Robustness Recipes for Proton Therapy

Polynomial Chaos Expansion as a tool to construct robustness recipes for proton therapy

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Radiotherapy is one of the key modalities to treat cancer. Due to the characteristic Bragg peak of protons, proton therapy is a kind of radiotherapy which has the ability to deliver high doses to tumors and at the same time have a relative small impact on the surrounding healthy tissue. However, uncertainties in patient setup and proton range can severely compromise the planned dose delivery. The conventional methods that are used in photon therapy to cope with these uncertainties cannot be applied to proton therapy due to the differences in dose deposition. Therefore, robust treatment planning has been introduced. Robust treatment plans are obtained by including several error scenarios at the same time in the plan optimization, and performing a worst-case-optimization over these. In order to be able to determine which error scenarios to include to ensure adequate target coverage, the effect of errors on the dose distribution must be quantified. To do this, dose recalculations for a large number of error scenarios are needed. Using the dose-engine to perform this recalculations is a very time-consuming task. Previous work by Van der Voort et al. has shown that it is possible to use Polynomial Chaos Expansion (PCE) as a meta model for the dose distribution, which drastically speeds up these calculations [27]. They used PCE to derive robustness recipes for oropharyngeal cancer patients. A robustness recipe describes which scenarios to include when performing robust optimization in order to obtain a treatment plan that meets the dose criterion for target coverage for a specified fraction of treated patients, given a specific setup and range uncertainty. Their recipe construction method had however a number of limitations. The range robustness settings were obtained by coarse steps and were not validated, furthermore inter-patient variability in plan quality was not taken into account.

The purpose of this study was to improve this robustness recipe construction method and expand the formulation to another treatment site, skull base meningioma patients. This work has shown and validated that PCE can indeed be used as a meta-model for the dose distribution of skull base meningioma patients. Several improvements and refinements have been implemented. The range recipe construction has been added to the existing methodology, which resulted in improved understanding of the effect of the range robustness setting RR on the resulting treatment plans. Furthermore, the application of a rescaling factor to account for inter-patient variance in the treatment plan quality, partly removed the patient-dependency of the recipe performance observed in the previous work.

The robustness recipes are constructed with the goal to ensure that at least 98% of the treated population receives a near-minimum dose $D_{98\%}$ of at least 95% of the prescribed dose $D_{\text{prescribed}}$. Setup robustness recipes were constructed under different range robustness settings, which resulted in no substantial differences. From this, it can be concluded that the setup and range recipes can be used independently. The recipes were validated for a total of 8 skull base meningioma patients, where for none of the patients did the percentage of the population that passed the coverage criterion deviate more than 1% from the required 98%. For the range robustness recipe, a linear relation between the range robustness setting RR and the range error $\rho$ was derived:

$$RR = 0.467\rho + 0.0177,$$

and the setup robustness recipe was expressed as a rational relation between the systematic setup error $\Sigma$, random setup error $\sigma$ and the setup robustness setting SR:

$$\Sigma = \frac{P_1(SR)\sigma + P_2(SR)}{\sigma^2 + Q_1(SR)\sigma + Q_2(SR)},$$

with the coefficients for the parameters $P_{1,2}$ and $Q_{1,2}$ given in Table 6.2 and in Table 6.3, corresponding to the final combination of all data points. Thus, these robustness recipes for skull base meningioma patients, derived for the treatment planning system Erasmus-iCycle using PCE, can be used independently, have been validated and provide adequate target coverage.
Introduction

1.1. Radiation therapy for cancer treatment
Cancer is the second leading cause of death globally, despite the fact that currently half of cancer patients survive for more than 10 years after their diagnosis. The three key modalities of treating cancer are surgery, chemotherapy and radiation therapy. Both chemotherapy and surgery can be used in combination with radiation therapy. For example, after surgical resection of the tumor, radiation therapy can be used to kill the remaining cells which are not manifested as gross tumor, but are microscopically still present. Apart from in combination with other treatments, radiation therapy can also be used as a stand-alone procedure for tumors which are inoperable.

Radiation therapy works by ionizing radiation which causes damage to the DNA of cancerous cells. The damaged DNA will result in direct cell death or reduced cell-growth. The quantity to measure radiation is dose, which indicates the amount of radiation received by a certain tissue, expressed in Gray (Gy). The higher the dose, the higher the chance of killing cancerous cells. It is inevitable that surrounding tissue is irradiated as well, resulting in damaged healthy DNA. Healthy tissue however has the ability to repair itself, when given some time, while cancerous cells have a much weaker capability of recovering. Therefore, radiation therapy is almost always given in multiple fractions, to give healthy tissue a chance to repair itself between treatments. Nonetheless, some normal cells will also be destroyed during treatment which can influence a patient's quality-of-life after treatment. Therefore, the aim of radiotherapy is to give as high a dose as needed to kill the tumor, while minimizing the dose to surrounding healthy tissue as much as possible.

Radiation can be delivered by radioactive material that is placed in the body near tumorous cells or by beams outside the body, which is called external beam radiation therapy. Several types of radiation are being used for external beam radiation therapy, such as photons, electrons and protons. The latter is the subject of this research.

1.2. Proton therapy and planning of proton treatments
Proton therapy has the ability to deliver high doses to tumors and at the same time have a relatively small impact on the surrounding healthy tissue. This is due to the finite range of protons, in contrary to photons which deposit dose along their entire path through the body. Proton therapy is therefore preferable over photon therapy in cases where a higher dose is needed or when high conformity is needed for the sparing of healthy tissue.

The downside of the narrow region of high dose delivery is that proton therapy is very sensitive to uncertainties [12, 13]. These uncertainties can originate from several sources, most importantly errors in the patient setup or in the proton range. The current practice of handling uncertainties in photon therapy is to expand the clinical target volume (CTV) by a margin, such that a planning target volume (PTV) is formed. This volume is then used to plan the treatment, such that coverage is ensured in the presence of uncertainties [28]. This method can however not be applied to proton therapy, due to the difference in dose deposition of protons and photons [11].

To be able to handle uncertainties in proton therapy, 'robust treatment planning' has been introduced. Robust treatment planning results in a treatment plan that ensures adequate target coverage, even with uncertainties. Typically, robust optimization has been used in two ways, either by minimizing an expected value or
by a worst-case optimization, which will be the focus of this research. Common practice to perform worst-case optimization is using minimax-optimization [8].

This method includes several error scenarios at the same time in the optimization, and performs a worst-case-optimization over these scenarios. This means that the worst-case values for the optimization objectives are optimized. An error scenario is a specific realization of the uncertainties resulting in a combination of errors. In order to determine which error scenarios to include to achieve a specified target coverage for a certain fraction of the treated patients, the exact effect of errors on the dose distribution must be quantified. The goal is then to derive a relation between the input error scenarios, and the errors the plan is able to cope with. To do this, dose recalculations are needed for a large number of error scenarios, to investigate the effect on the dose distribution. Dose recalculations performed by the exact dose engine that is used during the planning of proton treatments, are however very time-consuming.

1.3. Contributions

Previous work by van der Voort et al. [27] has shown that it is possible to use Polynomial Chaos Expansion, or ‘PCE’ as a meta-model for the dose distribution. This model can then be used to make very fast simulations of dose recalculations. Using their developed model they showed that so-called ‘robustness recipes’ can be derived. A robustness recipe describes which scenarios to include when performing robust optimization in order to obtain a treatment plan that meets the dose criterion for target coverage for a specified fraction of treated patients, given a specific setup and range uncertainty. They derived the relation between robustness settings and (setup and range) errors for oropharyngeal cancer patients, making use of the in-house developed treatment planning system Erasmus-iCycle. The robustness recipes were derived based on the data (CT image and treatment plan) of a single patient, and validated for other patients.

Their recipe construction research had numerous limitations. The range robustness settings were obtained by very coarse steps, without an upper limit on the target coverage criterion and no validation was executed. This method can have resulted in overly conservative range robustness settings. Another limitation is that the differences in treatment plan quality between patients were not taken into account during the recipe construction and validation. They observed a base-patient dependency during the validation of the derived recipe, i.e. the base patients practically met the exact dose constraint, whereas the results of the rest of the other patients were constantly much higher than the prescribed coverage. Additionally, the derived robustness recipes contained a constant term, suggesting that even if in the absence of setup and range errors, some robustness settings must be applied.

The purpose of this work is to improve the recipe construction method and expand the formulation of the robustness recipes to another treatment site, namely skull base meningioma patients. The goal is to gain more insight on the behavior of treatment plans under the influence of range robustness settings and errors, to improve the setup robustness recipe construction method and to show that the general method is applicable to another treatment site.

The research is a joint project of the Medical Physics & Technology section of the Department of the Radiation Science and Technology of Applied Sciences of the Technical University of Delft, the Radiotherapy Physics Department of the Erasmus MC Cancer Institute and the Holland Proton Therapy Center (HollandPTC) Delft.

1.4. Structure

The rest of this thesis is organized as follows. In Chapter 2, a background on proton therapy is given, starting with a comparison between proton and photon therapy, then discussing relevant uncertainties and concluding with some basic clinical information for skull base meningioma. Chapter 3 discusses the process of constructing treatment plans, together with the used treatment planning systems and methods of including robustness in the process. In Chapter 4, Polynomial Chaos Expansion is set out, ending with the specific application of PCE to dose distributions. In Chapter 5, the methods used during this research are described, explaining the construction of PCE, detailing several techniques for validating the obtained PCE, and finally discussing the adapted recipe construction method and the validation of the recipes. In Chapter 6, the results are presented, consisting of a validation of PCE as a meta-model, the constructed treatment plans, the robustness recipes for setup- and range errors and the validation of the recipes on the full patient set. Finally, Section 7 provides some concluding remarks, a discussion and directions for future work.
Proton therapy

In this chapter, first proton therapy is compared to photon therapy, then a brief introduction to Intensity Modulated Proton Therapy (IMPT) is given. Subsequently, the uncertainties that occur during radiation therapy will be discussed, and the conventional method to cope with these in photon therapy will be reviewed. The last section will cover the type of tumor which is the subject of this study, namely skull base meningioma.

2.1. Proton therapy vs. Photon therapy

As stated in the Introduction, radiation therapy is making use of ionizing radiation to kill cancerous cells. Traditional radiation therapy is delivered by photons. Proton therapy delivers the radiation to tissue by high energy protons ($\sim 200$ MeV), particles which do have a charge and are relatively massive (compared to the mass of electrons and photons). The difference in mass and charge is exactly what causes significant differences between the techniques. Because the dimensions of a photon are similar to an electron, a photon which travels through tissue will loose its energy at every collision with a particle. Therefore the dose is deposited in a very large region. A proton however is so ‘big’, that it will scatter inelastically and will be stopped at a certain point, where it will loose almost all its energy during the last collision. Most of the proton dose is therefore deposited in a very narrow region, which is called the Bragg peak. Figure 2.1 shows the relative dose as a function of depth in water for different particles. If the relative photon and proton doses are compared, the Bragg peak shows the potential advantage of protons over photons for therapeutic use: Protons can achieve a high dose with a very rapid distal dose fall-off behind the tumor, while photons deposit their dose along the full path.

By modifying the energy of the incoming protons, the position of the peak can be varied, and by combining multiple protons with varying energies a Spread-Out-Bragg-Peak (SOBP) can be formed. This results in a high dose for the full range of the tumor, while giving almost no dose to the tissue behind the target and having a relatively small impact on the tissue in front of it. An example of an SOBP is shown in Figure 2.2. Proton therapy is therefore preferable over photon therapy in cases where a high target dose is needed and/or when high precision is needed for sparing healthy tissues.
2. Proton therapy

Figure 2.1: Relative dose deposition as a function of penetration depth for various particles. The lighter particles such as photons and neutrons (first two graphs) show a broad and early peak, while the heavier ions show a much narrower region of high dose that is given at a greater depth [20].

Figure 2.2: The Spread Out Bragg Peak (SOBP) displayed in the graph is obtained by adding doses of protons with different energies, weighted such that the target is covered by the high dose plateau [20].

To further highlight the advantage of proton therapy, Figure 2.3 shows a CT slice with a proton dose distribution on the left and a photon dose distribution on the right. This figure illustrates the difference in dose deposition to the surrounding tissue. In order to achieve the same dose in the target, photons give a lot of dose to the rest of the brain while protons are modulated such that as much tissue is spared as possible. To summarize, proton treatments can be delivered with a larger dose conformity to the target in comparison to photon energy depositions, due to their characteristic Bragg peak.

2.2. Intensity Modulated Proton Therapy (IMPT)

The technique of delivering the proton dose that is considered during this research is pencil beam scanning. A pencil beam is a very narrow unscattered beam of protons, that can be aimed at any spot within the target volume. Due to the (positive) charge of protons, their path can be controlled by the use of magnetic fields. The aiming of the pencil beams can thus be done by both magnets and the energy of the protons which will determine the position and the depth of energy deposition. Each pencil beam is assigned a certain weight, which is proportional to the number of protons in the beam and thereby directly proportional to the deposited dose. The technique that combines multiple pencil beams with its own optimal weight and position
is called *Intensity Modulated Proton Therapy*, or IMPT, and can deliver doses very conformal to the tumor shape without making use of any patient or tumor specific hardware. The optimal weights and positions of the pencil beams are calculated during treatment planning, which is discussed in further detail in Chapter 3.

### 2.3. Uncertainties in proton therapy

Proton therapy gives the opportunity to deliver a high dose to the tumor while sparing healthy surrounding tissues, but this comes at a certain price: its sensitivity to uncertainties such as patient misalignment or errors in stopping power prediction. The stopping power of a medium is defined as its ability to absorb energy from protons while interacting. Because the position of the Bragg peak depends on the stopping power of tissue along the proton path, any change in the medium can shift the Bragg peak and therefore the dose will be deposited at another place than planned. An uncertainty can thus lead to an overshoot or undershoot of the target, which means that the dose will be delivered either in front or behind the target. This section will first cover the origin and type of uncertainties that may occur during treatment and afterwards briefly touch upon the methods to cope with uncertainties in photon therapy and the reason why these are not applicable to proton therapy. Chapter 3 will elaborate more on uncertainty handling in proton therapy.

This research addresses two types of uncertainties, *setup* and *range* uncertainty. Figure displays the coordinate system for a patient on a couch, that will be used to illustrate examples of these uncertainties. The couch is the ‘table’ on which the patient lies down while the treatment takes place.
2.3.1. Setup errors

Setup uncertainties can be split into two components, a systematic and a random one. Random errors are due to variations which occur during the execution of the treatment and variations which are due to preparation inaccuracies. They differ for every treatment and can not be predicted. An example of a random error can be a little shift in the patient setup between treatment fractions, which therefore differs day-to-day. The other class of errors is defined as *systematic* errors, which originate from the plan preparation and are the same throughout the treatment. Since the errors play an important role in this research, a more detailed description of both is given below.

- **Systematic setup error** \( \Sigma \)

In order to calculate and perform the optimal treatment for a patient, a treatment plan is made using a planning CT (Chapter 3 will go into more detail on treatment planning). Any systematic misalignment in the patient positioning with respect to the planning CT will cause a shift in the dose distribution. There are various ways to minimize this misalignment, from now on called the systematic setup error. Although there are various methods developed to minimize the standard deviation of the systematic setup errors down to a few millimeters [19], the errors are not completely eliminated and therefore need to be taken into account during treatment planning and evaluation. The standard deviation of the systematic setup error is expressed as \( \Sigma \) with millimeter (mm) as unit, and can be divided into components along the couch axes (\( \Sigma_x, \Sigma_y, \Sigma_z \)). Figure 2.5 shows an example of a systematic setup error, shifting the nominal scenario (black bullet) to an error scenario (red bullet).

- **Random setup error** \( \sigma \)

Random setup errors differ from fraction to fraction and can be caused by displacements of the patient between fractions, due to small errors in the positioning in relation to the planning CT. The standard deviation of the random setup error is expressed as \( \sigma \) with millimeter (mm) as unit, and can again be divided into components along the couch axes (\( \sigma_x, \sigma_y, \sigma_z \)). Figure 2.6 shows how for a treatment with a certain systematic setup error \( \Sigma \) (also displayed in Figure 2.5), three fractions have different random setup errors \( \sigma_1, \sigma_2 \) and \( \sigma_3 \).

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**Figure 2.5:** A systematic setup error \( \Sigma \), this error is constant over multiple fractions and can be divided into components along the couch axes.

**Figure 2.6:** A few examples of realizations of random setup errors \( \sigma_i \), given the systematic error \( \Sigma \) from Figure 2.5. Each fraction has a different random setup error. The random setup error can also be divided into components along the couch axis.
By comparing Figures 2.5 and 2.6, a clear distinction between the effects of systematic and random setup errors can be made. Random errors lead to blurring of the dose distribution, because for every fraction another distortion is applied on the intended distribution, while systematic errors will cause a shift of the intended dose distribution. Systematic and range errors can be combined to give the setup error, by simply adding the shifts and quadratically summing the standard deviations.

Apart from the alignment errors described above, also intra-fraction motion can cause errors. Intra-fraction motion means that the displacements take place during the treatment, which can be caused by organ movement or respiratory motion (breathing). Depending on the location of the tumor, the intra-fraction motion must also be taken into account. This research focuses on skull base tumors, where these types of uncertainties are negligible and thus only the setup errors which occur in between fractions are taken into account, i.e. the inter-fraction random and systematic setup errors.

2.3.2. Range errors

- Relative range error $\rho$
  The planning CT which is used as a basis for the treatment planning, is made with photons. This results in an image which can directly be used for photon treatment planning, for protons however, this is not the case. Due to the different interaction with matter for photons and protons, there is no direct way to relate the CT values to proton stopping power. In order to calculate the needed proton energy, first a conversion of Hounsfield Units must be done. The Houndsfield scale is a quantitative scale that is used to describe radio-density. This conversion is not analytic, but is based upon conducted measurements or Monte Carlo simulations. Errors in the conversion to the stopping power will lead to a systematic over- or undershoot of the wanted dose. The relative range error, which is also systematic, will be denoted by $\rho$ and is expressed in %.

- Absolute range errors $\rho_{abs}$
  Absolute range errors are due to uncertainties per fraction and do not originate from the CT image conversion. The absolute error is denoted by $\rho_{abs}$ and is also expressed in %.

This research takes only the relative range error into account.

The setup and range errors are assumed to have a Gaussian distribution, following the central limit theorem which states that combining many distributions asymptotically leads to normal Gaussian distribution. This is true for the kind of errors that are taken into account during this research, not for respiratory motion uncertainties. [28]

2.3.3. Conventional methods to deal with uncertainties

Now that the sources and characteristics of the setup and range uncertainties are set out, the conventional method to cope with the errors is be discussed. The goal of every treatment is to be robust against uncertainties, which means that the treatment plan is made such, that despite uncertainties, the treatment goals are achieved. Goals are defined as adequate target coverage and sparing of healthy tissues. This means that the errors must be taken into account in the treatment planning in some way. First the well-established method of handling uncertainties during treatment planning for photons will be discussed. Thereafter an explanation will be given why this method is not applicable to proton therapy.

Conventional treatment planning for photons

In order to explain conventional treatment planning for photons, first two definitions must be given; Gross Tumor Volume (GTV) and Clinical Target Volume (CTV). The GTV contains the gross extent and location of the tumor, visible on a CT image of the patient. The CTV is a volume that includes the GTV and where it is needed a small expansion is made to include microscopic tumor spread and sub-clinical malignant disease [23]. In order to account for uncertainties, photon treatment planning makes use of a geometrical expansion of the CTV, which results in the Planning Target Volume (PTV). Figure 2.7 shows the expansion from GTV to CTV to PTV, in a schematic way.

The extension is chosen such that it will contain the motion of the CTV due to both setup and range errors. When a treatment plan is now made based upon the PTV, which means that the high dose will be given to the full planning volume, which includes every shift of the CTV. The PTV must therefore be chosen such that it includes all the scenarios of the location of the CTV. This idea is making use of the dose cloud approximation, i.e. the almost static dose distribution of photons, in which the CTV moves due to range and
error uncertainties. Figure 2.8 shows the effect of different errors and the PTV. Important to note here is that for photons it suffices to look only at errors that origin from setup uncertainties, since the range has little influence.

Conventional treatment planning for protons

The crucial element of the treatment planning for photons is the assumption that the dose distribution is static in space. This is however not the case for protons, since the proton energy deposition is strongly dependent on the density variation along the path protons are traveling. The inadequacy of the PTV safety margins for proton therapy has been demonstrated [8], moreover for protons also range uncertainties have to be taken into account. This is illustrated in Figure 2.9, which displays the effect of a range shift on both treatment modalities. The first graph shows the effect of a shift in the photon dose, which will give almost no difference in dose at the CTV region (red region), while a shift in both the Bragg Peak and the Spread Out Bragg Peak result in a hot spot behind the CTV, and under-dosage in the CTV. [17]

To conclude, the photon procedure of handling uncertainties by expanding the CTV by a margin into the PTV, does not translate to proton therapy due to the non-static dose distribution and the sensitivity to range uncertainties [12, 24]. Chapter 3 will cover robust optimization, a method to handle uncertainties for proton therapy.

2.4. Skull base tumors

Proton therapy is used for various treatment sites, this research however focuses on skull base tumors. Two patient sets are used, initially 8 chordoma patients but for the majority of the research 8 skull base meningioma patients. This section discusses shortly skull base meningioma and the surrounding tissue. Since the tumors are located at roughly the same site the same theory can be applied to chordoma.
2.4.1. Proton therapy for skull base meningioma

Skull base meningiomas are located such that it is almost impossible to remove the whole tumor with a surgical resurrection. A combination of surgery and radiotherapy is therefore a logical choice [18]. Because of the characteristics of protons described in Section 2.1, they are preferred over photons, in order to spare the healthy surrounding tissue as much as possible. Several trials have proven that radiotherapy does improve the survival rate of patients with skull base meningioma [6, 15, 16, 29].

2.4.2. Organs-at-risk

Important healthy structures surrounding the target are called Organs-At-Risk, OARs. Figure 2.10 shows an illustrative patient to indicate the OARs surrounding the skull base tumor. Figure 2.10a shows the structures together with the CTV, where only the critical structures in close proximity of the tumor are displayed. Figure 2.10b shows a coronal (top-left), axial (top-right) and sagittal (bottom) view of the patient, where the typical location of a skull base meningioma is visible together with the organs-at-risk. The tumor can be located at the middle of the skull base but also on one of the sides.

Below, a short overview of the important surrounding OARs is given, together with possible consequences of overdosing the organs. The specific dose constraints per organ are discussed later, in Section 5.3.
• **Brainstem**
The brainstem connects the brain to the spinal cord and maintains vital control of the heart and lungs. It also coordinates many important reflexes. The brainstem is often located very close to the tumor and must therefore be taken into account during the treatment planning. If the brainstem receives too much dose, symptomatic necrosis will occur, which leads to a decrease in cognitive functioning.

• **Optical Nerves**
Optical nerves are the connection between the eyes and the brain, they transport pulses created by the retina. If the optical nerves are damaged by overdosing the tissue, this can lead to worsened sight or in some cases even complete blindness.

• **Chiasm**
The chiasm, or optic chiasm is also part of the optical system, just like the optical nerves. The chiasm has an X-shape, and indicates the place where the optical nerves cross each other. The consequences of overdose to the chiasm are the same as for the optical nerves.

• **Hippocampus**
The hippocampus consists of two hippocampi, located on the left and right side of the brain. The hippocampus is part of the limbic system and plays a role in the processing of new information, and consolidating memories. Damage to the hippocampi will lead to a decline in the neuro-cognitive functioning of the brain.

• **Pituitary gland**
The pituitary gland, or hypophysis, secretes hormones to control among other growth, blood pressure and temperature regulation. When the pituitary gland is overdosed, it can stop functioning completely. The pituitary gland is often located completely within the tumor volume and can therefore not always be saved.

Organs-at-risk can be classified as serial and/or parallel organs. A serial organ will loose its function, even if a small part of the structure is destructed. A parallel organ has some kind of redundancy built in, and the structure will keep on functioning even if a part of the organ is sacrificed. From the surrounding OARs of the skull base meningioma, the brainstem is an important serial organ, while for example the hippocampi are parallel structures. The type of constraints on the received dose can differ for serial and parallel organs.

### 2.5. Terminology

In order to be able to discuss the characteristics of proton therapy in the rest of this thesis, some definitions commonly used in radiotherapy are stated here. The concepts have already been discussed, but they are listed below as a quick reference list for later chapters.

• **Random setup error** ($\sigma$)
The random setup errors in the patient setup arise from setup uncertainties that occur during the execution of a treatment and differ per fraction.

• **Systematic setup error** ($\Sigma$)
Systematic errors in the patient setup originate from uncertainties that arise during the treatment preparation and are constant over the whole treatment.

• **Relative range error** ($\rho$)
The relative range error is due to uncertainties in the conversion of CT values to proton stopping power, the error is systematic and constant over the whole treatment.

• **Gross Tumor Volume (GTV)**
The Gross Tumor Volume contains the gross extent and location of the tumor, as visible on the CT image of the patient.

• **Clinical Target Volume (CTV)**
The CTV is a slightly larger volume than the GTV to include microscopic tumor spread and sub-clinical malignant disease [23].
• **Planning Target Volume (PTV)**
  Planning Target Volume, PTV, is the geometrically expanded volume based upon the CTV, which is used for photon treatment planning to mitigate setup uncertainties.

• **Organ-At-Risk (OAR)**
  Organ-At-Risk, OAR, is an organ or other critical structure in the proximity of the CTV. OARs must be included in the treatment planning such that the dose constraints are not violated. Typical OARs for skull base tumors are the brainstem, chiasm and optical nerves.
This chapter will first give a short overview of important treatment parameters that are used during treatment planning and evaluation, then treatment planning in general is set out, followed by the two treatment planning systems which were used during this research. Once the treatment planning has been outlined, the current methods to achieve robustness are discussed for photons as well as protons, leading to the formulation of the final goal of this research, the derivation of robustness recipes for proton therapy.

### 3.1. Treatment Parameters

To be able to construct and evaluate treatment plans, multiple treatment parameters can be used. This section describes the most commonly used treatment parameters, which are also used during this research.

- **D\text{prescribed}** - Prescribed dose
  The prescribed dose gives the dose that is to be given to the target volume during the treatment.

- **D\text{x}\text{%}** - Dose received by a certain volume
  This parameter gives the maximum dose that is received by at least \( x\% \) of the volume. For example: \( D_{20\%} = 30\) Gy, means that at least 20\% of the volume receives 30Gy or higher.

- **D\text{98\%}** - Near-minimum dose
  The near-minimum dose is given by the maximum dose that at least 98\% of the volume receives. The near-minimum dose is often used instead of the absolute minimum dose, because the absolute minimum dose can be fully determined by one voxel, this is unrealistically sensitive.

- **D\text{2\%}** - Near-maximum dose
  The near-maximum dose is given by the maximum dose that at least 2\% of the volume receives. The near-maximum dose is often used instead of the absolute maximum dose, because - similarly to the minimum dose - the absolute maximum dose can be fully determined by one voxel, this is unrealistically sensitive.

- **V\text{y}** - Volume receiving a certain dose
  This parameter gives the fraction of the volume that receives at least a specified dose \( y \cdot D\text{prescribed} \), and is expressed by
  \[
  V_y = \frac{1}{N_{\text{voxels}}} \sum_{i=1}^{N_{\text{voxels}}} \delta(D_i \geq y \cdot D\text{prescribed}),
  \]
  with \( N_{\text{voxels}} \) the number of voxels in the structure, \( D_i \) the dose in voxel \( i \) and \( y \) the fraction of the prescribed dose \( D\text{prescribed} \).

- **DVH** - Dose Volume Histogram
  The dose volume histogram (DVH) is a cumulative histogram that shows the fraction of a volume that receives at least a certain dose. A DVH is a very common way of evaluating treatment plans, because it displays the dose of multiple structures at once, and it is a convenient way of showing the 3D dose distributions in 2D graphs.
3.2. Treatment Planning

A treatment plan prescribes for a specific patient, which beams should be used and with which intensities in order to meet the desired coverage for the CTV and sparing of the healthy tissue, divided into a certain (prescribed) number of fractions.

The goal of treatment planning is to construct a treatment plan that delivers the prescribed dose to the target volume, the CTV (see Section 2.5), to maximize the probability of tumor control while minimizing the dose to surrounding healthy tissue, so as to minimize the normal tissue complication probability. A treatment plan for Intensity Modulated Proton Therapy (Section 2.2) consists of the needed beam directions and weights. The weight of a beam is proportional to the number of protons and thereby to the dose delivered. For treatment planning, different Treatment Planning Systems (TPS) can be used, two of which are discussed in the next section. First the general approach of treatment planning will be set out, as displayed in Figure

Figure 3.1: Schematic simplified overview of the process of treatment plan generation. First a planning CT is conducted and structures are delineated, together with the goals of the treatment formulated as constraints and objectives (objectives and constraints only show as example here), this is the input for the treatment planning system. The treatment planning system can be fully automated or (partly) manually operated. The output is a treatment plan that results in a to be delivered dose distribution.
First, a CT scan of the target volume and surrounding part of the patient's body is made. Subsequently, the structures are delineated within the CT image by a radiation oncologist. The result is a CT image with all relevant OARs and target volume(s) clearly indicated, as shown in the second step in the figure. The goals of the treatment are defined in the form of constraints and/or objectives. These are expressed in terms of the treatment parameters discussed in Section 3.1, the exact formulation differs per treatment planning system. The delineated CT image together with the list of goals for the treatment serves as input for the treatment planning system. The output is the treatment plan and the corresponding dose distribution. The treatment planner will examine the outcome and when the required CTV coverage or sparing of OARs is not achieved, the objectives and constraints are adjusted and a new treatment plan is generated. The generation of treatment plans is often an iterative process, executed by experienced treatment planners.

Not only the beam weights are optimized during treatment planning, but also the optimal beam angles can be calculated by treatment planning systems. This is however a very time-consuming option, therefore very often a beam-angle configuration is given as input together with the delineated CT and treatment goals. This configuration can be made either based upon the experience of a treatment planner or by following a treatment protocol for a certain tumor type or location which states a standard combination of beam-angles. Beam-angles are expressed in two components: the couch-angle and the gantry-angle. Both are displayed in Figure 3.2, together with the coordinate system of the couch.

Figure 3.2: Schematic illustration of couch- and gantry angles, together with the couch-coordinate system [5].

### 3.3. Treatment Planning Systems

The generation of treatment plans as described in the previous section considers the treatment planning system as a kind of black-box. Although this work uses two treatment planning systems, Erasmus-iCycle and RayStation, the main focus is on Erasmus-iCycle. Therefore this section will offer a more detailed insight in the process that takes place within Erasmus-iCycle, concluded by some short information on RayStation.

#### 3.3.1. Erasmus-iCycle

Erasmus-iCycle is an in-house developed fully automated treatment planning system, which makes use of multi-criteria optimization [4]. Multi-criteria optimization is based upon a wish-list. The wish-list, optimization method and used dose engine are set out below.

**Wish-list**

A wish-list consists of a combination of constraints and prioritized objectives. A constraint is a hard criterion that must be met, while an objective has to be met only whenever possible during the optimization [2]. The objectives are prioritized such, that the more important objectives are more likely to be met than the lower
priorities. For example the coverage of the CTV is often set as a constraint, while the sparing of a critical OAR is set as an objective with a very high priority. The lower priorities are included to push the dose distribution into the tumor volume and spare healthy tissue as much as possible. A wish-list is treatment and tumor specific, but usually patient independent. This means that the same wish-list can be used for patients within the same tumor type.

Optimization
The goal of the optimization is to find the optimal pencil beams and their corresponding weights. The selection of pencil beams is an iterative process, which uses a pencil beam re-sampling technique [25]. The iteration starts with randomly selecting a (by the input of the TPS predefined) number of candidate pencil beams from a fine grid. For the resulting subset, the dose matrix is calculated and an inverse optimization is performed to obtain the optimal weight for each pencil beam. After the optimization, beams with a low contribution are excluded to reduce the number of pencil beams. The next iteration starts with adding new random candidates to the existing reduced subset of pencil beams, and the optimization and exclusion of low contributing pencil beams is repeated.

The optimization that is performed to calculate the optimal pencil beams weights, is a multi-criteria optimization. The method used by iCycle is the 2-phase ε-constraint method, from now on 2pεc-method [3]. The optimization consists of two phases:

phase I
During the first phase, the objectives are minimized one-by-one as close to their goal (defined in the wish-list) as possible, within the given constraints. The objective with the highest priority is minimized first, until it either reaches its goal or can not go any further due to conflicting constraints. The obtained value of the objective will now be added as a constraint, such that during the next lower-prioritized objective minimization, the obtained result will not be jeopardized. The result is that for each subsequent objective that is being minimized, an extra constraint is added to the problem. At the end of phase I there is a plan where each objective has achieved a value that is either its goal-value or is as close as it can get due to constraints.

phase II
In the second phase, the objectives are again minimized, in order of decreasing priority. This time, the optimization is not stopped when the goal-value is reached, but is continued as far as possible such that for each objective the optimal value is obtained. At the end of phase II a Pareto-optimal plan is formed, which meets all the constraints and has attained objective values that are optimized to their fullest extent.

The iterative process of re-sampling and adding pencil beams and subsequently performing the 2pεc-optimization, is continued until the addition of extra pencil beams does no longer result in a significant improvement of the plan. A significant improvement is expressed as an improvement of an objective of at least 3%. This parameter can be increased or decreased in order to achieve either faster or better plans.

Dose engine
Each treatment planning system makes use of a dose calculation algorithm, the dose engine. Erasmus-iCycle uses a dose engine developed at Massachusetts General Hospital - Harvard Medical School [10].

3.3.2. RayStation
RayStation is a commercial treatment planning system developed by RaySearch Laboratories (Stockholm, Sweden). The input for RayStation contains just as for Erasmus-iCycle a combination of constraints and objectives. The objectives are however not prioritized, but each has to be given a specific weight. The higher the weight, the more contribution the objective will give during the optimization process. The optimization method that is used is also a multi-criteria optimization method, but with a weighted sum method. RayStation for proton therapy gives the opportunity to choose between two dose engines. First, there is a pencil beam algorithm, and second a Monte-Carlo dose engine for pencil beam scanning.

3.4. Robust Treatment Planning
Now that the process of generating treatment plans for proton therapy, or more specifically IMPT, has been discussed, the methods for coping with setup and range uncertainties will be addressed. This is an important
3.4 Robust Treatment Planning

part of treatment planning, since IMPT is highly sensitive to errors due to the stopping power dependency and steep gradients in the dose deposition of protons. Since margins that are used for photon treatment planning are inadequate for IMPT (see Section 2.3.3), another method must be applied. The method that both iCycle and RayStation use is minimax optimization.

3.4.1. Minimax optimization

Minimax optimization is a way to account for setup and range uncertainties in proton therapy [8]. During minimization optimization, a number of planning scenarios are used. A (planning) scenario, is a combination of the setup and range error. The nominal scenario is given by zero setup- and zero range error. During non-robust treatment planning, the optimization in the TPS is performed for the nominal scenario alone, where there are no errors. A limited number of predefined planning scenarios are also taken into account during robust treatment planning when using minimax optimization. For all included scenarios, the dose is evaluated and the worst-case value for each objective is optimized.

Planning scenarios and Robustness settings

Typically, a total of 9 planning scenarios are included during robust treatment planning [27]. These have to be given as input to the treatment planning system. The Setup Robustness setting (SR) and Range Robustness setting (RR) have to be entered. The SR is given in millimeter and the RR in percentage. The resulting nine scenarios are displayed in Table 3.1. The setup robustness SR is applied in each of the \((x, y, z)\)-directions, but depending on the treatment planning system separate values can also be used.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>(x) (mm)</th>
<th>(y) (mm)</th>
<th>(z) (mm)</th>
<th>(\rho) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Positive shift in (x)-direction</td>
<td>SR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative shift in (x)-direction</td>
<td>-SR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Positive shift in (y)-direction</td>
<td>0</td>
<td>SR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative shift in (y)-direction</td>
<td>0</td>
<td>-SR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Positive shift in (z)-direction</td>
<td>0</td>
<td>0</td>
<td>SR</td>
<td>0</td>
</tr>
<tr>
<td>Negative shift in (z)-direction</td>
<td>0</td>
<td>0</td>
<td>-SR</td>
<td>0</td>
</tr>
<tr>
<td>Range overshoot</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>RR</td>
</tr>
<tr>
<td>Range undershoot</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-RR</td>
</tr>
</tbody>
</table>

Erasmus-iCycle

Erasmus-iCycle uses minimax worst-case objective-wise optimization, which means that the worst-case value of each objective is minimized, under the worst-case value of each constraint. Erasmus-iCycle gives the option to choose which objectives and constraints to plan robustly and which not. Only the robust objectives and constraints are calculated for each scenario, the ‘normal’ objectives and constraints are only optimized for the nominal scenario. Erasmus-iCycle uses only one value for the setup robustness in all three directions.

RayStation

RayStation also uses minimax worst-case optimization. RayStation does however give the option of using direction-specific setup robustness settings. Furthermore, it has the option to not only include 9 planning scenarios, but also every combination of these scenarios. This does however lead to longer computation times.

3.4.2. Error simulation

In order to include planning scenarios in the robust optimization, the effects of setup and range errors on the dose distribution are simulated by the treatment planning system. The methods used by Erasmus-iCycle are stated below.

Setup error

The setup errors are simulated by shifting the pencil beams laterally with respect to the patient.
3. Treatment planning

Range error

There are two methods of modeling the range error, both are used in this work.

− Energy beam scaling
  Erasmus-iCycle changes the energy of the pencil beams, thereby influencing the range of the protons. The energy of the proton beams is thus scaled in this method. The draw-back of this way of scaling is that the available proton energies are limiting the scaling process. This means that when the scaled energy is not available, the next closest energy is chosen by an interpolation.

− CT image scaling
  The previous work by Van der Voort et al. (see Introduction for more information) used a different method of incorporating the range error, namely by scaling the CT image values instead of the proton beam energy.

3.5. Robustness recipes

Because robust optimization only takes 9 (or more) discrete scenarios into account, there is no actual knowledge about what happens for any other values and combinations of setup- and range errors. Consequently, the chance to be in exactly one of the planning scenarios is zero. In order to be able to predict how robust the treatment plan is against a certain set of errors, the intermediate behavior of the dose distribution has to be known. Ideally, one would like to know exactly which robustness settings have to be used to be robust against a certain set of specific setup and range errors.

The goal of this research is therefore to formulate so-called robustness recipes for skull base patients, which describe which scenarios to include when performing robust optimization to be able to handle a certain set of errors [27]. The robustness recipes are given by the robustness settings (SR,RR), as a function of the uncertainties in range and setup (Σ,σ,ρ). In order to be able to determine which error scenarios to include in the minimax optimization, the effect of errors on the dose distribution must be quantified. The next chapter will introduce a meta-model for the dose distribution that will be used for this and thereby for the construction of the robustness recipes.
This chapter will start off with stating the goal of making a Polynomial Chaos Expansion (PCE), thereafter the relevant theory will be covered. The last section will address the specific application of PCE for dose distribution calculations.

4.1. Polynomial Chaos Expansion

The goal of a Polynomial Chaos Expansion, from now on ‘PCE’, is to express the variability of a response or output of interest \( R \), with respect to the uncertain input parameters \( \vec{\xi} \). This is obtained by performing a series expansion with basis vectors \( \Psi_k \) and expansion coefficients \( r_k \). Expressed in an equation as:

\[
R(\vec{\xi}) = \sum_{k=0}^{\infty} r_k \Psi_k(\vec{\xi}) \quad (4.1)
\]

First, the used terms will be explained shortly, thereafter the underlying theory and methods are set out:

- **\( R(\vec{\xi}) \) - Exact output**
  The exact response \( R \) is the desired output, as a function of the uncertain input \( \vec{\xi} \).

- **\( \vec{\xi} = (\xi_1, \xi_2, ..., \xi_N) \in \mathbb{R}^N \) - Uncertain input**
  The uncertain input is a vector of \( N \) input parameters, originating from \( N \) distinct sources of uncertainties. Each random variable \( \xi_j \) has its own probability density function \( p_{\xi_j}(\xi_j) \). During this research, the probability density functions of the random variables \( \vec{\xi} \) are assumed to be independent Gaussians. A Gaussian distribution with a mean \( \mu \) and a standard deviation \( \sigma \), has the following form:

\[
p(\xi) = \frac{1}{\sigma \sqrt{2\pi}} e^{\frac{1}{2} \left( \frac{\xi-\mu}{\sigma} \right)^2} \quad (4.2)
\]

The sum of two random Gaussian distributed variables, \( \xi_1 \) and \( \xi_2 \), is again a Gaussian:

\[
\begin{align*}
\xi_{\text{com}} &= \xi_1 + \xi_2 \\
\mu_{\text{com}} &= \mu_1 + \mu_2 \\
\sigma^2_{\text{com}} &= \sigma^2_1 + \sigma^2_2 \\
p(\xi_{\text{com}}) &= \frac{1}{\sigma_{\text{com}} \sqrt{2\pi}} e^{\frac{1}{2} \left( \frac{\xi-\mu_{\text{com}}}{\sigma_{\text{com}}} \right)^2}
\end{align*} \quad (4.3-4.5)
\]

Because of the independence of the distributions, the joint probability density function \( p_{\vec{\xi}}(\vec{\xi}) \) for all uncertain input, is constructed by simply multiplying each individual probability density function as:

\[
p_{\vec{\xi}}(\vec{\xi}) = \prod_{j=1}^{N} p_{\xi_j}(\xi_j) \quad (4.7)
\]
With the joint probability density function, one can express the mean of the response, $\mu_R$ as:

$$
\mu_R = \int_{-\infty}^{\infty} R(\vec{\xi}) p_\vec{\xi}(\vec{\xi}) d\vec{\xi}, \tag{4.8}
$$

and the variance $\sigma_R^2$ is given by:

$$
\sigma_R^2 = \int_{-\infty}^{\infty} (R(\vec{\xi}) - \mu_R)^2 p_\vec{\xi}(\vec{\xi}) d\vec{\xi}. \tag{4.9}
$$

• $\sum_{k=0}^{\infty} r_k \Psi_k(\vec{\xi})$ - Series expansion

The series expansion is a representation of the exact output, and consists of expansion coefficients $r_k$ and basis vectors $\Psi_k(\vec{\xi})$. The basis vectors are multi-dimensional polynomials which depend on the random variables $\vec{\xi}$.

### 4.1.1. PC basis vectors

The polynomial chaos basis vectors, or PC basis vectors, are constructed via tensorization, they are a product of $N$ univariate polynomials. The polynomials are selected based upon the distribution of the uncertain inputs. The optimal polynomial family is orthogonal to the probability density functions $p_{\xi_j}(\xi_j)$ of the inputs. Because the PC basis vectors are constructed from the orthogonal univariate polynomials, they are also orthogonal:

$$
\langle \Psi_k, \Psi_l \rangle = \int_{\mathcal{D}(\Theta)} \Psi_k(\vec{\xi}) \Psi_l(\vec{\xi}) p_\vec{\xi}(\vec{\xi}) d\vec{\xi} = h_k^2 \delta_{k,l}, \tag{4.10}
$$

with $\mathcal{D}(\Theta)$ the full domain of the random variables. Equation 4.10 uses the orthogonality, with $h_k$ being the norm of basis vector $\Psi_k(\vec{\xi})$. Thus Equation 4.10 is equal to the norm of the basis vectors when $k=l$, and 0 when $k \neq l$ (indicated by the Kronecker delta function $\delta_{k,l}$).

The Wiener-Askey scheme, shown in Table 4.1 gives the optimal polynomials for common distribution types, by optimal meaning showing the fastest convergence [31]. Since this research focuses on Gaussian distributed random variables, the corresponding polynomial family that should be used is the Probabilist’ Hermite Polynomials. The Hermite polynomials are given by,

$$
H_n(\xi_j) = (-1)^n e^{\xi_j^2} \frac{d^n}{d\xi_j^n} e^{-\frac{1}{2} \xi_j^2}. \tag{4.11}
$$

They can also be constructed using the recurrence relation given in Equation 4.12 - 4.14.

$$
H_{n+1}(\xi_j) = \xi_j H_n(\xi_j) - n H_{n-1}(\xi_j) \tag{4.12}
$$

$$
H_{-1}(\xi_j) = 0 \tag{4.13}
$$

$$
H_0(\xi_j) = 1 \tag{4.14}
$$

<table>
<thead>
<tr>
<th>Random Distribution</th>
<th>Askey Polynomial</th>
<th>Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaussian</td>
<td>Probabilists’ Hermite Polynomials</td>
<td>$[-\infty, \infty]$</td>
</tr>
<tr>
<td>Uniform</td>
<td>Legendre Polynomials</td>
<td>$[a, b]$</td>
</tr>
<tr>
<td>Gamma</td>
<td>Laguerre Polynomials</td>
<td>$[0, \infty]$</td>
</tr>
<tr>
<td>Beta</td>
<td>Jacobi Polynomials</td>
<td>$[a, b]$</td>
</tr>
</tbody>
</table>

The consequence of the choice of orthogonal polynomials is illustrated by looking at the mean and variance of the response function $R(\vec{\xi})$. When Equation 4.1, 4.8 and 4.14 are combined, the following expression for the mean can be derived:
The series expansion given in Equation 4.1 is truncated to a limited amount of basis vectors, such that $O$ can define which orders to include in the expansion. The full $O$-th order PC basis set is given by:

$$\Gamma_O = \{ \prod_{j=1}^N \psi_{j \gamma_{k, j}}(\zeta_j) : \sum_{j=1}^N \gamma_{k, j} \leq O \}$$

where $\psi_{j \gamma_{k, j}}(\zeta_j)$ is a polynomial from the Hermite family, the first index $j$ indicates the uncertain input $\zeta_j$, the second index $\gamma_{k, j}$ stands for the order, specific to the given basis vector $\psi_k$. Using the multi-index $\vec{\gamma}$, one can define which orders to include in the expansion. The full $O$-th order PC basis set is given by:

$$\Gamma_O = \{ \prod_{j=1}^N \psi_{j \gamma_{k, j}}(\zeta_j) : \sum_{j=1}^N \gamma_{k, j} \leq O \}$$

The series expansion given in Equation 4.1 is truncated to a limited amount of basis vectors, such that

$$R(\zeta) = \sum_{k=0}^\infty r_k \psi_k(\zeta) \approx \sum_{k=0}^P r_k \psi_k(\zeta) = R_P(\zeta),$$

with $P + 1$ basis vectors in the expansion, expressed as

$$P + 1 = \frac{(N + O)!}{N!O!}.$$
with the basis set including all multidimensional polynomials having a combined order of maximum \(O \), where \(N\) is again the number of dimensions (uncertain inputs). For a truncated expansion, the expression for the variance derived in Equation 4.16 becomes:

\[
\sigma_R = \sum_{k=1}^{\infty} r_k^2 h_k^2 \approx \sum_{k=1}^{P} r_k^2 h_k^2
\]  

(4.20)

In case of the mean (Equation 4.8), the truncation applied to the series expansion has no effect.

### 4.1.2. Expansion coefficients

Now that the construction of the PC basis vectors is set out, the expansion coefficients are the only remaining unknowns. The next task therefore is to find a definition for the coefficients \(r_k\), which can be done using spectral projection of Equation 4.1, due to the orthogonality of the basis vectors:

\[
r_k = \frac{\langle R(\vec{\xi}), \Psi_k(\vec{\xi}) \rangle}{\langle \Psi_k(\vec{\xi}), \Psi_k(\vec{\xi}) \rangle} = \frac{\int_{D(\Theta)} R(\vec{\xi}) \Psi_k(\vec{\xi}) p_\vec{\xi} d\vec{\xi}}{\langle \Psi_k(\vec{\xi}), \Psi_k(\vec{\xi}) \rangle} = \frac{1}{h_k^2} \int_{D(\Theta)} R(\vec{\xi}) \psi_j(\xi_j) p_\vec{\xi} d\vec{\xi}.
\]

(4.21)

This expression for the coefficients contains the term \(R(\vec{\xi})\), which is the response as a function of the input, which is exactly the sought output of the whole model, and therefore not available during the construction of the PCE. The integral in 4.21 can therefore not be solved analytically and a way to approximate the multidimensional integral is given in Section 4.1.3.

### 4.1.3. Quadratures and cubatures

First the approximation of one-dimensional integrals is introduced, by using a finite sum method. Thereafter the generalization to multiple dimensions will be given.

**Quadratures**

The quadrature formula is a finite sum method that approximates an integral for a general function \(f(\xi)\), depending on a single variable \(\xi\) (thereby being a one-dimensional integral):

\[
I^{(1)} f = \int_{a}^{b} f(\xi) p_\xi(\xi) d\xi \approx Q^{(1)} f = \sum_{i=1}^{n_{lev}} f(\xi_{lev}^{(i)}) w_{lev}^{(i)}
\]

(4.22)

with

- \(I^{(1)} f\) the dimension of the integral
- \(\xi_{lev}^{(i)} \in [a, b]\) predefined quadrature points
- \(w_{lev}^{(i)} \in \mathbb{R}\) predefined weights.

The quadrature method is approximating the integral by evaluating the function at different predefined (quadrature) points and taking the weighted sum of the outputs. The index \(lev\) indicates the accuracy of the quadrature method, the higher the level \(lev\) gets, the more quadrature points \(n_{lev}\) are used to construct the approximation. Therefore, for a high accuracy, also a high number of points has to be evaluated. The points and weights must be chosen in such a way that the integration error is minimized. The choice of quadrature points and weights, depends on the probability density function \(p_\xi(\xi)\) of the random variable and the chosen quadrature rule.

There are various quadrature rules which can be used, each with its own accuracy and nestedness. Nestedness means the number of recurring points in each level of the quadrature. When a rule has a high nestedness, it means that for higher levels there are a lot of quadrature points overlapping with lower level points, such that they are already calculated and can be re-used. There are two extremes, full nestedness implies that every point is reused in the next level, and zero nestedness means that no double points occur within the full set of
The quadrature rule that will be used here, is the Gauss-Hermite rule, because of the Hermite polynomials which are used for the basis vectors. The Gauss-Hermite rule has a very low nestedness, only the point in the origin is being reused, and a very high accuracy: a polynomial exactness up to the order \(2n_{\text{lev}} - 1 = 4 \cdot \text{lev} - 3\). An example of the nestedness of the Gauss-Hermite rule versus the a rule with full nestedness, the Clenshaw-Curtis rule, is shown in Figure 4.1. This work uses the Gauss-Hermite rule with \(n_{\text{lev}} = 2 \cdot \text{lev} - 1\) functions evaluations.

### Cubatures

Now that the quadrature method for approximating a one-dimensional integral has been introduced, a cubature of dimension \(N\) can be derived by tensorization of the separate 1D-quadratures:

\[
Q^{(N_{\text{dim}})}_{\text{lev}} f = (Q^{(1)}_{\text{lev}_1} \otimes Q^{(1)}_{\text{lev}_2} \otimes \ldots \otimes Q^{(1)}_{\text{lev}_N}) f,
\]

with \(\text{lev}\) now being a multi-index, indicating the different quadrature levels along the different dimensions. The cubature, as a tensor product of the quadratures, contains all the combinations of the quadrature points. As an example, the cubature points for a three-dimensional cubature are shown in Figure 4.2a. The quadrature levels \(\text{lev}_j\) do not have to be the same in every direction, one can have for example a grid with three dimensions, having a third level in the first dimension and only two levels in the other two dimensions. A \(N\)-dimensional integral can be approximated by cubatures:

\[
I^{(N)} f = \int_{\Omega} f(\vec{\xi}) p_\xi(\vec{\xi}) d\vec{\xi} \\
\approx Q^{(N)}_{\text{lev}} f \\
= (Q^{(1)}_{\text{lev}_1} \otimes Q^{(1)}_{\text{lev}_2} \otimes \ldots \otimes Q^{(1)}_{\text{lev}_N}) f \\
= \sum_{i=1}^{n} f(\vec{\xi}^{(i)}) w^{(i)}
\]

\(\text{(4.24)}\)
Smolyak Sparse Grids

The polynomial chaos coefficients (Equation 4.21) can now be calculated, with the cubature method approximating the integrals of the response function. The expression shown in Equation 4.24 will however take many function evaluations, since the number of evaluations grows exponentially with the dimension of the problem, resulting in:

$$N_{\text{dim}} \prod_{j=1}^{N_{\text{lev}}} n_{\text{lev}_j}$$

evaluations. Therefore, one would like to decrease the number of cubature points, to limit calculation time.

Due to the ‘sparsity of effects’-principle, this can be achieved [30]. This principle states that responses are usually dominated by a few important parameters and more importantly by low order interactions. Cubature points corresponding to high integration levels in many parameters can therefore be excluded without a noticeable loss in accuracy. The grid that remains, contains only a few points for high integration levels and more points for low integration levels. There are various ways to select the exact points to be excluded, during this research the so-called Smolyak Sparse Grids will be used. Figure 4.2b displays an example of a sparse Smolyak grid, without the higher order interactions, greatly reducing the amount of functions to evaluate. The Smolyak sparse grid is obtained by using difference formulas of the quadratures, instead of the quadratures straight away. The difference formulas are given by:

$$\Delta^{(1)}_{\hat{\text{lev}} f} = Q^{(1)}_{\hat{\text{lev}} f} - Q^{(1)}_{0 f}, \quad \text{with} \quad Q^{(1)}_{0 f} = 0$$

When using the difference formulas as a basis, the cubature tensorization looks like:

$$Q^{(N)}_{\text{lev}} f = \sum_{l_{1} = 1}^{N_{\text{lev}}} \sum_{l_{2} = 1}^{N_{\text{lev}}} \ldots \sum_{l_{N} = 1}^{N_{\text{lev}}} (\Delta^{(1)}_{l_{1}} \otimes \Delta^{(1)}_{l_{2}} \otimes \ldots \otimes \Delta^{(1)}_{l_{N}}) f$$

$$= \sum_{\hat{\text{lev}} \in I(\text{lev})} \Delta^{(N)}_{\hat{\text{lev}}} f$$

with $\hat{\text{lev}}$ again being the different quadrature levels along different directions, $I(\text{lev})$ the set of included multi-indices and $\hat{\text{t}}$ the different grids. The set of included multi-indices for a full tensorization and a Smolyak sparse grid construction are given below.

$$I^{\text{Full}}(\text{lev}) = \{ \hat{\text{t}} : l_{j} \leq \text{lev} \ \forall j \in [1, ..., N] \}$$

$$I^{\text{Smolyak}}(\text{lev}) = \{ \hat{\text{t}} : \sum_{j=1}^{N} l_{j} \leq \text{lev} + N - 1 \}$$

A Smolyak sparse grid has a maximum dimension of the included grids at $\text{lev} - 1$. The amount of function evaluations needed for a certain number of dimensions is now largely reduced, thereby saving significant calculation time. The remained number of calculations per number of dimensions is given in Table 4.2, for different grid orders. The grid order, or GO, indicates the level of quadrature points that are included in the grid, i.e. $\text{GO} = \text{lev}$. 

---

Figure 4.2: Cubature points for a full grid and a Smolyak Sparse grid [26].

(a) Full three-dimensional cubature grid  
(b) Sparse Smolyak grid


4.1. Polynomial Chaos Expansion

Table 4.2: Number of function evaluations per grid order and number of dimensions.

<table>
<thead>
<tr>
<th>Grid order</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<td>4</td>
<td>9</td>
<td>49</td>
<td>201</td>
<td>1341</td>
</tr>
</tbody>
</table>

Extended Smolyak Sparse grids

Using the Smolyak Sparse grids to construct the cubatures for the evaluation of the integral resulting from the spectral projection of the expansion coefficients, one greatly reduces the number of evaluation points and subsequently the needed calculation time. The sparse grid can however be extended in a smart way, such that a higher accuracy is achieved without too much extra calculation cost. This can be done by extending the highest order one-dimensional grid with one extra level. This means that the maximum level included in the ‘normal’ Smolyak Sparse grid namely \( l_j = \text{lev} + N - 1 \) for one of the dimensions \( j \), becomes: \( l_j = \text{lev} + N - 1 + \text{lev}_{\text{extra}} \). Equation 4.29 with extended grid is given by:

\[
I_{\text{Extended Smolyak}}(\vec{\xi}) = I_{\text{Smolyak}}(\vec{\xi}) \cup \{ I : I_j = \text{lev} + N - 1 + \text{lev}_{\text{extra}} \} \setminus \{ I : I_j = \text{lev} + N - 1 \}.
\] (4.30)

The extended grid will give higher accuracy along the single dimension axes, with relatively a low number of added calculations: \( 2 \cdot \text{lev}_{\text{extra}} \cdot N \). The number of extra levels will from now on be notated as \( EL \).

Using the Gaussian quadrature rule in combination with the Extended Smolyak Sparse grids for the cubatures, the expansion coefficients of the Polynomial Chaos set (Equation 4.21) can now be expressed as:

\[
r_k = \frac{1}{h_k^2} \int_{\mathcal{D}(\Theta)} R(\vec{\xi}) \prod_{j=1}^{N} \psi_{j,\gamma_k}(\xi_j) p_{\xi_j} d\vec{\xi}
= \frac{1}{h_k^2} \sum_{l \in F_{\text{Sm}(\text{lev})}} \Delta_l^{(N)}(R \psi_k)
= \frac{1}{h_k^2} \sum_{i=1}^{n} R(\vec{\xi}_i^{(i)}) \psi_{k}(\xi_i^{(i)}) w^{(i)}.
\] (4.31)

4.1.4. Final construction of the PCE

The goal of constructing the PCE is to express the output response \( R \) as function of the uncertain input parameters \( \vec{\xi} \). In order to do this, a series expansion is constructed of the form: \( R(\vec{\xi}) \approx \sum_{k=0}^{P} r_k \psi_k(\vec{\xi}) \). The series expansion consists of the expansion coefficients \( r_k \) and the basis vectors \( \psi_k(\vec{\xi}) \). The basis vectors are constructed via tensorization of univariate polynomials, chosen from the Wiener-Askey Scheme. The expansion coefficients can be expressed via spectral projection and using orthogonality as a integral of the form

\[
r_k = \frac{1}{h_k^2} \int_{\mathcal{D}(\Theta)} R(\vec{\xi}) \prod_{j=1}^{N} \psi_{j,\gamma_k}(\xi_j) p_{\xi_j} d\vec{\xi}.
\]

This integral however contains the response as a function of the uncertain input variables \( \vec{\xi} \) and can not be solved analytically. Therefore an approximation of the integral is made, by using cubature grids as a weighted sum method. The result is an expression for the expansion coefficients, given in Equation 4.31, where now only a limited amount of function evaluations \( R(\vec{\xi}_i) \) is needed.

4.1.5. Hyperbolic Trim

The PC basis set formulated in the section above can also be truncated without losing much of its accuracy due to the sparsity of effects-principle. The set of basis vectors can be trimmed by excluding the polynomial basis vectors that represent high order interactions. A hyperbolic trimming is applied during this research, using the \( q \)-quasi-norm of the multi-index \( \gamma_{k,l} \) [1], defined as:

\[
\|\vec{\gamma}_{k,l}\|_q = \left( \sum_{j=1}^{N} \gamma_{k,j}^q \right)^{\frac{1}{q}}.
\] (4.32)
The factor $q$ is called the hyperbolic trim factor, and has a value between zero and one. The $q$-quasi-norm of Equation 4.32 has to meet: The factor $q$ is called the hyperbolic trim factor, and has a value between zero and one. The $q$-quasi-norm of Equation 4.32 has to meet:

\[ ||\vec{\gamma}_k||_q = \left( \sum_{j=1}^{N} \gamma_{k,j}^q \right)^{\frac{1}{q}} \leq GO, \tag{4.33} \]

since the number of basis vectors that can be in the expansion, depends also on the grid order $GO$. When the dimensionality of the polynomial basis vectors is bigger than the grid order, the expansion coefficients cannot be accurately determined. Therefore, the grid order $GO$ must always be equal to (or greater than) the polynomial order $PO$. When an extra level $EL$ following the extended Smolyak sparse grid is being used, the grid order can be $GO = PO - 1$, or:

\[ GO \geq PO \quad \text{or} \quad (GO + EL) \geq PO \tag{4.34} \]

### 4.2. PCE applied to proton therapy

During this research Polynomial Chaos Expansion will be applied to proton therapy, or more specific to dose distributions. This means that the PCE is used to model the dose distribution (exact output $R$) as a function of the uncertainties which influence it (uncertain input $\vec{\xi}$). The uncertain inputs are the setup and range errors as discussed in Section 2.3:

- Random setup errors
  \( \{\sigma_x, \sigma_y, \sigma_z\} \)
- Systematic setup errors
  \( \{\Sigma_x, \Sigma_y, \Sigma_z\} \)
- Range errors
  \( \rho \)

For the construction of the PCE, the random and systematic setup errors are combined for each direction, into \((X, Y, Z)\). Since both are assumed to be independently distributed, this is allowed. The final uncertain input vector is then given by:

\[ \vec{\xi} = (X, Y, Z, \rho) \tag{4.35} \]

Even if the PCE is constructed for this combined input, it is possible to deduce the full PCE afterwards for \((\sigma_x, \sigma_y, \sigma_z, \Sigma_x, \Sigma_y, \Sigma_z, \rho)\) [26].

### 4.3. Terminology

During the rest of this thesis the theory of PCE will be used. The following terms will be used:

- **PO** - *Polynomial Order*
  The polynomial order determines the set of basis vectors which is used for the PCE construction.

- **GO** - *Grid Order*
  The grid order indicates the level of quadrature points that are included in the grid.

- **EL** - *Extra Level*
  The extra level is the one-dimensional extension of the grid, which gives higher accuracy along the single dimension axis.

- **$q$** - *Hyperbolic trim factor*
  The hyperbolic trim factor $q$ is used in the $q$-quasi-norm to trim the set of polynomial basis vectors, to exclude basis vectors that represent high order interactions.
5

Method

This chapter starts with a general description of the method of constructing PCEs for dose distributions. Thereafter, various ways to validate the resulting PCE as a meta-model for the dose distribution are presented. Subsequently, the method to construct an iCycle wish-list resulting in clinically acceptable treatment plans is given, after which the recipe construction is explained. The latter is done for the case of iCycle as a treatment planning system but can be generalized easily for any other treatment planning system that is coupled to the PCE construction scripts. After the recipe construction, the way of validating the obtained recipes is detailed. The last section shows the method of coupling the PCE construction scripts to the RayStation planning system.

5.1. PCE construction

Polynomial Chaos Expansion (PCE) is used as a meta-model of the dose distribution. As discussed in Chapter 4, the PCE is constructed by choosing polynomial basis vectors and calculating the corresponding coefficients. During this research, the PCE is constructed using the Matlab package OpenGPC, a PCE package developed at TUDelft (for details see [21, 22]).

The basic steps of constructing the PCE are displayed in Figure 5.1. First, the input settings are given to the PCE scripts. These include the type of polynomials to be used, the maximum polynomial order $PO$, the grid order $GO$ (with optional an extra level $EL$ included) for the cubatures, the means and standard deviations of the uncertain input, the trim factor (for hyperbolic trimming of the PCE), the plan file and a dose cut-off value. The latter will be used in order to limit the PCE to represent only voxels with a dose value higher than a certain dose cut-off value $D_{cut-off}$, to save memory and time during the calculations. The standard deviations of the uncertain input are submitted in the following order: $[\Sigma_x \sigma_x \Sigma_y \sigma_y \Sigma_z \sigma_z \rho_{rel} \rho_{abs}]$, with $\Sigma$ and $\sigma$ being the standard deviations of the systematic and random setup errors respectively and $\rho$ being the range error standard deviation, relative or absolute. The same order applies for the means, if no means are given, a zero value is applied. The plan file is a string with the location of the treatment plan, based upon which the PCE will be made.

The provided input setting structure is checked and the additive errors are collapsed. In this case this means that the Gaussian random and systematic setup errors are merged, such that the standard deviation array becomes: $[\sqrt{\Sigma_x^2 + \sigma_x^2} \sqrt{\Sigma_y^2 + \sigma_y^2} \sqrt{\Sigma_z^2 + \sigma_z^2} \rho_{rel} \rho_{abs}]$. The means of the systematic and random setup errors are simply added.

Next, the generation of the cubatures is needed for the approximation of the integrals later on. First quadratures are created, following the chosen integration rule. By tensorization of the formed quadratures, and a summation of the sparse grids the final cubature is constructed and saved.

Then, the PCE object is initialized; the basis vectors are constructed from all multidimensional polynomials up to a maximum order $PO$, and the norm of each basis vector is calculated. When a hyperbolic trim factor $q$ is given in the input settings, the basis vectors representing high order interactions are cut out, following the method described in Section 4.1.5. The resulting PCE objects consists of basis vectors, the corresponding norms and for every voxel the coefficients. The input settings and some other details are also saved within the PCE.

Subsequently the dose mask is calculated, which is a logical array that indicates for every voxel if it should be
5. Method

Check and set PCE settings
Generate cubature
Initialize PCE object
Calculate dose mask
Calculate cubature responses
Construct the PCE

Figure 5.1: Flowchart of the PCE construction by OpenGPC-package in Matlab.

included in the PCE or not. A voxel is included if it receives a dose higher than the predefined \( D_{\text{cut-off}} \) in any of the 9 planning scenarios (Section 3.4.1). Thus, the dose per voxel is not only considered for the nominal scenario, but also for the worst case scenarios traditionally involved in robust optimization. In order to calculate the dose per voxel for these scenarios, the PCE scripts must be coupled to the dose engine which was used to produce the treatment plan. The dose engine is used as a black-box, with as input the (perturbed) scenarios, (i.e. the values for the combined (random and systematic) setup errors and range errors) and the treatment plan file, producing the dose per voxel for each scenario as output. The dose mask is then constructed by looking at the dose in every scenario, and only those voxels which receive a dose higher than the predefined \( D_{\text{cut-off}} \) in any scenario are included in the PCE.

The next step is to calculate the responses of all cubature points, for the voxels which are included in the PCE according to the dose mask. Every cubature point represents a perturbed scenario with a corresponding perturbed original dose distribution, which is calculated in the same way as for the dose mask scenarios, by using the dose engine. Once the responses for all cubature points are obtained, the coefficients in the PCE object are updated. The PCE is saved and can now be used to model the dose distribution as a function of the setup- and range errors.

5.1.1. Error simulation

In order to calculate the perturbed scenarios, the effects of setup and range errors are simulated by the dose engine and the resulting dose distributions are calculated. The method of simulating the errors is discussed in Section 3.4.2. During the PCE construction the setup errors are simulated in the same way as Erasmus-iCycle does automatically, for the range error however, a slight adaptation is made. The standard way of modeling range errors for iCycle is rescaling the proton beam energy, in this research this is changed to the rescaling of CT image values. The adaptation is made in two steps, first during the final calculation of the iCycle plans, second during the scenario calculations of the dose engine in the PCE construction.

5.2. Validation of PCE

Before the PCE can be used to construct robustness recipes, its accuracy as a meta-model for this specific treatment site must be validated. This section describes the various validation methods, results are shown in the next chapter.
5.2. Validation of PCE

5.2.1. Grid order
When constructing the PCE, it is important to use the right grid and polynomial order for the expansion. An overestimation of the needed order will slow down the construction significantly, while using an order which is too low may result in a model which is not a reliable representation of the dose distribution. Therefore, the optimal polynomial order must be examined. This is done by comparing the exact dose distribution as calculated by the dose engine, to the dose distributions resulting from multiple PCE’s of different orders. The dose comparison is performed by a gamma calculation, as will be further explained in Section 5.2.3. By comparing the calculation time and accuracy of several polynomial orders, the optimal order for this work can be chosen. For the cubatures in a PCE construction with a polynomial order of \( X \), one extra level (EL) is used, together with a grid order of \( (PO - 1) \):

\[
PO = X \\
EL = 1 \\
GO = X - 1
\]

5.2.2. Dose Volume Histograms
Dose Volume Histograms, DVHs, can be used to compare structure-wise the dose that is delivered by making use of both the exact dose engine and the PCE. The resulting dose distributions can be displayed together in a DVH and for a perfect meta-model, the DVHs will fully overlap. Important to note here is that the DVH is given as a fraction of the relative volume, such that structures of different sizes can be displayed together. This means that for a very small structure, even a small deviation can appear large in a DVH. The DVH can be used to compare doses in the nominal scenario as well as in error scenarios.

5.2.3. Gamma evaluation
Comparing two dose distributions can be done by simply calculating the dose difference in every voxel, this could however give a unfair result for a region with a large dose gradient. A more common and fair way of comparing two doses is using gamma evaluations [14]. In a gamma evaluation also neighboring voxels are taken into account up to a distance \( \Delta r \), from now on the ‘distance-to-agreement’, and a small dose difference \( \Delta D \) is allowed. In the end, every voxel will be scored a gamma value, which is defined as:

\[
\gamma(\vec{r}_e, \vec{r}_c) = \min\{\Gamma(\vec{r}_e, \vec{r}_c)\} \quad \forall \vec{r}_c
\]

with

\[
\Gamma(\vec{r}_e, \vec{r}_c) = \sqrt{\left(\frac{(\vec{r}_e - \vec{r}_c)^2}{\Delta r^2} + \frac{(D_e(\vec{r}_e) - D_c(\vec{r}_c))^2}{\Delta D^2}\right)},
\]

and

- \( \vec{r}_e \) = point in the exact dose distribution
- \( \vec{r}_c \) = point in the dose distribution that is being compared
- \( \Delta r \) = distance-to-agreement criterion
- \( \Delta D \) = dose difference criterion.

The gamma evaluation compares the voxels within a certain region, to find the best possible dose. Figure 5.2 shows a geometric representation of the gamma evaluation method. A voxel that meets both the distance-to-agreement criterion and the dose criterion, receives a \( \gamma \)-value lower than 1 (point a in the figure) and is accepted. When one of the criteria is violated, the voxel did not pass the test and receives a \( \gamma \)-value larger than 1 (point b in the figure) and is rejected. The result of a gamma evaluation is a failing or passing value for every voxel in the dose distribution. In this work the maximum dose difference is set at \( \Delta D = 0.1 \) Gy and the maximum distance-to-agreement at \( \Delta r = 1 \) mm.
5. Method

\[ \vec{r}_e - \vec{r}_c \text{ (mm)} \]

\[ \Delta r, \quad \Delta D \]

\[ \delta_a, \quad \delta_b \]

Figure 5.2: Two-dimensional geometric representation of the gamma calculation, with distance-to-agreement \( \Delta r \) and dose difference criterion \( \Delta D \). Point \( a \) does meet the criteria and is therefore scored a \( \gamma \)-value lower than 1, while point \( b \) exceeds the distance-to-agreement criterion and is therefore scored a \( \gamma \)-value bigger than 1.

5.2.4. Scenarios for validation

The scenarios which are used to test the distributions are chosen to be at the surface of the 99% confidence ellipsoid, constructed for systematic and random setup errors of both 2 mm and a relative range error of 2%. For these errors, a confidence ellipsoid is constructed from which 50 scenarios are chosen randomly. For every scenario the exact dose distribution is calculated as well as the distributions resulting from the Polynomial Chaos Expansion.

5.2.5. Voxel-wise comparison

Apart from the gamma evaluation, also a voxel-wise comparison is made. This can be done by calculating the exact dose of one single voxel as a function of a shift in the setup or range direction, such that a dose dependency is calculated. The same shifts are then calculated using the PCE and the resulting doses are then plotted together.

5.2.6. Beam-angle dependence

In Sections 5.2.1 - 5.2.5, the methods to test the validity of the PCE as a meta model for the exact dose engine are described. In order to prove that PCE works for every set of beam-angles, the accuracy as a function of beam angles used in the treatment plan is investigated. First the method used to examine the dependency on a three beam coplanar configuration is set out, thereafter a non-coplanar four-beam configuration is tested.

3 coplanar beam-angles

First, a coplanar setup is chosen with three equiangular beams, as shown in Figure 5.3a which shows the setup in the transverse plane. The displayed angles are the gantry angles, no couch angles are applied during this configuration. Subsequently two of the three beams are perturbed, by adding or subtracting 30, the beam at 180° is being kept fixed. For each of the resulting beam configurations, displayed in Table \( \xi \), a treatment plan is generated. Next, a PCE for each of the generated treatment plans is built, and gamma calculations are performed, using a set of error scenarios and the corresponding dose distributions calculated by the dose engine and the PCE. The gamma calculations yield an accuracy evaluation of the PCE for each treatment plan, and thereby for each beam angle configuration. When results are plotted together, a quality comparison of the PCE under different beam angles can be made.
5.2. Validation of PCE

(a) Initial beam setup  
(b) Two beam perturbation  
(c) Equiangular rotation

Figure 5.3: Different beam-angle configurations in the same plane, with two beam perturbations (a) and a full rotation with steps of 30° (b).

Table 5.1: Overview of the used beam angles for the coplanar setup with 3 beams.

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<tr>
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</table>

4 non-coplanar beam-angles

The starting point for the non-coplanar beam-angle configuration is displayed in Figure 5.4. For the evaluation the gantry angle of one beam is perturbed at a time, keeping the couch angle fixed. This is done for beams 1, 2 and 3, keeping the fourth beam fixed.

Figure 5.4: Beam-angle configuration starting point for the non-coplanar setup with 4 beams for skull base chordoma patient.
The first two angles (1 and 2) are perturbed twice, each time subtracting or adding 30°. The third beam (30) is rotated first by 35°, and thereafter by an extra 70°, to pass the fourth beam angle. The resulting beam angle configurations, given in Table 5.2, are then used to make treatment plans. Similar to the co-planar case, these treatment plans are used to construct PCEs and performing the gamma evaluation as described above.

<table>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Couch angles</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>290°</td>
<td>75°</td>
<td>200°</td>
<td>270°</td>
<td></td>
</tr>
</tbody>
</table>

5.3. iCycle wish-list construction

In order to construct realistic recipes, clinically acceptable treatment plans must be used. These treatment plans are depending on which treatment planning system is being used, for the sake of simplicity the focus of this section will be on iCycle.

5.3.1. Skull base chordoma

During the first phase of this research, the focus was on skull base chordoma. The protocol for organs at risk for skull base chordoma is given in Table 5.3a. The constraints on the CTV are displayed in Table 5.3b, consisting of a near-minimum dose $D_{98\%}$ and a near-maximum dose $D_{2\%}$ to prevent cold and hot spots. For the skull base chordoma patients, four non-coplanar beams were chosen, with the gantry and couch angles stated in Table 5.4. For the generation of wish-lists the Erasmus MC program Lucy was used. The search for an optimal wish-list is an iterative process, with adding and tuning constraints and objectives and each time calculating the resulting treatment plan.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem, surface</td>
<td>$D_{2cc} &lt;64$ Gy</td>
</tr>
<tr>
<td>Brainstem, center</td>
<td>$D_{2cc} &lt;53$ Gy</td>
</tr>
<tr>
<td>Spinal cord, center</td>
<td>$D_{2cc} &lt;64$ Gy</td>
</tr>
<tr>
<td>Spinal cord, surface</td>
<td>$D_{2cc} &lt;53$ Gy</td>
</tr>
<tr>
<td>Optical Nerves</td>
<td>$D_{2%} &lt;60$ Gy</td>
</tr>
<tr>
<td>Chiasm</td>
<td>$D_{2%} &lt;60$ Gy</td>
</tr>
<tr>
<td>Hippocampi, combined</td>
<td>$D_{40%} &lt;7.3$ Gy</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>$D_{mean} &lt;30$ Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structure</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV</td>
<td>$D_{98%} \geq 0.95 \cdot 74$ Gy = 70.3 Gy</td>
</tr>
<tr>
<td>CTV</td>
<td>$D_{2%} \leq 1.07 \cdot 74$ Gy = 79.2 Gy</td>
</tr>
</tbody>
</table>
Since proton therapy is not an established treatment method in the Netherlands yet, and chordoma is not a very common type of cancer, not much knowledge was available on the specifics of proton treatment plans for chordoma patients. Therefore, the wish-list had no starting or reference point. Another difficulty is the high dose needed to the CTV, in combination with constraints on the maximum dose values for the surrounding organs-at-risk. To illustrate this one can look at the brainstem, which has a hard constraint of $D_{\text{center,2cc}} < 53\text{Gy}$, while the CTV which is often located directly next to the brainstem must receive $D_{98\%} > 70.3\text{Gy}$. This results in having to make a trade-off between target coverage and sparing of organs-at-risk. The lack of experience combined with the forced trade-off eventually resulted in the decision to switch tumor sites, therefore from now on the focus of the research will be on skull base meningioma.

### 5.3.2. Skull base meningioma

The treatment protocol for skull base meningioma is significantly easier than that for chordoma discussed previously. This is due to a lower prescription dose to the target of $50.4\text{Gy}$. The tumor is located at roughly the same location as the chordoma, and therefore the same organs-at-risk are considered (Section 2.4). The dose constraints however are adjusted, due to the lower prescribed dose of the CTV. For the wish-list construction, the newly developed protocol of HollandPTC is used. The constraints on CTV coverage and the most important surrounding organs-at-risk are given in Table 5.5. The constraint on the near maximum dose $D_{2\%}$ is applied to prevent the occurrence of hot-spots. The most critical surrounding tissue consists of the brainstem, the optical nerves and the chiasm. Furthermore, the hippocampi are also to be taken into account in the optimization. When constructing the plans, two general beam configurations were used. The choice of beam angle configuration is based upon consultation with experienced treatment planners. They chose a configuration for a ‘left-sided’ CTV, for a CTV which is located at the ‘right-side’, the beam-angles are simply mirrored. The resulting beam-angles are given in Table 5.6. Only co-planar beams were used, and no couch angle is applied. The treatment is to be delivered in a total of 28 fractions.

### Table 5.5: Constraints on the CTV and OARs for meningioma

<table>
<thead>
<tr>
<th>Structure</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTV</td>
<td>$D_{98%} \geq 0.95 \cdot D_{\text{prescribed}} = 47.88\text{Gy}$</td>
</tr>
<tr>
<td>CTV</td>
<td>$D_{y%} \leq 1.07 \cdot D_{\text{prescribed}} = 53.93\text{Gy}$</td>
</tr>
<tr>
<td>Chiasm</td>
<td>$D_{\text{max}} &lt; 55\text{ Gy}$</td>
</tr>
<tr>
<td>Optical Nerves</td>
<td>$D_{\text{max}} &lt; 55\text{ Gy}$</td>
</tr>
<tr>
<td>Brainstem</td>
<td>$D_{\text{max}} &lt; 55\text{ Gy}$</td>
</tr>
<tr>
<td>Hippocampi (L+R)</td>
<td>$D_{40%} &lt; 7.3\text{ Gy}$</td>
</tr>
</tbody>
</table>

### Table 5.6: Beam angles used for skull base meningioma, the couch angle is zero in all cases

<table>
<thead>
<tr>
<th>Beam nr</th>
<th>Gantry angle - Left-sided CTV</th>
<th>Gantry angle - Right-sided CTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$180^\circ$</td>
<td>$180^\circ$</td>
</tr>
<tr>
<td>2</td>
<td>$230^\circ$</td>
<td>$130^\circ$</td>
</tr>
<tr>
<td>3</td>
<td>$290^\circ$</td>
<td>$70^\circ$</td>
</tr>
</tbody>
</table>

Now that the beam-angles are fixed, the wish-list is formulated such that the resulting plans meet the constraints set by the protocol. The wish-list construction was an iterative process, with every time tuning the objectives and constraints, and calculating the resulting plan. In order to receive a dose distribution which
5. Method

5.4. Recipe construction

When constructing the robustness recipe, a parameter which describes the dose distribution in the CTV must be chosen together with its desired criterion. In literature there are various suitable parameters discussed, but in this thesis the near-minimum dose $D_{98\%}$ was used, as described in Section 3.1. This was also used in previous research [27, 28]. A treatment is considered robust if at least 98% of the populations receives 95% of the prescribed dose in at least 98% of the CTV:

$$P(D_{98\%} \geq 0.95 \cdot D_{\text{prescribed}}) \geq 98\%$$ (5.6)

To prevent being too conservative, the recipes are constructed with a stricter constraint on the percentage of the population receiving sufficient target coverage, namely:

$$98.0\% \leq P(D_{98\%} \geq 0.95 \cdot D_{\text{prescribed}}) \leq 98.1\%$$ (5.7)

The recipe construction is split into a range robustness recipe and a setup robustness recipe. First the method to derive the range robustness recipe is explained, after which the method applied for setup recipe construction is detailed, together with the differences. The method is explained for iCyle recipes, but can easily be generalized for any other treatment planning system.

Range robustness recipe

The recipe construction consists of three main steps, which are shown in Figure 5.5. First, a treatment plan with a certain range robustness setting is generated. The iCyle wish-list that was constructed and clinically
accepted, is now used to construct a plan with a setup robustness setting of zero, and a range robustness setting of $x\%$ (i.e. SR = 0 mm and RR = $x\%$). For both recipes, the same single patient, the base patient is used to generate the treatment plans upon. Second, a Polynomial Chaos Expansion (PCE) is constructed based upon the treatment plan together with an initial guess of the range error $\rho$ that can be handled by the plan with range robustness setting $x\%$. Systematic and random setup errors are set at zero. In the third step 100,000 fractionated treatments are simulated and evaluated with the PCE, to determine the fraction of the treatments that received $D_{98\%} \geq 95\%$ of the prescribed dose. Each of the $10^5$ scenarios is a different realization of the range error, sampled using the known standard deviations and Gaussian distribution. Fractionation can also taken into account during the sampling, the range error however is a the systematic error and is constant over all fractions. The samples are multiplied with a scaling factor which will be explained into more details in Section 5.6. The result of the samples is the dose in the CTV for each scenario, and the corresponding $D_{98\%}$ values. From the $D_{98\%}$ of each scenario, a population histogram can be formed. Following Equation 5.7 between 98-98.1% of the treatments should receive a near minimum dose of at least 95% of the prescribed dose. If the amount of treatments is less than 98%, the range error is apparently too big and decreased for the next iteration. When more than 98.1% of the population achieves a good target coverage, the range error is increased. A new PCE is then constructed for the same plan and new range error, and treatments are simulated and evaluated again. Steps two and three are repeated until a range error is found for which exactly 98.0 – 98.1% of the population receives $D_{98\%} \geq 95\%$. This results in a combination of range robustness setting RR and range error $\rho$. All three steps are then repeated for multiple plans with different RR, such that a relation RR($\rho$) is found, the range recipe. The increase or decrease in range error in every step is calculated using the gradient method. The iteration of finding one range robustness setting and range error couple that satisfies Equation 5.7 is given in Figure 5.6.

![Figure 5.6: This figure shows an example of an iteration of 6 steps, that converges to the wanted percentage of the population passing Equation 5.7. Each next range error is determined by using the Newton gradient method. This method uses the gradient between two points to construct a tangent line, and the point where this line intersects with the wanted percentage of the passed population (y-axis), the corresponding value on the x-axis will be used as the next error. The arrow displays this step for the determination of the range error in the third iteration.](image)

In the graph the different iteration steps are displayed. First, the initial guess for the standard deviation of the range error is used to construct a PCE, the standard deviation of the range error is given along the x-axis. This PCE is then sampled and the population that passed the $D_{98\%} \geq 95\% D_{\text{prescribed}}$ is calculated, the resulting percentage is given along the y-axis. The first range error gave a percentage of 95.8% that passed the criterion, which is too low, therefore the range error is decreased for the next step. The PCE construction and sampling is repeated for the new range error, such that point two in the graph is reached, which is now too high. The next range errors are calculated using the gradient method, which results in a convergence towards the wanted percentage of the population to pass the dose criterion.
Setup robustness recipe
The setup recipes are constructed in a similar way, but now the maximum systematic and random setup error (\(\Sigma\) and \(\sigma\)) still giving adequate CTV coverage are the wanted outputs. The systematic setup error \(\Sigma\) is determined for a given set of random setup errors \(\sigma\), specifically (0, 0.5, 1, 1.5, 2, 2.5, 3) mm. Because now also random errors are involved, the fractionation must be taken into account. This is done by sampling the systematic setup error for 100000 scenarios, and for each of these scenarios sampling 28 different random setup errors. For the evaluation of the \(D_{98}\%\) of the population, the dose distributions are calculated for each scenario by taking the mean dose over the 28 fractions. The samples are, just as for the range recipe, multiplied by a scaling factor \(R_{\text{factor}}\) before the \(D_{98}\%\) is calculated (Section 5.6). The result of each iteration contains a combination of setup robustness setting, systematic setup error and random setup error such that in the end a relation \(SR(\sigma, \Sigma)\) is derived, called the setup recipe. Beyond the given set of random errors, an additional point for each Setup Robustness setting is calculated, the ‘end-point’ at which only a random setup error can be present to still meet precisely the population criterion. These points are calculated by applying a systematic setup error of 0, and by changing only the random setup error in every iteration step.

Last, setup recipes can be made for plans with both range and setup robustness settings and evaluated for fixed range error value, as obtained by the range recipe, and given the set of random error values as used before, to determine again the maximum systematic setup errors.

Base patient selection
First, a base patient is randomly chosen from the set of patients. This patient is then used to construct a setup recipe, without any range robustness settings or errors applied. This initial recipe is only used to select the optimal base patient and will further not be used. After a validation (the method of validation is described in the next section) of this recipe, the worst performing patient is selected as the final base patient. The final base patient is then used to construct the range and setup robustness recipes.

5.5. Recipe validation
As discussed in the section above, robustness recipes are constructed based on a single patient. The validation must however be done for more patients that the recipe works for a whole patient group with the same tumor site and type. The validation is conducted in a way similar to the recipe construction. First a validation point must be chosen, using the relations \(RR(\rho)\) and \(SR(\Sigma, \sigma)\). This means that a combination of robustness settings is chosen, \((RR, SR)\) together with a random setup error, \(\sigma\), and the recipes are then used to calculate the corresponding values for the systematic setup and range error \(\Sigma, \rho\). Ideally, one would choose a combination of errors \((\Sigma, \sigma, \rho)\), and calculate the corresponding robustness settings that have to be used. The recipes do give the opportunity to do this, Erasmus-iCycle however can only handle integer values for setup robustness settings. Afterwards treatment plans must be generated for each patient with the robustness settings according to the recipes for the validation point. Next a PCE is constructed for each patient with the treatment plan, and the range and/or setup errors as input. The (patient specific) PCE is now sampled for 100.000 scenarios, and the chance of achieving enough target coverage is calculated in the same way as in step II of the recipe construction, also including a \(R_{\text{factor}}\) multiplication (Section 5.4 and 5.6). The result of the validation is a percentage \(P_{\text{passed}}\) for each patient, which indicates which fraction of the sampled treatments passed the dose criterion on the CTV given in Table 5.5. The recipe is valid if this \(P_{\text{passed}}\) is for all patients above 98%.

5.6. Rescaling the dose
Because the recipe is built using only one patient, the base patient, the results depend on the plan quality of this specific patient. Each plan meets the CTV coverage constraint given in Table 5.5, but there are patients who barely meet this criterion and others who reach a much higher percentage of prescribed dose. This variance in plan quality can result in a variance in the resulting recipes. This is best explained by looking at two extreme (hypothetical) cases:

1. Base patient A \(D_{98}\% = 0.991 \cdot D_{\text{prescribed}}\)
   - Base patient A has a nominal plan where for the CTV \(D_{98}\% = 99.1\%\) of the prescribed dose is achieved. This is much higher than the needed 95% of the prescribed dose. The plan has therefore intrinsically more ‘room’ to make up for shifts in setup or range direction, since the recipe is formulated to achieve an exact \(D_{98}\% = 0.95 \cdot D_{\text{prescribed}}\). Due to the high level of coverage of the nominal plan, the plan in the presence of a small setup or range shift will still be acceptable.
2. Base patient $B$  
\[ D_{98}\%^B = 0.952 \cdot D_{\text{prescribed}} \]

For base patient $B$ it was harder to achieve enough target coverage, thus the nominal plan of this patient only barely meets the constraint of 95%: $D_{98}\%^B$ is 95.2% of the prescribed dose. A small shift in setup or range will therefore already result in insufficient tumor coverage and an unacceptable plan.

A recipe based on patient $A$ will therefore be less strict than a recipe based on patient $B$. Following this logic, the robustness recipes should be based on a patient who is representative for the whole patient group, without being too conservative and strict. One would ideally have the same plan quality for all the patients, to make a fair comparison and validate the working principle of the recipes. In order to approach this ideal situation as much as possible, rescaling of the plans can be applied. Rescaling means that the dose distribution is multiplied by the rescaling factor $R_{\text{factor}}$, which in this work is based upon the $D_{98}\%$ of the worst planning scenario. The plans are rescaled such that the worst planning scenario of each plan has a $D_{98}\%$ which is exactly 95% of the prescribed dose.

\[ R_{\text{factor}} = \frac{0.95 \cdot D_{\text{prescribed}}}{D_{98}\%_{\text{worst planning scenario}}} \]  

This results in a scaling factor lower than one for plans which are intrinsically ‘better’ than others, and lower than one for plans that barely meet the dose criterion in the nominal plan.

In this work, the rescaling is applied during both the recipe construction and the validation.

### 5.7. RayStation

The PCE construction as explained in Section 5.1, makes use of the dose engine as a ‘black-box’. Up until now, iCyle was always the dose engine fulfilling this role. Here a quick overview of the method of coupling another clinically used TPS, RayStation, to the PCE script as a black-box is given. Only the step where the PCE uses the black-box for the calculation of shifted dose distributions needs to be looked at. The construction as displayed in Figure 5.1 remains completely the same. The needed output of the dose engine in this step is the dose distribution of a certain treatment plan for a certain patient, given a set of error scenarios. The dose engine is used first to calculate the dose mask for which only the planning scenarios are included in this error set. Thereafter the set of error scenarios consists of all the cubature points, needed for the calculation of the expansion coefficients of the PCE. The dose calculations within RayStation are scripted using IronPython. The following steps must be made in order to construct the PCE using RayStation, from the existing Matlab scripts.

1. Create IronPython script ‘Calculate_Responses.py’

This script is adapted to contain all the patient and plan specific information needed for the dose calculation in RayStation of step 4. The script contains:

- Patient information
- Plan file
- Location of the error scenarios
- Location where the results should be saved

2. Open RayStation

3. Run ‘Calculate_Responses.py’

The script performs the following actions:

(a) Open the patient and plan file
(b) Perform the perturbations to the dose distribution as given by the error scenarios
(c) Calculate the resulting dose distributions
(d) Save the results at the specified location

4. Close RayStation

5. Load the calculated dose distributions into Matlab

6. Calculate expansion coefficients
This chapter starts with the validation results of PCE as a meta-model for the dose distribution for skull base meningioma patients. Subsequently, the constructed iCycle wish-list for skull base meningioma is described, together with an example of the resulting plans. After the validation of the model and the clinically accepted plan, the robustness recipe results of iCycle are shown. Thereafter, the results of the validation of both the setup and range robustness recipes are given, together with a validation of a combined recipe. The effects of the method of simulating errors in the scenario recalculations are illustrated, followed by the influence of the scaling factor $R_{\text{factor}}$. The final section of this chapter shows first results towards coupling the PCE-construction scripts to RayStation.

6.1. Validation of PCE for skull base meningioma

In this section the use of PCE as a meta-model for the dose distribution of skull base meningioma patients is checked and validated. First, the choice of the specific polynomial order $PO$ and the grid order $GO$ used during the research is illustrated. After that, a comparison between the two nominal dose distributions resulting from the exact dose engine and the PCE is made. The results of gamma evaluations for error scenarios are given and a voxel wise comparison is shown. The dependency of PCE quality on the beam-angles included in the treatment plan is investigated, for chordoma patients.

6.1.1. Polynomial order

The first step of validating the Polynomial Chaos Expansion is looking into the polynomial order required to construct a representative model of the dose distributions. This is done using the gamma evaluation method described in Section 5.2.3. Gamma calculations are performed for increasing polynomial orders and the corresponding grid orders (Section 5.2.1, Equations 5.1-5.3). The error scenarios that are used are taken from the 99% confidence ellipsoid, the dose criterion $\Delta D$ is set at 0.1 Gy and the distance-to-agreement criterion $\Delta r$ is 1 mm.

Figure 6.1 shows the amount of voxels which passed the gamma evaluation against the scenarios for which the gamma calculations are performed, for increasing polynomial orders. As can be seen in the figure, the amount of accepted voxels increases with the order of the PCE, thus the quality of the model enhances with the polynomial order. For a PCE of 3rd order, in only 3% of the scenarios are all the voxels accepted, while for the 4th order this is already 76% and for 5th for 98% of the scenarios all voxels are accepted. For the 6th order, this increases to 100% of the accepted scenarios for all voxels. The calculation time for constructing the PCEs of different orders is given in Table 6.1b, showing that the time to construct the PCE increases with polynomial order.

A trade-off is made such that the quality of the PCE as a meta-model is as high as possible while still having an acceptable construction time. By combining the timing and gamma evaluation results, the polynomial order that has been used during this research was set at 5, with an accompanying grid order of 4 with 1 extra level (GO4PO5EL1).
6.1.2. Nominal dose distribution

CT scan

The first thing to compare is the nominal dose distribution obtained by the exact dose engine and by the PCE, displayed on the (planning) CT scan. In the figure below, a single slice of the CT scan is displayed, together with the nominal dose distribution resulting from the dose engine (left) and the PCE (right).

Figure 6.2: Single axial CT slice of a meningioma patient, with dose distribution for the exact dose engine (left) and the PCE (right) for the nominal scenario.

There are no differences visible between the dose generated by the PCE and the dose resulting from the dose engine.

Dose volume histograms

Next, the dose distributions within the structures of the patient are compared using dose volume histograms. Figure 6.3 shows the dose volume histograms of the nominal dose distributions of both the exact dose engine and the PCE. In the graph, not only the CTV (clinical target volume) is displayed, but also the important...
6.1. Validation of PCE for skull base meningioma

Figure 6.3: Dose volume histogram of the nominal dose, resulting from the exact dose engine (continuous line) and the PCE (dashed line), for every structure the curves are overlapping which confirms the equal dose distribution.

organs-at-risk and other structures that were used for treatment planning. As can be seen in the figure, the dose distributions overlap for every structure. This confirms that the PCE resulted in the same nominal dose distribution as the exact dose engine. This confirms that PCE is a valid method to reconstruct the nominal dose distribution.

The next test is to see how PCE performs under dose shifts resulting from setup and range errors.

6.1.3. Dose distribution for error scenarios

In order to see whether PCE is still a valid model for a shifted dose distribution, gamma calculations for 50 different error scenarios are performed, using the same criteria as in Section 6.1.1. However, two sets of 50 error scenarios are added, with confidence levels of 95% and 90%. Figure 6.4 shows the resulting gamma evaluation, for each of the confidence levels. With increasing confidence, there is a slight decrease in the number of voxels that passed the gamma evaluation. The scale is however so small that the difference is only a few voxels. The PCE is thus also performing well for error scenarios.

Figure 6.4: Results of gamma calculations for different confidence intervals, the PCE dose distribution is compared to the distribution as produced by the exact dose engine.

A closer look at the worst performing scenario is also taken. This means that the dose volume histogram of the scenario in which the least voxels are accepted is inspected, to see how ‘bad’ this scenario actually was. For this evaluation the worst performing scenario of the 99% confidence level is taken. Figure 6.5 shows the dose volume histogram of the worst scenario, with the exact dose for every structure in a continuous line and PCE displayed by a dashed line. The graph shows that even for the worst scenario, only the right cochlea...
shows a little difference in dose. This structure however is only 0.04 cc, which is very small compared to for example 25 cc brainstem, thus even a small difference can have a large impact in a dose volume histogram.

Figure 6.5: Dose volume histogram of the worst performing scenario. Differences are only seen for the right cochlea, but even for that structure they are negligibly small.

The gamma evaluation has shown that PCE is a valid meta model for not only the nominal dose but also for different error scenarios. To see why, the dose in a single voxel is investigated under a shift of the dose distribution. This voxel is chosen to be in the CTV, and the doses of the PCE and the exact dose engine are compared, under different shifts along the $x$, $y$, $z$- or range directions. The dose dependence on the shift in a single direction is thus examined.

Figure 6.6: Dose dependence of a single voxel in the CTV on shifts in a single direction, of both the PCE dose distribution and the exact dose distribution. The curves for PCE and the exact dose engine are almost overlapping and the same dose dependence is observed.

Figure 6.6 displays the results, with the dose plotted against the applied shift along each directions. This figure is in agreement with earlier findings and shows that the dose dependence of a single voxel in the CTV shows the same behavior for the PCE and the exact dose engine. Furthermore, the shift results in a smooth dose distribution function, which is possible for polynomials to model.

6.1.4. Beam angle dependency
The beam-angle dependency of the accuracy of PCE was also investigated. This has been done in an early stage of the research and was therefore conducted for chordoma patients. However, this only was of minor influence on the results, since it is a qualitative investigation into the relation between the beam-angles in the treatment plan and the ability of the PCE to model this dose distribution. Furthermore, the location of the tumor and the surrounding anatomy is globally the same as for meningiomas. First, the results of a coplanar three beam configuration are shown, and second the results of a non-coplanar four beam setup are given.
3 coplanar beam-angles

The results for the different perturbations are given in Figure 6.10a. The gamma calculations show that the PCEs which are built for treatment plans with different beam angles, are performing similarly. The worst performing PCE of the 2-beam-perturbation is the setup where the angles are [150°, 180°, 210°]. A slice of the CT with the dose distribution (Figure 6.7b), shows that for this particular beam setup, the protons travel a very long path before they reach the CTV and all three beams end in the inhomogeneous nasal cavity.

![Figure 6.7](image)

For the equi-angular rotations, the gamma evaluations are plotted in Figure 6.10a. The worst performing PCE is constructed for the plan with [0°, 120°, 240°]. As can be seen in Figure 6.10b, this particular beam-angle setup causes all three beams to travel through very inhomogeneous tissue. Additionally, the 0° beam would never be used in clinical practice since it enters the skull frontally.

Overall the gamma evaluation shows a similar quality of PCE in modeling the dose distribution for different beam-angle configurations.

![Figure 6.8](image)

4 non-coplanar beam-angles

The results of the gamma calculations for different one-beam-perturbations of the non-coplanar configuration with four beam-angles are shown in Figure 6.9. The error scenarios for all configurations give similar results, the PCE performance does not differ significantly for specific configurations. This indicates that the PCE can be used for different non-coplanar beam-angle configurations as well.
6.2. Treatment plans for skull base meningioma

The final wish-list, constructed as described in Section 5.3 is given in Table 6.1. This wish-list had been used to make all the plans that were used during the robustness recipe construction and validation. The resulting treatment plans meet the dose constraints on the target coverage and sparing of organs-at-risk. An example of a resulting treatment plan is given in Figure 6.10. On the left the DVH is displayed and on the right a CT slice with the dose distribution, where the color indicates the dose. Additionally to the dose wash and delineated structures, an isodose line is shown for 95% of the prescribed CTV dose.

Table 6.1: Wish-list that is used to obtain the treatment plans for all skull base meningioma patients. The 4th column states the type of the constraint or objective. This determines whether the objective value should be linearly minimized or maximized, or the mean value of the objective. The last column indicates whether the constraints or objectives are optimized robustly. The last objective on the list, with the lowest priority is 'MU' (monitor units), which is always added in a proton wish-list to push down the dose to the patient as much as possible.
6.3. Robustness recipes

The robustness recipe results are separated into the setup robustness recipes and the range robustness recipes, concluding in a combination of the two. After constructing and validating the initial recipe, Patient 14 was selected as base patient for the final recipe construction (see Section 5.4). All the results shown below are obtained by constructing robustness recipes with Patient 14 as base patient, with the rescaling factor $R_{\text{factor}}$ applied during the construction and validation of the recipes.

6.3.1. Setup robustness recipe

The setup robustness recipe is constructed by fitting a function to the data points obtained by the recipe construction method. The recipe is given by a rational relation between the setup robustness $\text{SR}$, systematic setup error $\Sigma$ and the random setup error $\sigma$:

$$\Sigma = \frac{P_1(\text{SR})\sigma + P_2(\text{SR})}{\sigma^2 + Q_1(\text{SR})\sigma + Q_2(\text{SR})} \quad (6.1)$$

The parameters $P_1, P_2, Q_1$ and $Q_2$ are third order polynomial functions of the setup robustness setting $\text{SR}$ of the form:

$$P_i = x_1 \cdot \text{SR}^3 + x_2 \cdot \text{SR}^2 + x_3 \cdot \text{SR} + x_4 \quad (6.2)$$

$$Q_i = x_1 \cdot \text{SR}^3 + x_2 \cdot \text{SR}^2 + x_3 \cdot \text{SR} + x_4 \quad (6.3)$$

Figure 6.10: Example of a treatment plan generated by the constructed wish-list for skull base meningioma. In the DVH (a) the high dose to the CTV can be seen, together with the lower dose given to the organs-at-risk. The CT scan in the right figure (b), shows the dose wash (the color indicates the amount of dose), the delineated structures and an isodose line. The isodose line is plotted for the criterion of the CTV coverage, the near-minimum dose $D_{\text{98\%}}$ must be at least $0.95 \cdot D_{\text{prescribed}}$, indicated by the blue isodose line.
for $i = 1,2$. The values of $\vec{x}$ for each of the parameters are given in the first row of Table 6.2 and Table 6.3. The rational recipe function is plotted in Figure 6.11 together with the data points which were used to obtain the fit, for the four used robustness settings (SR = 2,3,4,5). The plot shows for different setup robustness settings (SR), the relation between the allowed systematic and random setup error in order to achieve the wanted target coverage (defined by Equation 5.7).

![Figure 6.11: Setup robustness recipe plotted together with the robustness settings and error-pairs which were used to fit the recipe upon. Every data point is a result of the recipe construction method as described in Section 5.4. This setup recipe is constructed using plans without any range robustness settings applied, and in the absence of range errors.](image)

### 6.3.2. Range robustness recipe

The range robustness recipe that is constructed by making use of the PCE construction and sampling is a linear relation:

$$RR = 0.467 \rho + 0.0177$$

(6.4)

Figure 6.12 shows this recipe together with the data points, with range robustness settings (RR) on the x-axis, and the allowed relative range error $\rho$ in order to achieve the wanted target coverage (Equation 5.7) on the y-axis.

![Figure 6.12: Range robustness recipes plotted together with the robustness setting and error pairs which were used to fit the recipe. The fitted line approaches a range error $\rho$ of 0% for a range robustness setting RR of 0%.](image)
6.3.3. Combination of range and setup robustness recipes

The results of the combination of the two recipes, the setup robustness recipes for different range robustness settings, are shown in Figure 6.13. For each range robustness setting, the corresponding range error $\sigma$ is applied, derived from the range robustness recipe as stated in Equation 7.1. The resulting recipes are fitted by the same function as Equation 6.1. The first 6 plots, (a) - (f), show the setup robustness recipes for different range robustness settings. The last figure (g) shows a fit of the same function, to all data points of the separate recipes combined.

Figure 6.13: Figures (a)-(f): Overview of setup robustness settings, SR, for various range robustness settings, RR. The graphs indicate for every specific SR, the combinations of systematic setup errors $\Sigma$ and random setup errors $\sigma$, which give adequate CTV coverage. The last graph (g) shows the fitted recipe for all data points combined.
Table 6.2: Parameter values for the setup robustness recipes plotted following Equation 6.1 in Figure 6.13g, for different range robustness settings RR. The parameters $P_1$ and $P_2$ are polynomial functions of SR, of the form $P_i = x_1 \cdot SR^3 + x_2 \cdot SR^2 + x_3 \cdot SR + x_4$. The values of $\vec{x}$ are listed in this table.

<table>
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<tr>
<th></th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$x_3$</th>
<th>$x_4$</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$x_3$</th>
<th>$x_4$</th>
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<td>RR = 0%</td>
<td>-2.37E+02</td>
<td>2.59E+03</td>
<td>-9.42E+03</td>
<td>1.04E+04</td>
<td>4.97E+02</td>
<td>-5.25E+03</td>
<td>1.83E+04</td>
<td>-2.09E+04</td>
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<tr>
<td>RR = 1%</td>
<td>8.93E+01</td>
<td>-1.01E+03</td>
<td>3.63E+03</td>
<td>-5.20E+03</td>
<td>-2.02E+02</td>
<td>2.18E+03</td>
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<tr>
<td>RR = 2%</td>
<td>9.94E+02</td>
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<td>3.81E+04</td>
<td>-3.72E+04</td>
<td>-3.06E+02</td>
<td>3.22E+04</td>
<td>-1.01E+04</td>
<td>7.33E+03</td>
</tr>
<tr>
<td>RR = 3%</td>
<td>-8.04E+01</td>
<td>3.13E+02</td>
<td>7.68E+02</td>
<td>-3.79E+03</td>
<td>4.04E+02</td>
<td>-2.93E+03</td>
<td>6.09E+03</td>
<td>-8.96E+02</td>
</tr>
<tr>
<td>RR = 4%</td>
<td>-1.44E+02</td>
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<td>-2.55E+03</td>
<td>1.10E+02</td>
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<td>1.23E+04</td>
<td>-8.37E+03</td>
</tr>
<tr>
<td>RR = 5%</td>
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<td>1.66E+03</td>
<td>-6.72E+03</td>
<td>6.25E+03</td>
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<tr>
<td>Combined</td>
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<td>1.67E+04</td>
<td>-5.41E+04</td>
<td>5.41E+04</td>
<td>4.25E+03</td>
<td>-4.26E+04</td>
<td>1.37E+05</td>
<td>-1.37E+05</td>
</tr>
</tbody>
</table>

Table 6.3: Parameter values for the setup robustness recipes plotted following Equation 6.1 in Figure 6.13g, for different range robustness settings RR. The parameters $Q_1$ and $Q_2$ are polynomial functions of SR, of the form $Q_i = x_1 \cdot SR^3 + x_2 \cdot SR^2 + x_3 \cdot SR + x_4$. The values of $\vec{x}$ are listed in this table.

<table>
<thead>
<tr>
<th></th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$x_3$</th>
<th>$x_4$</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$x_3$</th>
<th>$x_4$</th>
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<tbody>
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<td>RR = 0%</td>
<td>-2.33E+02</td>
<td>2.61E+03</td>
<td>-9.46E+03</td>
<td>1.04E+04</td>
<td>5.51E+02</td>
<td>-6.07E+03</td>
<td>2.20E+04</td>
<td>-2.42E+04</td>
</tr>
<tr>
<td>RR = 1%</td>
<td>1.03E+02</td>
<td>-1.24E+03</td>
<td>5.01E+03</td>
<td>-7.44E+03</td>
<td>-1.95E+02</td>
<td>2.25E+03</td>
<td>-8.48E+03</td>
<td>1.26E+04</td>
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<tr>
<td>RR = 2%</td>
<td>9.10E+02</td>
<td>-9.84E+03</td>
<td>3.29E+04</td>
<td>-2.89E+04</td>
<td>-4.33E+02</td>
<td>4.72E+03</td>
<td>-1.60E+04</td>
<td>1.47E+04</td>
</tr>
<tr>
<td>RR = 3%</td>
<td>5.39E+01</td>
<td>-1.06E+03</td>
<td>5.59E+03</td>
<td>-9.40E+03</td>
<td>9.42E+01</td>
<td>1.63E+03</td>
<td>-4.71E+03</td>
<td>1.20E+04</td>
</tr>
<tr>
<td>RR = 4%</td>
<td>-1.36E+01</td>
<td>-2.19E+02</td>
<td>2.35E+03</td>
<td>-5.59E+03</td>
<td>2.30E+02</td>
<td>-1.62E+03</td>
<td>2.29E+03</td>
<td>3.72E+03</td>
</tr>
<tr>
<td>RR = 5%</td>
<td>-1.41E+02</td>
<td>1.66E+03</td>
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<td>4.11E+03</td>
<td>2.92E+02</td>
<td>-3.79E+03</td>
<td>1.47E+04</td>
<td>-1.30E+04</td>
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<tr>
<td>Combined</td>
<td>-1.17E+03</td>
<td>1.21E+04</td>
<td>-3.95E+04</td>
<td>3.95E+04</td>
<td>3.41E+03</td>
<td>-3.49E+04</td>
<td>1.14E+05</td>
<td>-1.14E+05</td>
</tr>
</tbody>
</table>

6.4. Validation of the robustness recipes

Now that the robustness recipes for both the setup and range errors are given, the validation results will be shown. First, the results of the separate recipes are shown and second a validation of the combination is presented.

6.4.1. Setup robustness recipe

The validation for the setup robustness recipe is conducted for two combinations of $(SR, \Sigma, \sigma)$, given in Table 6.4. Since iCycle can only handle integer discrete values of setup robustness settings, a set of setup robustness setting SR and random setup error $\sigma$ is substituted into Equation 6.1, to obtain the corresponding systematic error $\Sigma$.

Table 6.4: Validation points for the setup robustness recipe

<table>
<thead>
<tr>
<th>Validation</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setup Robustness</td>
<td>3.00 mm</td>
<td>5.00 mm</td>
</tr>
<tr>
<td>Random setup error</td>
<td>0.75 mm</td>
<td>2.75 mm</td>
</tr>
<tr>
<td>Systematic setup error</td>
<td>0.96 mm</td>
<td>0.81 mm</td>
</tr>
</tbody>
</table>

Validation I

The results of the first validation are shown in Figure 6.14. The graph in Figure 6.14a shows the percentage of the population having a near-minimum dose $D_{98\%}$ in the CTV, against the received dose in Gy on the x-axis. The black dashed lines indicate the criterion that was set on the treatment plans for being robust: the horizontal line indicates the minimum percentage of the population having a $D_{98\%}$, which has to meet the dose constraint indicated by the vertical line at $0.95 \cdot D_{\text{prescribed}} = 47.88\text{Gy}$. The near-minimum dose of the population for Patient 14, the base patient, is given by the red dotted curve, the blue curves indicate the validation patients.
6.4. Validation of the robustness recipes

6.4.2. Range robustness recipe

The validation for the range robustness recipe is structured in the same way as the setup validation. The validation points are obtained by choosing either a range robustness setting or a range error. By making use of Equation 7.1, the corresponding range error or robustness setting is obtained. The two points that are used for the evaluation are given in Table 6.5.

Table 6.5: Validation points for the range robustness recipe

<table>
<thead>
<tr>
<th>Validation</th>
<th>I</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range Robustness RR</td>
<td>2.20%</td>
<td>3.80%</td>
</tr>
<tr>
<td>Range error $\rho$</td>
<td>1.05%</td>
<td>1.79%</td>
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</tbody>
</table>

Validation I

The results of the first validation are shown in Figure 6.16. The percentage of the population that passed the criterion for this combination of range robustness setting and range error, is not above 98% for every patient.
but it deviates not more than 0.34% (Table 6.16b). Additionally, a difference can be observed when the graph in Figure 6.16a is compared to the two previous setup validation graphs in Figures 6.14 and 6.15: the shape of the population graphs is less diverging and staying closer to 95% of the prescription dose for the range recipe validation.

Validation II
The results of the second validation point are shown in Figure 6.17. These illustrate the same behavior as for the first validation point.

6.4.3. Combination of robustness recipes
The combined validation is conducted for a 'full' combination of robustness settings and errors (SR, RR, Σ, σ, ρ), which is obtained by using Figure 6.13. One validation point is used, shown in Table 6.6. A setup robustness setting of 2 mm is used, in combination with a range robustness setting of 3%, this means that the SR=2mm line from Figure 6.13d is used to obtain the setup error combination.

Table 6.6: Validation point for the combined setup and range robustness recipe.

<table>
<thead>
<tr>
<th>Validation</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setup Robustness</td>
<td>3 mm</td>
</tr>
<tr>
<td>Range Robustness</td>
<td>2%</td>
</tr>
<tr>
<td>Random setup error</td>
<td>0.75 mm</td>
</tr>
<tr>
<td>Systematic setup error</td>
<td>0.64 mm</td>
</tr>
<tr>
<td>Relative range error</td>
<td>1.42%</td>
</tr>
</tbody>
</table>

The resulting population near-minimum dose for each patient is shown in Figure 6.18a, with the corre-
6.5. Error simulation

The way of calculating the dose for range error scenarios in the last step of the treatment plan optimization in Erasmus-iCycle has been adapted from its original way of modeling range errors. For iCycle, the standard way of simulating errors in the range is scaling the energy of the proton beams, while the adapted version uses CT value rescaling. The PCE construction scripts also use CT rescaling during the recalculation of error scenarios. The effects of both methods of simulating range errors are illustrated by the dose dependence graph in Figure 6.20, which displays the dose dependence of a single voxel, similar to Figure 6.6. The green solid line indicates...
the energy beam rescaling method, the red solid line the CT scaling method. The dashed lines correspond to the dose that is obtained when the rescaling factor \( R_{\text{factor}} \) is applied calculated according the same scaling method. Two important observations can be made. First, the effects of interpolation, needed due to the fact that not every energy and range error combination is available, can be seen in the step-wise pattern of the green curve. Second, the effect of the range error is decreased when CT image scaling is applied, since the dose dependence on the applied error decreases compared to energy beam scaling. This results in a rescaling factor lower than 1, thereby decreasing the dose when applied. The rescaling factor based upon the scaling of the beam energy is slightly bigger than 1 and therefore increase the dose.

Figure 6.20: Effects of the two different methods of simulating range errors. The graph displays the dose dependence of a single voxel. The effects of both methods of simulating range errors are illustrated by the graph in Figure 6.20. The green solid line indicates the energy beam rescaling method, the red solid line the CT scaling method. The dashed lines correspond to the dose that is obtained when the rescaling factor \( R_{\text{factor}} \) is applied calculated according the same scaling method. The rescaling factor decreases the dose for the CT-scaled range error with \( \sim 0.3 \text{ Gy} \), while it slightly increases the dose for the scaling of the proton beam energy.

6.6. Fractionation

Last, the effect of the number of fractions on the CTV coverage is examined. The results are plotted in Figure 6.21, as expected, for an increasing number of fractions, CTV coverage increases and approaches the line that indicates an infinite number of fractions. An infinite number of fractions implies that the random errors have no effects on the dose distribution anymore, resulting in better CTV coverage.

Figure 6.21: The number of fractions included in a treatment is plotted against the population that passed the dose criterion on the CTV, which is a measure for the level of target coverage. For an increasing number of fractions, the CTV coverage increases too and approaches the coverage infinite number of fractions would give. In the case of infinite number of fractions, the random setup errors are completely averaged out and thereby no more blurring the dose distribution resulting in better CTV coverage.
6.7. RayStation

Figure 6.22 shows the first results of coupling the PCE construction scripts to the dose engine of RayStation. The coupling between the PCE constructing scripts in Matlab and RayStation has been established and PCEs can be constructed.

```
Door:
The file has been saved as C:\Users\RayStation\Documents\Carlijn Data\Matlab\Patients\Schedelbesmettingencom_01\PCE\0011\0010\0021.mat

 sue =
       PCEClass with properties:
         Details: [1x1 struct]
         Rows: [5x4 double]
        Basis_Vectors: [5x1 MultivariateOrthogonalPolyonClass]
        Co effs: [5x13372 double]
        Poly_Type: {'hermite' 'hermite' 'hermite' 'hermite'}
```

Figure 6.22: The PCE script is coupled to RayStation and some first PCEs are constructed. The PCE script uses the dose engine as a black-box, in exactly the same way as it uses Erasmus-iCycle.
Discussion & Conclusion

7.1. Discussion
In this study the recipe construction method developed by Van der Voort et al. has been refined and expanded to another treatment site, skull base meningioma [27]. Multiple improvements have been implemented, which resulted in the formulated setup and range robustness recipes. This chapter first discusses the results, then presents recommended directions for future work, finishing with the main conclusions of the research.

7.1.1. Results
Recipe construction
During the recipe construction, a very narrow region of acceptance was created, i.e. the fraction of the population that had adequate target coverage had to be exactly between 98.00% and 98.10%. The previous work did not apply an upper bound. The gradient method in the iteration of the recipe construction, used to converge to this acceptance level is also a refinement with respect to the original method. Previous work assumed infinite number of fractions during the recipe construction, this study has added the fractionation to the recipe construction. However, the PCE model has been used to verify the assumption of infinite fractions and for a high number of fractions the level of CTV coverage indeed approaches the coverage that infinite fractions would give.

Setup robustness recipe
The setup robustness recipe of the previous work was built by applying an ellipsoid fit to the data points. For the setup robustness recipe in this work, this fit did not work and a rational fit is applied. A possible explanation of the difference lays within the calculation of the ‘end points’, i.e. the points where only random setup errors can be present to still meet the coverage criterion. The addition of these points to the graphs made the ellipsoid function unfit for the data. The downside of a rational function is that there is no simple way of expressing the setup robustness setting SR as a function of the random and systematic setup errors $\sigma$ and $\Sigma$. This means that for the application of the recipes, it is recommended to use the graphs in Figure 6.11 to look up robustness settings for specific random and systematic setup error combinations.

The validation results confirmed that the recipes do ensure adequate target coverage for most of the patients. When the criterion was not met, the fraction of the population deviated in none of the cases more than 1% from the wanted 98%. Erasmus-iCycle does not have the option to include setup robustness settings other than integers, so the recipe has not been tested for other setup robustness settings.

Range robustness recipe
This research has added the range recipe construction to the existing method. The previous research only determined range robustness settings for two specific range errors, being $\rho = 1\%$ and $\rho = 2\%$, with very coarse steps and without an upper limit on the target coverage criterion. This study has expanded the recipe construction to also include range robustness recipes, to gain more insight into the relation between the range robustness settings that are used and the resulting range error the treatment plans are able to cope with. As a result, the linear relation in Equation 7.1 was derived. The recipe does contain a constant, which implies
some robustness is needed, even without the presence of a range error. This behavior was also observed at the previous work. However, this constant term in Equation 7.1 is only 0.0177%, which is negligible. Therefore the robustness setting needed for a treatment plan without any range error, is practically zero.

Combination of range and setup robustness recipes
The recipes that are derived with both setup and range robustness settings applied, showed very little variance for different range robustness settings. Figure 6.13g verifies this, one function can be used to fit all data points resulting from setup recipes derived with different range robustness settings. This confirms the suggestion of the previous work, that setup and range robustness settings can be handled independently.

Rescaling factor
The rescaling factor that is used to make the different treatment plans of comparable quality has been added to the methodology. Not only did the inter-patient treatment plan variability decrease but also the intra-patient plan quality variance was reduced. The goal was to eliminate the dependency on the choice of base patient during for the recipe construction. The result is a recipe, which gives less conservative results for the other patients than observed in the previous work, Figure 6.19 illustrates this effect. However, by a scaling factor based upon the worst case scenario, one does not account for the dose in every scenario, so a plan can still be intrinsically less ‘robust’ than another. Thus the base patient dependency is still not fully handled by the rescaling. The recipe performs best if the ‘worst’ performing patient is used, which in this case was patient 14. This gives rise to the question which base patient one should use in a larger data set.

Range error simulation
As discussed, the effects of range and setup robustness settings and errors appeared to be almost independent, if looked at the different recipes. This could however partly be due to the fact that CT image scaling is used instead of the energy beam scaling which results in much smaller effects for the range errors. This influences the calculation of the planning scenarios and thereby automatically the rescaling factor. This factor is calculated based upon the worst planning scenario. The effect of range errors on CTV coverage is thus decreased by using CT image scaling, but the scaling factor is also decreased which automatically lowers the coverage of the CTV (Figure 6.20).

The difficulty of the range error is that there is no ‘exact’ way of defining it, as there is for the setup errors. The setup errors can be modeled as rigid body shifts when no anatomical motion is present, as is the case for skull base patients. Range errors however, can originate from several sources, and neither way of modeling the effects is fully correct.

7.1.2. Future research
These findings suggest various interesting directions for future research.
First, it would be interesting to use the patient data set of the Van der Voort. et al research, in combination with the adapted recipe construction and validation methods of this research. The resulting recipes then be compared to the original (ellipsoidal) recipes, such that the effects of the improvements in the method can be made clear.
Another direction is the construction of robustness recipes for RayStation in the same way this thesis did using Erasmus-iCycle. The method of robust optimization during the construction of a treatment plan differs per treatment planning system and the influence of these variations on the recipes is something to look into.
In order to do this, similar plans must be made for the same patient in iCycle and RayStation, such that a fair comparison can be made. Moreover, RayStation has two options for a dose engine, namely a pencil beam algorithm or Monte Carlo transport method. It would be very interesting to derive recipes based upon the two different dose engines and see if the way of performing dose calculation influences the robustness recipes.
The way of simulating the effect of range errors on the dose distribution is a further area of potential research. The CT image scaling may be an underestimation but the proton beam energy scaling together with the interpolation can be an overestimation. The definition of range error should be refined, together with the method of modeling its effects.
The validation results of the use of PCE as a meta model for skull base meningioma indicated that PCE can indeed be used for this treatment site. The use of PCE does not have to be limited to the construction of robustness recipes, but can also be expanded to an evaluation tool for constructed treatment plans. Although this research derived setup robustness recipes for several different range robustness settings, the construction of range and setup recipes remained separate. An improvement would be to include both range
and setup robustness settings and errors in one recipe construction methodology, i.e. instead of constructing
two recipes in series, make one in parallel.
Finally, the recipe construction is based upon achieving adequate target coverage for the CTV. The method
could however be expanded to include other criteria, such as dose constraints on critical surrounding organs-
at-risk. The resulting recipes will not only ensure that 98% of the treated population meets the target coverage
but also that the dose limits on the organs-at-risk are respected.

7.2. Conclusion
This work has shown that polynomial chaos expansion (PCE) can be used as a meta-model for the dose dis-
tribution of skull base meningioma patients. PCE has been used to construct setup and range robustness
recipes for robust treatment planning using Erasmus-iCycle for Intensity Modulated Proton Therapy.
Several improvements have been implemented, with respect to the method developed by Van der Voort et al.
[27]. The most important adaptations are the addition of the range recipe construction and the application
of a rescaling factor to account for inter-patient variance in the treatment plan quality. These adaptations re-
sulted in improved understanding of the effect of the range robustness setting RR on the resulting treatment
plans. Furthermore, the patient-dependency of the recipe performance observed in the previous work, could
partly be removed by applying the rescaling factor.
The robustness recipes are constructed with the goal to ensure that at least 98% of the treated population
receives a near-minimum dose $D_{98\%}$ of at least 95% of the prescribed dose $D_{\text{prescribed}}$. Setup robustness
recipes were constructed under different range robustness settings, which resulted in no substantial differ-
ences. From this, it can be assumed that the setup and range recipes can be used independently.
The derived setup robustness recipes are given by a rational relation between the systematic setup error $\Sigma$, random setup error $\sigma$ and the setup robustness setting $SR$. For the range robustness recipe, a linear relation
between the range robustness setting $RR$ and the range error $\rho$ was derived. The recipes were validated for a
total of 8 skull base meningioma patients, where for none of the patients did the percentage of the population
that passed the coverage criterion deviate more than 1% from the required 98%.
The final range recipe is given by:
$$RR = 0.467\rho + 0.0177, \quad (7.1)$$
and the setup robustness recipe is expressed as:
$$\Sigma = \frac{P_1(SR)\sigma + P_2(SR)}{\sigma^2 + Q_1(SR)\sigma + Q_2(SR)}. \quad (7.2)$$
with the coefficients for the parameters $P_{1,2}$ and $Q_{1,2}$ from Table 6.2 and Table 6.3, corresponding to the final
combination of all data points. These robustness recipes for skull base meningioma patients, derived for the
treatment planning system Erasmus-iCycle using PCE, can be used independently, have been validated and
provide adequate target coverage.
Bibliography


site=ro-journal.biomedcentral.com.


