axis are not equal, which we have done to represent the generated solutions more clearly and that the zero point is not the left corner of Figure 5.2 but lies further beneath.

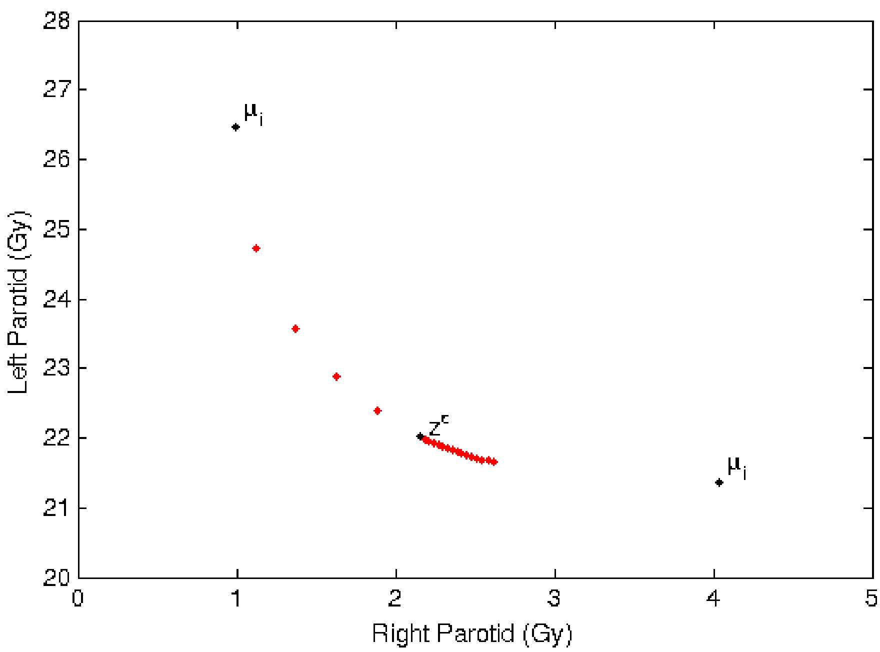

Figure 5.1: Pareto front generated with the zero point as second reference point, $s = 0.3$.

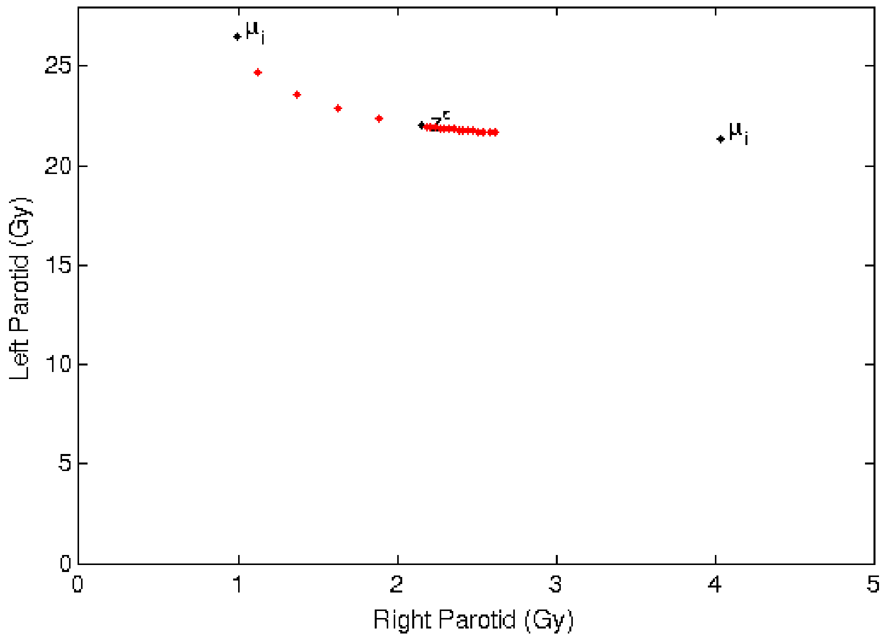

Figure 5.2: Pareto front generated with the zero point as second reference point, $s = 0.3$.

In Figure 5.1 it can be seen that the the solution space S generated with zero as the second reference point is clearly convex, which we expected since the reference point method generates a convex solution space. However, with zero as second reference point we see that the solutions do not form a very nice Pareto front. The explanation is that the Pareto front is not near to the zero. So the lines drawn from zero to the generated reference points give small differences in the solutions when optimizing the second objective, i.e. the left parotid. Higher differences in solutions occur when the first objective is optimized further, i.e. the left parotid. To clarify this we've added Figure 5.2.

5.2.2. The reference point method for the left and right parotid, using the ideal point

The reference points in this subsection are generated as discussed in Section 5.1.2. For this test case the ideal vector is given by $(z_1^*, z_2^*) = (0.9934, 21.3741)$. To generate the Pareto front we optimized both the first objective and the second objective further. With stepsize $s = 0.2$ the maximum number of iterations we could do optimizing the first objective, for the right parotid, was nine and we did three iterations while optimizing the second objective, for the left parotid. The results can be seen in Figure 5.3. Notice again that the axis are not equal.

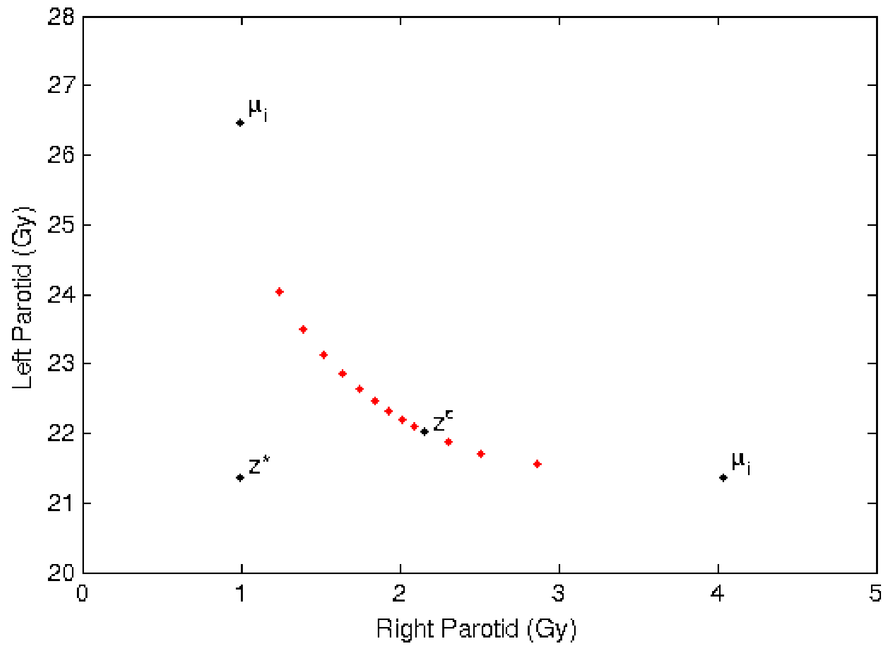

Figure 5.3: Pareto front generated with the ideal point as second reference point, $s = 0.2$

In Figure 5.3 it can be seen that with the ideal point as second reference point we gain a better shaped Pareto front than with the zero, since the ideal point is closer to the Pareto front than the zero point. Here again we can see that the solutions form a convex Pareto front. Also we see that with the ideal point the solutions from the reference point method are mainly located at the points where the Pareto front is most curved.

5.2.3. The reference point method for the left and right parotid, using the nadir point

Here again the method is as discussed in 5.1.3. For this test case the nadir vector is given by $(z_1^{nad}, z_2^{nad}) = (4.0404, 26.4702)$. We took stepsize $s = 0.5$ and did eighteen iterations in both the first objective and the second objective. This results in the Figure 5.4.

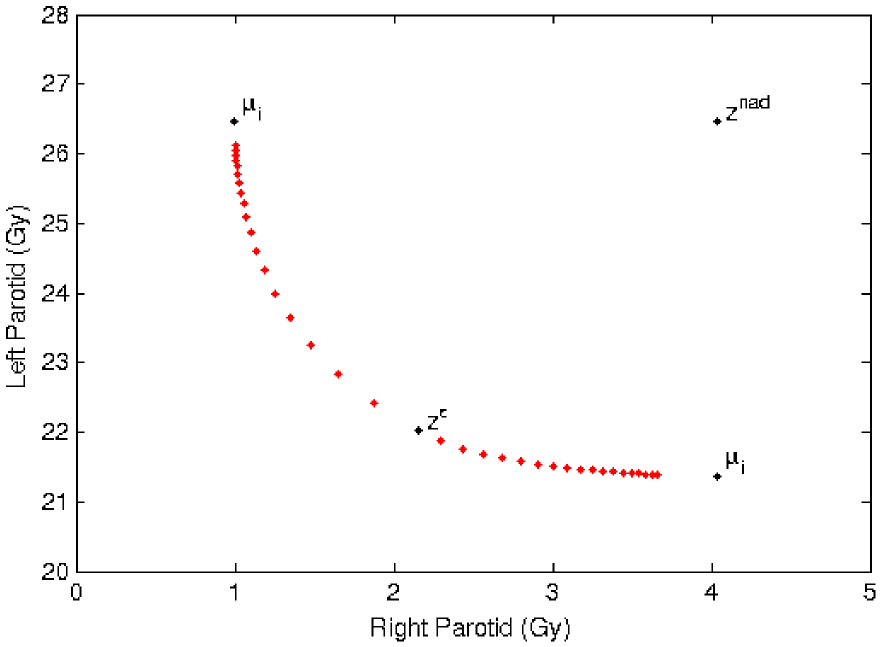

Figure 5.4: Generated Pareto front with the nadir point as first reference point, $s = 0.5$

In Figure 5.4 it can be seen that the reference point method with the nadir point as first reference point generates a nice Pareto front. In this case we can see that the most points are generated in the neighbourhood of the anchor points.

5.3. The reference method for the left parotid and left submandibular gland

Next, we considered an other test case. This test case involves the average doses in the right parotid (f_1) and the left submandibular gland (f_2). The wish-list for this test case can be seen in Table 5.6.

Table 5.6: Wish-list for two objectives, SMG stands for submandibular gland

Priority	Objective	Name	Goal
1	$f_1(x)$	Parotid Right	39
2	$f_2(x)$	SMG Left	39
3	$f_1(x)$	Parotid Right	20
4	$f_2(x)$	SMG Left	20
5	$f_1(x)$	Parotid Right	10
6	$f_2(x)$	SMG Left	10
7	$f_1(x)$	Parotid Right	2
8	$f_2(x)$	SMG Left	2

For these objective functions the ϵ-constraint solution is given by $(z_1^\epsilon, z_2^\epsilon) = (1.6824, 39.3118)$. The ideal vector is given by $(z_1^*, z_2^*) = (0.9934, 38.1668)$ and the nadir vector by $(z_1^{nad}, z_2^{nad}) = (5.7343, 42.3313)$. In exactly the same way as before we obtain Figures 5.5, 5.6 and 5.7.

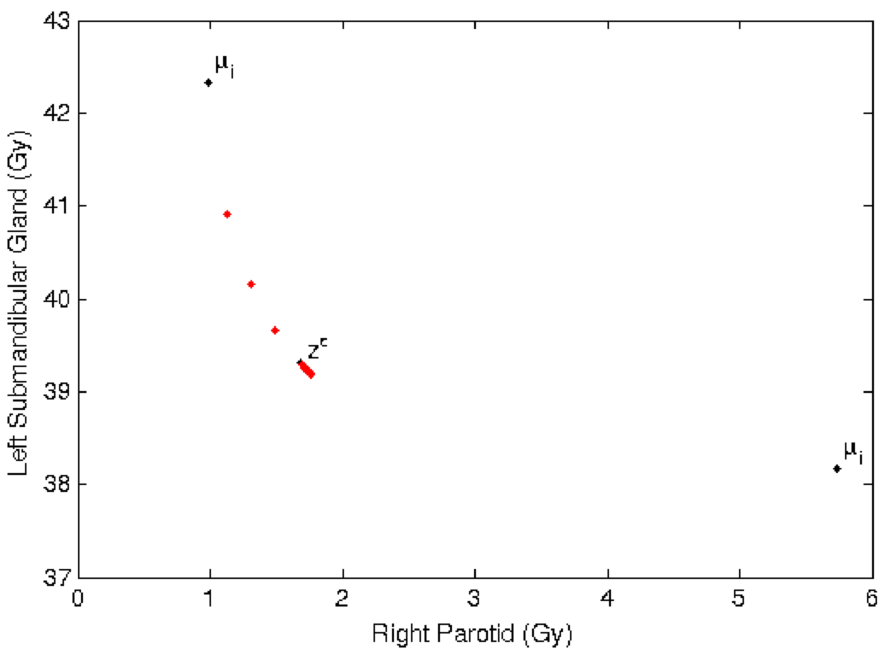

Figure 5.5: Pareto front generated with zero as first reference point, $s = 0.2$

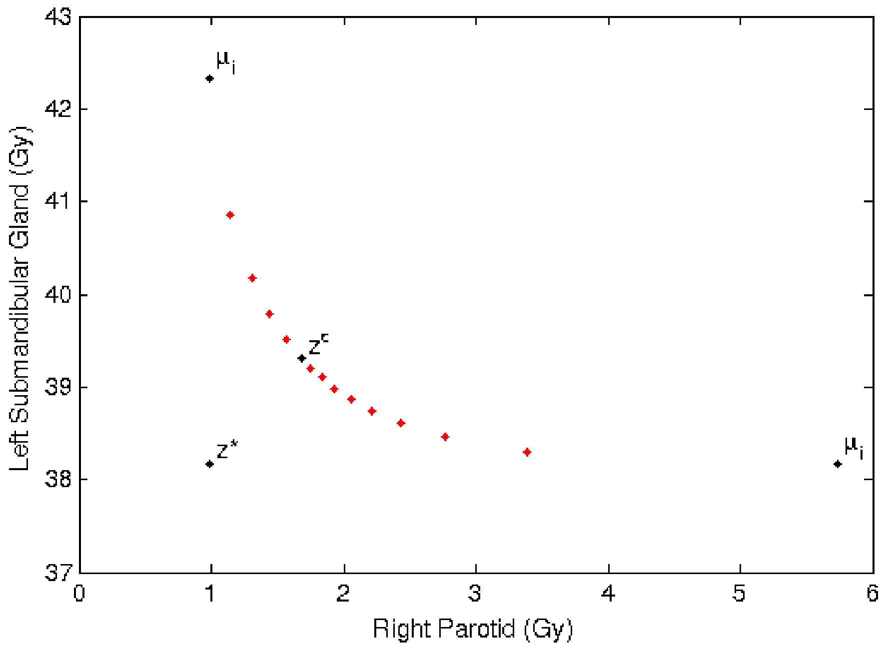

Figure 5.6: Pareto front generated with the ideal point as first reference point, $s = 0.2$

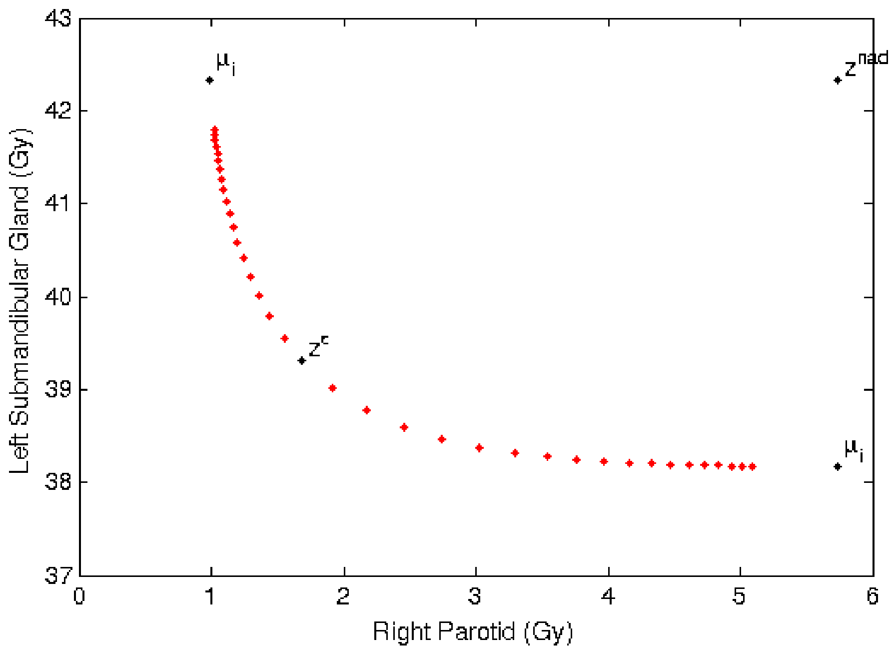

Figure 5.7: Pareto front generated with the nadir point as first reference point, $s = 0.5$

We can see that the same conclusions can be drawn as for the test case in Section 5.2. The method with the ideal point generates the most solutions in the most curved part of the Pareto front and the method with the nadir point generates the most solutions close to the anchor points. However, the figure with zero as a second reference point is slightly different (Figure 5.5). The Pareto front of this test case is located even further away from the zero than in the test case in Section 5.2. This results in more stacked solutions when optimizing the second objective, for the left submandibular grand.

5.4. Conclusions

As we have seen in the previous two subsections, the reference point method using the zero point does not generate a well-distributed Pareto front. This is caused by the fact that the Pareto front is not located near the zero; the further away the Pareto front, the more the solutions are stacked.

Since we are most interested in the points where we can gain something for one objective while giving in a little on the other objective, the most interesting part of the Pareto front is the part where the front is the most 'curved'. The reference point method using the ideal objective vector generates the most points in this part of the Pareto front.

Thus when we do an equal number of iterations, we can conclude that the ideal objective vector is the most ideal point to use with the reference point method.

All Pareto fronts formed in two-dimensional space are clearly convex, which we expected since the solution space S is convex.

A disadvantage of this method is that the calculations of the Pareto front simultaneously are very time consuming, because for each iteration an optimization has to be done before we can derive the new reference point. For n iterations thus n optimizations have to be done one after one other.

6

The reference point method for three objectives

6.1. The method for the left and right parotid and left submandibular gland

In this chapter we are going to extend the method of Chapter 5 to three objectives, the average doses the left parotid, the right parotid and the left submandibular gland. The wish-list for these objectives is shown in Table 6.1

Table 6.1: Wish-list for three objectives

Priority	Objective	Name	Goal
1	$f_1(x)$	Parotid Left	39
2	$f_2(x)$	Parotid Right	39
3	$f_3(x)$	SMG Left	39
4	$f_1(x)$	Parotid Left	20
5	$f_2(x)$	Parotid Right	20
6	$f_3(x)$	SMG Left	20
7	$f_1(x)$	Parotid Left	10
8	$f_2(x)$	Parotid Right	10
9	$f_3(x)$	SMG Left	10
7	$f_1(x)$	Parotid Left	2
8	$f_2(x)$	Parotid Right	2
9	$f_3(x)$	SMG Left	2

Again this is first solved with the ϵ-constraint method, which gives as solution $(z_1^\epsilon, z_2^\epsilon, z_3^\epsilon) = (2.7858, 23.4667, 39.3118)$. Since we concluded in Chapter 5 that the ideal point is the most useful to use as the second reference point, we will apply the method in three dimensional case only with the ideal objective vector. The ideal objective vector is given by $r^2 = (z_1^*, z_2^*, z_3^*) = (0.9934, 21.3741, 38.1668)$. When we take stepsize $s = 0.2$ and do ten iterations optimizing the first objective, fourteen optimizing the second and seven optimizing the third objective, we obtain the Pareto front as in Figure 6.1.

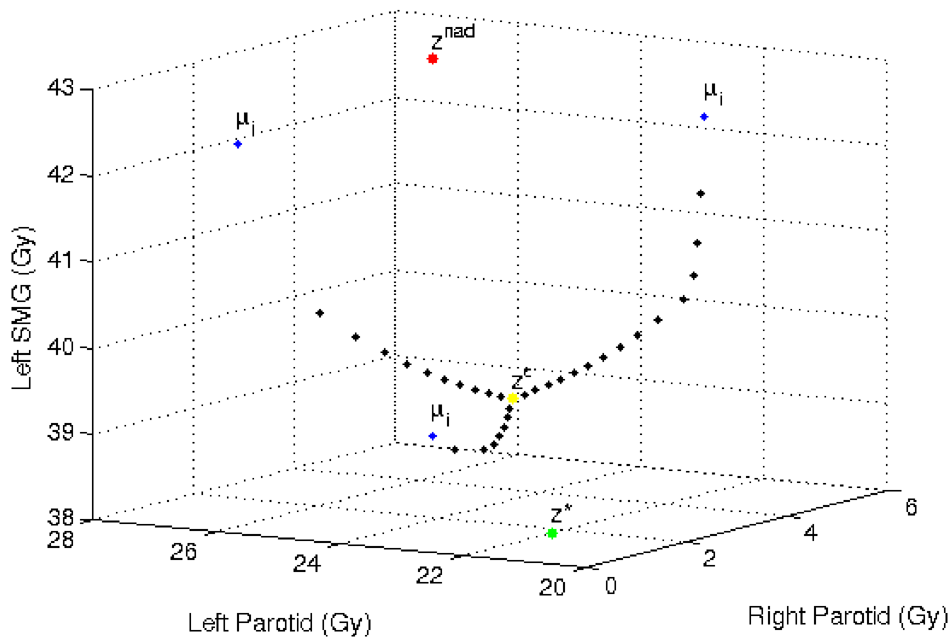

Figure 6.1: Three-dimensional Pareto front generated with the ideal point as second reference point, $s = 0.2$.

To determine whether the front is convex we will show a mesh plot of this Pareto front. This results in Figure 6.2.

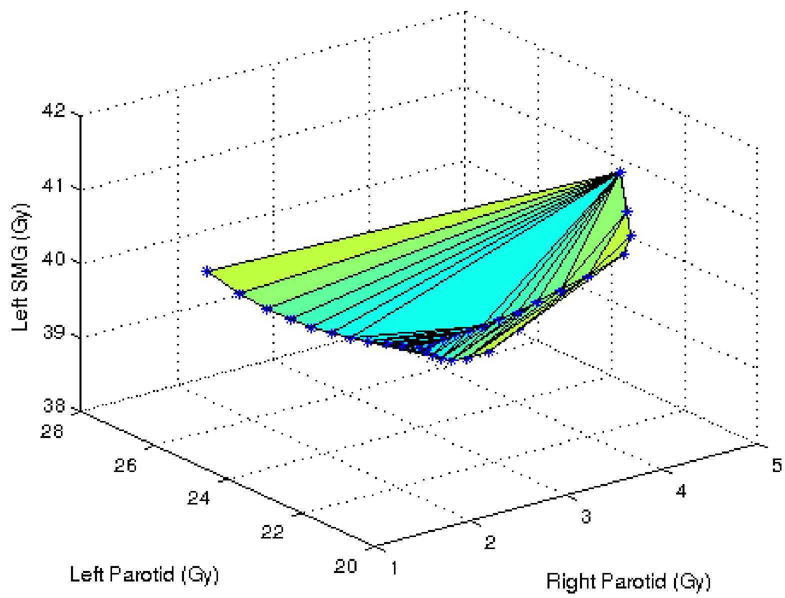

Figure 6.2: Three-dimensional mesh plot of the Pareto front generated with the ideal point as second reference point, $s = 0.2$.

We can conclude that the method from Chapter 5 also generates a convex Pareto front for three objective functions. Since the solutions for both two objectives and three objectives seem to work, we assume that it also generates a convex Pareto front for n dimensions. In Chapter 7 we will show some examples of the method applied to a realistic patient.

7

The reference point method for multiple objectives

In the previous two chapters the method was generalized to two or three objectives. In real life applications there are many more objectives to be considered. In this chapter the method of Chapter 5 is extended to a problem with a realistic number of objectives. A realistic wish-list is shown in table 7.1.

Table 7.1: Wish-list for a realistic patient.

Priority	Objective	Name	Type	Goal
1	$f_1(x)$	Parotid Left	Average	39
2	$f_2(x)$	Parotid Right	Average	39
3	$f_3(x)$	Submandibular Right	Average	39
4	$f_4(x)$	Submandibular Left	Average	39
5	$f_1(x)$	Parotid Left	Average	20
6	$f_2(x)$	Parotid Right	Average	20
7	$f_3(x)$	Submandibular Right	Average	20
8	$f_4(x)$	Submandibular Left	Average	20
9	$f_5(x)$	Oral Cavity	Average	39
10	$f_6(x)$	Cord	Maximum	40
11	$f_7(x)$	External Ring	Average	$A \cdot 0.9$
12	$f_8(x)$	Larynx	Average	$A \cdot 0.75$
13	$f_9(x)$	MCM	Average	$A \cdot 0.75$
14	$f_{10}(x)$	MCI	Average	$A \cdot 0.75$
15	$f_{11}(x)$	PTV Ring 1 cm	Maximum	$A \cdot 0.75$
16	$f_1(x)$	Parotid Left	Average	10
17	$f_2(x)$	Parotid Right	Average	10
18	$f_3(x)$	SMG Right	Average	10
19	$f_4(x)$	SMG Left	Average	10
20	$f_{12}(x)$	PTV Ring 4 cm	Maximum	$A \cdot 0.4$
21	$f_1(x)$	Parotid Left	Average	2
22	$f_2(x)$	Parotid Right	Average	2
23	$f_3(x)$	SMG Right	Average	2
24	$f_3(x)$	SMG Right	Average	2

Here $A = 46$ is the prescribed dose in Gray. Around the tumour, also called the planning target volume (PTV), some rings are delineated. The PTV rings are delineated around the PTV at 1 cm (f_{11}) and 4 cm (f_{12}) to realize a steep dose f all-off outside the PTV. Note from Table 7.1, that in the cord, PTV ring 1 cm and PTV ring 4 cm the maximum dose is used instead of the average dose.

For the realistic patient the method described in Chapter 5 can also be applied. In this chapter we will only do one iteration for comparison with the ϵ-constraint solution. It is also possible to optimize multiple objectives at the same time.

7.1. Optimizing the dose in the left parotid

When we optimize the average dose in the left parotid, we gain the following as first reference vector; $r^1 = (z_1^\epsilon - S, z_2^\epsilon, z_3^\epsilon, z_4^\epsilon, z_5^\epsilon, z_6^\epsilon, z_7^\epsilon, z_8^\epsilon, z_9^\epsilon, z_{10}^\epsilon, z_{11}^\epsilon, z_{12}^\epsilon)$. And for the second reference vector we again take the ideal vector, so $r^2 = z^*$. we can compare the ϵ-constraint solution and the reference point solution, with step size $S = 1$ the results are as in Table 7.2 .

Table 7.2: Solution for a realistic patient, optimizing the left parotid.

Objective	Name	z^ϵ	RPM
$f_1(x)$	Parotid Left	2.4986	1.5318
$f_2(x)$	Parotid Right	19.1684	19.2664
$f_3(x)$	Submandibular Right	10.4397	10.6621
$f_4(x)$	Submandibular Left	33.9262	33.9536
$f_5(x)$	Oral Cavity	28.0858	28.5243
$f_6(x)$	Cord	27.1355	26.5696
$f_7(x)$	External Ring	4.2773	4.2724
$f_8(x)$	Larynx	30.9777	31.3349
$f_9(x)$	MCM	33.5097	33.4689
$f_{10}(x)$	MCI	30.7560	31.1919
$f_{11}(x)$	PTV Ring 1 cm	40.3714	40.5106
$f_{12}(x)$	PTV Ring 4 cm	34.1791	34.6345

We can see that f_1 has been reduced by approximately 0.9668, while f_2 up to f_{12} have stayed the same approximately.

7.2. Optimizing the dose in the oral cavity and larynx

It is also possible to optimize certain objectives at the same time, so for example assume we want to obtain a lower average dose in the oral cavity (f_5) and the larynx (f_8). Then the first reference vector can be taken as $r^1 = (z_1^\epsilon, z_2^\epsilon, z_3^\epsilon, z_4^\epsilon, z_5^\epsilon - S, z_6^\epsilon, z_7^\epsilon, z_8^\epsilon - S, z_9^\epsilon, z_{10}^\epsilon, z_{11}^\epsilon, z_{12}^\epsilon)$. And for the second reference vector we again take the ideal vector. We compare the ϵ-constraint solution and the reference point solution, with step size $S = 1$, see Table 7.3 .

Table 7.3: Solution for a realistic patient, optimizing the left parotid.

Objective	Name	z^ϵ	RPM
$f_1(x)$	Parotid Left	2.4986	2.5132
$f_2(x)$	Parotid Right	19.1684	19.1943
$f_3(x)$	Submandibular Right	10.4397	10.4986
$f_4(x)$	Submandibular Left	33.9262	33.9335
$f_5(x)$	Oral Cavity	28.0858	27.1960
$f_6(x)$	Cord	27.1355	27.2204
$f_7(x)$	External Ring	4.2773	4.1728
$f_8(x)$	Larynx	30.9777	30.0664
$f_9(x)$	MCM	33.5097	33.6126
$f_{10}(x)$	MCI	30.7560	30.4482
$f_{11}(x)$	PTV Ring 1 cm	40.3714	40.4082
$f_{12}(x)$	PTV Ring 4 cm	34.1791	34.23984

Again f_5 and f_8 have been reduced by approximately 0.99, while the other f_i's have not changed much as well.

In this manner we can specify different objectives which we want to optimize further. The outcome of the method can be compared by a clinician. The different treatment plans that result can be compared by a clinician.

8
Conclusions

The main goal of this thesis was to generate a new method to form the Pareto front with the reference point method. We did research to look which points are the most optimal to use as reference points.

When we use zero as second reference point, the n optimizations have not to be done to calculate the ideal point. However, we concluded that the ideal vector is the most ideal vector to take as second reference point, since the applied method with the ideal vector of Chapter 5 generates most points in the most interesting region of the Pareto front. So, despite it takes more time to generate the Pareto front with the ideal point, we conclude that this results in a better distribution of Pareto optimal points on the Pareto front. If the ideal point is close to one of the anchor points, it might be better to use the reference point method with the nadir point.

The main advantage of this method is that, when a clinical isn't pleased enough about a certain objective from the ϵ-constraint solution. It is possible the optimize a certain objective some more.

Unfortunately we didn't have time to design a method where the optimizations can be calculated simultaneously. This method is introduced in the recommendations, Chapter 9.

9

Recommendations

Finally I have a few recommendations for further research. In this thesis we investigated a method which uses an iterative way of calculating the Pareto front. The disadvantage of this method is that the calculation of the Pareto front is very time consuming, because for each iteration an optimization has to be done before we can derive the new reference point. For n iterations thus n optimizations have to be done one after one other.

This can be prevented by choosing other reference points. In my research project I only implemented this method for two dimensions. The method goes as follows: draw line l with slope -1 through the first solution, the ϵ-constraint solution. Then you draw two other lines, l_1 and l_2, from the anchor points to the zero. Choose reference points on the segment of l that lies between l_1 and l_2. Then the solutions generated with the reference point method lie on the Pareto front. You then can generate n points on the line l, and solve the n optimizations with the reference point method in a parallel way.

A Pareto front of this method with 15 optimizations of the right and left parotid can be seen in Figure 9.1.

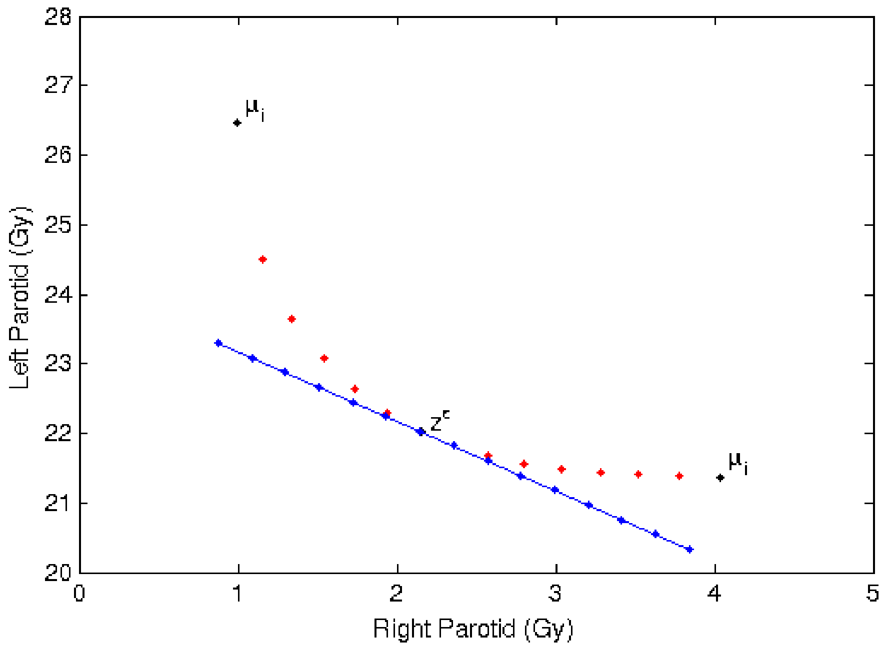

Figure 9.1: Pareto front generated with the ideal point as second reference point, and the first reference points on the blue line l

For three objectives the points should be generated on a sphere and for n objectives on a n-sphere centered around the ideal point. The advantage of this method is that the optimizations can be done at the same time, and thus the method is less time consuming.

Furthermore, the stepsizes S in this thesis where determined random, just such that a nice Pareto front was generated. In order to conclude which stepsize gives the most interesting solutions further research has to be done.

Bibliography

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A

Matlab codes

A.1. Calculating the ideal vector and nadir vector

```
function [anchor_pts, ideal_pt, nadir_pt] = compute_anchor_points(data_in,
    cons_in)
% Computes the ideal and nadir point and anchor points

% Gather all active objectives of the wish-list
[obj_uniq, obj_all] = gather_obj(cons_in);
n_obj = length(obj_uniq);

% Do the n_obj optimizations
ideal_pt = zeros(n_obj,1);
anchor_pts = cell(n_obj,1);
opt.DisplayExternal='';
opt.DisplayInfoWarn = 0;
opt.DisplayIter = 0;
opt.DisplayInfo = 0;
fprintf('\nComputing anchor points and the ideal/nadir point \nNeed to do
    %2d optimizations:\n', n_obj)

for i = 1:n_obj
    % copy constraints structure
    cons_temp = cons_in;

    % disable other objectives
    for j = 1:length(obj_all)
        if obj_uniq(i) ~= obj_all(j)
            cons_temp(obj_all(j)).Active = 0;
        end
    end

    % optimize
    fprintf('\nStarting optimization %2d of %2d\n', i, n_obj)
    xopt = primaldual(data_in.misc.size, data_in, cons_temp, opt);

    % evaluate objective values
    ev = evaluate_objectives(xopt, data_in, cons_temp);
    fprintf('Results:\n--------\n')
    for k = 1:n_obj
```

```
        fprintf('%-20s (%2d): %g\n', cons_in(obj_uniq(k)).VolName,
            obj_uniq(k), ev(obj_uniq(k)));
    end

    % save optimal value and anchor point
    ideal_pt(i) = ev(obj_uniq(i));
    anchor_pts{i} = ev(obj_uniq);
end

% Approximate nadir point
nadir_pt = anchor_pts{1};
for i = 1:n_obj
    if i > 1
        adept = find(nadir_pt < anchor_pts{i});
        nadir_pt(adept) = anchor_pts{i}(adept);
    end
end


end
```

A.2. Optimizing with the zero as second reference point.

```
function ev_zero = ref_zero(ev, constraints, objective, n_iter, stepsize, dataopt)
%REF_ZERO Generate reference points locally to the optimum and optimize
% with the single reference point method
% ----------------------------------------------------------------------------
% input:    ev: matrix which evaluates the objectives from the epsilon
%               constraint solution
%           constraints: constraints of the patient data
%           objective: the index of the objective you want to minimize
%           n_iter: the number of iterations you wish to make
%           stepsize: difference between the solution and reference point
% output:   ev_zero: matrix wich evaluates the objectives after applying the
%                   reference point method to different reference points
% ----------------------------------------------------------------------------


    options.DisplayIter = 0;
    options.DisplayInfoWarn = 0;
    [obj_act_uniq, obj_act_all, LTCP_all] = gather_obj(constraints);
    obj_act_uniq = gather_obj(constraints);

    % Some sensitivity parameter
    n_obj = length(obj_act_uniq);
    rho = zeros(1,n_obj);

    fprintf('\nThe max iterations you can do is: \n')
    n_iter_max = floor((ev(obj_act_uniq(objective)))/stepsize)

for j=2:n_iter+1

    point = ev(obj_act_uniq,j-1);


    % Generate the reference points
    for i=1:length(point)
        if i == objective && i == 1
            ref_pts = [point(1)-stepsize; 0];
        elseif i == 1
            ref_pts = [point(1); 0];
        elseif i == objective
            ref_pts = [ref_pts [point(i)-stepsize; 0]];
        else
            ref_pts = [ref_pts [point(i); 0]];
        end
        ref_pts
    end

    [weight, constant, wfull, cfull, val_lvls] = convex_pafs(constraints, obj_act_uniq, ref_pts, 1, 1);
```

```
    % Change the WS model to the LRPM model in the system and optimize
    [constraints_lrpm, dataopt_lrpm] = convert_to_lrpm(constraints,
       dataopt, obj_act_uniq, obj_act_all, weight, constant, rho);
    [xopt_lrpm, ofval, output, pddata, pdvars, constraints_out] =
       primaldual(dataopt_lrpm.misc.size, dataopt_lrpm, constraints_lrpm,
       options);
    xopt = xopt_lrpm(dataopt.misc.real);


    ev_temp = evaluate_objectives(xopt, dataopt, constraints);
    ev = [ev ev_temp];
end

ev_zero = ev;

end
```

A.3. Optimizing with the ideal vector as second reference point.

```
function ev_ideal = ref_ideal(ev, constraints, objective, obj_act_uniq, obj_act_all, n_iter, stepsize, dataopt, ideal_pt)
%REF_IDEAL Generate reference points locally to the optimum and optimize
% with the reference point method
% --------------------------------------------------------------------------
% input:    ev: matrix which evaluates the objectives from the epsilon
%               constraint solution
%           constraints: constraints of the patient data
%           objective: the index of the objective you want to minimize
%           n_iter: the number of iterations you wish to make
%           stepsize: difference between the solution and reference point
% output:   ev_zero: matrix wich evaluates the objectives after applying the
%                   reference point method to different reference points
% --------------------------------------------------------------------------


for j=2:n_iter+1
    % choose the index values from the wishlist you want to look at locally
    options.DisplayIter = 0;
    options.DisplayInfoWarn = 0;
    point = ev(obj_act_uniq,j-1);

    % Some sensitivity parameter
    n_obj = length(obj_act_uniq);
    rho = zeros(1,n_obj);

    fprintf('\nThe max iterations you can do is: \n')
    n_iter_max = floor((ev(obj_act_uniq(objective))-ideal_pt(objective))/stepsize)


    for i=1:length(point)
        if any(i == objective) && i == 1
            ref_pts = [point(1)-stepsize; ideal_pt(1)];
        elseif i == 1
            ref_pts = [point(1); ideal_pt(1)];
        elseif any(i == objective)
           ref_pts = [ref_pts [point(i)-stepsize; ideal_pt(i)]];
        else
            ref_pts = [ref_pts [point(i); ideal_pt(i)]];
        end
    end

    [weight, constant, wfull, cfull, val_lvls] = convex_pafs(constraints, obj_act_uniq, ref_pts, 1, 1);


    % Change the WS model to the LRPM model in the system and optimize
```

```
    [constraints_lrpm, dataopt_lrpm] = convert_to_lrpm(constraints,
       dataopt, obj_act_uniq, obj_act_all, weight, constant, rho);
    [xopt_lrpm, ofval, output, pddata, pdvars, constraints_out] =
       primaldual(dataopt_lrpm.misc.size, dataopt_lrpm, constraints_lrpm,
       options);
    xopt = xopt_lrpm(dataopt.misc.real);


    ev_temp = evaluate_objectives(xopt, dataopt, constraints);
    ev = [ev ev_temp];
end

ev_ideal = ev;
end
```

A.4. Optimizing with the nadir point as first reference point.

```
function ev_nadir = ref_nadir(ev, constraints, objective, obj_act_uniq, obj_act_all, n_iter, stepsize, dataopt, nadir_pt)
%REF_NADIR Generate reference points locally to the optimum and optimize
% with the single reference point method
% ---------------------------------------------------------------------------
% input:    ev: matrix which evaluates the objectives from the epsilon
%               constraint solution
%           constraints: constraints of the patient data
%           objective: the index of the objective you want to minimize
%           n_iter: the number of iterations you wish to make
%           stepsize: difference between the solution and reference point
% output:   ev_zero: matrix wich evaluates the objectives after applying the
%                   reference point method to different reference points
% ---------------------------------------------------------------------------



for j=2:n_iter+1
    % choose the index values from the wishlist you want to look at locally
    options.DisplayIter = 0;
    options.DisplayInfoWarn = 0;
    point = ev(obj_act_uniq,j-1);

    % Some sensitivity parameter
    n_obj = length(obj_act_uniq);
    rho = zeros(1,n_obj);

    fprintf('\nThe max iterations you can do is: \n')
    n_iter_max = floor((nadir_pt(objective)-ev(obj_act_uniq(objective)))/stepsize)

    for i=1:length(point)
        if i == objective && i == 1
            ref_pts = [nadir_pt(1); point(1)-stepsize];
        elseif i == 1
            ref_pts = [nadir_pt(1); point(1)];
        elseif i == objective
            ref_pts = [ref_pts [nadir_pt(i); point(i)-stepsize]];
        else
            ref_pts = [ref_pts [nadir_pt(i); point(i)]];
        end
    end

    [weight, constant, wfull, cfull, val_lvls] = convex_pafs(constraints, obj_act_uniq, ref_pts, 1, 1);


    % Change the WS model to the LRPM model in the system and optimize
```

```
    [constraints_lrpm, dataopt_lrpm] = convert_to_lrpm(constraints,
       dataopt, obj_act_uniq, obj_act_all, weight, constant, rho);
    [xopt_lrpm, ofval, output, pddata, pdvars, constraints_out] =
       primaldual(dataopt_lrpm.misc.size, dataopt_lrpm, constraints_lrpm,
       options);
    xopt = xopt_lrpm(dataopt.misc.real);


    ev_temp = evaluate_objectives(xopt, dataopt, constraints);
    ev = [ev ev_temp];
end

ev_nadir = ev;
end
```

A.5. Optimizing with the nadir point as first reference point.

```
function ev_line = ref_line_zero(ev, constraints, num_points, dataopt, anchor_pts, nadir_pt, ideal_pt)
%REF_LINE_ZERO Generate reference points on a line of 45 degrees through the
%epsilon constraint solution and solve this with the reference point method
% ----------------------------------------------------------------------------
% input:    ev:
%           constraints:
%           objective: the index of the objective you want to minimize
%           n_iter: the number of iterations you wish to make
% output: ev_zero: matrix wich evaluates the objectives after applying the
%                  reference point method to different reference points
% ----------------------------------------------------------------------------


    options.DisplayIter = 0;
    options.DisplayInfoWarn = 0;
    [obj_act_uniq, obj_act_all, LTCP_all] = gather_obj(constraints);
    obj_act_uniq = gather_obj(constraints);

    % Some sensitivity parameter
    n_obj = length(obj_act_uniq);
    rho = zeros(1,n_obj);


    % Generate lines from the zero points through the anchor points
    l1 = [0 0 anchor_pts{1}(1) anchor_pts{1}(2)];
    l2 = [0 0 anchor_pts{2}(1) anchor_pts{2}(2)];

    % Generate a line of 45 degrees, through te epsilon-constraint solution
    l3 = [0 ev(obj_act_uniq(1))+ ev(obj_act_uniq(2)) ev(obj_act_uniq(1))+ ev(obj_act_uniq(2)) 0];


   % Calculate the points where the lines intersect
    [x1, y1] = lineintersect(l3,l1);
    [x2, y2] = lineintersect(l3,l2);

  % generate n reference points on the line
  ref_pts_2 = points_line([x1 y1], [x2 y2], num_points);


  % Optimize for the n reference points
for j=1:num_points

    % Generate reference points
    ref_pts = [ref_pts_2(j,1) ref_pts_2(j,2); 0 0]

```

```
    [weight, constant, wfull, cfull, val_lvls] = convex_pafs(constraints,
       obj_act_uniq, ref_pts, 1, 1);


    % Change the WS model to the LRPM model in the system and optimize
    [constraints_lrpm, dataopt_lrpm] = convert_to_lrpm(constraints,
       dataopt, obj_act_uniq, obj_act_all, weight, constant, rho);
    [xopt_lrpm, ofval, output, pddata, pdvars, constraints_out] =
       primaldual(dataopt_lrpm.misc.size, dataopt_lrpm, constraints_lrpm,
       options);
    xopt = xopt_lrpm(dataopt.misc.real);


    ev_temp = evaluate_objectives(xopt, dataopt, constraints);
    ev = [ev ev_temp];
end

ev_line = ev;

end
```