Technische Universiteit Delft
Faculteit Elektrotechniek, Wiskunde en Informatica
Delft Institute of Applied Mathematics

# Slimme multi-criteria optimalisatie voor radiotherapie

## (Engelse titel: Smart multi-criteria optimization for radiotherapy)

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# "Slimme multi-criteria optimalisatie voor radiotherapie"

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# Abstract

For multi-criteria optimization of radiation therapy treatment planning, several methods can be used. One method, the 2-phase $\epsilon$-constraint method, is to optimize each criterium, one at a time, to find an optimal radiation plan. The disadvantage of this method is that it takes a lot of computation time.

The purpose of this thesis is to investigate a new multi-criteria method, the multiple reference point method, which takes just one optimization. The multiple reference point method is compared with the 2-phase $\epsilon$-constraint method and with the weighted-sum optimization method with equal weights. This because of the simplicity of this method and because it also takes just one optimization.

The multiple reference point method is tested for several test cases, and for five real patients. The plans from the multiple reference point method is for large lists better than the weighted-sum plans with equal weights, and are about as well, and even sometimes better than the plans from the 2-phase $\epsilon$-constraint method.

# Contents

# Chapter 1

# Introduction

Around half of the patients diagnosed with cancer is treated with radiation therapy in some stage of the disease. The goal is to destroy the tumor, while saving the healthy tissues as much as possible. This can be done by implanting radioactive sources inside the patient (brachytherapy) or by using an external radiation source (external beam radiation therapy). In this work we look at the latter.

To spare normal tissues (such as skin or organs which radiation must pass through to treat the tumor), radiation beams are aimed from several angles to intersect at the tumor, providing a much larger dose there than in the surrounding, healthy tissue. The plan for such a radiation treatment is made using optimalisation programs, to choose the many degrees of freedom from the radiation equipment as optimal as possible. The outcome of this is a treatment plan in which the beam angles and other parameters are given. To compare these plans with each other the resulting dose distribution is calculated, based on the patient's planning CT-scan.

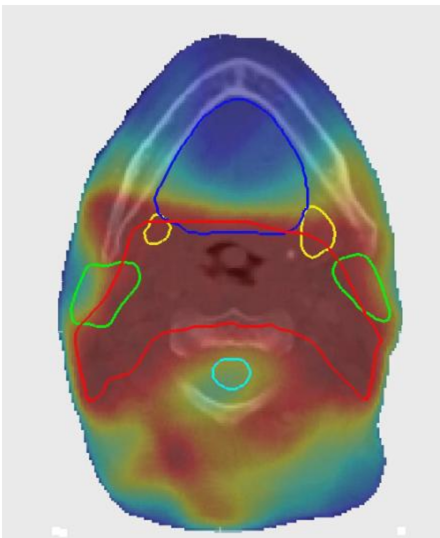

Figure 1.1: One slice of the dose distribution of a treatment plan.

Treatment plan optimization is a multiple criteria optimization problem, i.e. there are several treatment objectives. The most important one is that enough dose has to be delivered to the tumor. Besides that, you want the dose in the surrounding tissues to be as low as possible, to prevent complications. The number of criteria optimized on may even be larger, as often more than one criterion per structure may be involved. In a multiple criteria optimization problem trade-offs have to be made: some of the organs have a higher priority to be spared than other, every organ has its own sensitivity to radiation and sometimes one structure has to be sacrificed in order to keep more important structures functional.

All of these criteria are summarized in a list, the so-called 'wish-list'. One method is to optimize each criterium from the wish-list one at a time, to find an optimal radiation plan. The disadvantage of this method is that it takes a lot of computation time.

The purpose of this thesis is to investigate a new multi-criteria method, which needs fewer optimizations. The research project took place at the Erasmus MC - Daniel den Hoed Cancer Center in collaboration with the Delft Institute of Applied Mathematics.

In Chapter 2 several multi-criteria optimization methods are introduced. In Chapter 3 one of those, namely the multiple reference point method, is further explained. This is the multi-criteria method which is the main focus of this research project. In Chapter 4 some things are explained wich are necessarry to know before implementing the multiple reference point method. Next, in Chapter 5, 6, 7 and 8 the multiple reference point method is implemented for several kinds of simplified test cases, slowly building up to clinically relevant results. While doing this, the multi-criteria method is compared with the other multi-criteria optimization methods from Chapter 2 to investigate the quality. Finally, Chapter 9 concludes this report.

# Chapter 2

# Multi-criteria optimization methods

We consider a Multiple Criteria Optimization problem:

$$\begin{array}{ll} \text{minimize} & \{(f_1(\mathbf{x}),\ldots,f_m(\mathbf{x})) \quad : \mathbf{x} \in Q\} \\ \text{subject to} & \mathbf{g}(\mathbf{x}) \le \mathbf{0} \end{array} \tag{2.1}$$

where $\mathbf{x}$ denotes a vector of decision variables to be selected within the feasible set $Q \subset \mathbb{R}^n$. $\mathbf{x}$ represents a feasible treatment plan in which the beam angles and other parameters are given. $\mathbf{f}(\mathbf{x}) = (f_1(\mathbf{x}), f_2(\mathbf{x}), \ldots, f_m(\mathbf{x}))$ is a vector function that maps the feasible set $Q$ into the criterion space $\mathbb{R}^m$. The objectives are denoted by $f_i$, $i \in \{1, \ldots, m\}$. For readability, the constraints are summarized in a vector $\mathbf{g}(\mathbf{x})$, for which each element should be $\le 0$.

This multiple criteria optimization problem is a minimization problem because we want the dose in the tissue surrounding the tumor as low as possible, while giving the tumor enough dose. So, one of the constraints is that the tumor receives enough dose. $f_i$ for $i \in \{1, \ldots, m\}$ are the criteria for the dose in the tissues surrounding the tumor e.g. the maximum dose in the brainstem, or the mean dose in the larynx.

## 2.1 Weighted-sum optimization

The simplest way to solve an optimization problem in which there are several criteria to be considered, is the weighted-sum method (Breedveld et al. 2009). In the weighted-sum method, the objectives are weighted and summed together. Let the weights be denoted by $\mathbf{w} = (w_1, \ldots, w_m)$. The optimization problem to be solved becomes:

$$\begin{array}{ll} \text{minimize} & w_1 f_1(\mathbf{x}) + w_2 f_2(\mathbf{x}) + \cdots + w_m f_m(\mathbf{x}) \\ \text{subject to} & \mathbf{g}(\mathbf{x}) \le \mathbf{0} \end{array} \tag{2.2}$$

The sum of the weights is usually normalized to 1, to display the relative weights more clearly.

In this thesis we only use equal weights because this is the easiest way to distribute the weights. This is the solution where $w_1 = w_2 = \cdots = w_m$. The method is very quick. We use the results of the equal weights optimization to compare our results with. However, Breedveld et al. (2011) has proven that another optimization method gives clinically better results. So the results of the 2-phase $\epsilon$-constraint optimization method (section 2.2) are used as a golden standard.

## 2.2 2-phase $\epsilon$-constraint optimization

The second optimization method used in this thesis is the 2-phase $\epsilon$-constraint optimization method (Breedveld, 2009, 2012). For this method it has been proven that it gives clinically better results than the weighted-sum optimization method with equal weights (section 2.1).

This method is a multi-criteria optimization method in which the objectives, their priorities and goals are given in a prioritized list, the so-called wish-list. Each objective $f_i$ can occur several times in the list, with different goals. The basic idea behind this approach is to find a solution that satisfies the goal for the most important objective as well as possible before trying to meet the goals for the lower prioritized objectives. Each priority contains an objective and a goal. The list also contains (hard) constraints $\mathbf{g}(\mathbf{x})$ which are to be met at all times, see table 2.1.

Table 2.1: Wish-list.

| Priority | Objective | Goal |
|---|---|---|
| 1 | $f_1(\mathbf{x})$ | $b_1$ |
| 2 | $f_2(\mathbf{x})$ | $b_2$ |
| 3 | $f_3(\mathbf{x})$ | $b_3$ |
| | $\vdots$ | |
| m | $f_m(x)$ | $b_m$ |
| | $\mathbf{g}(\mathbf{x}) \leq 0$ | |

The optimization consists of two phases. If a goal is attainable ($f_i(\mathbf{x}) \leq b_i$), this objective is constrained to that goal before minimizing lower prioritized constraints. In a second run, this objective is minimized again, but now fully in order to obtain an optimal solution. If a goal is not obtainble, the objective is constrained to the value that was obtainable.

In the first iteration of the first phase, the objective having the highest priority is optimized:

$$\begin{array}{ll} \text{minimize} & f_1(\mathbf{x}) \\ \text{subject to} & \mathbf{g}(\mathbf{x}) \leq \mathbf{0} \end{array} \tag{2.3}$$

The result of this first minimization is plan $\mathbf{x}_1$. Depending on the result $\mathbf{x}_1$, a new bound is chosen. If the goal for $f_1$ is reached, so if $f_1(\mathbf{x}_1) \leq b_1$, then in further optimizations we set a new constraint: $f_1(\mathbf{x}) \leq b_1$, and go on to work on $f_2$. If the goal could not be reached, so if $f_1(\mathbf{x}_1) \geq b_1$, we set as a new constraint $f_1(\mathbf{x}) \leq \delta f_1(\mathbf{x}_1)$, where $\delta$ is usually set to 1.03 to create some space for further optimizations. So the new bound is chosen according to the following rule:

$$f_1(\mathbf{x}) \leq \epsilon_1 = \begin{cases} b_1, & \text{when} f_1(\mathbf{x}_1)\delta < b_1 \\ f_1(\mathbf{x}_1)\delta, & \text{when} f_1(\mathbf{x}_1)\delta \geq b_1 \end{cases} \tag{2.4}$$

where $\delta$ is usually set to 1.03.

In the next optimization $f_2$ is optimized, keeping $f_1$ constrained:

$$\begin{array}{lll} \text{minimize} & f_2(\mathbf{x}) & \\ \text{subject to} & \mathbf{g}(\mathbf{x}) & \leq \mathbf{0} \\ & f_1(\mathbf{x}) & \leq \epsilon_1 \end{array} \tag{2.5}$$

The result of this second minimization is plan $\mathbf{x}_2$. If the goal for $f_2$ is reached we set a new constraint: $f_2(\mathbf{x}) \leq b_2$. If the goal could not be reached we set a new constraint: $f_2(\mathbf{x}) \leq \delta f_2(\mathbf{x}_2)$, and go on to work on $f_3$.

This is repeated for all $m$ objectives. In general the new constraint is $f_i(\mathbf{x}) \leq \epsilon_i$ with

$$\epsilon_i = \begin{cases} b_i & f_i(\mathbf{x}_i)\delta < b_i \\ f_i(\mathbf{x}_i)\delta & f_i(\mathbf{x}_i)\delta \geq b_i \end{cases} \tag{2.6}$$

In the second phase of the multi-criteria optimization, all objectives which met their goals are minimized to their fullest, while keeping all others constrained. So, for each $f_i$ which met its goal $b_i$, solve, in order of priority:

$$\begin{array}{lll} \text{minimize} & f_i(\mathbf{x}) & \\ \text{subject to} & \mathbf{g}(\mathbf{x}) & \leq \mathbf{0} \\ & f_k(\mathbf{x}) & \leq \epsilon_k, \quad k \in \{1, \ldots, n\} \backslash i \end{array} \tag{2.7}$$

and then set $\epsilon_i = f_i(\mathbf{x}_i)\delta$ when optimizing for the lower order priorities.

## 2.3 The multiple reference point method

The purpose of this thesis is to investigate the multiple reference point method as a alternative to the 2-phase $\epsilon$-constraint optimization. The 2-phase $\epsilon$-constraint optimization method is our golden standard, because the results have clinically been proven to be better than the weighted-sum optimization method with equal weights. We also compare with the result of the weighted-sum optimization with equal weights, because of the simplicity of the method, and because it also takes one optimization (although the results are clinically inferior). With the multiple reference point method (MRPM), we want to get plans that are qualitatively comparible to the 2-phase $\epsilon$-constraint plans, (do much better than the weighted-sum plans with equal weights), but that have been obtained much faster than with the relatively slow 2-phase $\epsilon$-constraint method.

# Chapter 3

# The multiple reference point method

For the multiple reference point method (MRPM), we have to introduce a number of new quantities: reference points $\mathbf{r}^j$, value levels $v_j$, the partial achievement functions $a_i$, and the generic scalarizing achievement function $S$ (Ogryczak).

## 3.1 The reference points $\mathbf{r}^j$

Instead of the wish-list where for each priority level only one objective is optimized, at each priority $j$, we use a goal for each objective $i$: $\mathbf{r}^j = (r_1^j, r_2^j, \ldots, r_m^j)$. For example, the first priority level, $r_1^1$ is the goal for the first objective $f_1$, $r_2^1$ is the goal for objective $f_2$, ..., $r_m^1$ is the goal for the last objective $f_m$. With $K$ priority levels, we get $K$ reference points $\mathbf{r}^j$, $j = 1, \ldots, K$. This results in $K$ goals $r_i^j$ for each objective $f_i$. The goals in this minimization problem decrease with priority $j$: $r_i^j < r_i^{j-1}$.

## 3.2 The partial achievement functions $a_i(f_i(\mathbf{x}))$

The partial achievement functions $a_i$ are introduced to quantify how well the $i$-th objective has been met by current plan $\mathbf{x}$.

First introduce value levels $v_j$: $v_1 > v_2 > \cdots > v_K$ (so $v_K$ is the best level, with the lowest value). In section 3.3, extra conditions on the choice of $v_j$ are set to ensure convexity of the optimization problem. If in plan $\mathbf{x}$, the first priority for objective $i$ has been met exactly, so if $f_i(\mathbf{x}) = r_i^1$, the partial achievement function $a_i$ is set to $v_1$, so $a_i(f_i(\mathbf{x})) = v_1$. If plan $\mathbf{x}$ meets the second priority, $f_i(\mathbf{x}) = r_i^2$ (which is harder), the partial achievement function is set to $v_2$, so $a_i(f_i(\mathbf{x})) = v_2$.

If with plan $\mathbf{x}$ the objective $f_i(\mathbf{x})$ is not exactly a reference value, but lies in between two referene values, e.g. $r_i^2 < f_i(\mathbf{x}) < r_i^1$, the value of the partial achievement function is the linearly interpolated value between $v_1$ and $v_2$.

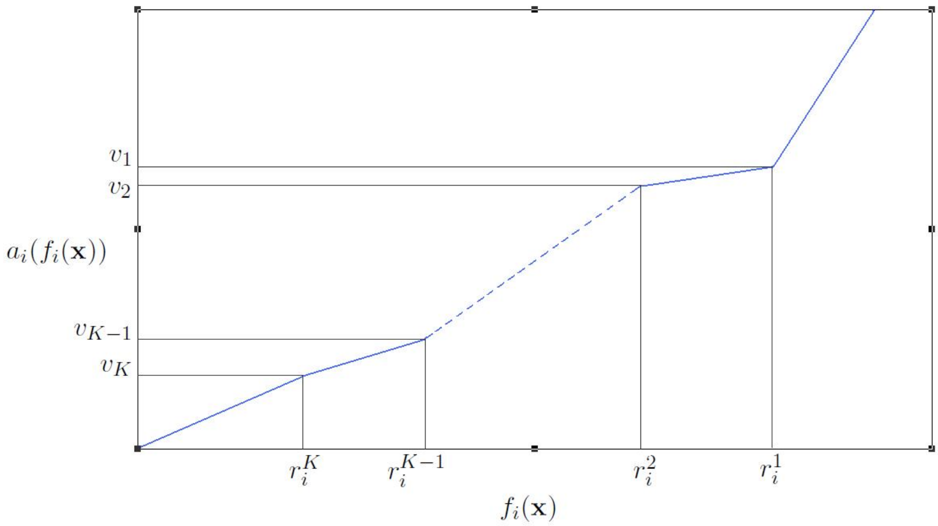


Figure 3.1: The partial achievement function.

This piece-wise linear increasing partial achievenment function takes the following form:

$$a_i(f_i(\mathbf{x})) = \begin{cases} v_K + \alpha(v_{K-1} - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^{K-1} - r_i^K), & f_i(\mathbf{x}) \le r_i^K \\ v_j + (v_{j-1} - v_j)(f_i(\mathbf{x}) - r_i^j)/(r_i^{j-1} - r_i^j), & r_i^j < f_i(\mathbf{x}) \le r_i^{j-1}, \quad j = 2, \ldots, K \\ v_1 + \gamma(v_1 - v_2)(f_i(\mathbf{x}) - r_i^1)/(r_i^1 - r_i^2), & f_i(\mathbf{x}) \ge r_i^1 \end{cases} \tag{3.1}$$

where $\alpha$ and $\gamma$ are arbitrarily defined parameters satisfying $0 < \alpha \le 1 \le \gamma$. Parameter $\alpha$ represents the additional increase of the satisfaction when the outcome is better than the last reference level $r_i^K$ . Parameter $\gamma$ represents the increase of dissatisfaction connected with outcomes worse than the first reference level $r_i^1$. Note that these parameters are unnecessary if $r_i^K \le f_i(\mathbf{x}) \le r_i^1$.

## 3.3 The generic scalarizing achievement function $S$

A special scalarizing achievement function is built which, when minimized, generates an efficient (Pareto optimal) solution to the problem. The generic scalarizing achievement function takes the following form:

$$S(\mathbf{a}) = \max_{1 \le i \le m} a_i + \frac{\epsilon}{m} \sum_{i=1}^{m} a_i \tag{3.2}$$

where $\epsilon$ is an arbitrary small positive number and $a_i$, for $i = 1, 2, \ldots, m$, are the partial achievements. The scalarizing achievement function is dominated by the worst partial (individual) achievement. The function is regularized by the sum of all partial achievements. The regularization term is introduced only to guarantee the solution efficiency in the case when the minimization of the main term (the worst partial achievement) results in a non-unique optimal solution.

Appropriately defined values $v_i$ allows one to guarantee convexity and thereby LP implementation. Namely, there is convexity whenever both $v_{K-1} > v_K$ and:

$$v_{j-1} > v_j + \max_{i=1,\dots,m} \frac{r_i^{j-1} - r_i^j}{r_i^j - r_i^{j+1}}(v_j - v_{j+1}) \quad j = 2, \dots, K-1 \tag{3.3}$$

Under this condition it is possible to express the MRPM (multiple reference point method) optimization as the following LP expansion:

$$\begin{array}{lll} \min & z + \frac{\epsilon}{m}\sum_{i=1}^{m} a_i & \\ \text{s.t.} & z \geq a_i & i = 1, \dots, m \\ & a_i \geq v_K + \alpha(v_{K-1} - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^{K-1} - r_i^K), & i = 1, \dots, m \\ & a_i \geq v_j + (v_{j-1} - v_j)(f_i(\mathbf{x}) - r_i^j)/(r_i^{j-1} - r_i^j), & i = 1, \dots, m, \quad j = 2, \dots, K \\ & a_i \geq v_1 + \gamma(v_1 - v_2)(f_i(\mathbf{x}) - r_i^1)/(r_i^1 - r_i^2), & i = 1, \dots, m \\ & \mathbf{x} \in Q & \end{array} \tag{3.4}$$

Where $z$ is the maximum of the $a_i$: $z = \max_{1 \leq i \leq m} a_i$.

# Chapter 4

# Preparation

With the MRPM-method, we want to get plans that are qualitatively comparable to that of the 2-phase $\epsilon$-constraint plans (do much better than the weighted-sum plans with equal weights) but that have been obtained much faster than with the relatively slow 2-phase $\epsilon$-constraint method.

## 4.1 Pareto optimality

We also want the solution to be *Pareto optimal*. Pareto optimality is a state of outcome in which it is impossible to improve any objective without worsening at least one other objective. Given an initial outcome, a change to a different outcome that makes at least one objective better without making any other objective worse is called a *Pareto improvement*. An outcome is defined as "Pareto optimal" when no further Pareto improvement can be made. If any outcome is not Pareto optimal, there is potential for a Pareto improvement: through reallocation, improvements can be made to at least one objective without making any other objective worse. Given a set of outcomes, the *Pareto front* is the set of outcomes that are Pareto optimal.

## 4.2 From wish-list to reference points

First the clinically used wish-list for the 2-phase $\epsilon$-constraint optimization method has to be translated into a set of reference points $\mathbf{r}^j$ (section 3.1). As an example we first consider a simple wish-list, where the objectives alternate (Table 4.1).

Table 4.1: A simple wish-list.

| Priority | Objective | Name | Goal |
|---|---|---|---|
| 1 | $f_1$ | Parotid R | 39 |
| 2 | $f_2$ | Parotid L | 39 |
| 3 | $f_1$ | Parotid R | 20 |
| 4 | $f_2$ | Parotid L | 20 |
| 5 | $f_1$ | Parotid R | 10 |
| 6 | $f_2$ | Parotid L | 10 |
| 7 | $f_1$ | Parotid R | 2 |
| 8 | $f_2$ | Parotid L | 2 |

The reference points would then look like this (Table 4.2):

Table 4.2: Reference points for the wish-list from Table 4.1.

| | $f_1$ | $f_2$ |
|---|---|---|
| $r^1$ | $r_1^1 = 39$ | $r_2^1 = 39$ |
| $r^2$ | $r_1^2 = 20$ | $r_2^2 = 20$ |
| $r^3$ | $r_1^3 = 10$ | $r_2^3 = 10$ |
| $r^4$ | $r_1^4 = 2$ | $r_2^4 = 2$ |

When the number of goals for one objective is not equal to those of another objective, creating the reference points is not so straightforward. Consider for example the following wish-list (Table 4.3) where the tumor dosage (PTV) is also an objective :

Table 4.3: Wish-list.

| Priority | Objective | Name | Goal |
|---|---|---|---|
| 1 | $f_1$ | PTV | 0.5 |
| 2 | $f_2$ | Parotid L | 39 |
| 3 | $f_2$ | Parotid L | 20 |
| 4 | $f_2$ | Parotid L | 10 |
| 5 | $f_2$ | Parotid L | 2 |

Then there is a problem, because the tumor (PTV) does not occur as often as the left parotid gland. To solve this, we looked at the following reference points (Table 4.4):

Table 4.4: Reference points for the wish-list from Table 4.3.

| | $f_1$ | $f_2$ |
|---|---|---|
| $r^1$ | 0.53 | 39 |
| $r^2$ | 0.52 | 20 |
| $r^3$ | 0.51 | 10 |
| $r^4$ | 0.50 | 2 |

This makes sure that $r_i^j < r_i^{j-1}, \ \forall i, j$. The first goal for the tumor is 0.53 instead of 0.50. We have investigated the results of the choice for these reference points in section 6.1.3.

## 4.3 An example of expressing reference points into an LP expansion

For example, let us consider a problem with two objectives and hierarchy of reference points:

| | $f_1$ | $f_2$ |
|---|---|---|
| $\mathbf{r}^1$ | $r_1^1 = 39$ | $r_2^1 = 39$ |
| $\mathbf{r}^2$ | $r_1^2 = 20$ | $r_2^2 = 20$ |
| $\mathbf{r}^3$ | $r_1^3 = 10$ | $r_2^3 = 10$ |
| $\mathbf{r}^4$ | $r_1^4 = 2$ | $r_2^4 = 2$ |

To reformulate the wish-list as a MRPM-problem, we start by choosing $v_4 = 0$ and $v_3 = 1$. Further we want to choose convex $v_2$ and $v_1$ according to condition (3.3). To do this we choose:

$$v_{j-1} = v_j + \max_{i=1,\dots,m} \frac{r_i^{j-1} - r_i^j}{r_i^j - r_i^{j+1}}(v_j - v_{j+1}) + 1 \qquad j = 2, \dots, K-1. \tag{4.1}$$

So $v_2 = v_3 + \max_{i=1,2} \frac{r_i^2 - r_i^3}{r_i^3 - r_i^4}(v_3 - v_4) + 1 = 1 + 1\frac{1}{4} + 1 = 3.25$ and $v_1 = v_2 + \max_{i=1,2} \frac{r_i^1 - r_i^2}{r_i^2 - r_i^3}(v_2 - v_3) + 1 = 3\frac{1}{4} + 1.9 \cdot (3\frac{1}{4} - 1) + 1 = 8.525$

We choose $\gamma = 10$, $\alpha = 0.1$ and $\epsilon = 2$. Then the MRPM model according to the model given in (3.4) takes the following form:

$$\begin{array}{lll}
\min & z + \frac{2}{2}(a_1 + a_2) & \\
\text{s.t.} & z \geq a_i & i = 1, 2 \\
& a_i \geq 0 + 0.1 \cdot (1 - 0)(f_i(\mathbf{x}) - 2)/(10 - 2) & i = 1, 2 \\
& a_i \geq 0 + (1 - 0)(f_i(\mathbf{x}) - 2)/(10 - 2) & i = 1, 2 \\
& a_i \geq 1 + (3.25 - 1)(f_i(\mathbf{x}) - 10)/(20 - 10) & i = 1, 2 \\
& a_i \geq 3.25 + (8.525 - 3.25)(f_i(\mathbf{x}) - 20)/(39 - 20) & i = 1, 2 \\
& a_i \geq 8.525 + 10 \cdot (8.525 - 3.25)(f_i(\mathbf{x}) - 39)/(39 - 20) & i = 1, 2 \\
& \mathbf{x} \in Q &
\end{array} \tag{4.2}$$

This problem is investigated in section 6.1.1.

# Chapter 5

# The multiple reference point method for two reference vectors

## 5.1 The reference point method model for two reference vectors

Real-life application of the reference poimt method usually deals with more complex partial achievement functions defined with more than one or two reference points. There is also a multiple reference point model for just two reference vectors. In this chapter this model for just two reference vectors is explained and implemented to see how the MRPM works.

The MRPM for two reference vectors is the same as the MRPM from chapter 3 with $v_1 = 1$ and $v_2 = 0$. For these value levels the partial achievement function for two reference levels looks like:

$$a_i(f_i(\mathbf{x})) = \begin{cases} \gamma(f_i(\mathbf{x}) - r_i^1)/(r_i^1 - r_i^2) + 1, & f_i(\mathbf{x}) \geq r_i^1 \\ (f_i(\mathbf{x}) - r_i^2)/(r_i^1 - r_i^2), & r_i^2 < f_i(\mathbf{x}) < r_i^1 \\ \alpha(f_i(\mathbf{x}) - r_i^2)/(r_i^1 - r_i^2), & f_i(\mathbf{x}) \leq r_i^2 \end{cases} \tag{5.1}$$

So it is possible to express this optimization as the following LP expansion:

$$\begin{array}{lll} \min & z + \frac{\epsilon}{m} \sum_{i=1}^{m} a_i & \\ \text{s.t.} & z \geq a_i & i = 1, \ldots, m \\ & a_i \geq \alpha(f_i(\mathbf{x}) - r_i^2)/(r_i^1 - r_i^2) & i = 1, \ldots, m \\ & a_i \geq (f_i(\mathbf{x}) - r_i^2)/(r_i^1 - r_i^2) & i = 1, \ldots, m \\ & a_i \geq \gamma(f_i(\mathbf{x}) - r_i^1)/(r_i^1 - r_i^2) + 1 & i = 1, \ldots, m \\ & \mathbf{x} \in Q & \end{array} \tag{5.2}$$

## 5.2 Results for two reference vectors

For this model we are going to look at some results to get some understandig how this model works. To do this, we tested the model on a test ase where we only looked at the left parotid ($f_1$) and submandibular gland ($f_2$). For these tests we took $r_i^2 = 0, i = 1, 2$. This to make sure that after the first goal is reached the objectives are further minimized.

Table 5.1: Results for different reference points.

| Reference points | $f_1$ | $f_2$ |
|---|---|---|
| $r_1^1 = 39$, $r_2^1 = 39$ | 17.449 | 33.346 |
| $r_1^1 = 20$, $r_2^1 = 20$ | 20.000 | 32.709 |
| $r_1^1 = 20$, $r_2^1 = 33$ | 18.406 | 33.000 |
| $r_1^1 = 10$, $r_2^1 = 10$ | 17.449 | 33.346 |

If we look at the results in Table 5.1, we see that if the first reference level is attainable for both objectives ($r_1^1 = 39, r_2^1 = 39$), the objectives both are minimized further. Next if the first reference level is attainable for just one objective, that objective is minimized to that level and the other one is minimized further ($r_1^1 = 20$, $r_2^1 = 20$). If the first reference level is attainable for both objectives but one of them restricts the other, this objective is optimized to the reference level and the other objective is minimized further ($r_1^1 = 20$, $r_2^1 = 33$). This is the case here because for lower values of $f_1$ the value of $f_2$ becomes higher. If the first referenc level is not attainable for both objectives, the objectives both are minimized as far as possible ($r_1^1 = 10$, $r_2^1 = 10$).

# Chapter 6

# The multiple reference point method for two objectives

## 6.1 Results for two objectives

For two objectives the Pareto front is given by the weighted-sum optimization method. Namely, if the weighted-sum optimization problem is solved for varying combinations of weights for two objectives, we get a Pareto front.

To calculate the results the objectives are imported from a wish list, and a function for adding constraints and variables is needed. These function can be found in Appendix C.1. Next, the goals are imported and the results are calculated according to the reference point model using the codes from C.2.

### 6.1.1 The multiple reference point method for the parotid glands

The MRPM has been tested on several kinds of simplified test cases. The first is a test case where we only look at the right and the left parotid gland. Here our wish-list is the one given in Table 4.1 so our model is the model in the example (section 4.3) .

If we look at the results in Figure 6.1 we can see that all solutions lie on the Pareto front, as expected. The result of our MRPM though differs quit a bit from our wish-point, but if you look closer you see that the difference is just 0.9 Gray for the right parotid gland and just 0.6 Gray for the left parotid gland. So, that actually looks promising. The only problem here is that the equal weights solution gives a relatively better result in comparison with the wish-point than our MRPM optimum. This because it is closer to the wish-point on the Pareto front than our MRPM optimum. Maybe that is just a coincidence, so to give a decent conclusion we have used the method in other configurations for this filtered patients.

### 6.1.2 The multiple reference point method for the parotid gland and the submandibular gland

The next test case involved the left parotid ($f_1$) and left submandibular gland ($f_2$). Here our MRPM model is again exactly the same model as in the example (section 4.3) but we are looking at different objectives.

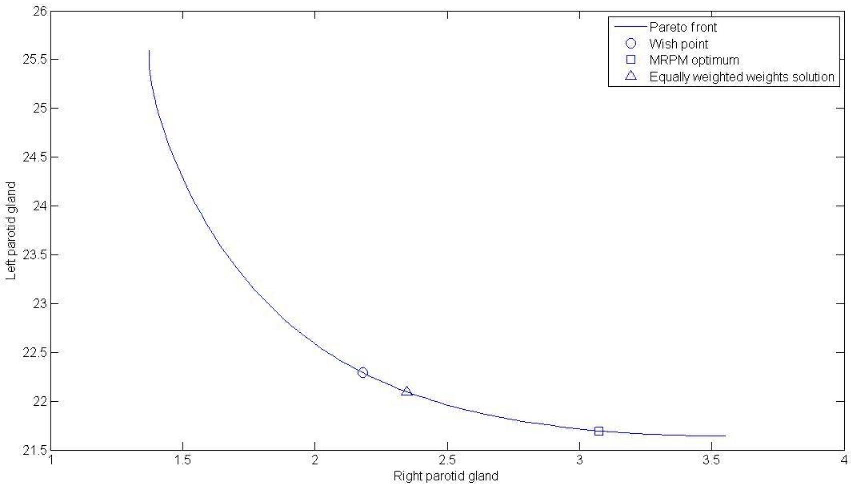


Figure 6.1: Comparison between the solution obtained by the MRPM and the wish-point on a Pareto front for the right and left parotid gland.

It can be seen in figure 6.2 that the MRPM solution also lies on the Pareto front, so it is a Pareto-optimal solution. The difference here with the wish-point is just 1.5 Gray for the left parotid gland and just 0.4 Gray for the left submandibular gland. Here we see again that the equal weights solution gives a slightly better result compared to the MRPM optimum.

### 6.1.3 The multiple reference point method for the parotid gland and the tumor

Next we consider an other kind of test case. With this case our first objective ($f_1$) (an exponential function) for the tumor should become 0.5. The lower the value of this function, the better the tumor is irraditated. Because this is an exponential function, the difference could become very large for a (somewhat) worse plan. The reference points have been shown in Table 4.4.

In Figure 6.3 we see again that the MRPM solution lies on the Pareto front, so it is a Pareto-optimal solution. The difference here with the wish-point is just 0.1 Gray for the left parotid gland and just 0.04 Gray for the tumor. Also, we see in this figure for the first time that the MRPM optimum gives a better result than the equal weights solution in comparison with the wish-point.

### 6.1.4 The multiple reference point method for the parotid gland and the 1-cm ring around the tumor

Next we look at the parotid gland ($f_1$) and a 1-cm ring around the tumor ($f_2$). With this patient our second objective is to get the dose in the 1-cm ring around the tumor to 34.5 Gray. This ring is used to improve the confirmity (i.e. less high dose outside the tumor). The wish-list is given in Table 6.1.

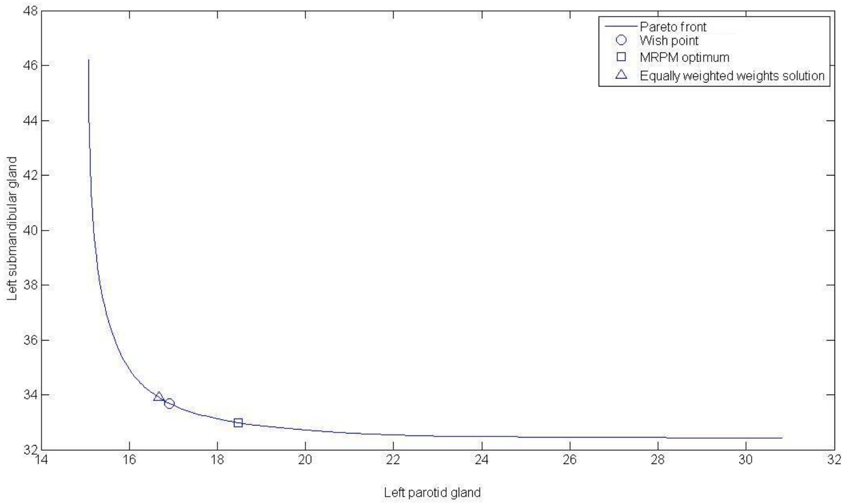


Figure 6.2: Comparison between the solution obtained by the MRPM and the wish-point on a Pareto front for the parotid and the submandibular gland.

Table 6.1: Wish-list for the parotid gland and the 1-cm ring around the tumor.

| Priority | Objective | Name | Goal |
|---|---|---|---|
| 1 | $f_1$ | Parotid | 39 |
| 2 | $f_1$ | Parotid | 20 |
| 3 | $f_1$ | Parotid | 10 |
| 4 | $f_1$ | Parotid | 2 |
| 5 | $f_2$ | PTV 1-cm ring | 34.5 |

Our reference points are therefore made in the same way as the reference points in Table 4.4:

Table 6.2: Reference points for the wish-list in Table 6.1.

| | $f_1$ | $f_2$ |
|---|---|---|
| $r^1$ | 39 | 34.53 |
| $r^2$ | 20 | 34.52 |
| $r^3$ | 10 | 34.51 |
| $r^4$ | 2 | 34.50 |

figure 6.4 gives the results for the right parotid gland and the 1-cm ring around the tumor. figure 6.5 gives the results for the left parotid gland and the 1-cm ring around the tumor.

Again the MRPM solution lies on the Pareto front in both figures, so the MRPM solution is a Pareto-optimal solution. The difference in figure 6.4 from the MRPM optimum with the wish-point is just 0.8 Gray for the right parotid gland and just 0.7 Gray for the 1-cm ring around the tumor.

In figure 6.5 the difference from the MRPM optimum with the wish-point is again small: 2 Gray for the left parotid gland and 1.3 gray for the 1-cm ring around the tumor. The equal weights in these cases give a better result than our MRPM optimum.

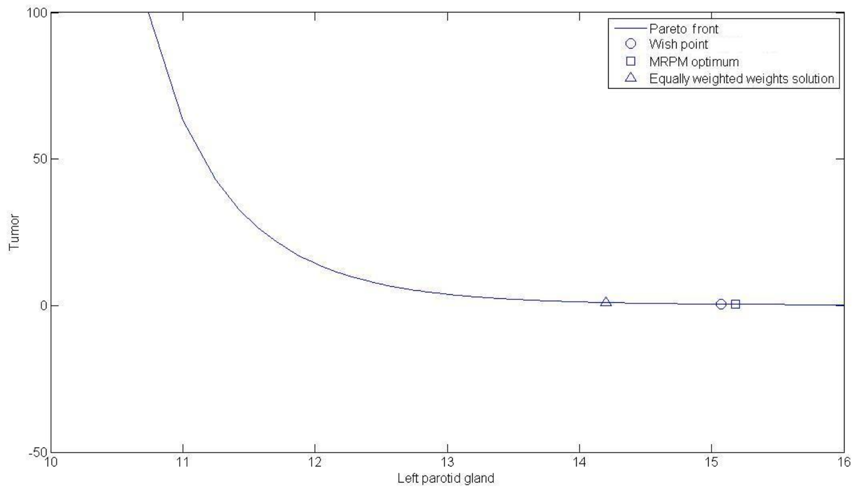


Figure 6.3: Comparison between the solution obtained by the MRPM and the wish-point on a Pareto front for the parotid gland and the tumor.

## 6.2 Moving the multiple reference point method optimum

The results from the MRPM are promising but we still can not prove that this method gives better results than the easiest way to solve multi-criteria optimaziation problems namely by using the quick weighted-sum optimization method. We want to find a way to get our MRPM optimum closer to our wish-point. Luckily, there are a lot things we have chosen along the way. Maybe a different choise will give better results.

### 6.2.1 Changing the parameters

In chapter 3, we could choose quite a few parameters if we make sure they satisfy their conditions. $\alpha$ and $\gamma$ can be chosen according to the condition $0 < \alpha \leq 1 \leq \gamma$. After some testing on a certain patient with a lot of different combinations of these two variables it seems that these parameters do not really have a lot of influence on our MRPM optimum.

For $\epsilon$ we know that $\epsilon$ has to be a small positive number. The first implementations were all with $\epsilon = 2$. Some testing shows that if $\epsilon$ gets a lot larger like 5 or 10, the MRPM optimum goes a little bit to the left on the Pareto front, but are values of 5 or 10 not to large for a supposed to be small number?

Our value levels $v_j$: $v_1 > v_2 > \cdots > v_K$ have to be choosen according to the condition given in (3.3) because we want to make sure that our problem is convex. The first implementations were all with $v_{j-1} = v_j + \max_{i=1,\ldots,m} \frac{r_i^{j-1} - r_i^j}{r_i^j - r_i^{j+1}}(v_j - v_{j+1}) + 1$ for $j = 2, \ldots, K-1$, so they were chosen according to condition (3.3). To make sure that the value levels are chosen according to the condition (3.3) there are several implementations possible. If $v_{j-1}$ is a lot bigger than the given condition, for example if $v_{j-1} = v_j + \max_{i=1,\ldots,m} \frac{r_i^{j-1} - r_i^j}{r_i^j - r_i^{j+1}}(v_j - v_{j+1}) + 100$ or $v_{j-1} = 10 \cdot (v_j + \max_{i=1,\ldots,m} \frac{r_i^{j-1} - r_i^j}{r_i^j - r_i^{j+1}}(v_j - v_{j+1}))$, it seems that the MRPM optimum goes to the right on the Pareto front. So this is something to investigate further. Unfortunately, as we have

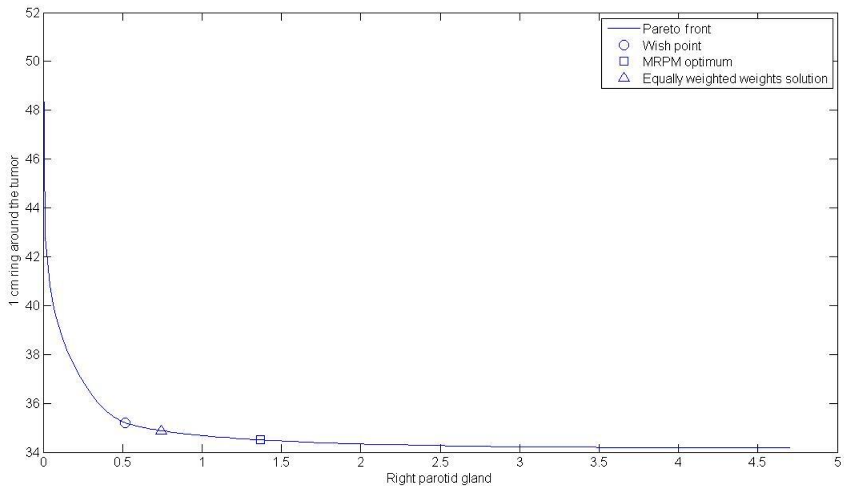


Figure 6.4: Comparison between the solution obtained by the MRPM and the wish-point on a Pareto front for the right parotid gland and the 1-cm ring around the tumor.

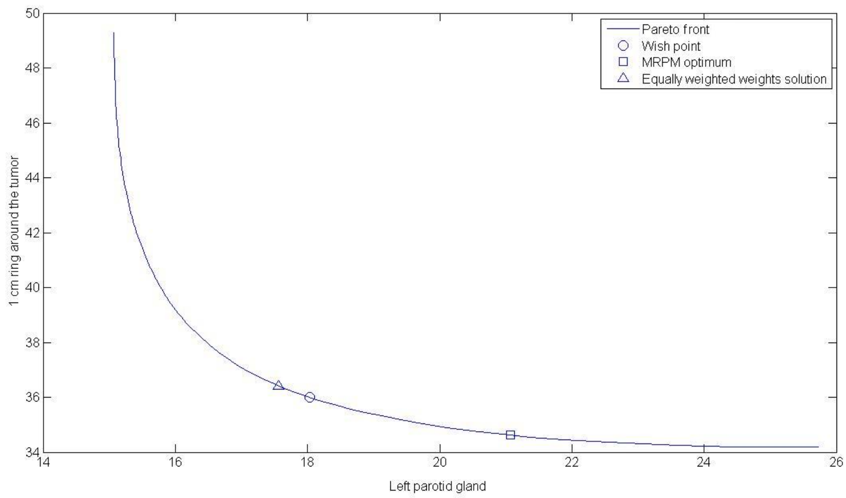


Figure 6.5: Comparison between the solution obtained by the MRPM and the wish-point on a Pareto front for the left parotid gland and the 1-cm ring around the tumor.

seen in section 6.1 the MRPM optimum is not always further to the left (or always further to the right) on the Pareto front.

The only parameters that have some influence are thus our value levels $v_j$. $\alpha$ and $\gamma$ had really no influence on our MRPM optimum, and $\epsilon$ a bit but this is supposed to be a small positive number. This is something to remember. First we want to make sure that the MRPM works for real patient cases. Maybe it is then necessary to change the MRPM optimum to get better results.

### 6.2.2 Introducing more reference points

Another way to get the MRPM optimum closer to our wish-point could be to introduce more reference points. If we look at the model from the example (4.2) we could introduce more reference points as follows:

Table 6.3: More reference points.

| | $f_1$ | $f_2$ |
|---|---|---|
| $\mathbf{r}^1$ | 39 | 39 |
| $\mathbf{r}^2$ | $20+e$ | $39-e$ |
| $\mathbf{r}^3$ | 20 | 20 |
| $\mathbf{r}^4$ | $10+e$ | $20-e$ |
| $\mathbf{r}^5$ | 10 | 10 |
| $\mathbf{r}^6$ | $2+e$ | $10-e$ |
| $\mathbf{r}^7$ | 2 | 2 |

To investigate the effect of more reference points, we looked at the left parotid ($f_1$) and submandibular gland ($f_2$) just as in 6.1.2 and in 5.2. For these objectives we see the results in Table 6.4. These are calculated with the same parameters as we used before. So $\alpha = 0.1, \gamma = 10, \epsilon = 2$ and the value levels are choosen according to equation (4.1).

Table 6.4: Results for more reference points.

| $e$ | $f_1$ | $f_2$ |
|---|---|---|
| 1 | 17.4488 | 33.3461 |
| 2 | 17.4488 | 33.3461 |
| 3 | 22.0816 | 32.5429 |
| 4 | 18.1791 | 33.0636 |
| 5 | 17.8327 | 33.1798 |
| 6 | 17.2270 | 33.4676 |
| 7 | 22.0816 | 32.5429 |

We have calculated the results up to $e = 7$ because for $e = 8$, $r_1^5 = r_1^6 = 10$ and $r_2^6 = r_2^7 = 2$ but we want to make sure that $r_i^j < r_i^{j-1}$, $\forall i, j$.

If we look at the results in Table 6.4 we see that the MRPM optimum first goes right on the Pareto front, then goes left on the Pareto front and then again goes right on the Pareto front. So introducing more reference points really influences the MRPM optimum.

This is thus something to consider if it necessary to change the MRPM optimum to get better results after we made sure that the MRPM works for real life patients. But then we have to implement this in some other way, because it is not always the case that $r_1^j = r_2^j$ for every $j$.

# Chapter 7

# The multiple reference point method for multiple objectives

So far the results of the MRPM were just for two objectives. In real life applications it rarely happens that there are just two objectives to be considered. In this chapter the MRPM is implemented for more than two objectives, to do this the codes from Appendix C.3 are used.

## 7.1 Results for four and five objectives

With the MRPM, we want to get plans that are qualitatively comparible to that of the 2-phase $\epsilon$-constraint plans, or are at least much better than the weighted-sum plans with equal weights. Besides that, we want that the MRPM plans to Pareto optimal. With two objectives we can easily check Pareto optimality by comparing them to the Pareto front. With more objectives this is no longer possible, because it becomes computationally too expensive to generate the Front. The MRPM plans are Pareto optimal by theory (section 3.3), and we have shown that our implementations does indeed deliver 8-optimal plans for bi-objective problems.

For more than two objectives it is easier to compare the results in a dose-volume histogram. In a dose-volume histogram the column height of the first bin ($0-1$ Gray, e.g.) represents the part of the volume of the structure that receives more than or equal to that dose. The column height of the second bin ($1.001-2$ Gray, e.g.) represents the volume of structure receiving at least that dose, etc. With very fine (small) bin sizes, the dose-volume histogram takes on the appearance of a smooth line graph. The curves always start at the top-left and end bottom-right. For the tumor the curve should be as high as possible, and decrease vere steeply at the highest dose. For surrounding tissues you want the curves to be as low as possible.

### 7.1.1 The multiple reference point method for the glands

For the first patient with multiple objectives we looked at the parotid and submandibular glands. For this patient the wish-list looks like:

Table 7.1: Wish-list for the glands.

| Priority | Objective | Name | Goal |
|---|---|---|---|
| 1 | $f_1$ | Parotid R | 39 |
| 2 | $f_2$ | Parotid L | 39 |
| 3 | $f_3$ | Submandibular R | 39 |
| 4 | $f_4$ | Submandibular L | 39 |
| 5 | $f_1$ | Parotid R | 20 |
| 6 | $f_2$ | Parotid L | 20 |
| 7 | $f_3$ | Submandibular R | 20 |
| 8 | $f_4$ | Submandibular L | 20 |
| 9 | $f_1$ | Parotid R | 10 |
| 10 | $f_2$ | Parotid L | 10 |
| 11 | $f_3$ | Submandibular R | 10 |
| 12 | $f_4$ | Submandibular L | 10 |
| 13 | $f_1$ | Parotid R | 2 |
| 14 | $f_2$ | Parotid L | 2 |
| 15 | $f_3$ | Submandibular R | 2 |
| 16 | $f_4$ | Submandibular L | 2 |

So the corresponding reference points for this patient look like:

Table 7.2: Reference points for the wish-list from Table 7.1.

| | $f_1$ | $f_2$ | $f_3$ | $f_4$ |
|---|---|---|---|---|
| $\mathbf{r}^1$ | $r_1^1 = 39$ | $r_2^1 = 39$ | $r_3^1 = 39$ | $r_4^1 = 39$ |
| $\mathbf{r}^2$ | $r_1^2 = 20$ | $r_2^2 = 20$ | $r_3^2 = 20$ | $r_4^2 = 20$ |
| $\mathbf{r}^3$ | $r_1^3 = 10$ | $r_2^3 = 10$ | $r_3^3 = 10$ | $r_4^3 = 10$ |
| $\mathbf{r}^4$ | $r_1^4 = 2$ | $r_2^4 = 2$ | $r_3^4 = 2$ | $r_4^4 = 2$ |

For these reference points the results look as follows:

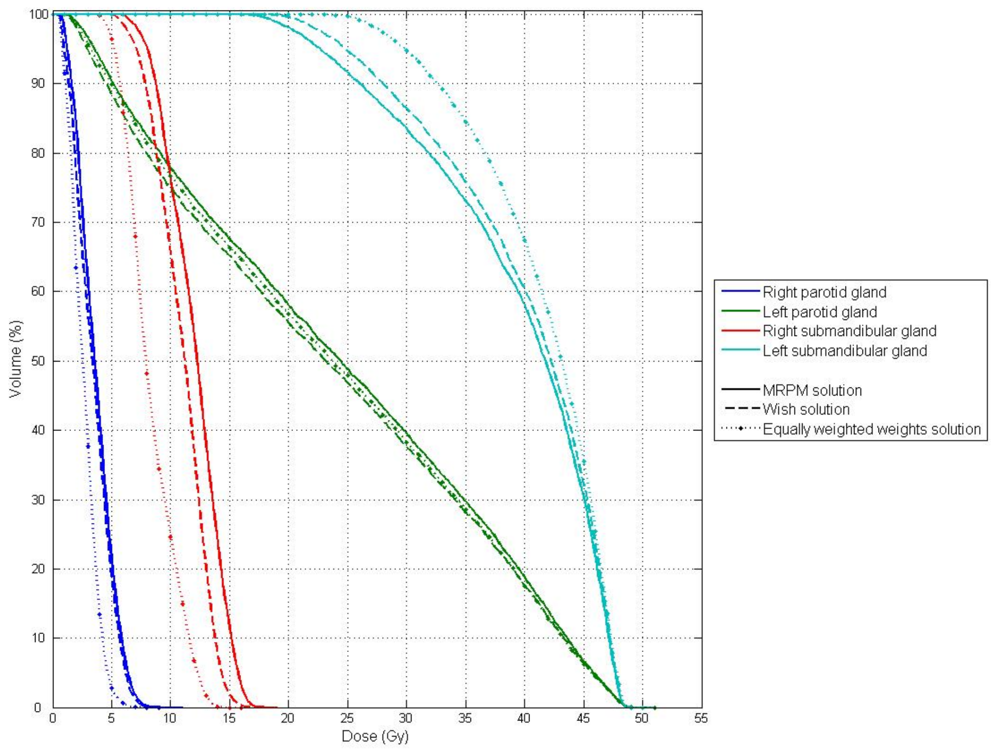


Figure 7.1: Comparison between the solution obtained by the MRPM, the wish-solution and the equal weights solution for the parotid and the submandibular glands in a dose-volume histogram. Curves close to the origin are generally prefered.

In Figure 7.1 we see that the three plans obtained with different methods are quite comparable. For the right parotid gland the MRPM solution and the wish-solution are almost the same, but the equal weights solution is a bit better, because it lies beneath the other curves, so there is more volume that receives less dose. For the left parotid gland all the solutions are almost the same. For the right submandibular gland, the MRPM solution is a little bit worse than the wish-solution, and the equal weights solution is a little bit better. For the left submandibular gland, the MRPM solution is a little bit better than the wish-solution, and the equal weights solution is quite a bit worse.

The results can also be summarised in Table 7.3. In this table the mean doses are shown.

Table 7.3: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for the wish-list from Table 7.1.

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| Parotid R | 3.433 | 3.652 | 2.613 |
| Parotid L | 23.517 | 24.383 | 23.904 |
| SMG R | 10.956 | 12.033 | 8.321 |
| SMG L | 39.795 | 39.040 | 41.434 |

In Table 7.3 we see that for the right parotid gland the MRPM solution lies very close to the wish-solution. For the left parotid gland the equal weights solution actually lies closer to the wish-solution than the MRPM solution. With the submandibular glands the MRPM solution lies again closer to the wish-solution than the equal weights solution. Also we see the same results as in the dose-volume histogram for example, for the right parotid gland the MRPM solution and the wish-solution are almost exactly the same, but the equal weights solution is a bit better. This because it has a lower value (we are minimizing the objectives).

### 7.1.2 The multiple reference point method for the glands and the tumor

Next we looked at a combination of the parotid glands, the submandibular glands and the tumor, where we have again an exponential function as an objective for the tumor, which makes it interesting as the order of magnitude behaves much differently compared to the other objectives. So the goal of 0.5 for $f_1$ is not in Gray but the value of the exponential function of the dose. The wish-list for this patient is shown in Table 7.4.

Table 7.4: Wish-list for the glands and the tumor.

| Priority | Objective | Name | Goal |
|---|---|---|---|
| 1 | $f_1$ | PTV | 0.5 |
| 2 | $f_2$ | Parotid R | 39 |
| 3 | $f_3$ | Parotid L | 39 |
| 4 | $f_4$ | Submandibular R | 39 |
| 5 | $f_5$ | Submandibular L | 39 |
| 6 | $f_2$ | Parotid R | 20 |
| 7 | $f_3$ | Parotid L | 20 |
| 8 | $f_4$ | Submandibular R | 20 |
| 9 | $f_5$ | Submandibular L | 20 |
| 10 | $f_2$ | Parotid R | 10 |
| 11 | $f_3$ | Parotid L | 10 |
| 12 | $f_4$ | Submandibular R | 10 |
| 13 | $f_5$ | Submandibular L | 10 |
| 14 | $f_2$ | Parotid R | 2 |
| 15 | $f_3$ | Parotid L | 2 |
| 16 | $f_4$ | Submandibular R | 2 |
| 17 | $f_5$ | Submandibular L | 2 |

The reference points for this patient are shown in Table 7.5

Table 7.5: Reference points for the wish-list from Table 7.4.

| | $f_1$ | $f_2$ | $f_3$ | $f_4$ | $f_5$ |
|---|---|---|---|---|---|
| $r^1$ | 0.53 | 39 | 39 | 39 | 39 |
| $r^2$ | 0.52 | 20 | 20 | 20 | 20 |
| $r^3$ | 0.51 | 10 | 10 | 10 | 10 |
| $r^4$ | 0.50 | 2 | 2 | 2 | 2 |

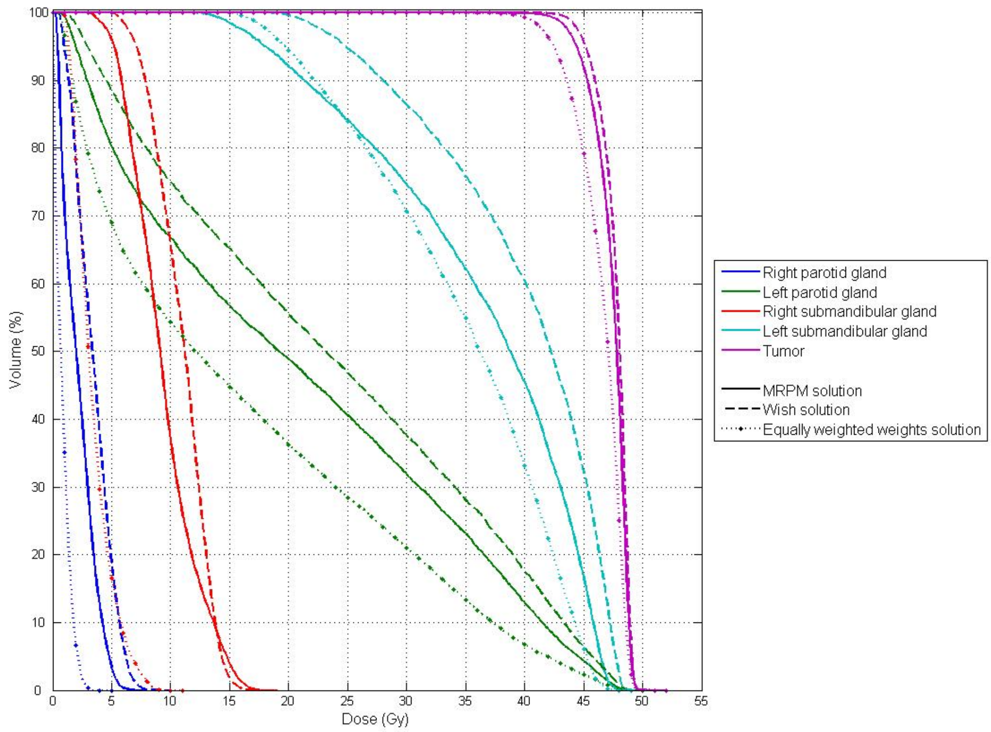


Figure 7.2: Comparison of the solution obtained by the MRPM, the wish-solution and the equal weights solution for the parotid and the submandibular glands in a dose-volume histogram.

In Figure 7.2 we now see some clear differences between the three plans. For the glands, the MRPM solution is quite a bit better than the wish-solution, but the equal weights solution is even better. For the tumor, the MRPM solution and the wish-solution are almost the same, but the equal weights solution is quite a bit worse. This because we want to maximize the dose in the tumor. In this case, the dose to the tumor is not sufficient, thus the pan is clinically unacceptable.

Table 7.6: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for the wish-list from Table 7.4.

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| PTV | 0.500 | 0.895 | 4.429 |
| Parotid R | 3.433 | 2.170 | 0.804 |
| Parotid L | 23.517 | 20.699 | 16.148 |
| SMG R | 10.956 | 9.347 | 3.391 |
| SMG L | 39.795 | 36.005 | 34.537 |

In Table 7.6 we also see the same results. First we see that the MRPM solution for the right submandibular gland and the tumor lies a lot closer to the wish-solution than the equal weights solution. For the parotid glands and the left submandibular gland the MRPM solution also lies closer to the wish-solution than the equal weights solution. Unfortunately, their are no hard conclusion that can be made from the results so far, because of the different trade-offs involved.

This example also clearly demonstrates the differences between the weightd-sum method and the others. Increasing the PTV objective by almost 4 gives room to reduce the sum of the other objectives over 20 compared to the WS solution. However, the increment of 4 for the PTV has a different impact than the gain of 20. The MRPM works goal-based, and better sticks to the desired solutions of interest.

## 7.2 Problem with a realistic number of objectives

To draw hard conclusions about the results of the MRPM, we want to calculate real clinically relevant plans for patients. For these patients there are often even more than four or five objectives to be considered, and the wish-list is usually a bit more complex than the wish-lists we looked at so far. An example of a clinical wish-list is shown in Table 7.7.

Table 7.7: An example of a clinical wish-list.

| Priority | Objective | Name | Goal |
|---|---|---|---|
| 1 | $f_1$ | Parotid R | 39 |
| 2 | $f_2$ | Parotid L | 39 |
| 3 | $f_3$ | Submandibular R | 39 |
| 4 | $f_4$ | Submandibular L | 39 |
| 5 | $f_1$ | Parotid R | 20 |
| 7 | $f_3$ | Submandibular R | 20 |
| 6 | $f_2$ | Parotid L | 20 |
| 8 | $f_4$ | Submandibular L | 20 |
| 9 | $f_5$ | Oral cavity | 39 |
| 10 | $f_6$ | Cord | 40 |
| 11 | $f_7$ | External ring | 41.4 |
| 12 | $f_8$ | Larynx | 34.5 |
| 13 | $f_9$ | MCM | 34.5 |
| 14 | $f_{10}$ | MCI | 34.5 |
| 15 | $f_{11}$ | PTV ring 1 cm | 34.5 |
| 16 | $f_1$ | Parotid R | 10 |
| 17 | $f_2$ | Parotid L | 10 |
| 18 | $f_3$ | Submandibular R | 10 |
| 19 | $f_4$ | Submandibular L | 10 |
| 20 | $f_{12}$ | PTV ring 4 cm | 18.4 |
| 21 | $f_1$ | Parotid R | 2 |
| 22 | $f_2$ | Parotid L | 2 |
| 23 | $f_3$ | Submandibular R | 2 |
| 24 | $f_4$ | Submandibular L | 2 |

It is a problem if we want to transform this wish-list into reference points, because there are several objectives that do not occur as often as for the parotid and the submandibular glands. To solve this while transforming this wish-list to reference points, we use the same technique as we used is section 4.3. The reference points then are given in Table 7.8.

Table 7.8: Possible reference points for the wish-list from Table 7.7.

| | $f_1$ | $f_2$ | $f_3$ | $f_4$ | $f_5$ | $f_6$ | $f_7$ | $f_8$ | $f_9$ | $f_{10}$ | $f_{11}$ | $f_{12}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\mathbf{r}^1$ | 39 | 39 | 39 | 39 | 39.03 | 40.03 | 41.43 | 34.53 | 34.53 | 34.53 | 34.53 | 18.43 |
| $\mathbf{r}^2$ | 20 | 20 | 20 | 20 | 39.02 | 40.02 | 41.42 | 34.52 | 34.52 | 34.52 | 34.52 | 18.42 |
| $\mathbf{r}^3$ | 10 | 10 | 10 | 10 | 39.01 | 40.01 | 41.41 | 34.51 | 34.51 | 34.51 | 34.51 | 18.41 |
| $\mathbf{r}^4$ | 2 | 2 | 2 | 2 | 39.00 | 40.00 | 41.40 | 34.50 | 34.50 | 34.50 | 34.50 | 18.40 |

In these reference points, we have lost a lot of priorities. For example $f_{12} = 18.43 \approx 18.4$ has the same priority in the reference points as $f_1 = 39$. In the wish-list $f_1 = 20$ and $f_1 = 10$ actually have a higher priority then $f_{12} = 18.4$. So it seems that this transformation is not the transformation we are looking for.

# Chapter 8

# Combining the multiple reference point method with the model for two reference points

## 8.1 Combined multiple reference point method model

It can happen that in the wish-list one of the objectives does not occur as often as one of the other objectives. To transform the wish-list to reference points without too much loss of priority we can use a different number of reference levels for different objectives. For example, if we look at the wish-list from Table 7.7 we could use the following reference points:

Table 8.1: Possible reference points for the wish-list from Table 7.7.

| | $f_1$ | $f_2$ | $f_3$ | $f_4$ | $f_5$ | $f_6$ | $f_7$ | $f_8$ | $f_9$ | $f_{10}$ | $f_{11}$ | $f_{12}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $r^1$ | 39 | 39 | 39 | 39 | | | | | | | | |
| $r^2$ | 20 | 20 | 20 | 20 | 39 | 40 | 41.4 | 34.5 | 34.5 | 34.5 | 34.5 | |
| $r^3$ | 10 | 10 | 10 | 10 | | | | | | | | 18.4 |
| $r^4$ | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

But now we do not have an equal amout of reference points for each objective. To solve this we look at a partial achievement function that is just like described in Chapter 3 for the objectives with more than two reference levels and resembles the function decribed in Chapter 5 for the objectives with just two reference levels. Because we want the priorities preserved we only use different value levels for the objectives with just two reference levels. Namely we still want $a_i(f_i(\mathbf{x})) = v_j$ if $f_i(\mathbf{x}) = r_i^j$ for $i = 1, \ldots, m$.

We introduce $p$ as the highest priority of a reference point, for an objective with just two reference levels, so $p = 2$ for $f_5$ in Table 8.1, and let $n$ be the number of the first objective with just two reference levels, so $n = 5$ in Table 8.1, the partial achievement function for $i = 1, \ldots, n-1$ becomes:

$$a_i(f_i(\mathbf{x})) = \begin{cases} v_K + \alpha(v_{K-1} - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^{K-1} - r_i^K) & f_i(\mathbf{x}) \leq r_i^K \\ v_k + (v_{j-1} - v_j)(f_i(\mathbf{x}) - r_i^k)/(r_i^{j-1} - r_i^j) & r_i^j < f_i(\mathbf{x}) \leq r_i^{j-1} \quad j = 2, \ldots, K \\ v_1 + \gamma(v_1 - v_2)(f_i(\mathbf{x}) - r_i^1)/(r_i^1 - r_i^2) & f_i(\mathbf{x}) \geq r_i^1 \end{cases} \tag{8.1}$$

The partial achievement function for $i = n, \dots, m$ becomes:

$$a_i(f_i(\mathbf{x})) = \begin{cases} v_K + \alpha(v_p - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^p - r_i^K) & f_i(\mathbf{x}) \leq r_i^K \\ v_K + (v_p - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^p - r_i^K) & r_i^K < f_i(\mathbf{x} < r_i^p \\ v_p + \gamma(v_p - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^p - r_i^K) & f_i(\mathbf{x}) \geq r_i^p \end{cases} \quad (8.2)$$

From this partial achievement functions we can derive the following optimization problem:

$$\begin{array}{lll} \min & z + \frac{\epsilon}{m}\sum_{i=1}^m a_i & \\ \text{s.t.} & z \geq a_i & i = 1, \dots, m \\ & a_i \geq v_k + \alpha(v_{K-1} - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^{K-1} - r_i^K) & i = 1, \dots, n-1 \\ & a_i \geq v_k + (v_{j-1} - v_j)(f_i(\mathbf{x}) - r_i^k)/(r_i^{j-1} - r_i^j) & i = 1, \dots, n-1; \quad k = 2, \dots, K \\ & a_i \geq v_1 + \gamma(v_1 - v_2)(f_i(\mathbf{x}) - r_i^1)/(r_i^1 - r_i^2) & i = 1, \dots, n-1 \\ & a_i \geq v_K + \alpha(v_p - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^p - r_i^K) & i = n, \dots, m \\ & a_i \geq v_K + (v_p - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^p - r_i^K) & i = n, \dots, m \\ & a_i \geq v_p + \gamma(v_p - v_K)(f_i(\mathbf{x}) - r_i^K)/(r_i^p - r_i^K) & i = n, \dots, m \\ & \mathbf{x} \in Q & \end{array} \quad (8.3)$$

## 8.2 Results

### 8.2.1 The multiple reference point method for real patients

If we use the derived model to calculate the MRPM solution for the patient with the wish-list from Table 7.7, using the codes from Appendix C.3, we get the following results.

Table 8.2: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for the wish-list from Table 7.7.

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| Parotid R | 2.361 | 2.086 | 0.872 |
| Parotid L | 19.279 | 21.547 | 20.417 |
| SMG R | 10.000 | 7.000 | 3.660 |
| SMG L | 33.690 | 34.694 | 39.978 |
| | | | |
| Oral cavity | 28.603 | 24.805 | 24.372 |
| Cord | 28.096 | 16.496 | 13.803 |
| External ring | 4.243 | 3.778 | 3.665 |
| Larynx | 30.237 | 21.639 | 19.311 |
| MCM | 32.225 | 22.217 | 17.125 |
| MCI | 29.668 | 17.312 | 14.944 |
| PTV ring 1 cm | 40.632 | 43.383 | 43.130 |
| PTV ring 4 cm | 35.209 | 25.718 | 24.987 |

If we look at the results in Table 8.2, the MRPM solution is clinically to be preferred over the other results. This because although the values for the left parotid and submandibular gland are a bit higher then those of the wish-solution, the values of the oral cavity, the external ring, the larynx, the MCM and the MCI are all substantially lower. Besides that, the cord even has a value below 20 Gray, what is preferable, if possible, because it allows irradiation in recurrent treatment. The MRPM optimum is also prefered over the solution of the weighted-sum optimization method with equal weights. This because the mean dose in the left submandibular almost 40 Gray for the equal weights solution, and this means a 20 percent higher chance on complications than with the other solutions.

To conclude, the results of five real patient calculated. These results can be found in Appendix B. One thing that really stands out is that for a little bit of loss for the glands there is a lot to win for the oral cavity, cord, brainstem, external ring and the esophagus. It depends on the patient and dose-interval if this loss is acceptable. For higher dose values a little change can result in a higher chance of complications. For example if the submandibular glands get 40 Gray the chance on complications is 20 percent higher than if it gets 39 Gray or less.

### 8.2.2 Weights

But what if you get a relatively good plan with just one value that is too high for your liking. Is it possible to reduce this value without to much loss of conformity?

So far we looked at the generic scalarizing achievement function $S$ wich looks like:
$S(a) = \max_{1\leq i\leq m} a_i + \frac{\epsilon}{m}\sum_{i=1}^{m} a_i$. The scalarizing achievement function is dominated by the worst partial achievement. The function is regularized by the sum of all partial achievements. We could see this as the worst partial achievement which is regularized by the sum of all partial achievements with weights $\frac{\epsilon}{m}$ (Ogryczak, 1997). To make one of the objectives more important we could change this weight.

Table 8.3: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS).

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| Parotid R | 4.198 | 5.258 | 1.468 |
| Parotid L | 17.438 | 17.744 | 17.341 |
| SMG R | 10.000 | 5.258 | 3.787 |
| SMG L | 30.300 | 31.460 | 37.662 |
| | | | |
| Oral cavity | 23.154 | 19.337 | 19.486 |
| Cord | 28.528 | 13.544 | 11.296 |
| External Ring | 4.711 | 3.875 | 3.633 |
| Larynx | 28.730 | 17.913 | 16.232 |
| MCM | 32.223 | 19.879 | 14.900 |
| MCI | 28.748 | 14.064 | 12.830 |
| PTV ring 1 cm | 34.559 | 39.087 | 36.270 |
| PTV ring 4 cm | 22.492 | 19.214 | 17.387 |

For example, if we look at the results in Table 8.3 the MRPM solution is a lot better for some objectives than the wish-solution, but the value of the PTV ring 1-cm is a bit too high. Maybe we can change this by changing the weights on the partial achievement of this objective.

In Table 8.4 the results are given for the results of the MRPM with different weights on the PTV ring 1-cm. We see that if the weight on the PTV ring 1-cm gets higher, the max dose gets lower.

Table 8.4: The MRPM solutions for a regular weight on the PTV ring 1 cm and for the weight twice and three times as big.

| Objective | Regular | 2x | 3x |
|---|---|---|---|
| Parotid R | 5.258 | 5.258 | 5.258 |
| Parotid L | 17.744 | 18.119 | 18.443 |
| SMG R | 5.258 | 5.258 | 5.258 |
| SMG L | 31.460 | 31.720 | 31.922 |
| | | | |
| Oral cavity | 19.337 | 19.748 | 20.142 |
| Cord | 13.544 | 14.579 | 14.950 |
| External Ring | 3.875 | 3.840 | 3.835 |
| Larynx | 17.913 | 17.857 | 18.065 |
| MCM | 19.879 | 20.130 | 20.509 |
| MCI | 14.064 | 14.407 | 14.842 |
| PTV ring 1 cm | 39.087 | 36.051 | 34.484 |
| PTV ring 4 cm | 19.214 | 18.613 | 18.356 |

Besides that, what is actually more important is that the rest of the values did not get much worse. So this gives us a way to reduce this value without too much loss of conformity. This is especially an advantage in comparison with the weighted-sum optimization method, because with that method you can also vary the weights but this can give completely different results.

# Chapter 9

# Conclusions

We were looking for a method with which we can get plans that are qualitatively comparible to that of the 2-phase $\epsilon$-constraint plans, do much better than the weighted-sum plans with equal weights, but can be obtained much faster than with the relatively slow 2-phase $\epsilon$-constraint method.

The multiple reference point method is at least a lot faster that the relatively slow 2-phase $\epsilon$-constraint method. Unfortunately, I had no time left to investigate the differences in depth but the multiple reference method finds an Pareto-optimal solution for the according reference points in just one optimization. This in comparison with the 2-phase $\epsilon$-constraint method, which needs at least one optimization for each objective in the wish-list.

Besides that, the plans from the multiple reference point method is for large lists better than the weighted-sum plans with equal weights, and are about as well, and even sometimes better than the plans from the 2-phase $\epsilon$-constraint method. It is hard to draw a hard conclusion about the quality because it differs per patient what is acceptable and desired. So this all depends on clinical considerations that have to be made.

One adventage of the multiple reference point method is that if you know that a certain value is too high you can get it lower without getting a totally different plan by putting different weights on the partial achievements. Besides that you could use more reference points or other choosen value levels to change the optimum, but this needs some more investigation. Changing the parameters $\alpha, \gamma$ and $\epsilon$ is also possible, but hardly influence the results.

# Appendix A

# References


1. Breedveld, S., Storchi, P.R.M. & Heijmen, B. (2009). The equivalence of multi-criteria methods for radiotherapy plan optimization. *Physics in medicine and biology*, 54, 7199 - 7209.

2. Breedveld, S. (2012). Prioritized multi-criteria optimization by sequential $\epsilon$-constraint programming - by example.

3. Ogryczak, W. Multiple reference point method as preemptive wish list.

4. Ogryczak, W. (1997). Preemptive reference point method. *Springer verslag*, 156-167.

5. Ogryczak, W. & Kozlowski, B. (2009). Referene point method with importance weighed ordered partial achievements.

# Appendix B

# Results

## B.1 Patient 1

Table B.1: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for patient 1.

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| Parotid R | 20.000 | 20.875 | 21.383 |
| Parotid L | 20.000 | 17.904 | 18.141 |
| SMG R | 28.253 | 34.083 | 33.830 |
| SMG L | 32.930 | 34.754 | 34.556 |
| | | | |
| Oral cavity | 22.538 | 15.647 | 13.427 |
| Cord | 30.000 | 11.489 | 10.967 |
| Brainstem | 19.883 | 5.463 | 5.445 |
| External Ring | 41.400 | 26.185 | 24.922 |
| Larynx | 45.870 | 44.216 | 45.664 |
| | | | |
| SCM | 46.146 | 44.216 | 45.296 |
| MCM | 46.917 | 44.216 | 44.895 |
| MCI | 47.086 | 44.216 | 44.766 |
| MCP | 34.500 | 29.023 | 29.260 |
| Esophagus | 24.890 | 17.491 | 17.794 |
| PTV ring 1 cm | 45.954 | 36.333 | 34.686 |
| PTV ring 2 cm | 39.973 | 28.045 | 24.717 |

## B.2 Patient 2

Table B.2: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for patient 2.

| Objective | WS | MRPM | EWS |
|---:|---:|---:|---:|
| Parotid R | 23.977 | 29.124 | 29.803 |
| Parotid L | 27.065 | 30.474 | 31.153 |
| SMG R | 41.783 | 43.212 | 44.880 |
| SMG L | 43.374 | 43.212 | 45.259 |
| | | | |
| Oral cavity | 39.000 | 33.395 | 32.073 |
| Cord | 29.926 | 8.430 | 8.164 |
| Brainstem | 29.451 | 6.045 | 5.502 |
| External Ring | 41.400 | 28.303 | 26.108 |
| | | | |
| SCM | 48.164 | 46.053 | 45.137 |
| MCM | 47.653 | 45.659 | 44.767 |
| MCI | 47.470 | 44.845 | 44.015 |
| MCP | 34.500 | 27.450 | 27.065 |
| Esophagus | 33.466 | 23.524 | 23.385 |
| PTV ring 1 cm | 47.793 | 35.074 | 32.863 |
| PTV ring 2 cm | 40.512 | 24.674 | 21.956 |

## B.3 Patient 3

Table B.3: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for patient 3.

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| Parotid R | 15,770 | 9,403 | 10,051 |
| Parotid L | 20,000 | 21,848 | 22,405 |
| SMG R | 21,853 | 26,869 | 26,862 |
| SMG L | 42,706 | 42,945 | 45,805 |
| | | | |
| Oral cavity | 26,437 | 20,352 | 18,399 |
| Cord | 30,000 | 8,226 | 8,406 |
| Brainstem | 21,668 | 6,398 | 6,720 |
| External Ring | 41,230 | 27,820 | 25,702 |
| Larynx | 48,084 | 48,084 | 47,458 |
| | | | |
| SCM | 39,721 | 42,409 | 41,104 |
| MCM | 46,166 | 45,248 | 44,338 |
| MCI | 46,727 | 45,399 | 44,526 |
| MCP | 38,141 | 35,924 | 35,155 |
| PTV ring 1 cm | 47,620 | 35,856 | 34,077 |
| PTV ring 2 cm | 44,301 | 26,361 | 23,121 |

## B.4 Patient 4

Table B.4: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for patient 4.

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| Parotid R | 8.053 | 6.421 | 7.049 |
| Parotid L | 10.000 | 19.547 | 21.305 |
| SMG R | 2.475 | 3.214 | 2.989 |
| SMG L | 3.262 | 3.423 | 3.356 |
| | | | |
| Cord | 28.023 | 7.683 | 5.837 |
| Brainstem | 29.849 | 9.760 | 6.799 |
| External Ring | 46.959 | 40.079 | 36.609 |
| Larynx | 0.132 | 0.132 | 0.128 |
| | | | |
| SCM | 14.778 | 14.119 | 13.238 |
| MCM | 0.206 | 0.191 | 0.184 |
| MCI | 0.000 | 0.000 | 0.000 |
| MCP | 0.000 | 0.000 | 0.000 |
| Esophagus | 0.000 | 0.000 | 0.000 |
| PTV ring 1 cm | 49.412 | 43.663 | 47.866 |
| PTV ring 2 cm | 33.073 | 40.874 | 35.542 |

## B.5 Patient 5

Table B.5: The MRPM solution, the wish-solution (WS) and the equal weights solution (EWS) for patient 5.

| Objective | WS | MRPM | EWS |
|---|---|---|---|
| Parotid R | 18,019 | 22,848 | 21,643 |
| Parotid L | 11,506 | 14,099 | 13,071 |
| Cord | 21,402 | 7,318 | 6,500 |
| Brainstem | 16,181 | 5,193 | 4,353 |
| External Ring | 34,844 | 27,404 | 26,915 |
| Larynx | 34,500 | 29,919 | 27,917 |
| PTV ring 1 cm | 34,497 | 30,671 | 34,078 |
| PTV ring 2 cm | 28,921 | 24,864 | 23,503 |

# Appendix C

# Codes

## C.1 Preparation

```
function [constraints] = add_rpm_constraint(constraints, idx, a, b, dvidx)
nidx = length(constraints)+1;
constraints(nidx) = constraints(idx);
constraints(nidx).VolName = sprintf('RPM helper for %s', constraints(nidx).VolName);
constraints(nidx).Objective = 0;
constraints(nidx).Minimize = 1;
constraints(nidx).Chain = [constraints(nidx).Type a b dvidx];
constraints(nidx).Type = 6;
constraints(nidx).Bounds = 1;
constraints(nidx).Priority = 0;
constraints(nidx).Active = 1;
constraints(nidx).numcons = 1;

% Disable this objective
constraints(idx).Active = 0;
```

```
function [constraints, data]= add_rpm_variable(constraints, data, name, dvidx, epsilon, obj)

nidx = length(constraints)+1;

% Adding constraints of new variable
constraints(nidx).datID = length(data.matrix)+1;
constraints(nidx).VolName = name;
constraints(nidx).Minimize = 1;
constraints(nidx).Type = 1;
constraints(nidx).Objective = 0;
constraints(nidx).ObjectiveMax = [];
constraints(nidx).ObjectiveSufficient = [];
constraints(nidx).Weight = 1;
constraints(nidx).Parameters = [];
constraints(nidx).Active = 1;
constraints(nidx).numcons = 1;
constraints(nidx).Chain = [];

% Should the new variable be minimized?
if strcmp(name,'RPM helper for z')
    constraints(nidx).Priority = 0;
    constraints(nidx).Bounds = 1;
else
```

```
    constraints(nidx).Priority = 1;
    constraints(nidx).Bounds = 0;

end

% Adjusting data to new variable
data.matrix(constraints(nidx).datID).A = zeros(1, data.misc.size);
data.matrix(constraints(nidx).datID).b = 0;
data.matrix(constraints(nidx).datID).c = [];
data.matrix(constraints(nidx).datID).Type = 0;
data.matrix(constraints(nidx).datID).numvox = 1;
data.matrix(constraints(nidx).datID).Z.UseMM = 0;
data.matrix(constraints(nidx).datID).Z.UseMV = 0;
data.matrix(constraints(nidx).datID).Z.B = [];

dvidxz = data.misc.size;
if strcmp(name,'RPM helper for z')
    data.matrix(constraints(nidx).datID).A([dvidx dvidxz ]) = [1 -1];
else
    data.matrix(constraints(nidx).datID).A([dvidx]) = 1 ;
    data.matrix(constraints(nidx).datID).A([dvidx+1]) = 1 ;
    data.matrix(constraints(nidx).datID).A([dvidxz]) = 1;

end
```

```
function[OIdx] = make_rpm_OIdx(constraints)

nidx = length(constraints);

A = zeros(nidx,1);
m = 1;
for k = 1:nidx
    if constraints(k).Active == 1
        if constraints(k).Bounds == 0
            for l = 1 : k -1;
                if constraints(l).Bounds == 0
                    A(l) = strcmp(constraints(l).VolName,constraints(k).VolName);
                end
            end
            B = (A == 0);
            if all(B)
                first(m) = k;
                m = m+1;
            end
        end
    end
end

OIdx = zeros(length(first),1);
for l = 1 : length(first)
    OIdx(l) = first(l);
end
```

## C.2 Two objectives

```
function [s,c] = make_rpm_constraints(OV)

% Er moet gelden 0 < alpha <= 1 <= gamma
```

```
alpha = 0.1;
gamma = 10;




p = size(OV);
n = p(2);
m = zeros(p(1),n);
v = zeros(n,1);

if p(2) == 1
    OV(:,2) = OV(:,1);
    n = n+1;
end


for j = 1 : p(1)
    for k = 1 : n -1
        if OV(j,n -k) - (1/100) <= OV(j,n -k +1)
            OV(j, n -k) = OV(j, n -k) + 1/100*k;
        end
    end
end


v(n) = 0;
v(n-1) = 1;


% v(k-1) is voorwaarde (5) + 1
for j = 1:p(1);
    for i = 2 : n-1
        m(j,n-i) = (OV(j,n-i)-OV(j,n-i+1))/(OV(j,n-i+1)-OV(j,n-i+2)) ;
    end
end

for i = 2: n-1
    v(n-i) = v(n-i+1) + max(m(:,i)) *(v(n-i+1)-v(n-i+2)) +1  ;
end



% w volgens (3)
% we nemen w gelijk voor alle objectives
w = zeros(n,p(1));
for k = 2 : n
    for i = 1 : p(1)
        w(k,i) = (v(k-1)-v(k))/(OV(i,k-1)-OV(i,k));
    end
end

s = w;
for q = 1 : p(1)
    s(1,q) = alpha*w(2,q);
    s(n +1,q) = gamma*w(n,q);
end


c = zeros(n+1,p(1));
for l = 1 : n
```

```
    for o = 1:p(1)
        c(l,o) = v(l)-s(l,o)*OV(o,l);
    end
end

for o = 1:p(1)
    c(n+1,o) = v(n)-s(n+1,o)*OV(o,n);
end
```

```
function [OV ] = make_rpm_OV(constraints, OIdx)

tel = zeros(length(OIdx),1);
for k = 1 : length(OIdx)
    for q = 1 : length(constraints)
        if constraints(q).Bounds == 0
            if strcmp(constraints(OIdx(k)).VolName, constraints(q).VolName)
                tel(k) = tel(k) + 1;
            end
        end
    end
end

lengte = max(tel);

OV = zeros(length(OIdx),lengte);
index = zeros(length(OIdx),lengte);
nidx = length(constraints);


for j = 1 : length(OIdx)
     l = 1;
     for i = OIdx(j) : nidx
        if strcmp(constraints(i).VolName, constraints(OIdx(j)).VolName)
            if constraints(i).Bounds == 0
                if j > 1 && l <= lengte - 1
                    if OV(j-1,l) ~= OV(j-1,l+1)
                        if  i < index (j-1,l+1)
                            OV(j,l) = constraints(i).Objective;
                            index(j,l) = i;
                            l = l+1;
                        else
                            OV(j,l+1) = constraints(i).Objective;
                            index(j,l+1) = i;
                            l = l+2;
                        end
                    else
                        if i > index(j-1,l) && index(j-1,l)~=0
                            OV (j,l) = constraints(i).Objective;
                            index(j,l) = i;
                            l= l+1;
                        else
                            l=l+1;
                        end
                    end
                else
                    OV(j,l) = constraints(i).Objective;
                    index(j,l) = i;
                    l = l+1;
                end
```

```
            end
        end
     end
    if l < lengte + 1
        for n = l : lengte
            OV(j,n) = OV(j, n-1);
            index(j,n) = index(j, n-1);
        end
    end
end

if lengte > 1
    if all(OV(:,1)>0)
    else
        hulp = OV;
        OV = zeros(length(OIdx),lengte - 1);
        for m = 1 : lengte - 1
            OV(:,m) = hulp(:,m+1);
        end
    end
end



end
```

```
function [constraints, data] = make_rpm_problem(constraints, data, OIdx, OV)

% Deactivating the other objectives
nidx = length(constraints);
for l = 1 : nidx
    if all(l ~= OIdx)
        if constraints(l).Bounds == 0
        constraints(l).Active = 0;
        end
    end
end

% Number of objectives
n = length(OIdx);

% Add decision variables
dvidx=zeros(n+1,1);
for i = 1 : n+1
    [constraints, data] = add_dv(constraints, data);
    dvidx(i) = data.misc.size;
end

% New constraint, based on constraint idx
[scalair, constant] = make_rpm_constraints(OV);

for k = 1 : n
    for j = 1: size(scalair,1)
        constraints = add_rpm_constraint(constraints, OIdx(k), scalair(j,k), constant(j,k), dvi
    end
end

% Add another new objective, which is to be minimized
for j = 1 : n
```

```
    [constraints, data] = add_rpm_variable(constraints, data, 'RPM helper for z', dvidx(j));
end

% add z variable
epsilon = 2;
[constraints, data] = add_rpm_variable(constraints, data, 'RPM minimizer', dvidx(1), epsilon, n);
```

## C.3 Multiple objectives

```
options.DisplayExternal=''; % Grafisch
options.DisplayIter=0;
options.DisplayInfo=0;
options.DisplayInfoWarn=0;


% In case we have to instantiate a file requestor, direct them to the
% patients dir
if exist(fullfile(pwd, 'patients'), 'dir')
    StartDir = 'patients';
else
    StartDir = '';
end

[PatFile, PatDir] = uigetfile(fullfile(StartDir, '*.xml'), 'Select patient file');
PatFile = fullfile(PatDir, PatFile);

% Import patient
fprintf('Importing patient.\n')
[Patient, constraints, data, metadata] = import_patient_data(PatFile);

% Set beams
Beams = setup_beams(metadata, 'MC');

% Combine all beams
fprintf('Generating %d beams.\n', Beams.Num);
[dataopt, constraints, data, metadata, Beams] = combine_beams(data, constraints, metadata, Patient,
[dataopt, constraints] = add_nonneg_constraint(dataopt,constraints);




% Calculating the rpm solution
OIdx = make_rpm_OIdx(constraints);
OV = make_rpm_OV(constraints, OIdx);


constraints_rpm = constraints;
dataopt_rpm = dataopt;

for i = 1 : length(OIdx)
   if constraints_rpm(OIdx(i)).numcons > 1
      [constraints_rpm, dataopt_rpm] = convert_to_minimax(constraints_rpm, dataopt_rpm, OIdx(i));
   end
end

[constraints_rpm, dataopt_rpm] = make_rpm_problem(constraints_rpm, dataopt_rpm, OIdx, OV);


[xopt_rpm, ofval_rpm, output_rpm, pddata_rpm, pdvars_rpm] = primaldual(dataopt_rpm.misc.size, dataop
```

```
ev_rpm = evaluate_objectives(xopt_rpm, dataopt_rpm, constraints_rpm);

return

% Calculating the mc solution

% Reorder data in mcopt
options_mc.ReorderData = 1;

[xopt_mc, ofval_mc, output_mc, pddata_mc, pdvars_mc, constraintsmc, xfeas_mc, dataopt_mc] = mco
ev_mc = evaluate_objectives(xopt_mc, dataopt_mc, constraintsmc);



% Calculating the weighted sum with equal weights
constraints_ws = constraints;
n = length(constraints);
a = zeros(n,1);
for j = 1:n
    for k = 1:n
        if strcmp(constraints_ws(k).VolName, constraints_ws(j).VolName)
            if constraints_ws(k).Bounds == 0
                if a(j) == 0
                    a(j) = 1;
                else
                    constraints_ws(k).Weight = 0;
                end
            end
        end
    end
end

[xopt, ofval, output, pddata, pdvars] = primaldual(dataopt.misc.size, dataopt, constraints_ws,
ev_ws = evaluate_objectives(xopt, dataopt, constraints_ws);



for j=1:length(ev_mc)
    if constraints(j).Active
        AcFlag = ' ';
    else
        AcFlag = '*';
    end
    fprintf('%-20s %s(%2d): %5.2g\t%5.2g\t%5.2g\n', constraints(j).VolName, AcFlag, j, ev_mc(j)
end
```

```
function [constraints] = make_rpm_constraints_combi(OV, constraints, OIdx, dvidx)

% Er moet gelden 0 < alpha <= 1 <= gamma
alpha = 0.1;
gamma = 10;




p = size(OV);
n = p(2); %number of priorities
k = p(1); %number of objectives
m = zeros(k,n);
```

```
v = zeros(n,1);
e = 0;

for q = 1:k
    if OV(q,2) == 0
        l(e+1) =  OV(q,1);
        e = e+1;
    end
end

for p = 1 : e;
    hulp = OV;
    k = k-1;
    OV = zeros(size(hulp,1) -1, size(hulp,2));
    for t = 1 : size(hulp,1)-1
        OV(t,:) = hulp(t,:);
    end
end



v(n) = 0;
v(n-1) = 1;


% v(k-1) is voorwaarde (5) + 1
for j = 1:k;
    for i = 2 : n-1
        m(j,n-i) = (OV(j,n-i)-OV(j,n-i+1))/(OV(j,n-i+1)-OV(j,n-i+2)) ;
    end
end

for i = 2: n-1
    v(n-i) = v(n-i+1) + max(m(:,i)) *(v(n-i+1)-v(n-i+2)) +1   ;
end




w = zeros(n,k);
for c = 2 : n
    for i = 1 : k
        w(c,i) = (v(c-1)-v(c))/(OV(i,c-1)-OV(i,c));
    end
end

s = w;
for q = 1 : k
    s(1,q) = alpha*w(2,q);
    s(n +1,q) = gamma*w(n,q);
end


c = zeros(n+1, k);
for b = 1 : n
    for o = 1: k
        c(b,o) = v(b)-s(b,o)*OV(o,b);
    end
end

for o = 1: k
```

```
    c(n+1,o) = v(n)-s(n+1,o)*OV(o,n);
end

for k = 1 : size(s,2)
    for j = 1: size(s,1)
        constraints = add_rpm_constraint(constraints, OIdx(k), s(j,k), c(j,k), dvidx(k));
    end
end

if e~=0
    for f = 5 : 11
        %vk = ri^k = 0
        s2 = zeros(3);
        s2(1) = alpha*v(2)/l(f-4);
        s2(2) = v(2)/l(f-4);
        s2(3) = gamma*v(2)/l(f-4);

        for d = 1 : 3
            constraints = add_rpm_constraint(constraints, OIdx(f), s2(d), 0, dvidx(length(dvidx
        end
    end

    f=12;
    s2 = zeros(3);
    s2(1) = alpha*v(3)/l(f-4);
    s2(2) = v(3)/l(f-4);
    s2(3) = gamma*v(3)/l(f-4);

    for d = 1 : 3
        constraints = add_rpm_constraint(constraints, OIdx(f), s2(d), 0, dvidx(length(dvidx)-1)
    end

end

end
```

```
function [OV ] = make_rpm_OV_combi(constraints, OIdx)

tel = zeros(length(OIdx),1);
for k = 1 : length(OIdx)
    for q = 1 : length(constraints)
        if constraints(q).Bounds == 0
            if strcmp(constraints(OIdx(k)).VolName, constraints(q).VolName)
                tel(k) = tel(k) + 1;
            end
        end
    end
end

lengte = max(tel);

OV = zeros(length(OIdx),lengte);
nidx = length(constraints);


for j = 1 : length(OIdx)
    n=1;
    for i = 1 : nidx
        if strcmp(constraints(OIdx(j)).VolName,constraints(i).VolName)
```

```
            if constraints(i).Bounds == 0
                if constraints(i).Active == 1
                    OV(j,n) = constraints(i).Objective;
                    n = n+1;
                end
            end
        end
    end
end



end
```

```
function [constraints, data] = make_rpm_problem_combi(constraints, data, OIdx, OV)

% Deactivating the other objectives
nidx = length(constraints);
for l = 1 : nidx
    if all(l ~= OIdx)
        if constraints(l).Bounds == 0
        constraints(l).Active = 0;
        end
    end
end

% Number of objectives
n = length(OIdx);

% Add decision variables
dvidx=zeros(n+1,1);
for i = 1 : n+1
    [constraints, data] = add_dv(constraints, data);
    dvidx(i) = data.misc.size;
end

% New constraint, based on constraint idx
[constraints] = make_rpm_constraints_combi(OV, constraints, OIdx, dvidx);





% Add another new objective, which is to be minimized
for j = 1 : n
    [constraints, data] = add_rpm_variable(constraints, data, 'RPM helper for z', dvidx(j));
end

% add z variable
epsilon = 2;
[constraints, data] = add_rpm_variable(constraints, data, 'RPM minimizer', dvidx(1), epsilon, n);
```