Dual-energy CT tissue segmentation methods for Monte Carlo dose calculations in proton therapy

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**Dual-energy CT
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ISABEL P. ALMEIDA

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Dual-energy CT tissue segmentation methods for Monte Carlo dose calculations in proton therapy

Dissertation

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Dr. Ronald Westra

Aos meus queridos pais
To my beloved parents

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1

Introduction

1.1 Introduction

Cancer is a group of diseases that originates from abnormal cell formation in an organ or tissue. Cancer cells divide indefinitely, in contrast to healthy cell mitosis which is started and stopped by means of chemical signals. Cell malformation typically originates at the level of the DNA, where alterations to critical genes may lead to changes in cell behavior. Gene mutation can be caused by external factors, such as chemical ingestion or radiation exposure, or might occur without any known exterior cause. Furthermore, these abnormal cells can divide by direct extension or by spreading to neighboring or distant parts of the body through blood or lymphatic vessels - a process called metastasis. 90% of the deaths due to cancer involve tumors that have spread to other body sites [1].

In 2016, cancer caused over 1.8 million fatalities, ranking as the sixth cause of deaths worldwide, equally affecting men and women [2]. Numerous therapies are constantly under development to improve cancer treatment, such as surgery, chemotherapy and radiotherapy, with the overall goal of killing the malign cells while limiting the damaged caused to healthy tissues. Depending on the tumor stage, site, as well as biological and physical characteristics, different therapies are used, either concurrently or sequentially. Prior to surgery, neoadjuvant chemotherapy and/or radiotherapy might be used to shrink the tumor, while after surgery adjuvant chemotherapy and/or radiotherapy can treat residual disease and decrease the risk of recurrence.

High energy ionizing radiation can sterilize cells by means of damaging and breaking their DNA structure. Also, the fact that cancer cells are biologically more sensitive to radiation than normal ones, due to their increased multiplication rate, makes radiation therapy (or *radiotherapy*) a viable option for cancer treatment both for curative and palliative cases. However, metabolic function and cell disorganization can lead to hypoxia and make the cancer radio-resistant [3]. Barton *et al.* [4, 5] and Tyldesley *et al.* [6] showed that approximately 50% of all cancer patients can benefit from radiotherapy treatment, of these, 50% for curative purposes.

Radiotherapy is commonly applied with external mega-voltage photon beams (typically ranging between 6 MV and 18 MV). Due to the specific photon dose distribution in matter as depicted in Figure 1.1, the use of numerous beam angles is required to ensure a higher dose in the tumor than in healthy tissues. For specific tumors, brachytherapy is also used, in which small radiation sources are placed near the tumor location allowing the delivery of very high doses at high rates in a short length, which could not be achieved with external photons beams. Brachytherapy can be combined with external radiotherapy or be used as stand-alone radiation treatment.

External radiation therapy can also be given with energy transferred by charged particles (hence called *particle therapy*), such as protons and carbon ions, that are accelerated up to 250 MeV and 430 MeV/u [8, 9], respectively. Fast ions pass through matter in almost straight trajectories, depositing their energy to the traversed medium mostly due to inelastic Coulomb interactions with electrons, secondly due to multiple Coulomb scattering with the atomic nuclei, and less frequently through inelastic nuclear interactions with atomic nuclei. These particles will come to a complete rest at a certain range, which is directly dependent on the initial energy and the composition of the traversed medium. The depth where most of the energy is deposited by these ions is called the Bragg peak. By combining beams with different energies resulting in a spread-out Bragg peak (SOBP), a uniform dose can be delivered to a volume, having the advantage of decreasing the volume of healthy tissue irradiated (Figure 1.1), compared to mega-voltage photon beams. The use of proton beams for therapy purposes is typically called *proton therapy* and it will be the main subject of the work presented in this thesis.

The following sections will focus on the clinical rationale to use proton therapy and on the uncertainties of the modality. For the latter, the use of dual-energy computed tomography (DECT) is introduced as a method to improve tissue segmentation and to increase the accuracy of Monte

Figure 1.1. Depth dose distributions of a 15 MV photon beam and a proton spread-out Bragg peak over a tumour volume (SOBP) (reproduced with kind permission [7]).

Carlo (MC) proton dose calculations.

1.1.1 Clinical context

Delayed consequences of radiotherapy will have a substantial impact on long term survivors, in particular for pediatric patients, which have higher radiation sensitivity than adults. This group will have an increased risk of adverse outcomes, such as early death, higher probability of the development of secondary tumours due to longer life expectancy, impairment of growth and cognitive functions, and overall decrease in quality of life [10].

Long term effects are especially related to dose received by healthy tissues, hence suggesting that the use of proton therapy (Figure 1.2) could decrease the treatment toxicity, first due to the discrete number of treatment fields used, second due to the characteristic dose distribution with a finite range. Furthermore, the use of intensity-modulated radiotherapy (IMRT), the state-of-the-art photon-beam technique able to irradiate complex tumours, increases the total dose deposited in the body, which may lead to significant risk of toxicity and risk of secondary cancers [11]. Miralbell *et al.* [12] showed in a retrospective study that proton therapy can reduce the risk of radiation-induced secondary cancer, using a model based on the recommendations of the International Commission on Radiological Protection (ICRP) [13], by a factor of 8 to 15 compared to IMRT for a medulloblastoma case. Similar to Miralbell *et al.*, Newhauser *et al.* [14] performed an *in silico* study for a craniospinal irradiation, reporting a higher risk of secondary cancer of 7 for IMRT compared to pencil beam proton therapy. Also for a group of seventeen pediatric medulloblastoma patients, Zhang *et al.* [15] showed *ratios of relative risk* (protons/photons) between 0.12 and 0.24 for risk of cardiac mortality using proton therapy compared to IMRT. Cotter *et al.* [16] showed a significant decrease in dose to normal tissues with proton therapy compared to IMRT for a cohort of seven children with bladder/prostate rhabdomyosarcoma, suggesting a decrease in long term side-effects.

In the last decades, several multicenter survivorship studies have been collecting data to characterize side effects of different radiotherapy modalities in different age groups and body sites

Figure 1.2. Illustration of the dose distribution of a head-and-neck tumour using proton therapy, on the right, and intensity-modulated photon radiotherapy (IMRT), on the left (adapted from [17]).

[10, 18–20], showing that there is not a clear trend that one modality is in all cases superior to the other, in part due to patient variability.

1.1.2 Proton therapy range uncertainties

Proton therapy decreases the dose to healthy tissues, due to the absence of dose beyond the Bragg peak and the use of a limited number of fields, however it has the downside of requiring a very precise prediction of where the protons will come to a complete rest. A shift in the SOBP position can cause irreversible damage to healthy tissues and OARs. For this reason, beams that stop immediately before a critical structure are avoided in treatment planning. Range uncertainties can be caused by patient set-up and anatomical changes, beam delivery, dose calculation engines and approximations and by imaging. The uncertainty on the latter is due to the conversion from a patient's computed tomography (CT) scan to physical properties, namely from CT numbers (CT#) to stopping power ratios (SPR) relative to water [21].

Current practice in proton therapy handles the uncertainties arising from the CT# to SPR conversion by adding treatment margins. An example of a margin recipe is $3.5\% + 1 \text{ mm}$, which adds 8 mm as margin for a 20 cm deep target, introduced at the Harvard Cyclotron Laboratory in 1985 [22] and still used by several institutes [21]. Applying conservative margin recipes to assure full target coverage may lead to substantial increase in dose deposition and toxicity in the critical structures near the tumour, potentially reducing the leverage of treatment with proton therapy.

For a charged particle beam, the average rate at which the charged particle loses its energy when crossing a medium, called mass collision stopping power (S_{col}/ρ), is described by the Bethe-Bloch formula [23]

$$\frac{1}{\rho} S_{\text{col}} = 4\pi N_A r_e^2 m_e c^2 \frac{1}{\beta^2} \frac{Z}{A} z^2 \cdot \left[\ln \left(\frac{2m_e c^2 \beta^2}{(1 - \beta^2)I} \right) - \beta^2 - \frac{C}{Z} - \frac{\delta}{2} \right] \quad (1.1)$$

where c is the speed of light in vacuum, m_e the electron mass, r_e is the classical electron radius, β the charged particle speed in units of c , Z and A the atomic number and atomic mass of the medium, z is the charge of the charged particle, N_A is the Avogadro's number, and I the mean

excitation potential of the medium. The density effect term $\delta/2$ corrects for the polarization caused by the projectile along its path, whereas the shell correction term C/z accounts for the decrease in interaction probability for projectiles with velocities similar or smaller than the orbital velocity of bound electrons. However, in the range of energies for therapeutic proton beams, these two correction terms $\delta/2$ and C/z are negligible, reducing the Bethe-Bloch formula to the Bethe equation used throughout the thesis and formulated in respect to the proton SPR relative to water

$$\text{SPR} = \rho_e \frac{\ln\left(\frac{2m_e c^2 \beta^2}{I(1-\beta^2)}\right) - \beta^2}{\ln\left(\frac{2m_e c^2 \beta^2}{I_{\text{water}}(1-\beta^2)}\right) - \beta^2} \quad (1.2)$$

Eq. 1.2 has two tissue-dependent variables: the relative electron density (ρ_e) and the mean excitation potential (I). The I of a medium can be determined by inverting Eq. 1.1, however experimental data is still difficult to collect with a low uncertainty. A clear example is the uncertainty around the mean excitation potential of water (I_{water}), for which the measured value has been ranging from 67 to 78 eV in the last decades, which can result in a shift in the SOBP position of 5 to 6 mm [24, 25]. For SPR calculation in clinical practice, tissue-dependent variables are extracted from CT images and empirical formulas, such as variations of Bragg's additivity rule.

A typical CT image is acquired by scanning an object with a single photon spectrum ranging from 70 to 140 kVp, therefore called single-energy CT (SECT) throughout this thesis. From a single image, an energy- and scanner-specific calibration curve is used (typically referred as Hounsfield units look-up-table), which correlates the CT# and SPR values of known tissues and by interpolating this function, the SPR for unknown tissues are calculated (Eq. 1.2). This relation can be directly calculated with tissue-mimicking plastics or by applying the stoichiometric method from Schneider *et al.* [26] to tabulated biological tissues. More recently, DECT scans have been also introduced in clinical practice, where two images of the same patient are extracted.

1.1.3 Dual-energy computed tomography for treatment planning

In 1976, Rutherford *et al.* [27] introduced the concept of extracting ρ_e and the effective atomic number (Z_{eff}) from DECT scans, which has been frequently explored in the last decade as an alternative to SECT. DECT can provide more information on the physical quantities ρ_e [28–30] and I [31, 32] used in the SPR calculation. The different ρ_e extraction methods from SECT and DECT are studied in detail in **Chapter 4**. Although it has been suggested in the literature that DECT leads to more accurate SPR prediction [30, 33–36], these techniques are not yet being implemented, as indicated by the recent publication of the results from a survey done by twelve particle therapy centers, showing that eight use the stoichiometric method for SPR prediction and three use the curve directly extracted from the tissue-mimicking plastics [37].

DECT images can be obtained at the level of the x-ray source, by producing different energy spectra (dual-spiral, dual-source and fast kV-switching) or using filtration to split a single spectrum in two (twin-beam); or at the level of the detectors, by dividing the photons in different energy bins (more details in Table 1.1). The DECT modalities dual-source, dual-spiral and twin-beam are described and studied in **Chapters 2 and 3**.

Furthermore, DECT can also be used to improve tissue segmentation in the two-dimensional space of ρ_e and Z_{eff} [38] using the Mahalanobis distance, which measures the distance between points in a multivariate space accounting for the covariance between variables. It is often used in different fields to find outliers in a set of data or, in this specific application, to assign a voxel with a certain ρ_e and Z_{eff} to the closest tabulated material. Additionally, DECT can potentially extract carbon and oxygen compositions for *in vivo* range verification with prompt gamma detection [39].

Table 1.1. Types of dual-energy CT scanners, representative models and main characteristics.

DECT modality	Model (manufacturer)	Number of x-ray tubes	Simultaneous acquisition	Energy range	Relevant remarks
Dual-spiral	SOMATOM Definition Confidence [®] RT Pro ^a Aquilion PRIME ^b	1	no	80-140 kVp	Limited temporal and spacial registration
Fast kV-switching	GSI Xstream on Revolution [®] CT ^c	1	no	80-140 kVp	
Twin-beam	SOMATOM Definition Edge ^a	1	yes	120 kVp with gold and tin filtration	
Dual-source	SOMATOM Definition Force ^a	2	yes	Multiple pair from 80 to 150 with tin filtration	Wider spectral separation; Limited field-of-view (33 to 38 cm).
Dual-layer detector	IQon Spectral CT ^d	1	yes	120 kVp or 140 kVp	Possibility to apply projection-based methods.

^a Siemens Healthineers, Forchheim, Germany.^b Toshiba Medical Systems, Otawara, Japan.^c GE Healthcare, WI, USA.^d Philips Healthcare, OH, USA.

1.1.4 Monte Carlo dose calculations

A validated Monte Carlo (MC) simulation model is often the gold-standard to perform dose calculations, since all physical interactions and transport of primary and secondary particles with matter are described in detail. MC simulations have been proposed for clinical practice in particle therapy [40]. Additionally, different radiobiological models can be used to estimate the biological effect caused by different particle beams. MC engines are especially important in regions with heterogeneities and steep gradients and in handling complex 3D and 4D geometries, and in using different biological models to estimate the biological damage caused by different particle beams.

Although the increasing availability of computational power is making TPS vendors move towards using MC dose engines for their calculations, in clinical practice most centers still rely on fast-performing pencil beam algorithms (PBA) to calculate the treatment plan. These are based on analytical models, which are not capable of handling well proton scattering and range mixing effects. The lack of accuracy of PBA can lead to poor tumour coverage, and over- or underestimation of dose to the organs-at-risk (OARs). Verburg *et al.* [41] presented a retrospective study for 10 head and neck patients with dose distributions calculated with a PBA and a MC model, showing an undercoverage of the clinical target volume (CTV) when using the MC model (average $\Delta D_{95} = -1.62\%$ of the prescription dose) due to range degradation. Dose volume histograms of OARs and CTV for a representative patient is depicted in Figure 1.3.

Figure 1.3. Difference in dose-volume histograms from a head and neck treatment plan calculated with pencil-beam algorithm (solid lines) and with a Monte Carlo simulation toolkit (dashed lines) for the clinical target volume (CTV) and six organs-at-risk (reproduced with kind permission [41]).

1.2 Objectives

The aim of this thesis is to investigate the potential of dual-energy computed tomography to decrease uncertainty in proton range and dose calculation due to CT numbers to tissue properties conversion. We hypothesize that DECT-extracted quantities ρ_e and Z_{eff} improve tissue segmentation at a voxel level, which combined with Monte Carlo dose calculations can more accurately predict proton energy deposition in tissues.

1.3 Thesis outline

Chapter 1 gives a general overview of the clinical rationale to use proton therapy and the potential role of DECT to decrease range uncertainty.

Chapter 2 presents a comparison study between two state-of-the-art DECT technologies (dual-source and twin-beam), quantifying their accuracy of extracting the physical properties ρ_e and Z_{eff} from two phantoms of known compositions. **Appendix A** complements the discussion on the methods used in **Chapter 2**. Additionally, SPR accuracy from different DECT methods is shown in **Appendix B**.

Chapter 3 describes a complete methodology to implement MC proton dose calculations based on fully segmented DECT images. Range accuracy was quantified for different SECT and DECT technologies in two phantoms of known compositions. Furthermore, the methodology was applied to SECT and DECT patient scans from the first RT-specific scanner with dual-spiral technology and differences in proton range were assessed.

Chapter 4 analyses five different methods of converting CT and DECT images from a neurological cancer patient to ρ_e , four of which are available in clinically approved software. Furthermore, using mass-density (ρ) images, calculated from ρ_e , in a TPS with a MC proton dose engine, differences in dose and range between the conventional piece-wise linear conversion from CT# to ρ_e and the other methods were quantified.

Chapter 5 details the MC modeling and experimental validation of the MEVION S250i with HYPERSCAN proton one-room system with an Adaptive Aperture™ for collimation. **Appendix C** demonstrates an application of the beam model, at its early stages, to treat small brain lesions with collimated beams.

Chapter 6 proposes the use of the MEVION S250i with HYPERSCAN for pre-clinical research by showing the feasibility of using this system to create small fields with the Adaptive Aperture™, while keeping a very low dose delivery time.

Chapter 7 gives a complete discussion of the work written in this thesis with a critical view on the challenges ahead to improve the current methods and to implement them in clinical practice.

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Dual-energy CT quantitative imaging: a comparison study between twin-beam and dual-source CT scanners

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Abstract

Purpose: To assess image quality and to quantify the accuracy of relative electron densities (ρ_e) and effective atomic numbers (Z_{eff}) for three dual-energy computed tomography (DECT) scanners: a novel single-source split-filter (i.e., twin-beam) and two dual-source scanners.

Material and methods: Measurements were made with a second generation dual-source scanner at 80/140Sn kVp, a third-generation twin-beam single-source scanner at 120 kVp with gold (Au) and tin (Sn) filters, and a third-generation dual-source scanner at 90/150Sn kVp. Three phantoms with tissue inserts were scanned and used for calibration and validation of parameterized methods to extract ρ_e and Z_{eff} whereas iodine and calcium inserts were used to quantify Contrast-to-Noise-Ratio (CNR). Spatial resolution in tomographic images was also tested.

Results: The third-generation scanners have an image resolution of 6.2, 0.5 lp/cm higher than the second generation scanner. The twin-beam scanner has low imaging contrast for iodine materials due to its limited spectral separation. The parameterization methods resulted in calibrations with low fit residuals for the dual-source scanners, yielding values of ρ_e and Z_{eff} close to the reference values (errors within 1.2% for ρ_e and 6.2% for Z_{eff} for a dose of 20 mGy, excluding lung substitute tissues). The twin-beam scanner presented overall higher errors (within 3.2% for ρ_e and 28% for Z_{eff} , also excluding lung inserts) and also larger variations for uniform inserts.

Conclusions: Spatial resolution is similar for the three scanners. The twin-beam is able to derive ρ_e and Z_{eff} , but with inferior accuracy compared to both dual-source scanners.

2.1 Introduction

Computed tomography (CT) is a crucial imaging modality for the future developments of quantitative imaging. However, CT numbers depend on the scanner characteristics and on the reconstruction model, meaning that the same material will show different CT numbers if the scanning and reconstruction settings are not the same [1, 2].

Dual-energy computed tomography (DECT) imaging has the potential to improve quantitative imaging by adding a second set of data to the same scanned material [3]. This imaging modality results in two 3-dimensional attenuation maps by scanning with two different photon spectra. Various methods have been described to transform these two sets of data from CT numbers to electron densities relative to water (ρ_e) and effective atomic numbers (Z_{eff}) [4–10], quantities suitable for quantitative imaging. The additional Z_{eff} information allows the distinction of different tissues types that have similar ρ_e [11]. DECT is not only a powerful technique to obtain material specific information, but it also reduces beam-hardening artifacts compared with conventional single energy CT (SECT) [12].

Moreover, SECT requires a calibration that is conventionally done with tissue-equivalent materials to obtain the ρ_e from the CT numbers. Uncertainties arise from the suitability of these tissue-equivalent materials and the number of tissue types needed to have a proper calibration (Figure 1 from Bazalova *et al.* [5]). The calibration in DECT is done by phantoms with known ρ_e and Z_{eff} values.

Different DECT modalities are commercially available and these are based on single or dual-source CT scanners [3]. A single-source CT scanner can provide DECT images by performing two consecutive spiral scans at different energies, scanning with a fast kilovolt-switching, using a dual-layer detector system or scanning with a split beam with different filters. The latter is a novel technique where a single beam is split using two filters, which results in two different photon spectra for the same source and thus producing DECT images [13]. Dual-source scanners produce DECT images by using two orthogonal tubes with different filtrations and voltages that can range from 70 kVp to 150 kVp [14]. The purpose of this study is to assess image quality and to quantify the accuracy of ρ_e and Z_{eff} for three DECT scanners: a third-generation single-source twin-beam and two dual-source scanners (second and third generations).

2.2 Materials and methods

2.2.1 CT scanners and image reconstruction

DECT imaging was performed with three DECT scanners (Siemens Healthineers, Forchheim, Germany): a third-generation twin-beam scanner (SOMATOM Definition Edge), a third-generation dual-source scanner (SOMATOM Definition Force) and a second generation dual-source scanner (SOMATOM Definition Flash). The dual-source scanner Force and the twinbeam scanner Edge were equipped with third-generation digital detectors (Stellar detector, Siemens Healthineers, Forchheim, Germany), which reduce electronic noise (on average by 30%) and cross talk, compared with conventional Ultra-Fast-Ceramic (UFC) solid-state CT detectors [15] used in the Flash scanner. Table 2.1 presents all scanning and reconstruction settings for three dose levels. Reconstructions were performed with filtered back projection (FBP) kernels and with equivalent iterative

kernels with strength five [16]. The use of the same settings for the three scanners was not possible due to different software versions that were installed on the different scanners. Figure 2.1 shows the spectral pairs of each scanner used in this work simulated with the software SpekCalc [17–19].

Table 2.1. Scanner voltage pairs, pitch, exposure and rotation times for a combined computed tomography dose index (CTDI_{vol}) of approximately 10 mGy, 20 mGy, and the maximum dose allowed by the scanner control software. The data for the three dose levels are separated by a semicolon for the CTDI_{vol}, exposure and rotation time. 512 x 512 images were reconstructed for 3 mm slices with filtered back projection (FBP) and advanced modeled iterative reconstruction (ADMIRE) or with sinogram affirmative iterative reconstruction (SAFIRE).

	Edge	Flash	Force
Voltage Pair (kVp)	120Au/120Sn	80/140Sn	90/150Sn
Pitch	0.3	0.6	0.7
CTDI _{vol} (mGy)	9.97; 19.64; 44.12	9.99; 20.02; 40.85	9.99; 20.02; 65.42
Exposure (mAs)	468; 936; 2088	260/100; 530/205; 1083/418	199/124; 398/249; 1304/815
Rotation Time (s)	0.33; 0.5; 1	0.28; 0.5; 1	0.28; 0.5; 1
Software Version	VA49	VA48	VA50
Reconstruction	FBP and ADMIRE	FBP and SAFIRE	FBP and ADMIRE
Kernel	B40 and Q34 ^a	B40 and Q34	Br40 and Qr40 ^b

^a The kernel nomenclature from the iterative reconstruction was recently redefined, in which the old Q34 is equivalent to the new Qr40 with beam hardening correction for bone and the old B40 is equivalent to the new Br40.

^b Qr40 with beam-hardening correction for bone selected.

The kernel nomenclature from the iterative reconstruction was recently redefined, in which the old Q34 is equivalent to the new Qr40 with beam hardening correction for bone and the old B40 is equivalent to the new Br40. Qr40 with beam-hardening correction for bone selected.

2.2.2 Phantoms

A Gammex RMI 467 phantom (Gammex Inc. Middleton, WI) was scanned with two different configurations. First, 16 tissue mimicking inserts (Gammex Inc. Middleton, WI) were placed and scanned in a certain load pattern (Figure 2.2a), in which bone-equivalent materials are spread out to minimized artifacts. A second scan followed using six iodine and six calcium inserts with different densities (Gammex Inc. Middleton, WI) and the remaining four holes filled with solid water inserts. Another set of five cylindrical inserts was scanned in two phantoms (Model 002H5 and Model 002HN; CIRS Inc., Norfolk, VA) with different sizes, but both made with identical water equivalent material (Figure 2.2a). The inserts consist of tissue mimicking material: lung (inhale), bone, muscle, adipose (product 002ED, CIRS Inc., Norfolk VA) and plastic water (002RW-S, CIRS Inc., Norfolk VA). Table 2.2 presents the density, ρ_e , and Z_{eff} of the Gammex RMI 467 and the CIRS tissue inserts (more detail can be found in Tables I and II of Landry *et al.* [9]). A Catphan 504 phantom (The Phantom Laboratory, Salem, NY) consisting of several modules was also scanned with the same settings to test image quality in terms of low contrast resolution of the axial plane.

The Edge scanner has a minimum object width requirement of 10 cm in the cranial-caudal direction, since the reconstruction is unreliable within 3 cm from the edges. This is due

Figure 2.1. Normalized X-ray photon spectra used in the Edge (a), Flash (b) and Force (c) scanners. All high energy spectra have a tin (Sn) filtration (0.6 mm for the Edge and Force and 0.4 mm for the Flash). The Edge low energy spectrum has a gold (Au) filter of 0.05 mm.

ID	Tissue inserts	Iodine and Calcium (mg/mL)
1	Solid water	Iodine 2.0
2	LN-300 Lung	Calcium 200
3	Solid water	Iodine 10
4	LV1 Liver	Solid Water
5	Solid water	Calcium 400
6	CB2-50% CaCO3	Iodine 5.0
7	B200 Bone Mineral	Solid Water
8	SB3 Cortical Bone	Calcium 600
9	LN-450 Lung	Solid Water
10	BRN-SR2 Brain	Iodine 15
11	AP6 Adipose	Calcium 300
12	IB Inner bone	Iodine 7.5
13	Solid water	Solid Water
14	CB2-30% CaCO3	Calcium 500
15	Water insert	Iodine 2.5
16	BR-12 Breast	Calcium 50

Figure 2.2. (a) Sketch of the Gammex RMI 467 scans with the respective load pattern with tissue mimicking inserts and with iodine and calcium inserts. (b) Sketch of the CIRS abdomen (top) and head sized (bottom) phantoms with respective insert load pattern. Not to scale.

Table 2.2. Density (ρ , in g/cm^3), relative electron density (ρ_e) and effective atomic number (Z_{eff}) of the inserts of the Gammex RMI 467 and of the CIRS phantoms. ρ_e and Z_{eff} (explained in Section 2.2.5) were calculated with the elemental compositions given by the manufacturers of both phantoms.

	Insert Name	ρ (g/cm^3)	ρ_e	Z_{eff}
Gammex RMI 467	LN-300 Lung	0.3	0.29	7.55
	LN-450 Lung	0.46	0.45	7.53
	AP6 Adipose	0.947	0.93	6.21
	BR-12 Breast	0.98	0.96	6.93
	Water insert	1	1.00	7.48
	CT Solid water	1.022	0.99	7.74
	BRN-SR2 Brain	1.051	1.05	6.09
	LV1 Liver	1.096	1.06	7.74
	IB Inner bone	1.134	1.09	10.42
	B200 Bone Mineral	1.152	1.10	10.42
	CB2-30% CaCO_3	1.331	1.28	10.90
	CB2-50% CaCO_3	1.559	1.47	12.54
	SB3 Cortical Bone	1.822	1.69	13.64
CIRS	Lung	0.21	0.20	7.24
	Adipose	0.967	0.96	6.44
	Plastic Water DT	1.039	1.00	7.55
	Muscle	1.062	1.04	7.59
	Bone	1.6	1.51	11.90

to the combination of the twin-beam design and the use of a flat object. On the one hand, due to penumbra effects a few detector rows close to the boundary of the filtered beams see a mixture of both Au and Sn spectra. These detector rows are considered in the computation of the average image, but not for the dualenergy evaluations. On the other hand, the use of flat objects causes the attenuation to change drastically in the flat-edges, which has an impact in the data processing and image quality. Our phantom, the Gammex RMI 467 phantom has a width of only 5 cm and its inserts have a length of 7 cm. For both these reasons, scans were made using two original 5 cm disks facing each other, thus assembling into a 10 cm wide phantom. The Gammex RMI 467 scans using tissue mimicking inserts were used to calibrate each scanner for ρ_e and Z_{eff} (following Saito *et al.* [8] and Landry *et al.* [9]), whereas scans with the CIRS head and abdomen sized phantoms were used for validation. CT numbers in Hounsfield Units (HU) from the low- and high-energy images were measured in circular regions of interest (ROIs) that covered the inserts, avoiding their edges, in a selected central slice of each phantom.

2.2.3 Spectral separation and CNR

DECT scans were reconstructed with iterative reconstruction (IR: SAFIRE and ADMIRE methods) and FBP of the iodine and calcium inserts in the Gammex RMI 467 phantoms from the three scanners. Merged images were obtained by mixing the low- and high-energy images with a weighted sum ($\omega_{\text{low}} \cdot \text{CT}_{\text{low}} + \omega_{\text{high}} \cdot \text{CT}_{\text{high}}$), where the vendor-recommended weight factors for each scanner were used ($\omega_{\text{low,high}}$). These images were

then used to calculate the Contrast-to-Noise-Ratio (CNR) for each insert as

$$\text{CNR} = \frac{\text{HU}_{\text{ROI}} - \text{HU}_{\text{surrounding}}}{\text{Noise}} \quad (2.1)$$

where HU_{ROI} and $\text{HU}_{\text{surrounding}}$ are the mean values of CT numbers (in HU) in the ROI and the medium surrounding the insert. The noise is the standard deviation inside the ROI.

2.2.4 Quantification of image resolution

The CTP528 module from the Catphan phantom consists of 21 sets of aluminum strips separated by equally sized gaps, which are quantified in terms of line pairs per cm (lp/cm). The image resolution can be obtained using a Modulation Transfer Function (MTF) that describes the reduction in the contrast between the strips and the gaps as the number of line pairs per centimeter increases [20, 21]. The MTF is calculated as

$$\text{MTF} = \frac{\text{Intensity}_{\text{strip}} - \text{Intensity}_{\text{gap}}}{\text{Intensity}_{\text{strip}} + \text{Intensity}_{\text{gap}}} \quad (2.2)$$

where the intensities are measures of the CT numbers (HU). Spatial resolution is quantified when MTF equals 10% (expressed as @10%MTF). The MTF was calculated for both iterative reconstructed and FBP DECT images for each scanner.

2.2.5 Relative electron density (ρ_e) and effective atomic number (Z_{eff})

For quantitative imaging, the ρ_e and Z_{eff} were obtained from images reconstructed with ADMIRE (Edge and Force) and SAFIRE (Flash), this choice was based on Landry *et al.* [16] results showing improved accuracy of IR compared to FBP. The ρ_e was derived using Saito's linear relation with respect to dual-energy subtracted CT numbers [8]:

$$\rho_e = a \cdot \frac{(1 + \alpha) \text{CT}_{\text{high}} - \alpha \text{CT}_{\text{low}}}{1000} + b \quad (2.3)$$

where CT_{low} and CT_{high} are the mean values of CT numbers (in HU) in each ROI from the low- and high-energy images, respectively, and a , b , and α are scanner and protocol specific fit parameters. The Z_{eff} was obtained using the relation formulated by Landry *et al.* [9] between the ratio of the attenuation coefficients (μ) for low- and high-energy, which resulted from the Rutherford *et al.* [4] parameterization of the linear attenuation coefficient as function of the scattering (coherent and incoherent) and the photoelectric effects. After converting the CT numbers into attenuation coefficients relative to water, the Z_{eff} equation is

$$\mu_{\text{high kVp}}^{\text{low kVp}} = \frac{A + BZ_{\text{eff}}^{n-1} + CZ_{\text{eff}}^{m-1}}{D + EZ_{\text{eff}}^{n-1} + FZ_{\text{eff}}^{m-1}} \quad (2.4)$$

where $\mu_{\text{high kVp}}^{\text{low kVp}}$ is the ratio between $\mu_{\text{low kVp, water}}^{\text{low kVp}}$ and $\mu_{\text{high kVp, water}}^{\text{high kVp}}$ and A , B , C , D , E , F , m , and n are fit parameters. A , B , and C are terms related to the low energy kVp and D , E , and F to the high energy kVp. The ratio $\mu_{\text{kVp, water}}^{\text{kVp}}$ is defined as $\mu_{\text{kVp, water}}^{\text{kVp}} = \text{CT}_{\text{kVp}} / 1000 + 1$.

Scans from the Gammex RMI 467 phantom were used to obtain the calibration fits (Eqs. 2.3 and 2.4) for each scanner and dose level. The values for atomic composition and mass density (ρ) provided by the manufacturer were used to calculate the reference values of $\rho_e = \rho \sum_i \frac{\omega_i Z_i}{A_i} Z_i^n / \rho_{e, \text{water}}$, and $Z_{\text{eff}} = \sqrt[n]{\sum_i \frac{\omega_i Z_i}{A_i} Z_i^n / \sum_i \frac{\omega_i Z_i}{A_i}}$, where ω is the relative weight of each element, Z is the atomic number, A is the atomic mass, $\rho_{e, \text{water}}$ is the electron density of water and the exponent value n was set to 3.3 [7].

2.2.6 Comparison analysis

Experimental based estimations of ρ_e , and Z_{eff} were compared with reference values and the relative mean errors were calculated. Accuracy was also calculated for the CIRS abdomen and head sized phantom scans. The same quantities were obtained using *syngo.via* software (Siemens Healthineers, Forchheim, Germany) from which Z_{eff} and ρ_e images are extracted. The conversion of CT numbers to Z_{eff} and ρ_e are described in detail by Hünemohr *et al.* [10]. The results from Saito and Landry *et al.*'s methods were compared with *syngo.via*, which can be found online (see Supplementary Data 2.8.C).

2.3 Results

Results are presented for the scans with a CTDI_{vol} of approximately 20 mGy, unless otherwise indicated.

2.3.1 Spectral separation for iodine and calcium inserts

Figure 2.3 shows low-kVp and high-kVp CT numbers for the iterative reconstructed scans with different iodine and calcium inserts. Figure 2.3a presents the scatter plots for the twin-beam scanner Edge, which are closer to the identity line (in black) than the plots for the dual-source scanners Flash and Force (Figures 2.3b and 2.3c). Specifically, the iodine inserts present poorly separated CT numbers in Figure 2.2a. The difference between the two generation detectors is apparent in the scatter clouds' size, where the images acquired with third-generation digital detectors show a smaller variation in CT numbers (Figures 2.3a and 2.3c). Figure 2.4 presents the CNR for the iodine (Figure 2.4a) and the calcium (Figure 2.4b) inserts for the FBP scans of the three scanners. Both figures show the results for CTDI_{vol} of approximately 10 mGy and 20 mGy. Both figures show higher values of CNR for the Force scanner. Although the Edge has similar noise levels, the difference between the mean CT numbers and the surrounding are lower, resulting in a lower CNR. Similar values of CNR are found for the Edge and the Flash.

Figure 2.4 presents the CNR for the iodine (Figure 2.4a) and the calcium (Figure 2.3b) inserts for the FBP scans of the three scanners. Both figures show the results for CTDI_{vol} of approximately 10 mGy and 20 mGy. Both figures show higher values of CNR for the Force scanner. Although the Edge has similar noise levels, the difference between the mean CT numbers and the surrounding are lower, resulting in a lower CNR. Similar values of CNR are found for the Edge and the Flash.

2.3.2 Spatial resolution

Figure 2.5 shows the MTF as function of the frequency (in lp/cm) for the three scanners for a CTDI_{vol} of approximately 20 mGy for two different reconstructions: FBP and IR. Image resolution @10%MTF is 6.2 lp/cm, 5.8 lp/cm and 6.2 lp/cm for the iterative reconstructed

Figure 2.3. Low and high energy # CT plots for the iodine (2, 2.5, 5, 7.5, 10, and 15 mg/ml) and calcium (50, 200, 300, 400, 500, and 600 mg/ml) inserts for CTDI_{vol} of approximately 20 mGy for the Edge (a), Flash (b), and Force (c) scanners. Inserts are numbered from low to high density, in which the iodine inserts have numbers 1 to 6 (iodine 2 mg/ml and 2.5 mg/ml overlap) and the calcium inserts are numbered from 7 to 12. The identity line is plotted in black and each scatter point corresponds to one pixel from each insert's ROI.

images from the Edge, Flash, and Force scanners, respectively. Slightly inferior values are found for the FBP reconstructed images (6.1 lp/cm, 5.7 lp/cm, and 6 lp/cm). Values for @10%MTF are constant for the three dose levels used (± 0.1 lp/cm).

2.3.3 Calibration of ρ_e and Z_{eff} for each scanner

For the assessment of ρ_e and Z_{eff} , iterative reconstructed scans were used (see Supplementary Data 2.8.A).

Saito's calibration fit parameters are presented in Table 2.3. The parameter α should be smaller for larger spectral separation (see Saito's eq. 3.8 [8]). The calibration fits for Z_{eff} as a function of the ratio of the attenuation coefficients ($\mu_{high\ kVp}^{low\ kVp}$) are shown in Figure 2.6. The Gammex RMI 467 phantom lung equivalent inserts were excluded from the fitting procedure, as reported also by Landry *et al.* [7] since they are heterogeneous and their low CT numbers lead to high standard deviation values. The interval range of $\mu_{high\ kVp}^{low\ kVp}$ differs between the twinbeam scanner, 0.1 and the dual-source scanners, 0.4 (Figure 2.6).

Figure 2.4. Contrast-to-Noise-Ratio (CNR) for the iodine (a) and calcium (b) 5 inserts for two CTDI_{vol} of approximately 10 mGy (solid) and 20 mGy (dashed line).

Table 2.3. Saito's fit parameters a , b , and α from Eq. 2.3 for the calibration phantom Gammex RMI 467.

	Edge	Flash	Force
a	1.04	0.98	0.99
b	0.99	0.99	0.99
α	2.06	0.44	0.35

2.3.4 Errors of measured ρ_e and Z_{eff}

The errors of ρ_e and Z_{eff} for the calibration (Gammex RMI 467) and validation phantoms (CIRS abdomen and head size) are shown in Figure 2.7. In Figures 2.7a and 2.7b a pattern is identified: the errors from the Edge are higher for the inserts in the inner ring of the phantom. For the dual-source scanners Flash and Force, the errors for ρ_e range between $[-0.6\%, 1.2\%]$ and $[-1.2\%, 0.4\%]$, and for Z_{eff} between $[-6.2\%, 3.8\%]$ and $[-5.2\%, 1.6\%]$. For

Figure 2.5. Modulation Transfer Function (MTF) for the three CT scanners at a CTDI_{vol} of approximately 20 mGy.

Figure 2.6. Fit results for Eq. 2.4 using the Gammex RMI 467 phantom with tissue mimicking inserts at equivalent dose. Both lung inserts were excluded from the fitting procedure. Error bars are the standard deviations for each insert.

the twin-beam scanner, the errors have wider ranges: $[-0.7\%, 15.3\%]$ for ρ_e and $[-28.1\%, 4.2\%]$ for Z_{eff} .

Figures 2.7c and 2.7d show the errors of Z_{eff} and ρ_e for the two validation phantoms. Relative differences between ρ_e values of the same insert in the two different phantoms are within 0.6% for the Flash and Edge, with the exception of the lung insert, whereas for the Force scanner all relative differences are within 0.5%. For Z_{eff} , discrepancies are observed in lung and adipose for the Edge scanner (14.5% and 6.9%) and also in adipose for the Force scanner (5.6%). All other relative differences between Z_{eff} are within $\pm 2\%$.

Figure 2.7. ρ_e and Z_{eff} errors (%) of measured values with respect to reference values of the Gammex RMI 467 phantom (a, b) and the CIRS abdomen and head sized phantoms (c, d).

2.3.5 Material attribution feasibility

Tissue composition segmentation can be done with the $[\rho_e, Z_{eff}]$ space (detailed in section 2.5 from Landry *et al.* [7]), which uses the two-dimensional Mahalanobis distance to assign each voxel to its closest reference material. For this method to be feasible, a proper separation in the $[\rho_e, Z_{eff}]$ space of the scatter plots for the different calibration materials should exist. Figure 2.8 presents the scatter plots from the scans with the calibration phantom for the three scanners. The data discretization observed for low Z_{eff} values (e.g. for the lung tissues) are a result of saving CT numbers' as integers by the vendors' software. In Figure 2.8a1, it is possible to observe in detail the cortical bone insert (insert number 8) for the Edge scanner, which shows the spread of ρ_e ($\Delta\rho_e$) and Z_{eff} (ΔZ_{eff}). Compared to the other two scanners, these ranges are wider for all inserts in the Edge, which is especially noticeable for the bone tissues.

All voxels from the lung and hard bone equivalent tissue were assigned to the correct material for the Gammex RMI 467 phantom (see Supplementary Data 2.8.B). The inner bone and bone mineral equivalent inserts have similar compositions and density, resulting in very close values of ρ_e and Z_{eff} (Figure 2.8).¹¹ The visible overlap of the soft tissues results in lower percentage of correct material attribution, which can be improved with lower spread of the $[\rho_e, Z_{eff}]$ clouds. The CIRS tissue inserts are well separated in the

Figure 2.8. (a) Edge, (b) Flash, and (c) Force $[\rho_e, Z_{\text{eff}}]$ scatter plots of the Gammex RMI 467 calibration phantom (CTDI_{vol} of approximately 20 mGy). (a1) shows the scatter plot for the cortical bone insert (insert number 8), where the spread on ρ_e and Z_{eff} are identified with $\Delta\rho_e$ and ΔZ_{eff} . The inserts are numbered according to Figure 2.2a. The solid water inserts 3, 5, and 13 were excluded from these plots, since they did not add any extra information.

$[\rho_e, Z_{\text{eff}}]$ space resulting in 100% correct material attribution, except for muscle and plastic water in the abdomen size phantom for the Edge scanner (93% and 98%, respectively). The errors of the ρ_e and Z_{eff} as well as the scatter plots of the $[\rho_e, Z_{\text{eff}}]$ space were obtained from the ρ_e and Z_{eff} images extracted from *syngo.via* (see Supplementary Data 2.8.C).

2.4 Discussion

The novel technology presented in this paper, the split-filter from the Edge scanner, has the advantage of using a single x-ray tube to do DECT scans, allowing for a possible upgrade on many clinical SECT scanners. In this work, a comparison of this new technique with the state-of-the-art dual-source DECT scanners was done to assess the performance of the twin-beam on quantitative imaging, knowing beforehand that the spectral separation of the twin-beam would not be as good as the one from the dual-source DECT scanners.

The twin-beam scanner has a width requirement of 10 cm in the craniocaudal direction, as explained in the section Section 2.2. Although the scans with the calibration phantom were made using two Gammex RMI 467 disks, it is important to point out that using the

syngo.via software, non-uniform ρ_e - Z_{eff} images along the phantom's profile were obtained for uniform inserts, whereas such non-uniformities were not seen in the CIRS phantoms, which have a width of 15 cm. Even then, the central slice of the Gammex RMI 467 disk with the inserts presented the most uniformly reconstructed image and it was used to perform the calibration.

A consequence of the twin-beam energy spectra (Figure 2.1a) is the poor CT number separation seen in Figure 2.3a for the iodine and calcium inserts. The two dual-source scanners, with well-separated spectra, present a noticeable distinction in CT numbers between the low and high energy scans for the iodine and calcium scans. The Force scanner with the third-generation detectors and the smaller spectral overlap (of only 10.5% of the area overlapping) shows scatter plots further away from the identity line and with lower variations.

The Flash and Edge have similar CNR results for both iodine and calcium materials. On one hand, the second generation dual-source scanner Flash has a good contrast due to its wider spectral separation, but higher noise levels due to the detector. On the other hand, the split-beam scanner Edge has low noise values, but also low contrast due to its narrower spectral separation. The Force has a CNR on average 1.5 times superior to the Flash and 1.4 superior to the Edge.

In terms of image resolution, the results for the @10%MTF are similar for both the Edge and the Force scanners and slightly lower for the Flash, since this is mostly related with the detectors' system.

The calibration of ρ_e and Z_{eff} was performed for the three scanners using the methods from Saito *et al.* [8] and Landry *et al.* [9] The Edge presented less robust calibration curves with higher fit residuals. This can be explained again by the reduced spectral separation of the twin-beam, that resulted in a high ρ_e parameter for the ρ_e fit (Table 2.3) and a low range of the attenuation coefficients ratio for the Z_{eff} fit (Figure 2.6a).

These results have a direct implication on the extraction of the ρ_e and Z_{eff} , which had overall higher differences with the reference values and spread out clouds in the $[\rho_e, Z_{\text{eff}}]$ scatter plots for this scanner. The same or higher deviations were obtained from *syngo.via*'s images, which use a different method to calculate ρ_e and Z_{eff} .

The ρ_e and Z_{eff} errors for the calibration phantom are noticeably higher for the Edge, especially for all inserts located in the inner ring of the Gammex RMI 467 phantom (inserts 9 to 16, Figures 2.7a and 2.7b). This can be related to the twin-beam requirement to reconstruct objects thicker than 10 cm. For this phantom, the Flash and the Force scanners presented lower errors for the tissue substitute inserts, specifically, errors for the soft tissues within 1.3% for ρ_e and 7% for Z_{eff} and for the bone tissues within 0.5% for ρ_e and 1.9% for Z_{eff} .

The validation was performed with a different set of tissue-equivalent inserts in two different sized phantoms, aiming also to assess the robustness of the calibration for a smaller phantom. Values of ρ_e for both phantoms have a relative difference within 0.6% for the three scanners. Higher discrepancies are observed for Z_{eff} , within 2% for bone, muscle and water and within 6% for adipose. From these results, it is possible to conclude that the calibration methods used for DECT are not phantom-size dependent, as long as

beamhardening effects are corrected during the image reconstruction.

Images acquired with the twin-beam technology resulted in widely spread ρ_e and Z_{eff} (Figure 2.8) values for the same material type, contrary to the results from the dual-source scanners. The use of different IR algorithms and detector systems and the lack of performance from the lung equivalent inserts are limitation from this study, but these do not change its overall conclusions.

2.5 Conclusion

The dual-source scanners measure ρ_e and Z_{eff} values closer to the reference ones, when compared with the twin-beam scanner, with a higher accuracy for the third-generation scanner Force. The dual-source third-generation scanner resulted in higher resolution and CNR than the other two scanners.

A comparison study between a scanner with a novel DECT technique, a split-beam, and dual-source DECT scanners is shown in this paper. Understanding the implications of using this new technique in terms of resolution, contrast and derivation of two quantities, ρ_e and Z_{eff} , seemed essential to assess the future of the twin-beam scanner for radiotherapy with photon and ion beams. The contrast and tissue material segmentation are necessary for a better contouring of body structures, organs and tumors. Also, an accurate calculation of these quantities is necessary to perform dose calculations and to be able to do in vivo range prediction for treatment verification for particle therapy. Finally, other features in quantitative imaging such as detailed texture analysis show the need for high-quality DECT images.

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2.7 References

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2.8 Supplementary data

2.8.A Gammex RMI 467 scanned with the twin-beam scanner Edge

Figure S2.1. Reconstructed images of low (a) and high (b) energy from Gammex RMI 467 scanned with the Edge scanner. The reconstruction was performed by the ADMIRE algorithm for a CTDIvol of approximately 20 mGy. The inserts positions match the ROIs sketched in Figure 2.2(a).

2.8.B Correctness of material assignment for Gammex RMI 467

Figure S2.2. Correctness of tissue attribution using the Mahalanobis distance for the Gammex RMI 467 (excluding the solid water and liquid water inserts). Tissues are ordered from low to high density.

2.8.C Comparison with *syngo.via*

Comparison between the results for the methods used in this work (Saito and Landry *et al.*'s calibrations) and the *syngo.via*'s ρ_e and Z_{eff} values presented overall higher errors using *syngo.via*'s methods for the Edge and Flash scanners, whereas for the Force, both methods are more consistent for the majority of the inserts (Figure S2.3). Further, Figure S2.4 shows the voxel spread for each insert in the $[\rho_e, Z_{\text{eff}}]$ space. Although the scatter plots are narrower than the results from Figure 2.8, these are located further away

from the reference values. Also, the conversion made by *syngo.via* from CT numbers to these quantities leads to a discretization of the scatter plots, which can cause the clear off-set between the measured and the reference values, in particular, for the bone equivalent inserts.

Figure S2.3. ρ_e and Z_{eff} errors (%) of measured values for the Gammex RMI 467 phantom using Saito/Landry methods and *syngo.via* for the Edge (a,b), Flash (c,d) and Force (e,f). The lung equivalent inserts were excluded, since *syngo.via* attributes $Z_{\text{eff}} = 0$ to materials with CT numbers inferior to -500 HU). Tissues are ordered from low to high density.

Figure S2.4. (a) Edge, (b) Flash and (c) Force [ρ_e , Z_{eff}] scatter plots of the Gammex RMI 467 calibration phantom (CTDI_{vol} of approximately 20mGy) extracted from *syngo.via*.

Monte Carlo proton dose calculations using a radiotherapy specific dual-energy CT scanner for tissue segmentation and range assessment

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Abstract

Proton beam ranges derived from dual-energy computed tomography (DECT) images from a dual-spiral radiotherapy (RT)-specific CT scanner were assessed using Monte Carlo (MC) dose calculations. Images from a dual-source and a twin-beam DECT scanner were also used to establish a comparison to the RT-specific scanner. Proton ranges extracted from conventional single-energy CT (SECT) were additionally performed to benchmark against literature values. Using two phantoms, a DECT methodology was tested as input for Geant4 MC proton dose calculations. Proton ranges were calculated for different mono-energetic proton beams irradiating both phantoms; the results were compared to the ground truth based on the phantom compositions. The same methodology was applied in a head-and-neck cancer patient using both SECT and dual-spiral DECT scans from the RT-specific scanner. A pencil-beam-scanning (PBS) plan was designed, which was subsequently optimized by MC dose calculations, and differences in proton range for the different image-based simulations were assessed. For phantoms, the DECT method yielded overall better material segmentation with > 86% of the voxel correctly assigned for the dual-spiral and dual-source scanners, but only 64% for a twin-beam scanner. For the calibration phantom, the dual-spiral scanner yielded range errors below 1.2 mm (0.6% of range), like the errors yielded by the dual-source scanner (< 1.1 mm, < 0.5%). With the validation phantom, the dual-spiral scanner yielded errors below 0.8 mm (0.9%), whereas SECT yielded errors up to 1.6 mm (2%). For the patient case, where the absolute truth was missing, proton range differences between DECT and SECT were on average in -1.2 ± 1.2 mm ($-0.5\% \pm 0.5\%$). MC dose calculations were successfully performed on DECT images, where the dual-spiral scanner resulted in media segmentation and range accuracy as good as the dual-source CT. In the patient, the various methods showed relevant range differences.

3.1 Introduction

Proton radiotherapy offers the potential of decreasing dose to normal tissues and to improve outcome by dose escalation, which may influence the patient's quality of life post treatment. Another promising potential of proton therapy is the modulation of the immune system, which may differ from photon therapy [1]. An issue in proton therapy is the uncertainty of proton range prediction, which requires the use of different techniques such as robust optimization or conservative margin recipes. These margin recipes are influenced by the piecewise linear conversion from single-energy CT (SECT) numbers (CT#), expressed in Hounsfield units (HU), to either mass-densities or stopping power ratios (SPR) relative to water [2, 3], after which materials may be assigned. Schneider *et al.* [4] proposed a stoichiometric method of calculating CT# of biological tissues from previously calculated scanner specific parameters using a phantom with known materials, resulting in a calibration curve from CT# of biological tissues to SPR. Later, [5] enhanced this method by extracting mass-density (ρ) tissue compositions of biological tissues from the stoichiometric-calculated CT#.

Dual-energy CT (DECT) has been proposed as an enhanced imaging modality for proton dose calculations, due to potential improvement of extracting more accurate information from the tissues' chemical composition [6, 7]. Also, the effective atomic number (Z_{eff}) and the relative electron density (ρ_e) are two physical quantities extracted from DECT that allow for a more accurate calculation of the SPR [8–11], thus potentially decreasing the uncertainty on the conversion from the patient images to quantities needed for treatment planning.

Proton dose calculations based on DECT imaging have been studied recently. Hünemohr *et al.* [7, 8, 12] showed how water equivalent path lengths could be predicted by ρ_e extracted from DECT and with a better accuracy than using the SECT HU to density look-up table based on the stoichiometric calibration [5]. Hudobivnik *et al.* [13] reported differences up to 3 mm in range between a pencil beam algorithm proton plan based on DECT and SECT images for the head region of a surrogate tumor patient. Wohlfahrt *et al.* [14] showed clinically relevant range deviations between using a conventional HU to SPR look-up-table and a patient-specific SPR prediction based on DECT, and their results were in agreement with those from Hudobivnik *et al.* [13].

DECT imaging can be performed using different technologies, either at the level of the x-ray detectors or at the level of the x-ray source [15]. By means of a single-source x-ray tube, DECT images can be obtained through fast kilovolt-switching, using a split beam geometry (twin-beam), by discriminating low and high-energy photons at the level of the detector, or by sequential scanning (dual-spiral). These DECT imaging modalities allow for large fields-of-view (FOV), however the dual-spiral CT can only scan sites with minimal motion (*e.g.* head and pelvis). With two perpendicular x-ray sources (dual-source) and detectors, a DECT scan can be made simultaneously, where one of the advantages is the possibility to add different extra filtration to both x-ray beams to increase spectral separation, whereas a disadvantage is the reduced FOV, due to one of the detectors being smaller than the other, which can be a constraint for larger sites.

This work focused on performing MC proton dose calculations using segmented DECT images in two phantoms of known composition for a DECT commercially available dual-

spiral scanner. The DECT segmentation procedure was developed to yield equivalent SPR to so-called direct-SPR methods for pencil beam algorithm (such as proposed by Yang [16]) dose calculations. Given the early adoption of dual-spiral technology in proton therapy clinics, emphasis was placed on this modality. Complementarily, a comparison with two other DECT modalities (the twin-beam and the dual-source) and with SECT was added. Furthermore, the same methodology was tested in a head-and-neck cancer patient scanned with DECT and SECT protocols, where range differences of a single-field PBS plan obtained from MC treatment planning [17] were assessed. To our knowledge this is the first study performing MC based proton treatment planning using DECT images.

3.2 Materials and methods

3.2.1 CT scanners and phantoms

DECT imaging was performed with three third-generation scanners (Siemens Healthineers, Forchheim, Germany): a twin-beam scanner at 120 kVp with gold and tin filtrations (SOMATOM Definition Edge), a dual-spiral scanner at 80-140 kVp (SOMATOM Definition Confidence[®] RT pro) and a dual-source scanner at 90-150 kVp with tin filtration (SOMATOM Definition Force). A SECT scan at 120 kVp was acquired with the same radiotherapy (RT) specific scanner, the Confidence[®] RT pro, at equivalent dose. Details of the phantom scans and reconstructions used are found in table Table 3.1.

Table 3.1. Values on the scanner total computed tomography dose index ($CTDI_{vol}$) for 32 cm, software version, reconstruction algorithm (advanced modeled iterative reconstruction (ADMIRE) or with sinogram affirmative iterative reconstruction (SAFIRE)) and kernel for the four sets of phantom scans. Images were reconstructed with a slice thickness of 3 mm, pixel size of 0.727 mm and with beam hardening correction for bone.

	Twin-beam	Dual-spiral	Dual-Source	SECT
$CTDI_{vol}$ (mGy)	19.6	19	20	20
Software Version	VA49A	VA62A	VA50A	VA62A
Reconstruction	ADMIRE	SAFIRE	ADMIRE	SAFIRE
Kernel	Q34	Q34	Qr40	Q34

An RMI 467 phantom with 16 tissue mimicking inserts (Gammex Inc. Middleton, WI) was scanned and used for calibration. For validation of the RT-specific scanner, a model 062M (CIRS Inc., Norfolk, VA) with 10 tissue mimicking inserts was used. Detailed information on the phantom compositions can be found in table Table 3.2.

Table 3.2. Mass-density (ρ) and composition of 16 tissues extracted from White *et al.* [18] and the CT# calculated with the stoichiometric method.

ID	Insert Name	ρ (g/cm ³)	Elemental Composition (%)												
			H	O	C	N	Cl	Ca	P	Na	Mg	Al	Si	S	Ba
1,3,5,13	Solid water	1.022	8	19.87	67.3	2.39	0.14	2.31							
2	LN-300 Lung	0.3	8.39	18.4	68.59	2.19	0.14	2.26			0.03				
			8.46	18.14	59.38	1.96	0.1				11.19	0.78			
4	LV1 Liver	1.096	7.43	20.71	57.86	1.96	0.08				11.19		0.77		
6	CB2-50% CaCO3	1.559	8.06	20.01	67.01	2.47	0.14	2.31							
			8.4	18.5	68.41	2.25	0.14	2.26			0.03				
7	B200 Bone Mineral	1.152	4.77	32	41.63	1.52	0.08	20.02			0.3				
			4.03	34.13	40.34	1.52	0.07	19.62							
8	SB3 Cortical Bone	1.822	6.65	23.64	55.52	1.98	0.11	8.87	3.24						
			6.94	19.82	56.62	1.81	0.11	6.39	8.31						
9	LN-450 Lung	0.46	3.41	36.5	31.41	1.84	0.04	26.81			0.41				
			2.66	39.08	30.34	0.99	0.04	26.48			11.21	0.58			
10	BRN-SR2 Brain	1.051	8.47	18.11	59.57	1.97	0.1				11.22		0.57		
			7.44	20.69	58.03	1.97	0.08								
11	AP6 Adipose	0.947	10.83	14.86	72.54	1.69	0.08								
			9.77	16.34	72.13	1.69	0.07								
12	IB Inner bone	1.134	9.06	16.27	72.3	2.25	0.13								
			9.44	14.86	73.5	2.07	0.13								
14	CB2-30% CaCO3	1.331	6.67	23.52	55.64	1.96	0.11	8.86	3.23						
			6.97	19.71	56.73	1.79	0.11	6.38	8.3						
15	Water insert	1	6.68	25.61	53.48	2.12	0.11	12.01			0.18				
			5.6	28.47	51.77	2.12	0.09	11.77							
16	BR-12 Breast	0.98	11.2	88.8											
			8.59	17.9	70.11	2.33	0.13	0.95							
a,l	Liver	1.072	8.97	16.45	71.36	2.14	0.13	0.93			0.01				
b,m	Lung (inhale)	0.195	9	17.1	69.4	2.1	0.1	2.2							
c,n	Breast 50/50	0.991	8.8	18.6	67.5	3.5	1.6								
d,j	Bone 1.53	1.53	9.6	17	70.3	1.9	0.2	0.9							
e,p	Muscle	1.062	5.7	25.9	40.8	1	0.1	17.9	8.3						0.3
f	Bone 1.16	1.161	9.1	16.8	69.7	2.1	0.1	2.2							
g,o	Adipose	0.96	7	22.7	56.3	2	0.2	8.5	3.3						
h	Bone 1.82	1.82	10	16.4	71.3	1.8	0.2	0.3							
i,k	Lung (exhale)	0.51	3.6	32	28.8	1.1	0.04	23.3	10.8					0.08	0.32
Bulk	Plastic Water-LR	1.029	8.9	20.4	66	2.4	0.6	1.7			9.29				
			7.91	27.21	53.62	1.74	0.23								

3.2.2 Study framework

For each DECT modality, as well as for SECT, the material and ρ images were computed and used for Geant4 MC proton dose calculations. The framework followed to obtain the MC input files from a DECT or SECT scan is presented in Figure 3.1.

Figure 3.1. Flowchart of procedures followed in this work: from a phantom scan to the input files for Geant4 MC proton dose calculations. In this work, phantom specific material lists were employed for segmentation.

DECT scans from the RMI 467 phantom were used to obtain a calibration in terms of ρ_e , Z_{eff} and mean excitation potential (I). ρ_e and Z_{eff} were derived from Saito *et al.* [19] weighted difference in CT numbers (CT#) and from Landry *et al.* [20] ratio of attenuation coefficients, respectively (fit coefficients in table Table 3.3). The lung inserts were excluded from Landry's fitting procedure, due to their heterogeneity and high standard deviation, as reported in previous studies [20, 21]. The I_{values} were obtained from Yang [16] empirical relationship between the logarithm of I_{values} and ρ_e of human tissues, $\ln(I_{value}) = cZ_{eff} + d$, where the fit parameters c and d were obtained using 74 human biological tissues from [18, 22]. This set of tissues was divided in soft tissues ($Z_{eff} \leq 9$) and bone tissues ($Z_{eff} > 9$) and the fit results are shown in table Table 3.4 (consistent with Figure 3 from [16]). Z_{eff} and I_{values} for the tabulated biological materials were calculated with Bragg's additivity rule.

Using all media of the RMI 467 phantom, for SECT, the calibration was obtained by using a direct CT# to ρ curve. The mean CT# per insert used for calibration for all DECT and SECT

Table 3.3. Fit parameters obtained from the images of the calibration phantom, following section 2.5 from Almeida *et al.* [21].

		Twin-beam	Dual-spiral	Dual-source
Saito	a	1.037	1.001	1.011
	α	2.064	0.881	0.357
	b	0.991	0.993	0.992
	r^2	0.999	0.999	0.999
Landry	A	0.176	0.207	0.207
	B	0.012	0.003	0.002
	C	3.00×10^{-5}	2.59×10^{-5}	3.07×10^{-5}
	D	0.167	0.211	0.207
	E	0.013	0.004	0.003
	F	2.17×10^{-7}	1.29×10^{-7}	2.64×10^{-7}
	m	4.534	4.529	4.568
	n	2.898	2.856	2.886
	r^2	0.979	0.999	0.998

Table 3.4. Fit parameters for Yang [16] parameterization between the logarithm of I and Z_{eff} , divided in two regions (soft and bone tissues).

	$Z_{\text{eff}} \leq 9$	$Z_{\text{eff}} > 9$
c	0.126	0.1
d	3.365	3.33
r^2	0.971	0.949

scans can be found in Supplementary Data 3.8.A.

The dual-spiral DECT calibration curves obtained for the RMI 467 phantom were applied to the model 062M phantom, used for validation. The SECT calibration was also evaluated with said phantom. The material and ρ maps needed for the Geant4 proton dose calculations were produced for both phantoms, using the total number of media for each one to later compare with the reference phantoms (see Supplementary Data 3.8.B with reference material maps). For the DECT scans, materials were assigned to each voxel using the 2D Mahalanobis distance in the $[\rho_e, Z_{\text{eff}}]$ -space (explained in section 2.5 from [23]) to find the closest reference material. Next, using the material and ρ_e maps, the ρ maps were computed from the relation

$$\rho_e = \rho \sum_i \frac{\omega_i Z_i}{A_i} Z_i^n / \rho_{e, \text{water}} \quad (3.1)$$

where ω is the relative weight, Z is the atomic number and A is the atomic mass. For SECT, the calibration was used to obtain the ρ maps, and from these densities, the materials were assigned by means of a look-up table. The linear relationship between Z_{eff} and the logarithm of the I was used in this work to assign one I to each voxel. For SECT and the reference phantom, the I_{values} were calculated with the Bragg additivity rule from the tissue

compositions, resulting in one I per material.

To minimize material misassignment due to artifacts from the image reconstruction of the different scanners, the geometries used in the simulations were derived from the middle slice of the scanned phantoms with a slice thickness of 1.5 mm, which was replicated ten times to obtain a uniform volume.

All calculations to produce input files for the MC simulations were made in Matlab® v. R2016b (The MathWorks Inc., Natick, MA).

3.2.3 Direct-SPR *versus* composition-SPR

To avoid eventual systematic range differences between treatment plans optimized on the basis of DECT images which are directly converted into SPR (named 'direct-SPR', see for example Yang [16]) and plans optimized on the basis of ρ and composition estimation from DECT (named 'composition-SPR'), it is necessary to ensure that both approaches yield the same stopping power (or SPR) values for a given voxel.

In the direct-SPR, ρ_e and I images obtained from DECT are inserted in the Bethe equation

$$\text{SPR} = \rho_e \frac{\ln\left(\frac{2m_e c^2 \beta^2}{I(1-\beta^2)}\right) - \beta^2}{\ln\left(\frac{2m_e c^2 \beta^2}{I_{\text{water}}(1-\beta^2)}\right) - \beta^2} \quad (3.2)$$

where c is the speed of light, I_{water} is the I of water, m_e is the electron mass, and β is the proton speed in units of c . SPR values can subsequently be directly used in some types of pencil beam algorithm treatment planning systems.

In the case of composition-SPR used as input to Geant4 MC dose calculations (or other dose calculation algorithms requiring composition for the computation of stopping power), one should pay attention to the MC code's internal conversion of density and composition into stopping power.

We ensured that composition-SPR matched direct-SPR by computing the mass-densities from the DECT-obtained ρ_e and composition by inverting equation 3.1, and by overwriting I_{values} in Geant4 (more details in section 3.2.5) to match the ones from the direct-SPR.

SPR-maps (calculated for 100 MeV protons and with $I_{\text{water}} = 78$ eV) were extracted from Geant4 during the process of defining the geometry materials in a voxel by voxel basis, and we verified that the mean values of SPR per phantom insert agreed with those from the direct-SPR approach. The process is illustrated in Figure 3.2.

3.2.4 Geant4 simulations

Each phantom was irradiated with independent mono-energetic single rectangular fields pencil beams with no energy spread passing through different tissue mimicking inserts (Figure 3.3) and the corresponding dose [24] was calculated with Geant4 (version 10.02.p02 [25]) and physicslist 'QGSP_BIC_HP'. Dose to water in medium was scored [26] by simulations using the DECT- and the SECT- computed material and ρ maps, as well as using the voxelized reference phantom. The proton range, determined at the depth of the 80% dose distal fall-off (R80), was evaluated. 25×10^6 protons were used in beams 1-5 and 10^6 protons in beams 6-11 achieving a range uncertainty in R80 limited by the pixel size of

Figure 3.2. Flowchart of the elements used to calculate the direct-SPR and the composition-SPR.

0.727 mm. To assess the number of protons, the same beam geometries (beams 1-11) were simulated in a water phantom with different number of protons. The number of protons was increased until the maximum deviation in R80 (difference between maximum and minimum R80) was lower than the pixel size. Beams irradiating the lung inserts for both phantoms were excluded from this study, since the heterogeneity of these regions leads to very large discrepancies compared to the reference, which were not observed in other tissue equivalent inserts.

Figure 3.3. Schematic view of the mono-energetic proton beams passing through different inserts in the calibration (left) and validation (right) phantoms. For the calibration phantom (left), five 175 MeV beams (1-5) 10 cm wide were used. For the validation phantom (right), 5 cm wide beams (6-11) with different initial proton beam energies were used.

3.2.5 Geant4 tissue segmentation using one I per voxel

In typical Geant4 simulations, the geometry is defined by inputting the voxelized information of ρ and material number, as well as the definition of a list of base materials, which have at least a given ρ , composition and I . During the process of reading the information of each voxel, new materials are created using the base materials and the mass-densities coupled within a certain binning (in this work, 0.001 g/cm³), for example, a new material could be 'Solid_Water_1.025', which refers to base material 'Solid Water' with density 1.025 g/cm³. In this work, in addition to mass-densities, I_{values} per voxel were also

given as input, overwriting the ones in the base materials. This leads to a second binning process: for all new sets of materials defined by a certain ρ binning, new sub-sets are defined by the I binning (bin width: 0.5 eV), for example 'Solid_Water_1.025_77.5', which refers to base material 'Solid Water' with density 1.025 g/cm³ and I of 77.5 eV.

3.2.6 Patient case

A head-and-neck cancer patient treated for a T4aN2cM0 squamous cell carcinoma was scanned (Institutional Review Board approval P0153) with two different imaging protocols with the Confidence[®] RT pro scanner: a conventional SECT scan (120 kVp), followed by a dual-spiral DECT scan (80-140 kVp), with equivalent CTDI_{vol} (32 cm) of 13 mGy. Images were acquired with an extended FOV of 650 mm to cover the shoulders and reconstructed with an iterative reconstruction kernel (SAFIRE I30 kernel with metal artifact reduction iMAR for dental fillings and strength 3) resulting in a voxel size of 1.27 mm. Non-rigid image registration of the dual-spiral scans is performed by the scanner's software [27–29]. An in-house developed 3-step multiresolution deformable image registration algorithm, based on the Elastix toolbox [30], was applied on both the low and high energy DECT datasets to overlap the planning SECT, on which the clinical delineations of the relevant structures done by a radiation oncologist and a radiotherapy technician were made. The RMI 467 phantom was scanned with the same imaging protocol and was used for calibration for the DECT tissue segmentation method explained in section 3.2.2. For the SECT calibration, section 2.2 of Schneider *et al.* [5] was followed: the materials of the RMI 467 phantom yielded CT model parameters $k_1 = 2.30 \times 10^{-4}$ and $k_2 = 2.34 \times 10^{-5}$ ($r^2 = 0.999$); the stoichiometric parameters (k_1, k_2) were applied to a list of 16 ICRU tissues selected for this study (Table 3.5), returning a CT# for each material, finally resulting in a calibration curve CT# to ρ . After applying the calibration curves to obtain the ρ_e and Z_{eff} images for DECT and the ρ image for SECT, the material segmentation was done using a set of 16 ICRU tissues selected for this head-and-neck case plus air.

Table 3.5. Mass-density (ρ) and composition of 16 tissues extracted from White *et al.* [18] and the CT# calculated with the stoichiometric method.

Tissue Name	ρ (g/cm ³)	Elemental Composition (%)										CT# (HU)	
		H	C	N	O	Na	Mg	P	S	Cl	K	Ca	Fe
Adipose lo Z	0.93	11.6	68.1	0.2	19.8	0.1			0.1	0.1			-85
Adipose mean Z	0.95	11.4	59.8	0.7	27.8	0.1			0.1	0.1			-64
Bone marrow yellow	0.98	11.5	64.4	0.7	23.1	0.1			0.1	0.1			-35
Gland lo Z	0.99	10.9	50.6	2.3	35.8	0.1		0.1	0.1	0.1			-26
Yellow-red marrow	1	11	52.9	2.05	33.5	0.05		0.05	0.15	0.15	0.1	0.05	-14
Brain fluid	1.01	11.1			88	0.5				0.4			12
Eyes	1.02	10.7	6.9	1.7	80.3			0.1	0.1		0.2		16
Brain white	1.04	10.6	19.4	2.5	66.1	0.2		0.4	0.2	0.3	0.3		35
Blood whole	1.06	10.2	11	3.3	74.5	0.1		0.1	0.2	0.3	0.2	0.1	55
Skin mean Z	1.09	10	20.4	4.2	64.5	0.2		0.1	0.2	0.3	0.1		76
Skin hi Z	1.09	10.1	15.8	3.7	69.5	0.2		0.1	0.2	0.3	0.1		79
Cartilage	1.1	9.6	9.9	2.2	74.4	0.5		2.2	0.9	0.3			96
Whole column	1.33	7.1	25.8	3.6	47.2	0.1	0.1	5.1	0.3	0.1	0.1	10.5	445
Cranium	1.61	5	21.2	4	43.5	0.1	0.2	8.1	0.3			17.6	855
Mandible	1.68	4.6	19.9	4.1	43.5	0.1	0.2	8.6	0.3			18.7	953
Cortical bone	1.92	3.4	15.5	4.2	43.5	0.1	0.2	10.3	0.3			22.5	1301

A PBS plan based on the DECT images was made following three steps:

1. First, an initial plan was made with a proton therapy extension of the research tool CERR [31, 32]. This plan was created with CERR's particle extension double Gaussian pencil beam algorithm (PBA) based on the DECT direct-SPR image for water equivalent thickness calculations, and with a prescribed dose of 2 Gy per fraction to the planning target volume (PTV). Pencil beams were placed on a 3.5 mm grid in the lateral direction and with 1 mm spacing between Bragg peaks from adjacent energies. The PBA plan was first used to ensure the feasibility of the beam arrangement prior to treatment planning based on MC dose calculations.
2. Second, the coupling to Geant4 from Resch *et al.* [24] was used. This approach is based on a similar procedure as in Mairani *et al.* [17]. The dose distributions of each pencil beam were recomputed with MC by simulating each one in the patient geometry with Geant4 (version 10.02.p01, physics list 'QGSP_BIC_HP', 10^5 primary protons). The pencil beam doses to water in medium were scored and used to replace the initial PBA doses in CERR. Throughout this manuscript, MC treatment planning refers to this method, where the dose of each pencil beam was calculated by means of MC and optimized using the gradient based optimizer implemented in CERR.
3. Using the new MC pencil beam doses, CERR's particle extension optimizer recalculated the pencil beam weights to achieve a homogeneous dose to the PTV (detailed description in appendix B from [24]) and, finally, the optimized plan was exported.

Final MC dose distributions were calculated for the DECT segmented images in Geant4. The final plan was also recalculated in the SECT image using the same number of protons (approx. 10^7 primary protons) to avoid any potential artefacts caused by performance optimizations such as dose thresholds in the treatment planning tool. Differences in range between the SECT and DECT were evaluated.

3.3 Results

3.3.1 Material maps

Figure 3.4 shows the binary map of voxels correctly assigned for the different DECT modalities. For the calibration phantom, the twin-beam showed a poor material assignment (64% of the voxels, excluding air around the phantom, were correctly assigned), especially for the soft tissue-equivalents, which was prominent in the bulk material (solid water). For the same phantom, the dual-spiral and the dual-source material maps were the closest to the reference with 86% and 90% correct material assignment, respectively. Lower percentages were observed in the SECT material map (39%). For the validation phantom, the dual-spiral yielded over 89% of the voxels correctly assigned, while SECT assigned less than 48% voxels correctly.

3.3.2 Validation between direct-SPR and composition-SPR

Figure 3.5 shows the SPR values per insert from each scanner and the reference SPR calculated from the phantom specifications for an energy of 100 MeV. All scanners showed a maximum difference between both methods (direct- SPR and composition-SPR) below 0.6%. Detailed explanation and SPR-maps from the three DECT modalities and computed

Figure 3.4. Map of assigned materials with respect to the reference for the different imaging modalities (white voxels: correctly assigned, black voxels: wrongly assigned). Calibration phantom (top row and bottom left); validation phantom (bottom middle and right panels).

with both methods, as well as the difference between them are found in Supplementary Data 3.8.C.

Figure 3.5. Top row: SPR computed with the direct-SPR method and the composition-SPR method (for 100MeV protons). Middle row: difference between direct-SPR and composition-SPR methods. Bottom row: difference between composition-SPR and reference.

As explained in section 2.5, materials in Geant4 were created with a density binning of 0.001 g/cm^3 and with one I per material, for the reference phantoms and SECT images), and with one I per voxel with a binning of 0.5 eV for the DECT images. Table 3.6 presents the number of materials created for each modality and phantom.

Table 3.6. Number of materials created by Geant4 for the different scanners and geometries.

	RMI 647	062M	HN Patient
Twin-beam	15954	-	-
Dual-source	9319	-	-
Dual-spiral	13163	14905	18354
SECT	1259	1268	399

3.3.3 Differences in R80 for both phantoms

Figure 3.6 shows the R80 profiles for the reference and DECT and SECT segmented images for the calibration phantom (beams 1-5) and for the validation phantom (beams 6-11).

Figure 3.7 shows the mean of the absolute R80 errors for the 11 beams and the different imaging modalities. For the three DECT scanners and the calibration phantom, the twin-beam showed errors between (1.1-2.2) mm, whereas the dual-source and the dual-spiral scanners showed comparable values under 0.8 mm, except for beam 1, which has a larger mean error (1.2 mm). Dual-spiral DECT based simulations showed errors under 0.8 mm for all beams impinging on the validation phantom and of 1.1 mm for the calibration phantom. The SECT method had errors between 0.1 and 2.2 mm for the 11 beams.

3.3.4 Differences in proton range between SECT and DECT imaging for the patient case

Figure 3.8 shows the dose from the DECT-MC based-plan for a representative slice and the differences between the dose distribution of the same plan based on DECT and SECT images, and R80 profiles for the single field for the head-and-neck patient case. Figure 3.9 presents 2D maps in the beam-eye-view (BEV) of the range distributions from the DECT and SECT calculations and the absolute differences in R80 between both plans, with a mean R80 variation of $-1.2 \pm 1.2 \text{ mm}$ (equivalent to $-0.5 \pm 0.5 \%$).

3.4 Discussion

To decrease the normal tissue complication probability (NTCP) of a proton treatment plan, it is essential to minimize margins by decreasing range uncertainties.

The DECT material assignment method shows distinct differences between the twin-beam and the dual- spiral/dual-source modalities. In the twin-beam material maps, there was a systematic misassignment of the five different soft tissues (AP6-Adipose, BR12-Breast, Solid Water, SR2-Brain and LV1 Liver) for the calibration phantom, due to the very close ρ values (Figure 3.4). The main cause for this is the lack of spectral separation between the low and high voltages (see [21]), which results in noisy Z_{eff} images and, consequently, the misassignment of the soft tissue mimicking media. Overall, the edges of the phantoms are misassigned, but this is expected, since the reconstruction algorithms have difficulties with sharp-edges, resulting in a gradient in HU.

Figure 3.6. R80 profiles for the calibration (beams 1-5) and validation phantom (beams 6-11). R80 calculated from the reference phantom are plotted in black. The x -axis runs along the width of the beams, perpendicular to the beam direction, excluding the edges due to sensitive range mixing effects.

The dual-source material assignment exhibited only 10% of incorrect materials for the calibration phantom, which is mainly due to a ring of misassigned materials around the phantom's edge. This ring is visible only for the dual-source scanner, which may be caused by its smaller FOV. This effect is not observed in any of the dual-spiral material-

Figure 3.7. Mean of the absolute R80 errors in mm (y-axis) and in % (labels) for the calibration (beams 1-5) and the validation (beams 6-11) phantoms.

maps, which yielded over 86% correct material assignment. Tissue assignment has a direct impact on all dose calculation composition-based engines, since SP are calculated based on the material and the ρ of each voxel where a particle crosses. As expected, the material assignment method performed better for the DECT than for the SECT procedure (Figure 3.4), SPR-maps computed directly from the DECT segmented images for all scanners were compared to the SPR-maps printed from the MC dose engine. A difference up to 0.6% is found between both methods for each insert (Figure 3.5), due to the material list created by Geant4 given a certain ρ and I binning (detailed explanation in section 3.2.5 and in Supplementary Data 3.8.C). In terms of R80 accuracy, decreasing the binning in Geant4 of ρ and I returned a difference in the order of 0.01 mm for all beams, which is negligible given the image resolution.

MC is known for its superior accuracy of dose calculations to other algorithms due to its consideration of all particle interactions and physical processes and it has been proposed for clinical practice in particle therapy (*e.g.* [33]). The MC framework presented enables the use of fully segmented DECT images. DECT has the potential to predict more accurately the tissues ρ_e and perform tissue segmentation in the 2D $[\rho_e, Z_{\text{eff}}]$ -space. In addition, DECT has also the potential advantage of extracting the medium I_{values} from Z_{eff} images [16]. In this work, the extracted DECT I_{values} per voxel are implemented in Geant4 to be used in the geometry creation and in the proton dose calculation. This step was carefully done to ensure that the stopping powers which were calculated for proton transport in Geant4 were equivalent to those obtained from the direct-SPR methods originally published. This is crucial to ensure equivalent range when switching from PBA to MC dose algorithms. With respect to the I , the optimal I binning was found (0.5 eV), since this new segmentation process dramatically increases the number of materials

Figure 3.8. Top row: dose distribution of the uni-directional proton beam based on the DECT (dual-spiral) image. The PTV is outlined with a green contour. Top-left: absolute dose distribution. Top-right: differences between DECT- and SECT- (stoichiometric)-based plans (zoomed-in, as indicated by the white box on the left plot). Bottom plot: R80 profiles for a representative slice.

created (Table 3.6) and consequently the memory use.

The differences in R80 for the three investigated DECT modalities showed that the twin-beam had an inferior accuracy than the dual-source and dual-spiral CT, as expected from the noisy Z_{eff} images, which impacted on the calculation of the I . In Figure 3.6 (beams 1-5) it is possible to observe a good agreement between the dual-spiral and dual-source R80 profiles, while the twin-beam systematically results in deeper penetrating beams.

Looking at the overall effect, for all five beams used (beams 1-5 in Figure 3.7), the dual-source has the lowest errors, which is expected and directly related to its wider spectral separation and lower residuals in both the Saito [19] ρ_e and the Landry *et al.* [20] Z_{eff} fits. Nevertheless, the dual-spiral performs almost as well as the dual-source, with the advantage of scanning with a wider FOV for a rigid anatomy. For this reason, the dual-spiral performance was further evaluated in a validation phantom.

Figure 3.9. BEV 2D map R80 distribution for DECT (left) and SECT(middle) plans. Right plot: BEV 2D map of the absolute R80 differences between DECT and SECT.

For the validation set and in terms of the mean R80 error (Figure 3.7), the dual-spiral consistently showed an accuracy under 0.8 mm, confirming the results obtained with the calibration phantoms. Beam profiles (Figure 3.6) for the beams 6, 9 and 11 showed a very good agreement with the reference, although the other 3 beams are also within a 1 mm difference. SECT shows a wider range of result, with a 0.1 mm accuracy for beam 8 and rising to 1.7 mm in beam 9. Previously to this work, Wohlfahrt *et al.* [34] reported range differences bellow 1 mm for two DECT direct-SPR methods using PBA in an anthropomorphic phantom. Since the use of MC in proton therapy is generally acknowledged to be necessary for proper modelling of the impact of lateral heterogeneities, not range in homogeneous media, we expected that similar range accuracy with DECT/MC would be achieved as with DECT/PBA.

The patient study presented here aims at illustrating the differences in proton range and dose when using two distinct imaging modalities for the same patient and a PBS plan optimized based on MC dose calculations. In section 3.2.6 the PBA based plan was not strictly necessary to obtain the final MC treatment plan. This step was performed to make sure the initial beam arrangements led to a viable PBA plan before committing computer resources to calculate the dose distribution of each pencil beam with MC. Figure 3.8 gives the dose difference and the difference in R80 in a CT slice. For the whole plan, the dose distribution re-calculated on SECT constantly showed an overshooting with respect to DECT (dual spiral), expressed by the (mostly) negative differences shown in Figure 3.9 (right plot) with a mean deviation of -1.2 ± 1.2 mm. This value using DECT/MC agrees with previously published results using DECT/PBA plans with a cohort of patients: Wohlfahrt *et al.* [14] reported a mean water-equivalent range shift of -1.1 mm between a SECT and DECT dual-spiral plans, and Hudobivnik *et al.* [13] found mean differences of -1.7 mm between SECT and DECT dual-source plans, also for a head case.

Although no conclusion can be drawn on the accuracy of each method in the patient geometry (contrary to the phantoms), range differences shown in Figure 3.8 are clinically relevant and they support the aim of this work, showing that further research is needed to decrease the range uncertainty and, consequently, decrease the conservative margin recipes used in proton therapy.

With respect to the three DECT modalities, the dual-source scanner's limited FOV is a constraint for radiotherapy, while the twin-beam scanner seems to yield similar results to the conventional SECT scanner. The dual-spiral scanner with its good spectral separation (although with no additional filtration in the high energies) and a wide FOV, seems to be the recommended DECT modality for radiotherapy if a proper image registration between the two images is performed. It is likely that the dual-spiral approach will be sufficient for cases located in sufficiently rigid anatomy, such as brain, and head and neck cases.

3.5 Conclusion

In this work, a clear framework for the input of DECT images in MC was implemented for accurate range calculation, including I per voxel or per material and consistent with direct-SPR. Furthermore, this study tested the performance of different DECT modalities using the same methodology in terms of tissue segmentation and proton range (R80), which were compared with two phantoms with known compositions. Complementary, a comparison with SECT is given. Between the three DECT scanners, the twin-beam typically showed less accuracy compared to the dual-spiral and dual-source modalities, which yielded very similar results. The improved DECT tissue segmentation, which comes directly from the quality of the DECT information, has a direct impact on the R80 accuracy, since the tissue composition and ρ are crucial for the protons energy loss calculation and errors will accumulate until the beam distal fall-off. Moreover, a patient case was tested and DECT and SECT dose distributions yielded clinical relevant differences in range.

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3.8 Supplementary data

3.8.A Measured CT# per insert

Table S3.7. Mean value of CT# per insert for the DECT and SECT scans. The inserts ID match the ones in table Table 3.2

ID	Twin-beam		Dual-spiral		Dual-source		SECT
	120 kVp/Au	120 kVp/Sn	80 kVp	140 kVp	90 kVp	150 kVp/Sn	
1	2	6	13	5	14	2	4
2	-707	-695	-684	-696	-700	-701	-692
3	5	5	6	-2	15	4	4
4	77	77	76	70	82	70	70
5	3	4	37	31	44	32	4
6	802	692	1064	753	1115	641	831
7	219	186	305	200	312	163	224
8	1237	1058	1679	1158	1710	961	1278
9	-541	-534	-509	-523	-522	-526	-518
10	32	37	1	26	12	37	20
11	-79	-70	-105	-83	-98	-74	-87
12	209	169	292	186	299	155	213
13	14	7	7	1	5	-4	4
14	465	395	569	419	604	359	459
15	6	2	-7	-3	5	1	-3
16	-35	-35	-53	-44	-46	-39	-45

3.8.B B. Material maps from the RMI 467 and the 062M phantoms

Figure S3.1. Reference material maps using all the assigned media available for each phantom. The water insert from the RMI 467 phantom was assigned as solid water, due to very close values of density.

3.8.C C. Direct-SPR versus composition-SPR

MC dose calculations use the values of ρ , composition and I in each voxel to calculate the SPR. Once the material, density and I images are given to the MC dose engine, it will create a new set of list materials which combines all voxels in a certain interval of ρ and I (explained in section 3.2.5). Figure S3.2 shows the following data for the dual-source scanner: the ρ , I and SPR calculated directly from the DECT method and the same values

printed out by the MC dose engine. Using a $\Delta\rho = 0.001 \text{ g/cm}^3$ and $\Delta I = 0.75 \text{ eV}$, the MC engines computes the SPR within 0.6% from the direct-SPR method.

Figure S3.2. Dual-source values of density, I and SPR per insert computed directly from the DECT method ("direct") and printed out by the MC dose engine ("composition"). Bottom plots: difference between the composition and the direct values for each quantity.

Figure S3.3 shows the difference between the two methods after varying the $\Delta\rho$ and ΔI independently. In both cases, the difference between both methods changes in the sub-percent level. To achieve a higher accuracy, one would have to use very low values of $\Delta\rho$ and ΔI which would lead to computer memory issues and increased simulation time. With respect to R80 accuracy, decreasing the uncertainty in ρ and I lead to changes of the order of 10^{-2} mm , which is lost in the image resolution.

The SPR-maps from both methods (direct-SPR and composition-SPR) for each scanner are shown in Figure S3.4 with the respective difference-map.

Figure S3.3. Differences between the direct-SPR *versus* composition-SPR for different ΔI and $\Delta\rho$. Left plot: $\Delta\rho$ was kept at 0.001 g/cm^3 and ΔI varied, as indicated in the legend. Right plot: two values of $\Delta\rho$ were used with a ΔI of 1 eV . Note that, the orange squares represent the same data in both plots ($\Delta\rho = 0.001 \text{ g/cm}^3$ and $\Delta I = 1 \text{ eV}$)

Figure S3.4. SPR-maps from the direct method (top row) and composition method (middle row) and the difference between both with respect to the composition method. Left column: Twin-beam, middle column: dual-source, right-column: dual-spiral.

**A comparison study between single- and
dual-energy CT density extraction
methods for neurological proton Monte
Carlo treatment planning**

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Abstract

Purpose: Monte Carlo proton dose calculations requires mass densities calculated from the patient CT. This work investigates the impact of different single-energy CT (SECT) and dual-energy CT (DECT) to density conversion methods in proton dose distributions for brain tumors.

Material and methods: Head CTs for four patients were acquired in SECT and DECT acquisition modes. Clinical software was used to reconstruct DirectDensityTM images and to obtain DECT based pseudo-monoenergetic images (PMI). All CT datasets were converted into ρ_e by means of different calibration methods (one method based on SECT called "CT2RED", and three methods based on DECT called "PMI2RED", "Hünemohr-15it" and "Saito-15it") using a head-sized phantom. ρ_e images were converted to mass-densities (ρ) to investigate ρ differences and one representative patient case was used to make a proton treatment plan. Using CT2RED as the clinical standard, differences in dose distributions in the target and in five organs-at-risk (OARs) were quantified.

Results: . The proton plan evaluated in the Saito-15it and Hunemohr-15it datasets showed the largest relative differences compared to initial CT2RED plan down to -6% of the prescribed dose. Compared to CT2RED, average range differences were calculated: -0.1 ± 0.3 mm for PMI2RED; -0.8 ± 0.4 mm for Hünemohr-15it, and -1.2 ± 0.4 mm for Saito-15it. In the phantom study, Saito-15it and Hünemohr-15it produced the lowest ρ_e root-mean-square error (0.7%) and DirectDensityTM the highest error (2.7%).

Conclusions: Given the wide choice of commercially available conversion methods, studies investigating the ρ_e accuracy for proton dose calculations are necessary. However, there is still a gap between performing accuracy studies in reference ρ_e phantoms and applying these methods in human CT images. For this treatment case, the PMI2RED method was equivalent to the conventional CT2RED method in terms of dose distribution, CTV coverage and OAR sparing, whereas Hünemohr-15it and Saito-15it presented the largest differences.

4.1 Introduction

In a conventional radiotherapy workflow, single-energy computed tomography (SECT) images are used to perform dose distribution calculations for treatment planning due to their capability of identifying tissue attenuation characteristics. In the treatment planning procedure, sufficient tumor coverage and healthy tissue sparing are desired. The more advanced photon therapies and proton therapy can lead to conformal tumor dose distributions, allowing optimal sparing of organs-at-risk (OARs) [1–3]. With increasing conformity of tumor dose, the accuracy of the dose calculation algorithm and its input from CT imaging becomes more critical. In this study, we will focus on the accuracy of proton dose calculations based on various information extraction methods from CT images.

In a treatment planning system (TPS) for proton radiotherapy the dose calculation engine requests material properties from the patient CT scan, such as stopping power ratios (SPR) or mass densities (ρ), depending on the type of dose calculation algorithm. Most proton centers today base their treatment plan on ρ extracted from SECT images, although it has been suggested in the literature that dual-energy CT (DECT) can lead to more accurate proton range prediction [4–8].

In proton radiotherapy, various methods are available to convert SECT and DECT images into relative electron densities (ρ_e), which can be linearly converted into ρ [9]. In this study, the ρ_e accuracy of the five conversion methods were evaluated in a phantom study with known material properties. Additionally, two SECT based and three DECT of these ρ_e conversion methods were studied in brain CT scans of four patients. For one proton treatment plan, differences in dose distribution, particularly target coverage and sparing of OARs, were quantified.

4.2 Materials and methods

4.2.1 Phantom study and CT protocols

Two certified ρ_e phantoms (PMMA and 062M) were scanned with a SOMATOM Confidence[®] RT pro 64-slice CT scanner (Siemens Healthineers, Forchheim, Germany) in SECT acquisition mode at 120 kVp and dual-spiral DECT acquisition mode at 80 and 140 kVp. All phantom scans were reconstructed with sinogram affirmed iterative reconstruction (SAFIRE, Siemens terminology) whereby the beam hardening correction for bone was enabled (Q34 kernel, strength 3). The SECT scan was also reconstructed with the commercially available iterative DirectDensity[™] (Siemens Healthineers) reconstruction algorithm (F30 kernel, strength 3) [10]. For all acquisitions, the X-ray tube current (mAs) was manually set to have a constant CT dose index (32 cm) of approximately 30 mGy. Compared to the clinical scanning protocols, a higher CT dose index was chosen to limit noise influences in the phantom study. Instead of a 16 cm CT dose index, the 32 cm dose index was reported because the shoulders were also imaged according to our clinical neurological scan protocol. In the manufacturer's neurological scan protocol (16 cm), the patient's shoulders exceed the limited field-of-view.

The first phantom was a head-size home-made PMMA cylinder (diameter = 15.0 cm, length = 28.0 cm) consisting of one central hole (diameter = 2.8 cm) drilled through the entire cylinder length to fit four RMI 467 tissue characterization inserts (Gammex Inc.,

Middleton, WI) simultaneously. Different insert combinations were inserted in the PMMA phantom so that a total of 14 tissue mimicking inserts were scanned. The second phantom was the central bulk and the inserts of the 062M phantom (CIRS Inc., Norfolk, VA). The mean CT_{HU} numbers of each insert from both phantoms were computed in a cylindrical region-of-interest. The PMMA phantom was used for the calibration of four ρ_e conversion methods, and the validation of DirectDensity™, whereas the 062M phantom was used for the validation of all five conversion methods.

4.2.2 ρ_e conversion methods

4.2.3 Single-energy CT

This paper examines two SECT methods to convert CT_{HU} numbers to R, where the symbol CT_{HU} was used to denote CT numbers in Hounsfield Units (HU). In the first conversion method, the cylindrical PMMA phantom was used to obtain the energy dependent CT_{HU} number to R conversion curve for the 120 kVp acquisition (called "CT2RED" onwards). The CT to R conversion curve was then applied to the 062M validation phantom.

In the second conversion method, the 120 kVp acquisition of both phantoms was reconstructed by DirectDensity™, which should be independent of the X-ray tube potential and reconstructs directly into CT_{RED} numbers. CT_{RED} denotes CT numbers in units that are linearly scalable to ρ_e using a fixed linear relationship: $\rho_e = CT_{RED}/1000 + 1$ [10]. No additional ρ_e calibration procedure was required and therefore, the ρ_e values of both phantoms were used for validation of this method.

4.2.4 Dual-energy CT

This paper examines three DECT based CT_{HU} number to ρ_e conversion or extraction methods. In the first method, Saito's methodology [11] was used to convert the DECT images into ρ_e . This method uses a linear fit procedure between a weighted subtraction of the 80 and 140 kVp CT images to obtain scanner and protocol specific fit parameters a , b and α ,

$$\rho_e = a \cdot \frac{(1 + \alpha)CT_{HU}^{high} - \alpha CT_{HU}^{low}}{1000} + b \quad (4.1)$$

The mean 80 and 140 kVp CT_{HU} numbers of the PMMA phantom inserts (CT_{HU}^{low} and CT_{HU}^{high} respectively), computed in cylindrical regions-of-interest, were used in the calibration procedure. As validation, the CT_{HU}^{low} and CT_{HU}^{high} of the 062M validation phantom were combined according to Eq. 4.1. Furthermore, a denoising algorithm was applied in the resulting ρ_e images, which consisted of an edge-preserving curvature flow image filter (time step = 0.05, iterations = 15) implemented in the Insight Segmentation and Registration Toolkit (ITK) [12].

In the second DECT based extraction method, Hünemohr's methodology [4] was used to calculate the ρ_e image: "Hünemohr-15it", which starts from the same equation as Saito [13–15], performing a weighted subtraction of the 80 and 140 kVp CT images, but bases its calibration on one single fit parameter (c_e) according to equation Eq. 4.2. This is the method implemented in *syngo.via*'s RHO/Z package (Siemens Healthineers, Forchheim,

Germany) and was therefore added to this study as the best-case scenario possible to achieve with *syngo.via* as a clinical approved software. Our denoising and calibration procedures were also applied to "Hünemohr-15it" (Supplementary Data 4.7.A).

$$\rho_e = c_e \cdot \left(\frac{CT_{HU}^{high}}{1000} + 1 \right) + (1 - c_e) \cdot \left(\frac{CT_{HU}^{low}}{1000} + 1 \right) \quad (4.2)$$

The third and last DECT based ρ_e extraction method used a pseudo mono-energetic CT_{HU} number to ρ_e conversion curve. Here the pseudo mono-energetic image (PMI) was calculated by *syngo.via*'s (VB30_HF01) monoenergetic plus algorithm: "PMI2RED" onwards [16]. Following Wohlfahrt *et al.* [5], the PMI was reconstructed at 79 keV. The calibration procedure used to obtain the CT2RED conversion curve was also applicable to obtain the PMI2RED conversion curve. In Figure 4.1 the entire workflow of the phantom study is summarized.

Figure 4.1. Study workflow.

4.2.5 Brain tumor CT

A mass-density comparison was performed for all patients and one patient dataset was used to perform proton dose calculations on the mass-density datasets. A detailed explanation is given in the following sub-sections (Figure 4.1).

4.2.6 CT protocol and post-processing

To evaluate ρ differences between the different ρ_e conversion methods, brain CTs of four patients were acquired with a contrast-enhanced SECT imaging protocol and a dual-spiral 80 and 140 kVp DECT imaging protocol using the SOMATOM Confidence[®] RT pro CT scanner. After the contrast medium injection (iodine), a latency time of 5 minutes was considered before starting the SECT scan, after that the DECT scan was directly acquired (< 1 minute). The impact of the contrast medium was investigated for one of the patients

and was found to be negligible in this application (Supplementary Data 4.7.B). All scans were acquired with a constant CT dose index (32 cm) of 20 mGy and reconstructed with a voxel dimension of $0.64 \times 0.64 \times 1.00 \text{ mm}^3$.

The SECT acquisitions were reconstructed with the SAFIRE technique whereby the beam hardening correction for bone was enabled (Q34 kernel, strength 3). Reconstruction of the SECT acquisitions with the iterative DirectDensity™ algorithm (F30 kernel, strength 3) was performed for one representative patient, since this algorithm is not recommended for proton therapy (private correspondence with Siemens Healthineers). The DECT acquisitions were reconstructed with the Q34 kernel (strength 3). The DECT reconstructions were registered using deformable image registration software (Elastix) [17], and post-processed to calculate the ρ_e images based on Saito's and Hünemohr's method. Additionally, *syngo.via*'s DECT software package was used to calculate the PMIs at 79 keV.

A proton treatment was planned for one of the four brain CTs and prior to the planning stage, the five ρ_e images were converted to ρ by using a linear fit relationship (maximum fit error < 1%) based on human tissues and recommended in TG186 [9]: $\rho = -0.1746 + 1.176\rho_e$ ($r^2 = 0.99992$). Between the CT acquisitions, the anatomy of the patient can change due to motion, therefore all ρ images originating from the DECT conversion methods were elastically deformed to the ρ image originating from the SECT 120 kVp scan. Finally, the same values of ρ for the voxels outside the body structure were assigned in all sets to assure that the differences found in the treatment plan were caused only by the ρ values of the patient geometry.

4.2.7 Proton treatment planning

The Clinical Target Volume (CTV) corresponding to a brain tumor (craniopharyngioma), as well as the OARs were delineated by a radiation oncologist in the conventional 120 kVp SECT scan. A pencil beam scanning treatment plan was made in RayStation v8A Monte Carlo (RaySearch Laboratories AB, Stockholm, Sweden) using the CT2RED ρ -image. Three coplanar fields (one posterior and two lateral) were aimed at the CTV with a prescription dose of 54 Gy (RBE) in 30 fractions (Figure 4.2). The beam angles (80°, 180°, 290°) were chosen to avoid crossing the right and left hippocampi, which have a low dose tolerance ($D_{40\%} \leq 7.3 \text{ Gy}$) [18]. The optical chiasm with a tolerance of $D_{0.03\text{cc}} \leq 55 \text{ Gy}$ is located at the distal edge of the posterior beam [18].

After using the optimization tool box and the Monte Carlo dose engine to compute the final dose with 0.5% uncertainty in the CT2RED ρ image, the final plan was recalculated, without performing a new optimization, in the other four sets of images (DirectDensity™, PMI2RED, Hünemohr-15it and Saito-15it) and relative differences between the CT2RED and the other dose distributions were assessed. Furthermore, dose volume histograms (DVH) for the CTV and selected OARs (optical chiasm, brainstem, hippocampi and pituitary gland) were analyzed. Finally, a plan with a single posterior beam was made with the purpose of quantifying differences in proton range (defined as the 80% distal fall-off) between the different methods.

Figure 4.2. Proton treatment plan and dose distribution on the CT2RED image set.

4.3 Results

4.3.1 Evaluation of relative electron density accuracy in phantoms

The relative difference between the determined ρ_e by the five conversion methods and the certified ρ_e for the PMMA and 062M phantoms is illustrated in Figure 4.3(a). In both phantoms, the largest ρ_e errors were found in the high-density bone inserts for the DirectDensityTM image reconstruction method. DirectDensityTM overestimated the ρ_e of ‘Bone 1.55’ with 3.9% and ‘Bone 1.82’ with 5.5%. The lowest root-mean-square (RMS) errors for ρ_e were found for the Saito-15it ($a = 0.999$, $b = 0.995$, $\alpha = 0.864$) and the Hünemohr-15it ($c_e = 0.873$) methods, which were below $\pm 1.0\%$. Overall, the RMS errors for the 062M inserts were 2.7% for DirectDensityTM and 1.0% for CT2RED and PMI2RED.

The standard deviations calculated in the inserts for the Saito-15it and the Hünemohr-15it methods were larger compared to the other conversion methods, although edge-preserving denoising was already applied as post-processing (Supplementary Data 4.7.A). The CT2RED and PMI2RED methods showed comparable errors; only in the middle and high-density bone inserts, the ρ_e errors were larger than 1.4% for both methods.

4.3.2 Mass-density differences in the patient geometry

Absolute ρ differences (g/cm^3) in arbitrary cranial slices between the conventional CT2RED conversion method and three other methods are depicted in Figure 4.4 for the different brain CTs. In the right column of Figure 4.4, a histogram indicates the normalized probability distribution of the absolute ρ differences in bins of 0.01 g/cm^3 between the conventional CT2RED method (as standard) and the PMI2RED, Hünemohr-15it and Saito-15it conversion methods. For each of the four brain CTs, Figure 4.5 shows the average ρ differences for all tissues (excl. air cavities), but also for the soft tissue and for bone tissue. The DirectDensityTM results for patient #1 were added in Supplementary Data 4.7.C.

With respect to CT2RED, the PMI2RED ($-0.010 \pm 0.006 \text{ g/cm}^3$), Hünemohr-15it ($-0.038 \pm 0.036 \text{ g/cm}^3$) and Saito-15it ($-0.025 \pm 0.020 \text{ g/cm}^3$) conversion methods resulted in overall higher bone densities (*i.e.* negative differences compared to CT2RED) averaged

Figure 4.3. The relative difference (%) ± 1 standard deviation for ρ_e for the five conversion methods (a). On the left of the vertical black line, the relative differences were calculated for the 062M phantom. On the right, the relative differences were calculated for the PMMA phantom with the RMI 467 tissue mimicking inserts. The measurement setup of both phantoms is illustrated in (b) and (c).

over the four brain CTs. For the same conversion methods, overall positive differences were observed for the soft tissues: $0.003 \pm 0.001 \text{ g/cm}^3$, $0.011 \pm 0.002 \text{ g/cm}^3$ and $0.018 \pm 0.01 \text{ g/cm}^3$, respectively.

4.3.3 Differences in proton dose distributions

Relative dose differences between the CT2RED and the other three conversion methods for a representative slice of the transversal plane are shown in Figure 4.6(a-c). The plan evaluated on the Saito-15it image shows the largest differences compared to the initial plan (down to -6%), followed by the Hünemohr-15it method (down to 4%) and the PMI2RED method (almost no visible differences). The DVHs resulting from each plan are depicted in Figure 4.6(d) for the CTV and five selected OARs, with the DVH of the CTV zoomed-in on Figure 4.6(e).

For the plan with one posterior beam, differences in range resulted in an average of $-0.1 \pm 0.3 \text{ mm}$ for PMI2RED; $-0.8 \pm 0.4 \text{ mm}$ for Hünemohr-15it, and $-1.2 \pm 0.4 \text{ mm}$ for Saito-15it.

4.4 Discussion

The recent availability of scanners with DECT capabilities in addition to the standard SECT mode, and different methods of converting CT_{HU} or CT_{RED} numbers to ρ_e in radiotherapy facilities raises the question of which one to use and its impact on treatment planning. This study aims to investigate the differences in dose calculation for proton treatment planning depending on which conversion method is used: CT2RED, PMI2RED, Hünemohr-15it and Saito-15it, from which the first two methods are part of commercially

Figure 4.4. Absolute ρ differences between the CT2RED method and DirectDensityTM (a), PMI2RED (b), Hünemohr-15it (c), and Saito-15it (d). (e) ρ line profile in the cranial body region. (f) mean values of absolute ρ differences (± 1 standard deviation) for all voxels and separated in soft and bone tissues.

available software.

Initially, the ρ_e accuracy was assessed in two phantoms. The 062M phantom was used as validation phantom for all methods and relative errors with respect to the reference ρ_e showed a higher discrepancy in the high-density materials (Figure 4.2). Saito-15it and Hünemohr-15it had the lowest root-mean-square (RMS) error of 0.7%, whereas DirectDensityTM showed the highest RMS error of 2.7%. This study used head-sized phantoms, but it should be noted that the DirectDensityTM algorithm is optimized and calibrated on an abdominal-sized phantom (private correspondence with Siemens

Figure 4.5. Mass-density differences ($\Delta\rho$) (± 1 standard deviation) between the conventional CT2RED conversion method and the PMI2RED, Hünemohr-15it and Saito-15it methods calculated over the entire patient geometry excluding air and dental fillings, for all tissues (left), only for bone tissues (middle) and only for soft tissues (right panel).

Healthineers).

With SECT and DECT scans from four patients, ρ_e images were created using each conversion method (Figure 4.1) and converted in ρ using the recommendation from TG186 [9]. Lacking a ground truth, the CT2RED ρ images were used as reference, since it is the standard method clinically used, and differences with the other conversion methods were assessed (Figure 4.4 and Figure 4.5).

The Hünemohr-15it method aims to reproduce the results that the *syngo.via* RHO/Z package would give, for which the proper scanner-, size- and energy-specific calibration were used. This was not the case for the *syngo.via* version installed in our institution, therefore our own implementation of the method had to be used. The use of a RHO/Z package without an optimal calibration might result in relative electron density discrepancies and dose distribution differences. The ability to specify scan-specific fit parameters in clinical software would not only be of benefit for the accuracy of the relative electron density images.

To further understand the impact of the ρ images, a proton treatment plan was created for one of the four patients and the dose distributions calculated on the different ρ images were compared. A plan, originally made and optimized in the CT2RED set, was recalculated in the other three image sets, without performing any further optimization.

Saito-15it yields high accuracy in our phantom study agreeing with previous phantom studies, but also with animal tissue studies, such as Bär [19], Möhler [20] and Taasti [21], showing higher accuracy in predicting SPR, that depends on the ρ_e of the medium, for

Figure 4.6. Top panel: dose differences between the plan calculated on the CT2RED images and the same plan evaluated on PMI2RED (a), Hünemohr-15it (b) and Saito-15it (c) datasets. Bottom panel: (d) dose volume histograms of the five evaluated methods for the CTV (solid line) and five organs-at-risk; (e) zoomed-in CTV dose volume histogram.

animal tissues using DECT-based methods than SECT. Nevertheless, the CT2RED patient image was used as reference for comparison in this work, due to its status of clinical standard. Robust planning was considered for this study, to follow the trend in clinical practice to account for set-up and range uncertainties, but it was found that a robust plan did not alter the main conclusions shown [22].

Results in Figures 6(a-c) agree with the ρ differences observed in Figures 4 and Figure 4.5. Using a thresholding technique of the ρ values, the contributions of bone and soft tissues to these dose differences were assessed and it was found that, although bone tissues show the higher absolute ρ differences between methods, it has a negligible contribution for this patient case. Dose differences found for PMI2RED can be expressed as a proton range variation in the posterior beam direction below 0.2 ± 0.4 mm, which falls within the voxel size of $1 \times 1 \times 1$ mm³ typically used in radiotherapy for head scans. The obtained mean proton range difference between CT2RED and Saito-15it (-1.1 ± 0.4 mm) agrees with the published values by Wohlfahrt *et al.* ([8]) and Hudobivnik *et al.* [6], where a comparison between SECT and DECT plans was performed for a cohort of patients with head tumours.

The optical chiasm and pituitary gland show the largest differences in DVH for the three methods, because of their location in the distal-edge of the posterior beam and their small

volume, making them more sensitive to small variations. In contrast, the brainstem and hippocampi show similar dose coverages for all methods, since these organs are not in the beam paths. To follow up on this study, a larger cohort of patients and different sites should be analysed to confirm the robustness and consistency of each method.

Given the wide choice of commercially available methods for converting SECT and DECT images to ρ_e , studies are needed to assess the accuracy of these methods, as well as its impact for proton dose calculations. However, there is still a gap between performing accuracy studies in certified ρ_e phantoms with known compositions and applying these methods in human CT images. Furthermore, full-DECT treatment planning is currently not an option in commercial TPS, where the only solution for the user is to pre-process the DECT images and use the resulting ρ (or SPR) image as input. This work quantifies the differences in ρ for four patients and quantifies differences in dose and proton range for a neurological patient between the conventional CT2RED method and three other SECT- or DECT- based conversion methods. For this treatment site, the PMI2RED method was equivalent to the conventional CT2RED method in terms of dose distribution, CTV coverage and dose to the OARs, whereas Hünemohr-15it and Saito-15it led to proton dose and range differences. Which method approximates best reality in a patient cannot be determined in this study.

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4.7 Supplementary data

4.7.A A. Impact of noise in Saito's and Hünemohr's methods

Saito's and Hünemohr's methodologies were used to convert the DECT images into ρ_e . Both methods combine the 80 and 140 kVp CT datasets according to Eq. 4.1 and Eq. 4.2 in the manuscript. To reduce the influence of noise after combining the 80 and 140 kVp CT datasets, a denoising algorithm was applied to the resulting ρ_e images, which consisted of an edge-preserving curvature flow image filter implemented in the Insight Segmentation and Registration Toolkit (ITK). The influence of the iteration number on the ρ_e accuracy was investigated for 3 different iteration numbers: 5, 10, and 15 iterations.

Figure S4.1. Relative difference (%) ± 1 standard deviation in ρ_e for two methodologies and for different iteration values of the edge-preserving curvature flow image filter in the post-processing step (0, 5, 10 and 15). Zero iterations correspond to no denoising.

After applying the edge-preserving denoising algorithm as post-processing step, the

relative differences were computed between the ρ_e from the reference and the ones obtained by the two methods (Figure S4.1). For the 062M tissue mimicking inserts, the mean value remained the same after the post-processing step, while the standard deviations reduced by 50% between Saito-0it and Saito-15it or Hünemohr-0it and Hünemohr-15it.

4.7.B B. Impact of the presence of contrast medium in the patient scans

In clinical practice, when a contrast-enhanced CT is necessary for delineation, a second scan without contrast is performed and used for planning. However, this study was part of a clinical trial where multiple CT scans were acquired from a patient; a DECT scan prior to contrast injection, a SECT scan after contrast injection and a DECT scan after contract injection. For the dose calculations presented in the paper, only the contrast enhanced SECT and DECT scans were used. The individual DECT images (80 and 140 kVp) without contrast were compared to the ones with contrast. Results of the mean differences between both images are shown in Figure S4.2, highlighting the slices through which the beams crossed. In the slices of interest, the maximum difference in mean CT number was 7 HU and 5 HU for the 80 kVp and 140 kVp, respectively.

Figure S4.2. Mean difference in CT numbers (1 and 2 standard deviations) between the image with and the image without contrast, for 80 kVp (left) and 140 kVp (right). The right top panel: sagittal plane of the patient illustrating with a red box the slices crossed by the three proton beams showed in Figure 4.2. The same slices are highlighted in both plots..

4.7.C C. DirectDensity™ results for patient #1

The CT acquisitions for patient #1 were reconstructed using DirectDensity™. The resulting ρ_e -images were converted to ρ as explained in subsection "CT protocol and post-processing". The average ρ difference (± 1 standard deviation) between the CT2RED image

and the DirectDensityTM image was $-0.005 \pm 0.023 \text{ g/cm}^3$. The dose differences for the plan calculated in the CT2RED set and recalculated with DirectDensityTM were within 1%. Figure S4.3 summarizes the results for DirectDensityTM: absolute ρ differences with respect to the CT2RED image for a representative slice, the probability histogram calculated over all slices and the resulting dose difference for the proton plan with three beams.

Figure S4.3. Left panel: Absolute mass-density differences ($\Delta \rho$) between the conventional CT2RED conversion method and the DirectDensityTM. Middle panel: Probability histogram calculated over the entire CT. Right panel: dose differences between the plan calculated on the CT2RED images and the same plan evaluated on the DirectDensityTM set.

**Monte Carlo beam model validation of a
proton pencil beam scanning system with
a dynamic collimator**

Isabel P Almeida *et al.*

5.1 Introduction

The interest in proton therapy as a treatment modality for cancer has been growing worldwide. To overcome the high cost of building a stand-alone multi-room proton therapy centre, many centers consider the solution either to integrate a proton therapy system in a fully-functional pre-existing health-care facility or to construct a single-room proton therapy centre [1]. For this purpose, several vendors have put efforts into launching compact systems with one treatment room, such as the Proteus[®] ONE (IBA, Louvain-la-Neuve, Belgium) and the ProBeam[®] (Varian Medical Systems, Inc., Palo Alto, CA, USA). Mevion Medical Systems, Inc. (Littleton, MA, USA) presented a novel solution for a compact system with the release of the MEVION S250[™] passive scattering proton therapy system with minimum footprint required, in which the world's smallest clinical synchrocyclotron for particle radiotherapy applications is mounted on a moving gantry that rotates around the patient. The Monte Carlo beam model of this machine was developed by Prusator *et al.* [2] showing a very good agreement with measured data. The same group investigated the neutron contamination of the MEVION 250[™], in which all beamline components are very close to the patient. More recently, Mevion upgraded their passive scattering system to the MEVION S250i HYPERSCAN with pencil beam scanning (PBS) and with a novel Adaptive Aperture[™] (AA) for beam collimation.

Due to the novelty of the MEVION S250i HYPERSCAN with an Adaptive Aperture[™], beam modelling with current treatment planning systems is required, hence the need of using a Monte Carlo (MC) platform to generate the beam model and to simulate numerous scenarios with and without the use of the AA component. In this work, we modelled the MEVION S250i HYPERSCAN with AA installed at the Zuid-Oost Nederland Protonen Therapie Centrum (ZON-PTC), Maastricht, and we validated the simulated data with dose measurements. The results presented in this chapter were limited due to the very recent assembling of the machine and the lack of beam time to perform all the necessary measurements.

5.2 Materials and methods

5.2.1 Clinical system description

The MEVION S250i with HYPERSCAN is a compact one-room delivery system with high-field superconducting fifteen-ton synchrocyclotron mounted on the gantry as shown in Figure 5.1a. All components in the beam path are placed in the nozzle (Figure 5.1b) and these are:

Magnetic quadrupole - dual axis scanning magnet air core iron free, which steers the beam in the x - and y -directions.

Dosimetry system - composed of six transmission ion chambers (TICs) placed between the synchrocyclotron exit and the energy modulation system. The TICs are responsible for measuring the beam spot position, shape and charge.

Energy modulation system (EMS) - composed of 18 plates made of a single Lexan block to ensure the same material properties, with optimized thicknesses and air gaps, where 162 plate-combinations provide degradation of the nominal range in water in multiples of 2.1 mm (Figure 5.2a).

Adaptive Aperture™ (AA) - two opposite banks (left/right) with dynamic non-divergent leaves made of Nickel 200 (99.6% pure) [3, 4], for beam collimation with minimal neutron production, moving as a block in the y-direction. Each side of the AA is composed of top and bottom jaws and five leaves, parallel to each other (Figure 5.2b,c). The jaws of the AA are 20.75 mm thick (y-direction, Figure 2c) and their shape minimizes leakage when both jaws (e.g. top-left and top-right) are closed. The five middle leaves have a physical thickness of 5 mm and are currently used to shape the edges of the irradiated volume (Figure 5.2b,c). The AA has a total length in the beam path (z-direction) of 10 cm, its positioning in both x- and y-directions has a 0.5 mm resolution and it can move to any position (including crossing the middle axis) in the full 20 x 20 cm² treatment field.

Exit window - made of Lexan with a nominal thickness of 1.6 mm, covers the end of the nozzle (Figure 5.1b).

5.2.2 Monte Carlo beam model

This system produces a pencil beam with a proton range of 32.2 cm in water, measured as the 90% distal fall-off (R90) of the Bragg peak, according to the PSTAR data base from the National Institute of Standards and Technology (NIST) [5]. The frontal part of the nozzle includes the EMS, AA and exit window and can be extended towards the isocenter from 33.6 cm to 3.6 cm (called "nozzle extension" onwards and defined as the distance from the down-stream end of the exit window to the isocenter). The magnetic quadrupole and dosimetry system are placed in a fixed position with respect to the beam exit of the synchrocyclotron. Another characteristic of this system is the mechanical EMS, which produces shifted Bragg peaks with equal widths for the whole energy range, in contrast to other energy selection systems that use a percentage of the energy to define an energy selection window, causing the Bragg peak width to increase for higher energies [6]. The measured virtual source to axis distance (SAD) to the isocenter for this system is 182.1 cm.

5.2.2.1 Modelling of beamline components

The beam model was made using the MC platform TOolkit for PArticle Simulation (TOPAS) based on the Geant4 Monte Carlo code and libraries [7]. The default physics list 'QGSP_BERT_HP' validated for proton therapy applications [8] was used throughout this work, with all particle transport cut-offs set at 0.5 mm. TOPAS has also been validated for PBS by Lin *et al.* [9].

The dosimetry system was modelled only in terms of the water equivalent thicknesses (WETs), taken from the technical specifications of each TIC, and positioning each in the beam line according to the Mevion blueprints (purple rectangles in Figure 5.3a).

The EMS plates were modelled with Lexan (atomic composition: weight percentages 5.5491% hydrogen, 75.5751% carbon and 18.8758% oxygen, and a mean excitation energy of 73.1 eV) and with plate-specific densities ranging from 1.159 g/cm³ and 1.205 g/cm³. The physical thicknesses and airgaps between the EMS plates were taken from the blueprints provided by Mevion (Figure 5.2a).

The exit window is also modelled with the same material Lexan, a physical thickness of 1.6 mm and a density of 1.2 g/cm³.

Figure 5.1. (a) Sketch of the complete system, with all components mounted on the gantry, that rotates from -5 to 185 degrees around the isocenter in the gantry plane with a 0.1 degree accuracy. (b) Inner gantry with the modelled extendable part of the nozzle containing the energy modulation system (EMS), the Adaptive ApertureTM and the exit window.

Each component of the AA was independently modelled according to detailed blueprints from Mevion and using pure Nickel with a mean excitation energy of 331 eV [10]. The AA

Figure 5.2. (a) Lateral view of the EMS with all plates (numbered from 1 to 18) retracted from the beam path, with the right (blue) side in beam's-eye-view (BEV) of the Adaptive Aperture™ (AA) visible on the right. (b-c) Diagonal and frontal view of the AA, which moves as one block in the y -direction, but each leaf and jaw can have a different position in the x -direction. Note: the red and blue colours of the AA are merely for illustration purposes and to indicate the left and right side in the BEV.

is positioned according to the center of the middle leaf and all the other leaves and jaws move as a block with respect to this position, meaning that the left and right sides have always the same y -coordinate.

5.2.2.2 Proton source modelling

A particle beam can be characterized in terms of its transverse emittance (ϵ), which is defined as the area of an ellipse on the (x, θ_x) -space (Figure 5.3a) [11, 12]. The beam of a PBS system is designed and tuned to have the smallest spot size at the isocenter (called the beam "waist"). However, interactions with air in the beam path need to be considered since they change its shape in terms of spatial and angular distribution. The generalized Fermi-Eyges theory describes the Gaussian angular-spatial distribution of a pencil beam by means of three parameters A_0 , A_1 and A_2 , called moments of distribution [13]. The angular-spatial distribution (ASD_x)¹ represents the Eyges solution to Fermi's diffusion equation as function of depth z ,

¹The theory is described for the xz -plane, however the same methodology is followed for the yz -plane.

$$\text{ASD}_x(x, \theta, z) = \frac{1}{\pi \sqrt{A_0(z)A_2(z) - A_1^2(z)}} \exp \left(-\frac{A_0(z)x^2 - 2A_1(z)x\theta_x + A_2(z)\theta_x^2}{A_0(z)A_2(z) - A_1^2(z)} \right) \quad (5.1)$$

where the angular (θ_x) and spatial (x) distribution of protons within a spot are projected onto the xz -plane at a given longitudinal position z (Figure 5.3b). The integral of ASD_x over the angle θ_x delivers the Gaussian spatial distribution of the particles at depth z . The $A_1(z)$ is the covariance and it describes the correlation between particle's transverse position and direction,

$$A_1(z) = 2 \text{Cov}(x, \theta, z) \quad (5.2)$$

the $A_0(z)$ and $A_2(z)$ are the double angular and spatial variance, respectively, from which the angular (σ_x) and spatial spread (σ_θ) can be extracted [14, 15]:

$$A_0(z) = 2\sigma_\theta(z)^2 \quad (5.3)$$

$$A_2(z) = 2\sigma_x(z)^2 \quad (5.4)$$

where σ_x is used to describe the beam size (or *spot size*). With the assumption that protons suffer low multiple Coulomb scattering in air, the propagation between the system's virtual source position and the isocenter can be expressed as it would in vacuum, with

$$A_2(z) = A_0(0)z^2 + 2A_1(0)z + A_2(0) \quad (5.5)$$

where A_0 , A_1 and A_2 represent the initial moments of the angular-spatial distribution. Experimentally, these coefficients can be determined by measuring $A_2(z)$ in at least three different z positions. These values are typically measured with high resolution *beam monitor profiles* that sample the beam laterally in x and y , integrating over the longitudinal direction, and from these, the spot size (σ_x) can be extracted from the σ -parameter of a single Gaussian

$$y = a \cdot \exp \left(\frac{x-b}{\sigma_x} \right) \quad (5.6)$$

Notably, an isoline given by Eq. 5.1 is an ellipse in the (x, θ_x) -space and the beam emittance ε is defined as the area of this ellipse, which stays constant and obeys the conservation law of the phase-space (Liouville's theorem). ε can be calculated from the moments of distribution

$$\varepsilon = \frac{\pi}{2} \sqrt{A_0(z)A_2(z) - A_1^2(z)} \quad (5.7)$$

Finally, the beam emittance parameters to be input in the TOPAS MC model are $\sigma_x = \sqrt{A_2(0)/2}$, $\sigma'_x = \sqrt{A_0(0)/2}$ and $\text{correlation}_x = A_1(0)/(\sigma_x \cdot \sigma'_x)$ for a type source

"emittance". The correlation parameter indicates if a beam is diverging (< 0), converging (> 0) or if the beam has a minimum or maximum ($= 0$). This procedure was followed to obtain the σ_x , σ'_x and correlation_x and for the xz -planes and the analogue for yz -planes.

Figure 5.3. (a) Ellipse parameters used to define the angular and spatial distribution in the (x, θ_x) -space. (b) Diagram illustrating the xz - and yz -planes used to define the beam source and the different positions in z with respect to the virtual source position. (c) Diagram of the beam model with the positions of the beam monitor profiles used for the spot measurements and simulations (blue rectangles) at -31.1 , -20 , -10 , 0 , $+10$ and $+20$ cm in the z -direction with respect to the isocenter. In white: the range modulation system, in blue and red: the Adaptive Aperture™, and in purple: transmission ion chambers

5.2.3 Measurements without the Adaptive Aperture™

To define the beam emittance parameters (Eq. 5.5), single static beam spots in air at maximum energy, *i.e.* no EMS plates are placed in the beam path, aimed at the isocenter were measured at six positions in the axial direction: -31.1 cm (the most upstream position possible), -20 cm, -10 cm, 0 cm (isocenter), $+10$ cm and $+20$ cm using both the Lynx® detector (IBA, Louvain-la-Neuve, Belgium) consisting of a scintillation screen of gadolinium-based plastic coupled with a CCD camera for high precision relative dosimetry, and EBT3 radiochromic film orthogonal to the beam, represented by the blue rectangles in Figure 5.3c. The gantry was placed at 90 degrees (horizontal beam), with a nozzle extension of 33.6 cm and 80 monitor pulses were used for each spot measurement, with a charge of 4 pC per pulse, corresponding to a total of 2×10^9 primary protons. To validate the emittance parameters extracted from the measurements, the detector was simulated as a water slab with $300 \times 300 \times 20$ mm³, and bin size of $5 \times 5 \times 20$ mm³, placed

at the same six positions as the measurements, scoring dose to water in medium (as for all other simulations performed in this work), and 2×10^6 primary protons were simulated to ensure a statistical uncertainty of the dose value of less than 1%.

With the same set-up as described in the previous paragraph, but with the detector fixed at the isocenter and a nozzle extension of 10 cm, 2D dose profiles for single beam spots for fifteen selected energies (Table 5.1) were measured and compared to simulations in terms of spot size, defined as the σ -parameter of the single Gaussian fit. The σ -parameter was extracted for the x - and y -directions.

Table 5.1. List of fifteen selected energies and the EMS plate combination (1 = placed in the beam path, 0 = retracted, *e.g.* for the nominal energy, all plates are retracted). The plate numbers are indicated in Figure 5.2a.

Energy (MeV)	Plate number																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
227	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
217.8	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
208.1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
198.1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
187.8	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
177	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
165.7	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	0
153.9	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	1
141.3	1	1	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0
127.8	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	1	1
113.1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	0
96.8	1	1	0	1	1	1	1	1	1	1	1	1	0	0	0	0	0	1
78.2	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0
55.6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1
45.4	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1

Integrated depth dose (IDD) profiles for the fifteen energies were measured also with the MP3-PL Therapy Beam Analyzer T41050 system (PTW-Freiburg), which is a perspex tank with a moving system for recording dose distributions, and PTW Bragg peak chamber 34070 (PTW-Freiburg), with 0.3 mm steps in the Bragg peak region and 5 mm in the plateau region, and a nozzle extension of 16 cm (Figure 5.4a). A water cylinder with the same radius of the PTW Bragg peak chamber 34070 (4.08 cm) and 34.8 cm length was simulated in TOPAS (Figure 5.4b), using a 0.25 mm scoring bin and 2×10^7 primary protons (statistical uncertainty $< 0.1\%$). The final curves were compared in terms of the R90, R80 and the Bragg peak width defined as the distance between the 80% proximal to the 80% distal fall-off (R_{80-80}).

At maximum energy, a $10 \times 10 \text{ cm}^2$ field with equidistant spots (Figure 5.5a) was measured in air at the isocenter, without the exit window of the nozzle and with the gantry at 90 degrees, and a charge per spot equivalent to 2.5×10^9 protons. Measurements were performed with the Lynx detector and this was modelled as previously described. Simulations with 4.55×10^5 primary protons per spot were used to ensure a statistical uncertainty $< 0.32\%$. The dose profiles were normalized to the average value of a central region of $7.5 \times 7.5 \text{ cm}^2$ and the lateral penumbra (LP), the lateral flatness (LF) and the lateral symmetry (LS) of were used to evaluate both fields. The LP, LF and LS are measured

Figure 5.4. Longitudinal profile measurement (left) and simulation (right) set-up for the maximum energy case. The PTW Bragg peak chamber (green) was modelled as a cylinder inside the water tank (blue). The same set-up was repeated for the other selected energies, in which only the energy modulation system plates in the beam path change.

as

$$LP = \frac{|R80_1 - R20_1| + |R80_2 - R20_2|}{2} \quad (5.8)$$

$$LF = \frac{D_{PLmax} - D_{PLmin}}{D_{PLmax} + D_{PLmin}} \cdot 100\% \quad (5.9)$$

$$LS = \frac{D_2 - D_1}{D_2 + D_1} \cdot 100\% \quad (5.10)$$

where $R80_{1,2}$ and $R20_{1,2}$ are the location of the 80% and 20% distal fall-offs for each side (1,2) of the lateral profile, D_{LPmax} and D_{LPmin} are the maximum and minimum relative doses in the target region (red box in Figure 5.5b), and D_1 and D_2 are the integrated doses in each half of the field illustrated in Figure 5.5c.

5.2.4 Measurements with the Adaptive Aperture™

Due to lack of beam time and other technical constraints of the recently assembled ZON-PTC system, the AA experiments described in this section and the corresponding results were performed at the Mevion factory (Littleton, MA, USA) and the simulations were done with the specific parameters of that machine (*e.g.* energy and energy spread, emittance parameterization, EMS plate thicknesses).

A 3D treatment plan to deliver 2 Gy to a spherical target of 1000 cc (called "1l-sphere" onwards) was developed and the dose to water was measured with the OCTAVIUS®

Figure 5.5. (a) Spot map of the $10 \times 10 \text{ cm}^2$ single plane fields, composed of 1681 spots with 2.5 mm spacing, the red lines illustrate the x- and y-profiles used in the analysis. (b) Definition of lateral penumbra (Eq. 5.8) and target width used to calculate the lateral flatness (Eq. 5.9). (c) Illustration of the D_1 and D_2 integrated doses of each half of the field size (Eq. 5.10).

1500XDR two-dimensional detector (PTW-Freiburg) consisting of 1405 vented ionization chambers uniformly placed in a $27 \text{ cm} \times 27 \text{ cm}$ matrix with a 7.1 mm spacing between centers, inserted in an OCTAVIUS® 4D phantom (PTW-Freiburg) with the detector positioned at the isocenter, orthogonal to the beam path and using the AA to decrease the lateral penumbra (Figure 5.6). Additionally, the same plan was measured with the AA retracted. The plan was composed of thirteen energy layers, ranging from 135.7 MeV to 183.9 MeV.

5.3 Results

5.3.1 Source emittance parameterization

Figure 5.7 shows the spatial variance ($A_2(z)$) of the measured spots calculated with Eq. 5.4 for different positions in z . The dashed and solid lines show the resulting fits from equation 5, with fit parameters $A_0(0)$, $A_1(0)$ and $A_2(0)$ presented in Table 5.2. To validate the emittance parameterization, simulations were performed with the same set-up as the measurements and are plotted as empty markers in Figure 5.7. Table 5.3 indicates the emittance parameters used to define the source of the beam model described in this manuscript.

Figure 5.6. (a) Set-up for the 11-sphere simulation, with the OCTAVIUS® 1500XDR detector (green) inside the OCTAVIUS® 4D phantom (blue). (b) Spot map and Adaptive Aperture™ (AA) position in the beam's-eye-view for a representative energy layer of the 11-sphere, with the AA dynamically following the spot positions to trim the edges of the irradiated volume.

Figure 5.7. The A_2 parameter calculated from the σ_x (Eq. 5.4) of measured 2D transverse profiles (solid markers) at maximum energy as function of the virtual source axis distance (SDA) for both xz - and yz - planes. Empty markers show the A_2 for simulated profiles using the resulting source parameterization extracted from the fits (dashed and solid lines, Table 5.2 and Table 5.3) and scored at the same positions as the measured profiles. The location of the isocenter in terms of the beam path is indicated by the vertical dotted line.

5.3.2 Longitudinal and transverse profiles validation

The spot sizes measured and simulated in a 2D plane of a 300 x 300 mm² detector placed at the isocenter and extracted as the sigma (σ) of a single Gaussian fit are depicted in Figure 5.8 for two orthogonal profiles (x and y), as well as the difference between

Table 5.2. Fit parameters from Eq. 5.5 for both xz - and yz -planes.

	A_0 (mrad ²)	A_I (mrad mm)	A_2 (mm ²)	r^2
xz -plane	1.9×10^{-5}	-0.0013	4.90	0.997
yz -plane	2.3×10^{-5}	-0.0029	6.00	0.998

Table 5.3. Emittance source parameters extracted from the fit results from Figure 5.7.

	σ (mm)	σ' (mm)	Correlation
xz -plane	0.0031	1.57	-0.1297
yz -plane	0.0034	1.73	-0.2433

experiment and simulations. Due to a very good agreement between the EBT3 film and the Lynx detector measurements, only the results of the latter are used in this analysis. The average differences between measured and simulated spot sizes are 0.2 ± 0.2 mm and 0.3 ± 0.2 mm, for the x - and y -profiles, respectively.

Figure 5.8. Top and middle panels: Spot size (defined as the σ of a single Gaussian) as function of the proton energy for the x - and y -profile of measured (solid markers) and simulated data (open markers). Bottom panel: Difference in spot size between measurement and simulations for the x - and y -profiles, and the average differences indicated in the legend ($\pm$ standard deviation).

Experimental and simulated IDD, integrated laterally over a radius of 4.08 cm, normalized to the maximum for the fifteen energies of Table 5.1 are depicted in Figure 5.9. The source energy and energy spread of the MC model were fine-tuned, yielding the values 228.65 MeV and 0.497 MeV. Table 5.4 shows the absolute values in R90, R80 and R₈₀₋₈₀ and the respective difference between these parameters for experiment and simulation. The differences between D_{80-80}^{exp} and D_{80-80}^{sim} are within the measurement resolution of 0.3 mm for all energies, with the experimental data showing an average D_{80-80}^{exp} of 8.2 ± 0.2 mm and the simulations an average of 8.3 ± 0.2 mm. Maximum differences between $R80^{\text{exp,sim}}$ and $R90^{\text{exp,sim}}$ are 0.7 mm, yielding an average difference of 0.2 ± 0.3 mm for both R80 and R90.

Figure 5.9. Experimental and simulated integrated depth dose curves of for fifteen energies. The dose was normalized to the maximum of each curve.

5.3.3 Validation of 2D without the Adaptive Aperture™

Figure 5.10 shows the results for the 10×10 cm² field covered with 1681 spots equally spaced and with the Lynx detector positioned at the isocenter, and Table 5.5 shows the comparison in lateral penumbra (LP), lateral flatness (LF) and lateral symmetry (LS) between experiment and simulation. The x -profile (dashed line) yielded a difference in LP of 0.1 mm between experiment and simulation, while the y -profile has a difference of 0.5 mm. The experimental data presents a LF of 0.9% and a LS of 1.2% for the x -profile and 1.5% and 1% for the y -profile, while the simulation yielded a 1.7% LF for both profiles and 0.5% and 0.3% LS for the x - and y -profiles, respectively.

5.3.4 Validation of 3D fields with the Adaptive Aperture™

Figure 5.11a-d shows the measured and simulated doses (with 2% statistical uncertainty) for the 1l-sphere with and without the AA for collimation, and Figure 5.11e-h depicts two

Table 5.4. Analysis of the experimental and simulated integrated depth dose curves in terms of 90% distal fall-off (R90), 80% distal fall-off (R80) and Bragg peak width (D_{80-80}) for fifteen energies. The last row indicates the averages over the fifteen energies of R90, R80, D_{80-80}^{exp} and D_{80-80}^{sim} and D_{80-80} .

Energy (MeV)	R90 ^{exp} (mm)	R90 ^{sim} (mm)	Δ R90 (mm)	R80 ^{exp} (mm)	R80 ^{sim} (mm)	Δ R80 (mm)	D_{80-80}^{exp} (mm)	D_{80-80}^{sim} (mm)	ΔD_{80-80} (mm)
227	322	322.1	-0.1	323	323.1	-0.1	8.4	8.5	-0.1
217.8	299.5	299.7	-0.2	300.4	300.6	-0.2	8.4	8.5	-0.1
208.1	276.4	276.6	-0.2	277.5	277.6	-0.1	8.3	8.6	-0.3
198.1	253.6	253.5	0.1	254.6	254.5	0.1	8.5	8.5	0
187.8	231	230.9	0.1	232	231.9	0.1	8.4	8.6	-0.2
177	208.2	208	0.2	209.1	209	0.1	8.4	8.5	-0.1
165.7	185.4	185.3	0.1	186.4	186.2	0.2	8.2	8.4	-0.2
153.9	163	162.8	0.2	163.8	163.6	0.2	8.3	8.4	-0.1
141.3	140.3	140	0.3	141.2	140.9	0.3	8.2	8.2	0
127.8	117.6	117.3	0.3	118.5	118.3	0.2	8.1	8.3	-0.2
113.1	95	94.5	0.5	95.9	95.5	0.4	8.1	8.3	-0.2
96.8	72.5	71.9	0.6	73.5	72.8	0.7	8.1	8.1	0
78.2	50	49.2	0.8	50.8	50.2	0.6	8	8.1	-0.1
55.6	27.3	26.8	0.5	28.3	27.8	0.5	7.8	8	-0.2
45.4	19.1	18.7	0.4	20.1	19.6	0.5	8	8	0
Average			0.2 ± 0.3			0.2 ± 0.3	8.2 ± 0.2	8.3 ± 0.2	-0.1 ± 0.1

Figure 5.10. Left panels: Dose distributions of the 10×10 cm² field covered with spots with 2.5 mm spacing for the measured (top) and the simulated (bottom) data. The doses were normalized to the average value of the 7.5 x 7.5 cm² middle region of each field. Right panels: the profiles drawn on the dose distributions (x-profile = dashed line, y-profile = solid line).

orthogonal profiles for both scenarios. The doses were normalized to the mean dose value in a central region of interest of 7 x 7 cm².

Table 5.5. Analysis of the $10 \times 10 \text{ cm}^2$ field measured at the isocenter using the parameters in terms of lateral penumbra (LP), lateral flatness (LF), lateral symmetry (LS), target size, field size, $D_{LP\max}$ and $D_{LP\min}$, which correspond to the maximum and minimum relative doses in the target region (red box in Figure 5.5b). The LP, LF and LS were calculated using Eqs. 5.8, 5.9 and 5.10.

	x-profile			y-profile		
	Exp	Sim	Diff	Exp	Sim	Diff
LP (mm)	7.5	7.3	0.1	7.7	7.2	0.5
Target width (mm)	72.5	73	-0.6	71.1	73.5	-2.4
Field size (mm)	102.3	102.3	0	101.9	102.4	-0.5
$D_{LP\max}$ (%)	100.8	101.7	-0.9	101.6	101.6	0
$D_{LP\min}$ (%)	98.9	98.5	0.4	98.6	98	0.6
LF (%)	0.9	1.6	-0.7	1.5	1.8	-0.3
LS (%)	1.2	0.5	0.7	1	0.3	0.8

5.4 Discussion

The MC beam model of the proton beam installed at ZON-PTC was presented and validated against measurements performed in-loco, except for the AA validation, which used data from the manufacturer's factory. This system is characteristic for its short beam line, the use of a mechanical energy selection system close to the patient, the energy-invariant width of the Bragg peak and the additional AA component to decrease lateral penumbra.

The characterization of the beam source emittance was challenging, due to the short range of distances where beam profiles could be measured (-31.1 cm, -20 cm, -10 cm, isocenter, +10 cm and +20 cm). The fit parameters presented in Table 5.2 were obtained by constraining the lower and upper boundaries, until acceptable values would be reached. The emittance parameterization was validated with simulations with the same set-up as the measured 2D-profiles. However, it is recommended that more spots should be measured, especially in the region upstream towards the virtual source location, to improve the fit results and hence the model of our source. These extra measurements were still not done due to the lack of beam on time in the current system.

The transverse and longitudinal dose profiles were studied for fifteen selected energies. The spot sizes extracted from the transverse profiles yielded an average difference of $0.3 \pm 0.2 \text{ mm}$ between experimental and simulated data (Figure 5.8). For the IDD, overall there is a very good agreement at the Bragg peak and plateau region for both experimental and simulated data (Figure 5.9). Differences in R80 and R90 for the simulated and measured IDD are within the measurement resolution for the nine higher energies (Table 5.4). For the lower energies, differences increase with the addition of EMS plates in the beam path, reaching a value of 0.7 mm. As expected, the beam width (R_{80-80}) of the measured data is constant for all energies ($8.2 \pm 0.2 \text{ mm}$), and the same is observed for the simulated IDD ($8.2 \pm 0.3 \text{ mm}$). The average D_{80-80} falls below the measurement resolution of 0.3 mm.

The decrease in agreement between measurements and simulations for the lower energies for both transverse and longitudinal profiles, with deviations up to 1 mm and 0.8 mm, respectively, indicates that the EMS model needs to be improved, for instance, the

Figure 5.11. Left panels: 2D doses of the 11-sphere without (w/o) and with the Adaptive ApertureTM (AA) of the measured and simulated plans. Right panels: x- and y- profiles of the dashed and solid lines drawn in (a-d) and indicating the lateral penumbra (LP) for each case (using the definition in Eq. 5.8).

parallelism between the EMS plates needs to be confirmed.

The 3D plan with the 11-sphere placed at the isocenter was the first test of the AA component and using the measurements performed at the Mevion factory, due to the lack of beam time in the commissioning phase of ZON-PTC. Initial results are satisfactory, showing a reasonable agreement between x- and y-profiles when using the AA (Figure 5.11g-h). An average difference in LP of 4.5 mm and 4.1 mm is observed between

the plans without and with the AA for the measurements and simulations, respectively. To continue and improve this work, the following measurements would need to be added:

- Perform EBT3 film measurements in positions closer to the beam exit of the synchrocyclotron, to improve the emittance characterization and make it more robust.
- Transverse dose profiles measured in a water tank at different depths (*e.g.* 1/4, 2/4 and 3/4 of the IDD peak) for the fifteen energies and compare them with simulations.
- Longitudinal dose profiles measured with a lower step than 0.3 mm in the Bragg peak.
- $10 \times 10 \text{ cm}^2$ field measurements performed at other distances in the axial direction (*e.g.* -20 cm, -10 cm, 10 cm and 20 cm) to ensure a good agreement outside the isocenter.
- Plans of complex 3D-geometries with and without the AA.
- Perform measurements with the AA at different distances of the isocenter.
- Comparison with the treatment planning system recently released.

5.5 Conclusion

Preliminary results of the Monte Carlo beam model of the MEVION S250i HYPERSCAN with an Adaptive Aperture™ assembled at the ZON-PTC clinic in Maastricht show an acceptable agreement between experimental and simulated data. More detailed measurements are needed to complete the fine-tuning of the MC model and to perform further validation. Furthermore, the MC model will also be compared with the treatment planning system RayStation v8B (RaySearch Laboratories AB, Stockholm, Sweden) released in January 2019, since it includes their model of the multi-layer Adaptive Aperture™.

5.6 Acknowledgments

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Exploring the feasibility of a clinical proton beam with an adaptive aperture for pre-clinical research

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Abstract

Objective: To investigate whether the MEVION S250i with HYPERSCAN clinical proton system could be used for pre-clinical research with millimetric beams.

Methods: The nozzle of the proton beam line, consisting of an energy modulation system (EMS) and an Adaptive ApertureTM (AA), was modelled with the TOPAS Monte Carlo (MC) Simulation Toolkit. With the EMS, the 230 MeV beam nominal range can be decreased in multiples of 2.1 mm. Monte Carlo dose calculations were performed in a mouse lung tumour CT image. The AA allows fields as small as $5 \times 1 \text{ mm}^2$ to be used for irradiation. The best plans to give 2 Gy to the tumour were derived from a set of discrete energies allowed by the EMS, different field sizes and beam directions. The final proton plans were compared to a precision photon irradiation plan. Treatment times were also assessed.

Results: Seven different proton beam plans were investigated, with a good coverage to the tumour ($D_{95} > 1.95 \text{ Gy}$, $D_5 < 2.3 \text{ Gy}$) and with potentially less damage to the organs-at-risk (OARs) than the photon plan. For very small fields and low energies, the number of protons arriving to the target drops to 1-3%, nevertheless the treatment times would be below 5 seconds.

Conclusions: The proton plans made in this study, collimated by an AA, could be used for animal irradiation.

Advances in knowledge: This is one of the first study to demonstrate the feasibility of pre-clinical research with a clinical proton beam with an adaptive aperture used to create small fields.

6.1 Introduction

The number of ion beam therapy centers has been growing rapidly in the last decade, making ion beam therapy a possible cancer treatment. To advance the understanding of ion beam therapy, pre-clinical research is needed combining different tumour models and ion beam irradiation [1].

Also in recent years, specialized image-guided irradiation platforms for conventional photon radiotherapy were installed in over one hundred research departments worldwide, an order of magnitude more than in 2011 [2]. Such platforms are radically changing the field of pre-clinical animal research in radiobiology by using image-guided irradiation with millimetric beams [3]. Furthermore, specific treatment planning systems were developed, where the physics of low-energy x-ray beams was modelled to deliver accurately the prescribed dose to the target, while considering the constraints in dose to the organs-at-risk (OARs) [4–6].

Integrating the existing state-of-the-art photon platforms with ion beams will initiate a completely new field in pre-clinical research. Greubel *et al.* [7] presented a study where 24 subcutaneous tumours in mice were irradiated with 20 Gy using 23 MeV proton beams and tumour growth was evaluated. Moreover, Constanzo *et al.* [8] published a radiobiological study, where a 4 MeV mini-proton beam was used to irradiate tumour cells and survival curves were comparable to the ones obtained with x-ray irradiation. In 2017, Ford *et al.* [9] demonstrated the feasibility of integrating a 50 MeV proton beam with a commercially available x-ray pre-clinical platform. The same group developed a Monte Carlo (MC) model for a small animal proton beamline and investigated the relative biological effectiveness (RBE) in tissues using fractionated proton minibeam [10].

Since it is unlikely that dedicated small animal ion beam therapy facilities will be built due to cost, current clinical and non-clinical ion beam facilities look for solutions to adapt their beams for image-guided pre-clinical research [11–13] while making use of platforms with existing x-ray beams for imaging and positioning [2]. For this reason, the work here presented investigates the possible use of a clinical proton beam, which has a unique Adaptive Aperture™ to create small fields with sharp beam penumbras and low proton energies, for small animal research. The study will focus on dose calculations with proton beams, and will not consider any effects of relative biological effectiveness at low proton energies. This would require extensive studies of the RBE in small proton beams in *in vivo* systems.

6.2 Materials and methods

6.2.1 Clinical system

The MEVION S250i with HYPERSCAN proton system (Mevion Medical Systems Inc., Littleton, MA, USA) is a commercially available one-room compact system with a synchrocyclotron proton accelerator mounted on the gantry, which rotates in the treatment room around the patient (Figure 6.1a). The beam line consists of a dual axis scanning magnet, transmission ion chambers, a fast energy modulation system (EMS) and an Adaptive Aperture™ (AA) for beam collimation (Figure 6.1b). These components are mounted on the Nozzle, that can rotate between -5° and 185° in the gantry plane (Figure 6.1a). Furthermore, the module that contains the EMS and AA can be extended

towards the isocentre, ranging from 3.6 to 33.6 cm.

Figure 6.1. (a) Treatment room sketch with the synchrocyclotron mounted on the gantry, which rotates around the isocentre from -5° and 185° ; (b) close view of the Adaptive Aperture™ (AA) module in the beam's-eye-view; (c) MC model of the module with the 16 plates of Energy Modulation System (EMS) in the beam path, indicating the range shifter plates, the AA and the exit window (the beam goes from right to left) with a representative slice of the micro cone-beam CT of the mouse in front of the nozzle. The dotted box is zoomed-in on the right.

The system produces a pencil beam with a fixed energy of 230 MeV and uses the EMS to decrease the pencil beam energy. This device consists of eighteen Lexan plates with specific thicknesses and air gaps that allow for a decrease of the pencil beam residual range in multiples of 0.21 cm in water, covering a depth from 32 cm (90% distal fall-off) to the surface. The AA is located at the end of the beam line and it consists of two opposing blocks of seven leaves made of Nickel [14] moving in a $20 \times 20 \text{ cm}^2$ treatment field enabling collimation of each pencil beam per energy layer. The AA moves as a block in the y-direction and each leaf can move in the x-axis direction (Figures 6.1b and 6.1c). Furthermore, the one nominal proton energy combined with the type of EMS, results in Bragg peaks with a constant range straggling (the full-width half maximum (FWHM) in the beam direction of approximately $27 \pm 1 \text{ mm}$ measured in integrated depth doses (IDDs)).

6.2.2 Beam model

The beam model of the S250i with HYPERSCAN system was created using the MC platform TOolkit for Particle Simulation (TOPAS)[15] (Figure 6.1c). The model was validated with data provided by the manufacturer.

6.2.3 Simulation set-up

The submillimetric cone beam CT (μ CBCT) image of a mouse with an orthotopic lung tumour was acquired with the X-RAD 225Cx system (Precision X-ray, North Branford, CT, USA) at a tube voltage of 80 kVp and with a $0.1 \times 0.1 \times 0.1 \text{ mm}^3$ voxel size. The main structures (tumour in the right lung, right and left lungs, spinal cord and heart) were delineated by a radiation oncologist. Using a dedicated small animal radiotherapy planning system SmART-Plan [6] (research v. 1.5, Precision X-ray), an optimal photon irradiation plan was designed to administer a prescribed dose of 2 Gy to the tumour (Figure 6.2a).

Figure 6.2. (a) Photon dose distribution, micro cone-beam CT image and structure contours for the photon plan with two opposed 225 kVp photon beams using a 5 mm circular collimator to deliver a prescribed dose of 2 Gy to the tumour (statistical uncertainty of 0.1%, equivalent to approximately 10^8 histories per beam). The tumour is indicated in green in the right lung. (b) Illustration of the three proton treatment fields (and corresponding inner gantry rotation) used to create seven different proton plans.

For the proton plans, simulations of a single spot proton pencil beam aimed at the tumour centre were performed combining two or three treatment fields (TF), using different energies and five field sizes (Table 6.1, Figure 6.2b). The choice of energy was limited by the EMS discrete steps. Treatment scenarios T1 to T6 use treatment fields with low energies (29.14 MeV, 32.97 MeV, 36.46 MeV and 39.72 MeV), in which the Bragg Peak stops inside the tumour, while T7 uses two opposed 158.87 MeV beams to "shoot-through" the tumour. The minimum field size in the y -direction (axis in Figure 6.1b) is limited by the leaf thickness of 5 mm, however in the x -direction, any opening is possible with 0.5 mm resolution. The default physics list from TOPAS, validated for proton beams [15, 16], was used and dose-to-water-in-medium (physical dose) was scored in a $0.2 \times 0.2 \times 0.2 \text{ mm}^3$ grid (double the original μ CBCT voxel size). A primary 230 MeV proton beam with an energy spread (standard deviation) of 0.2174 MeV and a virtual source-axis-distance (SAD) of 185 cm, was simulated with 1.75×10^9 protons per TF.

Each treatment scenario resulted in 64 (T1 - T4) or 16 (T5 - T7) dose distributions

Table 6.1. Simulation set-up for seven different treatment scenarios (T), using two or three treatment fields (TF1 - TF3) defined by the gantry rotation 0°, 90° and 180° (explicitly in Figure 6.1a), respectively.

Treatment scenario #	Treatment fields (MeV)			Field size (mm ²)
	TF 1	TF 2	TF 3	
T1	39.72	29.14	36.46	5 x 2.5 5 x 3 5 x 3.5 5 x 4
T2	39.72	32.97	39.72	
T3	39.72	29.14	36.46	
T4	39.72	32.97	39.72	
T5	39.72	-	36.46	
T6	39.72	-	39.72	
T7 shoot-through	158.87	-	158.87	

(Table 6.2), for each of these the dose volume histogram (DVH) metrics D95 and D5 (dose given to 95% and 5% of the tumour volume, respectively) were calculated to select the best plan for each treatment. Furthermore, the DVH metrics V90 and V10 were used to evaluate the volume of OARs that received 90% and 10% of the prescribed dose, respectively. Finally, the best dose distributions from the seven different scenarios were compared, arriving at the plan that best covers the tumour with the prescribed dose.

6.2.4 Clinical system output

6.2.4.1 System's delivery efficiency

The EMS can decrease the beam nominal range to zero. However, the use of almost all the 18 range shifter plates decreases the number of protons that exit the EMS. To quantify the protons lost due to the use of these plates, simulations with a single-beam aimed at the isocentre were performed with the system's nominal energy (230 MeV) and the energies chosen for treatments T1 - T7. The AA was added to the simulations with the field sizes ranging from 5 x 1 mm² to 5 x 5 mm². The number of protons that arrived at the nozzle's exit window (Figure 6.1c) was scored and compared to the number of 10⁷ primary protons generated.

6.2.4.2 Calculation of the dose rate and treatment time

For practical reasons, it is important to assess whether the system would be able to deliver the prescribed dose of 2 Gy in an acceptable irradiation time [17], since the animal is under deep anaesthesia and the common workflow includes imaging, treatment planning and irradiation. With a maximum beam current of 10 nA, the MEVION S250i with HYPERSCAN, can produce 6.24×10^{10} protons per second. From the simulations described in Subsubsection 6.2.4.1, the time needed to deliver 2 Gy as function of energy and field size was estimated.

Table 6.2. Field size for each TF corresponding to each combination number (grey columns), *e.g.* the field size for combination 1 is (5 x 2.5, 5 x 2.5, 5 x 2.5); for combination 2 is (5 x 2.5, 5 x 2.5, 5 x 3). T1 to T4 yielded 64 combinations of field sizes, whereas T5 to T7, only 16 combinations, since only two TF were used (Table 6.1).

Combination	TF1 (mm ²)	TF2 (mm ²)	TF3 (mm ²)	Combination	TF1 (mm ²)	TF2 (mm ²)	TF3 (mm ²)
1	5 x 2.5	5 x 2.5	5 x 2.5	33	5 x 3.5	5 x 2.5	5 x 2.5
2			5 x 3	34			5 x 3
3			5 x 3.5	35			5 x 3.5
4			5 x 4	36			5 x 4
5		5 x 3	5 x 2.5	37		5 x 3	5 x 2.5
6			5 x 3	38			5 x 3
7			5 x 3.5	39			5 x 3.5
8			5 x 4	40			5 x 4
9		5 x 3.5	5 x 2.5	41		5 x 3.5	5 x 2.5
10			5 x 3	42			5 x 3
11			5 x 3.5	43			5 x 3.5
12			5 x 4	44			5 x 4
13		5 x 4	5 x 2.5	45		5 x 4	5 x 2.5
14			5 x 3	46			5 x 3
15			5 x 3.5	47			5 x 3.5
16			5 x 4	48			5 x 4
17	5 x 3	5 x 2.5	5 x 2.5	49	5 x 4	5 x 2.5	5 x 2.5
18			5 x 3	50			5 x 3
19			5 x 3.5	51			5 x 3.5
20			5 x 4	52			5 x 4
21		5 x 3	5 x 2.5	53		5 x 3	5 x 2.5
22			5 x 3	54			5 x 3
23			5 x 3.5	55			5 x 3.5
24			5 x 4	56			5 x 4
25		5 x 3.5	5 x 2.5	57		5 x 3.5	5 x 2.5
26			5 x 3	58			5 x 3
27			5 x 3.5	59			5 x 3.5
28			5 x 4	60			5 x 4
29		5 x 4	5 x 2.5	61		5 x 4	5 x 2.5
30			5 x 3	62			5 x 3
31			5 x 3.5	63			5 x 3.5
32			5 x 4	64			5 x 4

6.3 Results

6.3.1 Proton plan that best covers the target

Simulations of the seven treatments described in Table 6.1 were performed. All DVHs were scaled to the prescribed physical dose $D_{90} = 2 \text{ Gy}$ ¹. Figure 6.3a presents the D95 and D5 extracted from each of 64 dose distributions from T1. The field size that produced the minimum difference between D95 and D5, *i.e.* the steepest slope of the tumour's

¹ All doses reported in this work are physical doses (Gy) and not RBE-weighted absorbed doses (GyE).

DVH, is marked with a black line and hence chosen as the best combination for each treatment. Figure 6.3b shows the V10 and V90 for the right lung and heart for the 64 field size combinations (explicitly in Table 6.2), where the horizontal lines represent the V90 and V10 extracted from the photon plan. From the Supplementary Data 6.7, Figure S6.1 gives the results for T3, T5 and T7.

Figure 6.3. (a) D95 and D5 for all field combinations for T1, where the combination with the steepest slope between D95 and D5 is indicated with a black vertical line (combination 54). The x-axis shows the 64 combinations for T1: the first point on the x-axis has the field size (TF1 = 5 x 2.5 mm², TF2 = 5x2.5 mm², TF3 = 5 x 2.5 mm²) and the last (TF1 = 5 x 4 mm², TF2 = 5 x 4 mm², TF3 = 5 x 4 mm²). All the 64 field-size combinations are shown in Table 6.2. (b) representation of the ipsi-lateral right-lung V10 and the V90, and the heart V10. Horizontal lines show in both panels, as indicated, the D5, D95, V10 and V90 values extracted from the photon plan (Figure 6.2).

The best case for each treatment scenario is described in Table 6.3 in terms of the AA opening and the DVH metrics: D95, D5 for the tumour, V10 and V90 for the ipsi-lateral right lung, and the V10 for the heart. Figure 6.4 shows the DVHs for the seven proton treatments, including the tumour, right lung and heart. The DVH extracted from the photon plan is shown in black.

Figure 6.5 shows the dose distributions for three different types of proton irradiation: using three fields and low energies, using two opposing fields and low energies, and using two opposing "shoot-through" fields with high energies. Dose differences between these three irradiations are shown in Figure 6.6.

6.3.2 Clinical system output

Figure 6.6a-f show the number of protons scored at the exit window of the nozzle for different field sizes, using a representative energy of 39.72 MeV. The fraction of protons for each energy that arrive to the exit window for an open field is shown in Figure 6.7a, while Figure 6.7b gives these values as function of the field size.

Table 6.3. Combinations that best covered the tumour found for each treatment scenario, indicating the Adaptive Aperture™ (AA) size for each treatment field (TF) and the dose volume histograms metrics D5, D95, V10 and V90.

Treatment scenario #	AA size for each TF			D95	D5	V90 Lung (%)	V10 Lung (%)	V10 Heart (%)
	TF1	TF2	TF3					
T1	4	3	3	1.95	2.26	13	69	8
T2	4	3	3	1.95	2.27	13	69	8
T3	4	4	3	1.96	2.18	12	72	2
T4	4	4	3	1.96	2.21	12	72	19
T5	4	-	3	1.98	2.2	19	7	5
T6	4	-	3.5	1.96	2.18	19	69	5
T7	4	-	3	1.96	2.27	23	8	17
Photons	-	-	-	1.99	2.07	32	48	0

Figure 6.4. Dose volume histograms of the seven treatments for the tumour (solid line), ipsi-lateral right lung (dashed line) and heart (dotted line).

Considering the number of protons that the system produces per second at the exit of the cyclotron ($\approx 6.24 \times 10^{10}$ protons for 10 nA beam current), the efficiency of each beam with respect to its energy and field size (Figure 6.7b), the time to cover a 2 Gy target was determined and the results are shown in Figure 6.8.

6.4 Discussion

This work presented a dosimetric study on the feasibility of pre-clinical irradiations with the compact proton system S250i with HYPERSCAN. Exploring the capabilities of the system EMS for range modulation, and AA for collimation, seven different proton irradiation scenarios were simulated in a MC platform to irradiate a mouse lung tumour. To perform the experiments simulated here, a high precision positioning

Figure 6.5. Proton dose distributions in transverse, coronal and sagittal planes for the field size combinations depicted in Table 6.3 from irradiations T3, T5 and T7 (a, b and c panels, respectively). Dose differences between irradiation T7 and T3 (d), between T7 and T5 (e), and between T5 and T3 (f).

platform with a coupled high-resolution CBCT imager would be necessary to assure a sub millimetric uncertainty of the mouse positioning, while keeping the gantry at a fixed angle (Figure 6.1a). This has already been achieved by coupling commercially available small animal x-ray imaging platforms to a fixed proton beam line [9]. On a gantry-based system, extra care has to be taken to position the beam nozzle in a reproducible fixed position.

The AA allows the creation of very small fields, limited to a minimum of 5 mm in the y -direction (axis in Figure 6.1b), but down to 0.5 mm in the x -direction. Considering the size of the tumour and without explicitly adding any margin, a range of five AA openings were simulated, resulting in 16 or 64 different field size combinations. In the field of pre-clinical radiotherapy research, no guidelines are given for margins, which is an important study point recommended by the ESTRO ACROP report from Verhaegen *et al.* [3]. In this respect, Vaniqui *et al.* [18] published a method of calculating the optimal collimator diameter from

Figure 6.6. Number of protons scored at the exit window for a 39.72 MeV beam, with different collimations (b-f) and with no collimation (a).

a set of fixed diameters depending on the parameters of a cost function, especially relevant for tumours affected by the breathing motion. Such an approach could be implemented in a follow-up study to this work, adapting the recipe proposed to the constraints of the AA of this system.

Figure 6.3a plots the DVH metrics D5 and D95 for one scenario (T1), where the worst tumour coverage is seen for the smallest field ($5 \times 2.5 \text{ mm}^2$, $5 \times 2.5 \text{ mm}^2$, $5 \times 2.5 \text{ mm}^2$) while generally improving for the largest fields. The best-case tumour coverage, taken as the DVH with the steepest slope between D5 and D95, for T1 was achieved for a field of ($5 \times 4 \text{ mm}^2$, $5 \times 3 \text{ mm}^2$, $5 \times 3 \text{ mm}^2$). The same analysis for all seven treatments resulted in the seven best case scenarios that were shown in Table 6.3 and in Figure 6.4. The "shoot-through" technique, with a similar beam arrangement as in the photon plan (Figure 6.2a), would be expected to give a better coverage of the target. However, the use of a single spot beam resulted in a non-uniformity of the dose distribution in the lateral direction. Using an optimizer and smaller side-by-side-beams may improve this result.

For benchmarking, a photon plan (Figure 6.2a) was made by a commercially available treatment planning system for small-animal research. In contrast, in this work, single spot proton beams with equal weight were aimed at the isocentre. Nevertheless, Figure 6.4 and Table 6.3 show that the proton plans could be used for animal irradiation with a less optimal tumour coverage, but for most cases with an improved sparing of the

Figure 6.7. Fraction of protons that arrive at the exit window in an open field (no collimation) as function of the energy (a), and as function of the energy and field size (b). The field sizes used: 5 mm², 10 mm², 12.5 mm², 15 mm², 17.5 mm², 20 mm², 25 mm², correspond to an Adaptive ApertureTM opening of 5 x 1 mm², 5 x 2 mm², 5 x 2.5 mm², 5 x 3 mm², 5 x 3.5 mm², 5 x 4 mm² and 5 x 5 mm², respectively.

Figure 6.8. Beam-on time to deliver 2 Gy as function of the energy and field sizes.

OARs. Specifically, 32% of the right lung volume receives 90% of the prescribed dose in the photon plan, which decreases to 12% in T3 and T4 proton plans. Furthermore, in Figure 6.2a it is possible to observe a very high photon dose (three times the prescribed dose) in bone tissues, due to the predominance of the photoelectric effect for low energy

x-ray beams. Protons in tissue also have a lower mass stopping power for bone than water, in contrast with the factor of about three higher mass-energy absorption coefficient at low energy photon beams.

The proton treatments designed in this study used two strategies: low energy fields that stop in the tumour or high energy beams to shoot through. Dose differences show that the former allows for a decrease in dose to healthy tissues observed in Figure 6.5d-f, with respect to the "shoot through" strategy. This would allow to study potential RBE effects [10]. The latter has the potential interest of performing small animal proton CT imaging that could be used for pre-treatment position verification or to improve range uncertainty by directly measuring the animal relative stopping power maps [19].

A special component of this beamline is the EMS, which is characterized by a constant range straggling at the Bragg peak for all energies. This might be a disadvantage for pre-clinical work, since it prevents the easy production of sharper beams. Another effect of the EMS is the increase in lateral beam spot size with the decrease in energy, caused by the many plates in front of the beam. For the low energies used in this work (T1- T6), the beam spot size, taken as the standard deviation of a double GaussianGaussian fit, is approximately 16 mm. The AA can collimate the beam, however there is an intrinsic loss in efficiency by using large spot sizes with small fields, since most of the beam will be absorbed by the AA, clearly seen in Figure 6.7b. The central beam axis also suffers a decrease in intensity (Figure 6.6b-f), since the very small angular deflections in proton trajectories are not negligible for small fields. Nevertheless, Figure 6.8 shows the estimated irradiation time needed to deliver a 2 Gy dose with different energies and field sizes. For the lowest energy (29.14 MeV) and the smallest field size ($5 \times 1 \text{ mm}^2$), the prescribed dose can be delivered in less than 5 s. The high dose rate of this system allows for 30 Gy to be delivered in less than a minute.

6.5 Conclusion

The feasibility of the MEVION S250i with HYPERSCAN proton irradiation system for pre-clinical research was affirmatively tested, using different strategies in the choice of energies, field directions and sizes. Moreover, the system would be able to give very high doses in a short period of time, due to the system's high beam current. With the use of a movable platform equipped with μ CBCT imaging and a table with accurate positioning, the clinical proton system could be used to perform proton irradiation in small animals for a wide range of studies.

6.6 References

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6.7 Supplementary data

Figure S6.1. Top panels: D95 and D5 for all field combinations for T3, T5 and T7 (left, middle, right, respectively), where the combination with the steepest slope between D95 and D5 is indicated with a black vertical line. Bottom panels: representation of the ipsi-lateral right-lung V10 and the V90, and the heart V10 for T3, T5 and T7. Horizontal lines show in both panels, as indicated, the D5, D95, V10 and V90 values extracted from the photon plan (Figure 6.2).

Discussion

7.1 Summary and discussion

Dual-energy computed tomography (DECT) is currently an important topic of research for several applications in radiotherapy. For proton therapy, DECT is studied particularly to improve range prediction and tissue segmentation, to extract tissue compositions, to predict prompt-gamma and positron emission, and to move towards automated organ delineation. Understanding the advantages and current limitations of DECT technology is crucial for clinical implementation, which we believe will happen at many centers in the near future.

Due to the wide choice of DECT technologies available on the market, such as dual-source and twin-beam, this thesis started in **Chapter 2** by quantifying and extracting, for these two different DECT systems, tissue-specific physical properties: the relative electron density (ρ_e) and the effective atomic number (Z_{eff}) following the methods from Saito [1] and Landry *et al.* [2] respectively. In a quantification point-of-view, DECT benefits immensely with a system with a wide spectral separation (within the clinical range of energies), whereas a twin-beam technology with two strongly overlapping low- and high-energy spectra with the same maximum photon energy produces similar images and results in higher discrepancy between reference and calculated values for ρ_e and Z_{eff} in phantom tests. For this reason, the dual-source system with the additional filtration in the high-energy x-ray source has the potential of yielding the lowest root-mean-square (RMS) errors for these physical properties for both third, but also, second generation detectors. This was also explored in **Chapter 2** of this thesis, comparing two dual-source systems with different detectors.

However, the current commercially available dual-source DECT systems have a fundamental physical limitation on the size of the detectors placed inside the scanner structure, resulting in a combined field-of-view (FOV) of maximum 35 cm diameter. In the external-beam radiotherapy field, the complete image of a patient is required depending on the tumour location, which would not fit this limited FOV. The dual-spiral technology with a single x-ray tube and imaging detector appears as the compromise between a system with a good spectral separation (although no extra filtration) and the capability of producing images with the typical 50 cm FOV of SECT scanners. We studied in detail the first CT scanner specifically manufactured for radiotherapy that includes a DECT dual-spiral capability (**Chapter 3**). In this chapter, we extracted the Z_{eff} from DECT with two purposes: assign a material per voxel using the two-dimensional $[\rho_e, Z_{\text{eff}}]$ -space, and extract the mean excitation potential (I) necessary for collision stopping power calculation using the method developed by Yang *et al.* [3]. Additionally to analyzing this radiotherapy specific dual-spiral technology and comparing it to the twin-beam and dual-source systems, a comparison with the SECT methodology was added to complement the results of this work and investigate relevant differences in range.

A complete framework was developed to use DECT images in Monte Carlo (MC) proton dose calculations, which will be discussed further in this chapter. Two main conclusions resulted from this work: first, the dual-spiral yielded results as good as the dual-source in terms of tissue segmentation and range prediction (defined as the 80% distal fall off, R80) for the non-moving phantoms used; second, absolute differences in R80 for a single-field head & neck patient case between the DECT dual-spiral and the SECT-stoichiometric based dose calculations yielded a mean value of 1.2 ± 1.2 mm. The later was consistent

with the work presented by Wohlfahrt *et al.* [4] reporting a mean water-equivalent range shift of -1.1 mm between a SECT and DECT dual-spiral plans, and Hudobivnik *et al.* [5] who found mean differences of -1.7 mm between SECT and DECT dual-source plans, also for a head case.

Meanwhile, radiotherapy clinics and hospitals rely on treatment planning systems (TPS) to perform dose calculations based on CT images, which currently are not capable of handling a set of two DECT images as input and lack the necessary tools to extract from these the different tissue properties. Since these systems rely on a single-input, a pseudo-monoenergetic image (PMI), presents itself as a hybrid solution: created from a weighted sum of the two DECT acquisitions ($\alpha\text{CT}_{\text{low}} + (1 - \alpha)\text{CT}_{\text{high}}$), but using the same conversion methodology from CT# to SPR or ρ as the conventional SECT. The choice of α -parameter can be optimized depending on the application: *e.g.* a higher contrast-to-noise ratio and edge enhancement can decrease inter-observer variability for contouring, while a smoother image with minimal beam-hardening effect can be used for SPR or ρ calculation. A 79keV-PMI was successfully implemented as clinical standard in the Universitäts Protonen Therapie Dresden for all body sites except lung and head & neck, basing this decision on the results presented by Wohlfahrt *et al.* [4, 6, 7] that compared 79keV-PMI- and SECT-based SPR prediction in a anthropomorphic ground-truth phantom and later evaluated the differences in a cohort of head and pelvic patients. Nevertheless, the 79keV-PMI is not able to achieve the accuracy in SPR of the full DECT based methods.

Scanner manufacturers have also been developing their own software to facilitate the radiotherapy work-flow. One example was the launching of the DirectDensity™ algorithm by Siemens Healthineers (Forchheim, Germany) in 2016, which reconstructs an image directly in scaled relative electron densities. Another product of Siemens Healthineers is the RHO/Z package from their own *syngo.via* software, that calculates ρ_e and Z_{eff} images from the two DECT scans.

At our institute, we are supplied with two DECT scanners (a dual-source SOMATOM Definition Drive and a dual-spiral SOMATOM Definition Confidence© RT pro), the latest software version for each scanner with the DirectDensity™ algorithm, and RHO/Z package in *syngo.via*. The large offer of clinically available methods of extracting ρ_e led to the on-going study in **Chapter 4**. Additionally, since Saito's [1] method has been recurrently shown to yield the lowest RMS for ρ_e extraction, its implementation was also added to this study, applying an additional post-processing denoising algorithm with fifteen iterations (called *Saito-15it*). Five ρ_e -extraction methods (CT2RED, DirectDensity™, PMI2RED, *syngo.via*-RHO, and Saito-15it) were tested first in two phantoms and later applied to a neurological patient scanned with both DECT and SECT protocols. The ρ_e -images for the patient case were converted to ρ -images (detailed explanation in section 4.2.6), so this could be used directly as input in the TPS. The ρ -images for the patient computed from the CT2RED, DirectDensity™ and PMI2RED methods (all methods based in a look-up-table conversion) yielded very similar ρ values, with differences within $0.005 \pm 0.023 \text{ g/cm}^3$. The two full DECT-based methods (*syngo.via*-RHO and Saito-15it), that start from the same equation, although following different post-processing algorithms, as discussed closely with Siemens and Saito (**Appendix A**), yielded higher discrepancies compared to the other three methods. Notably, opposite values were observed for the bone tissues, which was

explained after an direct correspondence with Siemens, and it was due to the fact that the *syngo.via*-RHO software used was not optimized for the scanner at our institution. Additionally, the effect of using the different ρ -images for proton dose calculations was quantified in terms of dose and range differences, where, for instance, differences of 1.5 ± 0.5 mm in R80 between CT2RED and *syngo.via*-RHO were found in a single patient example. We are continuing this study by adding a considerable number of patients to investigate if the variability between methods is seen in other cases and, up to now, the same trend is observed in the ρ -images.

Chapters 3 and 4 confirm that proton dose calculations are sensitive to the CT modality (single or dual-energy), the DECT technology, and even the post processing algorithm used to compute the tissue properties. In this respect, we believe that MC techniques play an important role in decreasing the systematic uncertainty and in scrutinizing the numerous possibilities available.

A full framework was developed to use DECT images to create the necessary material-, ρ - and I -maps needed as input for Geant4 MC dose calculations. We wanted to investigate if DECT combined with a MC dose engine would yield a higher accuracy in terms of proton range compared to a material-based ground-truth simulated phantom than SECT conventional methodology. The hypothesis was confirmed and it is presented as one of the main results of **Chapter 3**. Furthermore, a plan calculated on the patient geometry had the individual pencil beams optimized with MC instead of using the pencil beam doses calculated by the analytical pencil beam algorithm. In this way, we account for the effect of inhomogeneities in the proton beam path.

These studies on the accuracy of DECT were especially relevant in our radiotherapy clinic, since its recent construction of the Zuid-Oost Nederland Protonen Therapie Centrum (ZONPTC), adding proton therapy as another available treatment modality. Our institution will start to treat patients either with intensity modulated radiotherapy (IMRT) or with scanned proton beam therapy. The choice of radiotherapy modality (IMRT or proton therapy) will be made according to a *model-based approach* from official Dutch scientific and health care governance bodies, which uses different normal tissue complication probability models to calculate the tissue-toxicity predicted for each treatment and, with these results and based on some thresholds, selects the modality that most benefits the patient [8]. For this reason, every patient is scanned with a single imaging protocol (depending on the body site), which has to suit both radiotherapy modalities.

ZONPTC decided to acquire the MEVION S250i with HYPERSCAN compact proton system (Mevion Medical Systems Inc., Littleton, MA) with the Adaptive Aperture™ (AA) beam collimation system. Aiming to have an independent dose (re)calculation engine, the MC beam model of this system was developed and it is described in detail in **Chapter 5**, showing a very good agreement for the integrated depth dose curves and the spot dose profiles for fifteen selected energies, for a single 10×10 cm² field at the isocenter and a 3D geometry tested with and without the AA. We are already partially integrating the framework developed in **Chapter 3** with the beam model of our center, in particular, the implementation of DECT maps, so that DECT and SECT-based simulations can be performed and, additionally, compared with experiments measured in-house.

The AA component of our system makes it theoretically possible to create very small fields, either for treatment of small lesions (**Appendix C**), or even for pre-clinical *in vivo* small animal research. A first proof of concept to show the feasibility of performing pre-clinical research using the S250i with HYPERSCAN system was done *in silico* and it is presented in **Chapter 6**. This study helped us to understand the implications of degrading the nominal 230 MeV proton beam to very low energies and its effect on spot size and dose homogeneity, and also to investigate the system's dose rate. We proved that this system can deliver doses of 2 Gy to a target volume of 27 mm³ in under half a minute, achieving a good tumor coverage for several research scenarios.

7.2 Considerations and future perspectives

7.2.1 Advances in proton range prediction techniques

As shown for a subset of centers by the survey done by Taasti *et al.* [9], most particle therapy centers worldwide base their CT# to SPR (or ρ) curve on one of two methods: interpolation between measured tissue mimicking plastics or CT# prediction by means of the stoichiometric calibration proposed by Schneider *et al.* [10]. For the latter, a scanner specific parameterized model is created based on the compositions of tissue equivalent materials and it is used to predict the CT# of tabulated human tissues.

A recent study in which we participated (Gomà *et al.*) looked carefully at the statements made in the 1996 publication from Schneider *et al.* and presented a critical review of the method [11]. First, for the stoichiometric calibration, Schneider claimed that a set of materials with known compositions, not necessarily biological tissue-like, could be used for the calibration and extraction of k_1 and k_2 fit-coefficients for the CT scanner model (equation A.20 from [11]). Gomà *et al.* shed new light on this by showing that the use of different phantoms, scanned with the same protocol and scanner, yields different fit results and, as consequence, different CT# prediction for the set of tabulated tissues (see table 2 from [11]). Secondly, the stoichiometric calibration seems to be a redundant step in converting CT# to ρ_e when using an interpolation between the tissue mimicking inserts from the RMI 467 phantom (Gammex Inc. Middleton, WI), as shown in Figure 7.1. The same is not observed for the 062 M phantom, since it contains Barium in the elemental compositions of the bone inserts and this element is not present in biological tissues. These results were confirmed by an independent implementation of the stoichiometric method and using another set of CT images scanned at our institution with a different CT scanner, different protocols and reconstruction methods. On the other hand, the results published by Hansen *et al.* [12] do not reflect the same agreement between SPR extracted from the stoichiometric calibration *versus* the interpolation between the RMI 467 tissues.

Additionally, the list of human tissues used for the stoichiometric calibration and numerous other studies, reported in the International Commission on Radiation Units and Measurements (ICRU) and the International Commission on Radiological Protection (ICRP) publications, refer back to the early 50s, and have since been recompiled, republished and re-normalized by different sources. The true accuracy of these tabulated human tissues is unknown and it will have a direct impact on the accuracy of the CT# conversion to SPR, because mass-densities and compositions are used for SPR calculation methods for:

Figure 7.1. CT# of tabulated tissues calculated with the stoichiometric calibration based on the RMI 467 (Gammex) and 062M (CIRS Inc., Norfolk, VA) phantoms, and measured CT# of the tissue mimicking materials from the same phantoms (with kind permission from [11]).

- ρ_e calculation from the ρ and material composition ($\rho_e = \rho \sum_i \frac{\omega_i Z_i}{A_i} Z_i^n / N_{e,water}$) or from a linear fit of the relating ρ_e and ρ ($\rho_e = a + b\rho$), as explained in **Chapters 3** and **4**, respectively;
- I calculation with the Bragg additivity rule or with the linear relationship between I and Z_{eff} [3], which is also calculated with the Bragg additivity rule;
- tissue segmentation in the $[\rho_e, Z_{eff}]$ -space, where both quantities are calculated using the known compositions from reference tissues;

Moreover, these tabulations represent, at best, a mean human tissue composition and it is known that this varies for individual patients. There is a need to develop methods able to extract patient-specific tissue compositions from dual-energy or even multi-energy CT images to overcome this source of uncertainty.

Recently De Smet *et al.* [13] discussed the effect of the I uncertainty in SPR calculation, by splitting and analyzing the contribution of the I_{water} and the I_{medium} (called "water based formalism"), since the group hypothesizes that a higher accuracy could be achieved if water molecules in tissues could be treated separately applying the experimentally determined I_{water} . Besides, De Smet *et al.* used three different I_{water} values: 75.3 eV (calculated from the Bragg additivity rule), 75 eV [14] and 78 eV (most recent recommendation [15]). By being consistent in the choice of I_{water} in both parts of the

Bethe equation and using the *water based formalism*, relative deviations of SPR caused by I ranged between 0.1% to 0.8%, in which the uncertainty is higher for tissues with the lower water content. For tissues with high water content, the deviation in SPR is negligible in terms of proton range, in contrast to the reported value of 1.5% range uncertainty caused by I from the work of Paganetti *et al.* [16]. Nevertheless, this study assumes that water molecules in tissues are equivalent to pure water, disregarding the different molecule interactions, and it lacks experimental validation to support their hypothesis. Also recently, Bär *et al.* [17] showed that an improved optimization of elemental I used in the calculation of I_{medium} of known human tissues yielded a maximum deviation in SPR of 0.44% and of 0.47% in proton range.

Overall, studies to understand SPR uncertainty used either the pre-existing set of human data and the Bragg additivity rule, or methods based on different x-ray imaging modalities. For the second case, methods are often applied in phantoms, where ground truth is known, but these are difficult to translate to patients. This gap between unrealistic phantoms made of tissue mimicking plastics and patients, from which a ground-truth lacks, needs to be overcome.

The use of animal tissues has been tested to validate the accuracy of the SE- and DECT SPR prediction methods. Taasti *et al.* [18] compared SPRs predicted from the DECT ρ_e and Z_{eff} images (as explained in section 3.2.2) of 'homogeneous' tissue samples against experimental data and found an accuracy of 0.75% / 1.69% for soft and bone tissues, respectively, whereas the SECT prediction yielded an accuracy of 1.41% / 8.69%. Bär *et al.* [19] compared range uncertainties between these two methods against range measurements of inhomogeneous animal tissues samples, and found an accuracy of 0.19% / 1.06% for DECT and 0.53% / 1.37% for SECT. Studies from Xie *et al.* [20] and Möhler [21] also showed the superior range and SPR prediction of DECT over SECT. Nevertheless, animal tissues do not solve the lack of ground truth needed to perform MC dose calculations, since exact tissue compositions are unknown and the use of frozen and/or *ex vivo* samples do not model accurately live tissues.

One step towards decreasing the gap between phantom studies and translation to clinical reality is the 3D printing of very complex and accurate geometries with known composition, and the production of 3D printer filaments with biological properties similar to human tissues [22–24].

An alternative to converting x-ray attenuation coefficients to SPRs is the concept introduced in 1963 by Cormack *et al.* of using a high-energy proton beam that crosses the patient's body to perform proton radiography and tomography, and directly extract SPR from the tissues in terms of water equivalent path length [25]. At the time, this technique was not considered for clinical application due to physical and technological limitations in achieving a spatial resolution comparable to x-rays caused by multiple Coulomb scattering of protons.

The increased number of proton facilities and the need to improve current methods of range prediction, made pCT reappear as a possible solution, besides being also considered for pre-treatment verification of patient positioning. Two main systems have been studied and developed, one that creates a pCT image by integrating over a number of incident protons (*proton integrating system*), another that tracks the trajectory and energy of

individual protons (*proton tracking system*).

Proton integrating systems are affected by the multiple Coulomb scattering, resulting in an intrinsic limitation of the spatial resolution achievable. At the Heidelberg ion beam therapy center, Rinaldi *et al.* [26–28] developed and tested an ion-based transmission imaging system, using parallel-plate ionization chambers, as well as a method to increase range resolution without increasing the imaging dose.

Proton tracking systems aim to overcome the lack of spatial resolution of pCT by tracking individual protons before and after the scanned object. Schulte *et al.* [29] proposed a method of estimating the protons most likely path from the measured positions. Based on this formalism, Rit *et al.* [30] developed a filtered backprojection algorithm to reconstruct the recorded proton paths, where a clear gain in spatial resolution is seen compared to assuming proton straight paths. Additionally, its fast on-the-fly reconstruction was seen as an advantage to implement this method clinically over iterative reconstructions algorithms, since it would allow for in-room patient anatomical check prior to irradiation. Other pCT systems are under development aiming to improve spatial resolution by minimizing multiple Coulomb scattering in the proton tracking system [31], while decreasing the imaging dose. The Proton Radiotherapy Verification and Dosimetry Applications (PRaVDA) pCT consortium formed in 2013 developed the first solid-state pCT scanner for clinical implementation composed by two sets of trackers to capture the position before and after the object, and a range telescope that estimates the energy loss suffered by each proton when crossing the object [32]. For a cylindrical phantom with 7.5 cm diameter, this system recorded 1080 projections in 360° measuring the range of 280 million protons in less than one second and yielding less than 1.6% difference in SPR.

Also, current systems have proved their added value and accurate SPR prediction for small objects, where the spatial resolution decreases with depth. Also at the level of software, the question is on how a TPS would be able to integrate pCT images and successfully use them for treatment planning

In this thesis, DECT for range prediction was studied in static phantoms and for body sites with minimum movement, however there is a need to quantify the accuracy of the methods presented in this work for moving geometries and couple them to treating moving targets with pencil beam scanning proton therapy.

7.2.2 Advances in proton range verification techniques

After improving range prediction techniques for treatment planning, range verification is needed to ensure that treatments are accurately delivered. For this purpose, secondary particles produced by nuclear interactions between the beam and the medium and that escape the patient's body can be detected in real-time or post-treatment. Nuclear interactions will occur along the beam path until the projectile's kinetic energy drops below the nuclear Coulomb barrier, shortly before the Bragg peak.

From the nuclear decay of positron (β^+) emitters ^{11}C , ^{13}N and ^{15}O created during biological tissue irradiation, the emitted photons produced by the $\beta^+\beta^-$ annihilation can be detected by a positron emission tomography (PET) scanner and this image can be compared to the expected activity based on the proton dose distribution planned. The principle of using PET for range verification has been studied since 1969 and has

been used clinically in a few centers, namely, at the carbon ion tumor therapy facility operating at the GSI Helmholtzzentrum für Schwerionenforschung GmbH, Germany, and at the Francis H. Burr proton beam therapy center operating in the Massachusetts General Hospital, USA. Fiedler *et al.* [33] demonstrated that the in-beam PET system developed and used at GSI was able to detect range deviations of 6 mm in water equivalent thickness for carbon ions with sensitivity and specificity values of 94% and 87%, respectively, for 81 patients. For proton beams, Parodi *et al.* and Knopf *et al.* [34, 35] showed that patients could highly benefit from offline PET/CT imaging for range verification for a number of treatment sites.

However, due to the short half-lives of the isotopes (20, 10 and 2 minutes, for the ^{11}C , ^{13}N and ^{15}O , respectively) and the low induced activity, this technology requires a dedicated PET device and data acquisition should be, preferably, during the irradiation. PET imaging for range verification can provide information for quality control post-treatment, however its outcome depends on the biological washout, on the induced activity depending on the charged particle beam used, dose per fraction, irradiated volume, body site, and the type of particle therapy delivery system (double passive scattering or pencil beam spot scanning). Moreover, when using MC calculations to predict the production of β^+ emitters, the results are dependent on the physics model and the cross-sections data used [36]. These constraints and the high cost of a dedicated PET device seem to be discouraging new particle therapy centers from considering this option.

For a real-time *in vivo* range verification, quasi-instantaneous photons (called prompt gamma, PG) emitted resulting from target nuclei de-excitation can be detected after leaving the patient body, and it was proposed in 2003 by Stichelbaut and Jongen [37]. PGs have characteristic spectra up to 10 MeV and depend strongly on the nucleus of origin and the projectile's energy. A phantom study from Janssen *et al.* [38] analyzed the factors that could influence PG measurements for range prediction, such as ρ , phantom diameter, and detector acceptance angle and cut-off energy. In 2012, IBA (Ion Beam Applications, Belgium) presented the first knife-edge shaped slit camera able to detect PG along the beam path resulting in a one-dimension depth profile [39, 40], showing its feasibility with the MC code MCNPX and its capability of acquiring 3 to 6 MeV PG in a clinical environment for different proton beam energies. Richter *et al.* [41] tested the first prototype of the IBA slit camera during seven fractions of a head & neck tumour case treated with proton therapy and verified that the range variations were negligible and below the range uncertainty of $3.5\% + 2 \text{ mm}$.

Limitations of PG imaging rely mostly on the detector technology, and on its time-, spatial- and energy resolution. Background radiation from neutrons and secondary gammas can be reduced with the application of time-of-flight analysis with respect to the arrival of the primary particle, while energy resolved detectors allow for a discrimination of PGs and their nuclei of origin [42].

Groups worldwide are developing different detector systems and there seems to be a need for a compromise between the range deviations relevant in clinical practice and its cost, since it still needs to be reasonable for a clinical institution to acquire [43].

Also for the purpose of *in vivo* range verification, other more exotic approaches are under development, such as measuring thermoacoustic waves created during particle

irradiation [44], and detecting bremsstrahlung photons and correlating them with the beam path [45–47].

Ultimately, the development and clinical implementation of range verification methods, combined with the improvement of range predictions, will allow for the decrease of the conservative margin recipes used and to give focus on how to improve proton therapy delivery in moving targets.

7.3 References

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A

**Reply to: "Comment on: Dual-energy CT
quantitative imaging: A comparison
study between twin-beam and
dual-source CT scanners [Med. Phys.
44(1), 171–179 (2017)]"**

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A.1 Correspondence

To the Editor,

First, the authors would like to thank Dr Saito for his careful reading of our paper and the insightful comments on the comparison between the two methods found in the supplementary materials of our study. In supplementary material 2.8.C, we compared two methods to derive relative electron density ρ_e : Saito [1] and *RHO/Z*, as implemented in *syngo.via* (Siemens Healthineers, Forchheim, Germany). Secondly, the authors would like to add further information and point out differences between both methods of extracting relative electron density ρ_e from dual-energy CT (DECT) images.

Saito [1] started by assuming a linear relation between ρ_e and the weighted difference (ΔHU) of the two DECT images:

$$\rho_e = \Delta HU / 1000 + 1,$$

$$\text{where } \Delta HU = (1 + \alpha) HU_{\text{high}} - \alpha HU_{\text{low}}$$

where $HU_{\text{low,high}}$ are the CT numbers for the low and high energies. In addition, to consider variabilities of different CT scanners and imaging protocols used, two fit parameters were added to the previous equation:

$$\rho_e = a \Delta HU + b$$

Dr Saito is correct in stating that Eq. (14) from Hünemohr *et al.* [2], as used in the Siemens *syngo.via* *RHO/Z* method, can be rewritten as Eq. (3) from Almeida *et al.* [3] for the case $a = b = 1$, where the α in Almeida *et al.*s equal to $(c_e - 1)$ in Hünemohr *et al.*. Dr Saito points out correctly that his method, on average, results in smaller discrepancies between extracted and reference ρ_e values for phantoms. However, the differences between Saito and *RHO/Z* are not only due to the fitting equations. Following personal correspondence with Siemens we can confirm that *syngo.via* makes use of specific DECT calibrations before producing the ρ_e images. The *syngo.via* software applies different calibrations depending on the object's diameter, the CT energy pair used, and the source-detector distance, which are all used to extract the single-fit parameter (c_e) from Eq. (14) from Hünemohr *et al.* [2] In other words, in the *RHO/Z* method c_e is also dependent on scanner variables.

In addition to the calibrations done prior to the calculation of the ρ_e images, *syngo.via* also applies an edge preserving denoising algorithm, in which the optimal contrast-to-noise ratio from the merged¹ DECT images is transferred to the resulting ρ_e images. Note that in our paper, the *Saito* method was applied on the images extracted from the scanner software without further postprocessing, as we believe was also done in Saito 2012.

To help the reader understand the differences between the methods, a model 062M phantom (CIRS Inc., Norfolk, VA) was scanned with the dual-spiral mode of the

¹The merged DECT images are obtained by mixing the low- and high-energy images with a weighted sum ($\omega_{\text{low}} \cdot HU_{\text{low}} + \omega_{\text{high}} \cdot HU_{\text{high}}$), where the optimal weighting factors are recommended by the vendor for each specific scanner.

SOMATOM Definition Confidence[®] RT pro (Siemens Healthineers, Germany) at 80–140 kVp (without tin filtration for the high-energy voltage) with a CTDI_{vol} of approximately 20 mGy and reconstructed with kernel Q34 strength 3, which includes beam-hardening correction for bone. The *Saito* and *RHO/Z* methods were used to extract the ρ_e images. For *Saito*, a RMI 467 phantom (Gammex Inc. Middleton, WI) was also scanned with the same protocol and used for calibration, yielding the fit parameters: $a = 1.0014$, $b = 0.9901$, and $\alpha = 0.9207$. Figure A.1 shows the errors between the calculated and the reference values of the model 062M, calculated from the manufacturer compositions (left panel), and ρ_e images using *Saito* (middle panel) and *RHO/Z* (right panel). The values in Figure A.1 result in a root-mean-square error over the whole set of 0.88% for *Saito* and 1.72% for *RHO/Z*. In addition to the point made by Dr Saito on the average discrepancies, we wish to point out that the standard deviation per insert is on average a factor three higher for *Saito* when compared to *RHO/Z*.

Figure A.1. Left panel: relative difference, $(\rho_e^{\text{ref}} - \rho_e^{\text{calc}})/\rho_e^{\text{ref}}$, per insert between the mean value of the calculated ρ_e and the reference, where the error bars represent the standard deviation. Middle and right panels: middle slice of the ρ_e images of the 062 M phantom using both methods, with a narrow window to visualize noise.

The authors appreciate the advantage of the Saito three-parameter fit to characterize better the combination of CT scanner, scan protocol and object dimensions and, consequently, to produce more accurate ρ_e values, as seen in Figure S2.3(e) of the supplementary materials of Almeida *et al.* and in Figure A.1 (left panel). However, the authors believe that an edge preserving denoising algorithm could also be applied to the *Saito*- ρ_e images to yield a comparable noise level to the images produced by *RHO/Z* (Figure A.1, middle and right panels).

A.2 Acknowledgments

Dr Chistian Hofmann from Siemens Healthineers is thanked for providing detailed information on the *syngo.via* algorithm.

A.3 References

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B

Evaluating clinical stopping power estimation from a radiotherapy dual energy CT scanner

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Abstract

The use of dual energy computed tomography (DECT) is increasingly considered in particle therapy (PT) to reduce the range of uncertainties attributed to the conversion of X-ray linear attenuation coefficients into relative stopping power (RSP). DECT scanners equipped with clinically available image conversion software can now be found in PT centers. In this work, RSP calculated on the basis of clinical DECT scanner software (*syngo.via*) was compared to a validated published procedure (*Hudobivnik*) for calibration and pediatric head phantoms. Based on material inserts, the average difference between RSP values calculated using *syngo.via* (*Hudobivnik*) against reference values were 1.0% (0.7%). This difference excludes the lung inserts as the *syngo.via* method does not provide Zeff values for CT numbers < -500 HU. An analysis of the head phantom showed overall a good agreement with all RSP differences within 1% between the *syngo.via* and *Hudobivnik* methods. The use of clinically available *syngo.via* provides equivalent accuracy as a validated RSP calculation method.

B.1 Introduction

Range uncertainties in proton therapy (PT) [1] are partially attributed to the conversion of x-ray linear attenuation coefficients obtained from computed tomography (CT) scans to relative (to water) proton stopping power (RSP), which is used for treatment planning. Currently RSP uncertainties from single energy CT (SECT) are estimated at 3.5% [2]. The use of dual energy CT (DECT) to separate the contributions of Compton scattering and photoelectric absorption to photon attenuation provides RSP values with 1% accuracy [3, 4] via relative electron density (ρ_e) and effective atomic number (Z_{eff}) estimation. While several methods for RSP estimation have been published [3–7], few are currently available clinically. DECT scanners have been recently installed at PT facilities [8] and clinical software allowing ρ_e and Z_{eff} calculation from DECT images has been made available. Differences in scanner and software performance suggest that careful validation is necessary before using a clinical DECT scanner [9]. In this study the RSP accuracy from a clinical DECT scanner equipped with such software was evaluated against the validated DECT RSP evaluation methods of Hudobivnik *et al.* [6].

B.2 Material and methods

A SOMATOM Definition Open AS scanner with sequential DECT capability (Siemens Healthineers, Forchheim, Germany) installed at the Loyola Univ Medical Center in Maywood, IL, was employed to scan a custom made calibration phantom and a pediatric head phantom. The calibration phantom consisted of a 15 cm diameter PMMA cylinder centrally housing the tissue mimicking inserts of the Gammex RMI 467 electron density calibration phantom (Gammex, Middleton, WI, USA). The inserts' mass density (ρ), ρ_e , Z_{eff} , mean excitation potential I and RSP are found in Table B.1 and were calculated using the elemental compositions and equations from [6]. The pediatric head phantom, model 715 HN from CIRS (Norfolk, VA, USA), is constructed of materials simulating bone and soft tissue. DECT scans of both phantoms were performed with sequential 80 kVp and 140 kVp acquisitions. CT number (CT#) images were reconstructed with the H20f kernel. The scanner software (*syngo.via*) was used to obtain ρ_e and Z_{eff} images. The Z_{eff} was calculated with exponent 3.1 using equation 2 from [6]. Alternatively the low and high kVp CT# images were converted to ρ_e and Z_{eff} using the methods presented in [6]. Subsequently the Bethe equation was used to calculate RSP following conversion of Z_{eff} to the logarithm of I using the piecewise linear fits from [3]. RSP from the calibration phantom inserts and from homogeneous parts of the pediatric phantom were obtained using elliptical regions of interest (ROI) and used to compare the two methods.

B.3 Results

Table B.1 reports the measured CT# as well as the errors compared to the reference of the DECT derived quantities for the *syngo.via* and *Hudobivnik* methods (referred to as M1 and M2, respectively) for the Gammex phantom inserts. The mean of the absolute value of insert RSP errors were 1.0% and 0.7% for M1 and M2, respectively. For intermediate quantities ρ_e and Z_{eff} , M1 had mean errors of 0.8% and 2.9 % respectively, while for M2 ρ_e and Z_{eff} had lower mean errors of 0.4 % and 1.5 %.

Figure B.1 shows RSP for different slices of the pediatric head phantom where we observed that the RSP predictions from the two methods agreed within 1%. Due to the

Table B.1. Reference values for the Gammex phantom inserts. RSP is calculated for 175 MeV protons using $I_{\text{water}} = 75 \text{ eV}$. ρ was taken from the inserts' calibration sheet.

Insert ID	$\rho \text{ (g/cm}^3\text{)}$	ρ_e	Z_{eff}	$I \text{ (eV)}$	RSP
LN-300 lung	0.27	0.261	7.36	76.3	0.261
LN-450 lung	0.42	0.409	7.49	73.8	0.410
AP6 adipose	0.947	0.928	6.16	66.5	0.942
BR-12 breast	0.981	0.959	6.82	68.0	0.970
CT solid water	1.017	0.987	7.53	70.2	0.995
BRN-SR2 brain	1.051	1.046	6.06	63.6	1.067
LV1 liver	1.104	1.075	7.49	69.5	1.085
IB inner bone	1.144	1.103	9.45	74.5	1.104
B200 bone mineral	1.153	1.104	10.15	80.3	1.095
CB2-30% CaCO ₂	1.333	1.278	10.60	80.7	1.267
CB2-50% CaCO ₂	1.556	1.466	12.26	93.1	1.428
SB3 cortical bone	1.823	1.693	13.38	105.6	1.626

Table B.2. Mean CT# at 80 kVp and 140 kVp for the calibration phantom along with the mean relative error $\Delta X = (X_{\text{measured}} - X_{\text{reference}})/X_{\text{reference}} \cdot 100\%$ of DECT derived quantities for the *syngo.via* method (M1) and *Hudobivnik* method (M2). The mean of the absolute value of insert errors is additionally reported, excluding the lung inserts from the calculation for both M1 and M2, since M1 does not calculate Z_{eff} for CT# ≤ 500 HU (due to the low signal to noise ratio of lung tissues).

Insert ID	CT# ₈₀ (HU)	CT# ₁₄₀ (HU)	$\Delta\rho_e$ (%)		ΔZ_{eff} (%)		ΔRSP (%)	
			M1	M2	M1	M2	M1	M2
LN-300 lung	-753.9	-754.8	-	3.0	-	1.9	-	-2.3
LN-450 lung	-577.1	-582.7	-	-2.7	-	-0.3	-	-2.6
AP6 adipose	-127.2	-100.0	0.6	-0.3	-2.3	1.2	-0.1	-1.1
BR-12 breast	-69.5	-58.3	0.8	0.2	-2.6	1.4	0.8	0.1
CT solid water	4.9	-8.6	0.7	0.5	-3.6	0.1	1.4	1.2
BRN-SR2 brain	-10.3	15.3	0.8	0.2	-7.3	-3.4	0.8	0.2
LV1 liver	93.1	81	0.7	0.3	-4.2	0.6	1.5	1.0
IB inner bone	349	219.1	0.5	0.7	-5.8	-4.6	0.4	0.8
B200 bone mineral	365.6	236.4	-1.3	-0.8	1.5	3.1	-2.3	-1.7
CB2-30% CaCO ₂	689.5	483.6	-0.7	-0.4	-0.9	0.0	-0.8	-0.5
CB2-50% CaCO ₂	1284.9	873.7	-1.0	-0.4	0.5	0.0	-1.1	-0.2
SB3 cortical bone	1968.6	1321.2	-0.5	0.4	0.6	-0.1	-0.6	0.6
mean error	-	-	0.8	0.4	2.9	1.5	1.0	0.7

heterogeneous nature of the pediatric head phantom it was not possible to compare the ROI RSP values to reference values, and only the comparison of M1 and M2 is reported here.

B.4 Discussion and conclusion

The generally higher errors for the *syngo.via* method are attributed to the fact that the scanner software calibration is valid for a wide range of DECT protocols and phantom diameters scanned at 80 and 140 kVp, while the *Hudobivnik* method was calibrated

Figure B.1. RSP slices for the pediatric head phantom with ROIs used to calculate the mean value and standard deviation (in brackets) of the ratio of RSP from the *syngo.via* and *Hudobivnik* methods.

specifically for this phantom and scan parameters. In general, the RSP accuracy of both methods is at the level which is desired for PT ($\approx 1\%$). We can thus conclude that both methods are acceptable for PT dose calculations, and that the added convenience of using the clinically available *syngo.via* is warranted.

B.5 Acknowledgements

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C

**Potential benefits of using an adaptive
aperture in treating small lesions in the
brain with proton therapy**

Adapted from poster P173 from PTCOG57, May 2018, Cincinnati, USA

C.1 Introduction

In the last few years, compact proton therapy centers have appeared in the market as an option with reduced cost and offering the possibility to integrate into working clinics.

Proton therapy has the potential to treat small brain lesions, aiming to spare important structures and increase the patient's quality of life post treatment [1].

The purpose of this work is to evaluate the possible gain of collimating a scanned proton beam to treat small brain lesions using a unique commercially available Adaptive ApertureTM (AA).

C.2 Material and methods

The beam line described in **Chapter 5** and validated against measurements was used for this *in silico* study. This system has a component responsible for beam collimation, the AA, consisting of moving leaves, which travel from spot to spot to shape the beam in the lateral direction (see Figures 5.1 and 5.2).

From a patient with a small volume (9 cc) craniopharyngioma (Figure B.1a), an IMPT plan with two opposing beams was designed with Raystation 7a (RaySearch Laboratories, Sweden) with a total prescribed dose of $D_{95} = 54\text{Gy}$ (30 fractions of 1.8 Gy). In an independent software, the AA positions were defined as an expansion of 1 cm from the CTV (Figure B.1b-c). The CT data files were imported into TOPAS and the IMPT plan was simulated, with and without the use of the AA component. The resulted dose distributions of both cases were compared and the dose volume histograms (DVH) were analysed for critical organs.

Figure B.1. (a) Sagittal plane from the patient CT and CTV (in pink); Two positions of the Adaptive ApertureTM (AA) for a given energy layer, (b) or (c), and for two representative spots (in blue). For each spot and energy layer, an optimal positioning of the AA is used.

C.3 Results and Discussion

An average decrease in dose of $17\% \pm 2.3\%$ to healthy tissues is observed when using the AA (Figure B.2). A margin of 1 cm was investigated, however a lower value could decrease the dose to the critical organs that are closer to the CTV, while keeping an homogeneous dose distribution (Figure B.3). An optimal value for the margin needs to be investigated.

Figure B.2. Dose distribution of the same plan with (a) and without (b) using the Adaptive Aperture[™] for a representative slice. (c) Relative dose differences between both plans.

Figure B.3. DVH with and without the use of the Adaptive Aperture[™] (AA).

Collimating the proton beam with the AA has the potential to reduce the beam penumbra and to reduce dose to OARs in treating small brain lesions.

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Addendum

List of abbreviations

ρ	mass-density
I	mean excitation potential
ρ_e	relative electron density
Z_{eff}	effective atomic number
ADMIRE	advanced modeled iterative reconstruction
CBCT	cone beam computed tomography
CNR	contrast-to-noise-ratio
CT#	CT number
CTDI _{vol}	computed tomography dose index
CTV	clinical target volume
DECT	dual-energy computed tomography
FBP	filtered back projection
FOV	field-of-view
HU	Hounsfield units
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
IDD	integrated depth dose
IR	iterative reconstruction
ITK	Insight Segmentation and Registration Toolkit
MC	Monte Carlo
MTF	modulation transfer function
NTCP	normal tissue complication probability
OAR	organ-at-risk

PBA	pencil beam algorithm
pCT	proton computed tomography
PET	positron emission tomography
PG	prompt gamma
PMI	Pseudo mono-energetic images
PT	proton therapy
PTV	planning target volume
R80	80% dose distal fall-off
RBE	relative biological effectiveness
RMS	root-mean-square
ROI	region-of-interest
RSP	relative (to water) proton stopping power
RT	radiotherapy
SAD	virtual source to axis distance
SAFIRE	sinogram affirmative iterative reconstruction
SECT	single-energy computed tomography
SOBP	spread-out Bragg peak
SPR	stopping power ratio
TIC	transmission ion chamber
TOPAS	TOol for PArticle Simulation
WEPL	water equivalent path length
WET	water equivalent thickness
ZONPTC	Zuid-Oost Nederland Protonen Therapie Centrum

Valorization

Background

Cancer is a leading cause of death worldwide. The causes, characteristics, risk factors and occurrence of cancer can vary greatly, requiring a constant development of new therapies. Radiotherapy is one of the main treatments for cancer, in which different technologies and types of radiation can be used, such as proton therapy.

In the last decennia, the number of proton therapy centers treating and under construction has increased exponentially, as a measure to provide more precise treatment modality for malign tumours. The characteristic dose distribution of a proton beam in the human body has the potential to decrease short and long term secondary effects of radiation. However, there is a lack of evidence supporting this theoretical advantage of proton therapy, only a few comparison studies indicate its superior outcome compared to x-ray radiotherapy (partially summarized in **Chapter 1**), mostly for children. A new patient selection system that can help bring light to this topic is the dutch model based approach: for each patient with a proton indication, photon (x-ray) and proton treatment plans are calculated and compared, and based on the radiation toxicity levels to the main organs-at-risk (OARs), a choice is made between both radiotherapy modalities. This model might have an important role in providing quantitative evidence of proton therapy's ability to better spare the OARs near a tumour.

Computed tomography (CT) imaging plays a crucial role in radiotherapy treatments, since the treatment plan is made based on the tissue compositions and densities extracted from the processing of each patient CT image. Nevertheless, there is an uncertainty associated with the different CT imaging, scanners and post-processing methods, which are specially relevant for proton therapy, when compared to conventional x-ray radiotherapy, because proton beams deposit most of their energy at the end of a track. To account for such uncertainties, margins are added to the tumour volume to assure that the whole malign mass is irradiated with the necessary dose, however this measure has the cost of increasing the dose to the surrounding healthy tissues.

Monte Carlo (MC) methods are considered the gold-standard for simulations of particle transport and interactions with matter, due to its complex implementation of physical models and libraries. In radiotherapy, MC techniques are needed to better predict the dose distribution in a patient, using directly or indirectly the information extracted from a CT image. While analytical methods may overlook small differences caused by tissues' miss-assignment of atomic composition and density, using MC methods these effects will be taken into account and contribute for the final dose. Besides, MC techniques are used to obtain the linear-energy-transfer (LET) distribution of different particle beams, and can also deal with moving geometries and help to understand inter-play effects between a

moving beam and a moving target. MC's biggest down-side is the computational time needed for accurate simulations, which is highly dependent on the geometry complexity and size, and the number of particles simulated. Nevertheless recent developments in the computer industry have made it possible for vendors of treatment planning systems (TPSs) to start implementing (fast) MC models.

Products and innovation

In this thesis, methodologies of improving accuracy in proton therapy have been studied.

Dual-energy CT dose calculations: We were the first group to develop a platform where dual-energy computed tomography (DECT) images could be used from end-to-end to perform MC dose calculations, a method still not implemented in any commercially available TPS. With this platform, differences in the range of protons using standard images and this new up-rising technology were investigated for phantoms, in which ground truth is known, and on a patient case. For the latter, clinical relevant differences were observed.

Moreover, different DECT modalities and methods were studied through-out this thesis, aiming to investigate the impact of DECT imaging on proton range and dose calculations, and to provide recommendations between DECT systems.

Full implementation of DECT in a TPS is not trivial if the vendor decides to use both DECT images as input. For this, DECT-specific calibrations are needed and the vendor needs to choose one from the different methods published in the last decade, for which validation has been performed in phantom studies using tissue mimicking inserts and animal tissues. An alternative is to calculate a weighted sum of both DECT images (called pseudo-monoenergetic image, PMI), or using CT scanners' own software to convert the DECT images into mass-densities or relative electron densities, that can also be given as input for the TPS.

The wide choice of possibilities dealing with DECT images makes it more difficult for DECT to be implemented on clinical practice, since numerous software and methods are available, and for a TPS vendor to choose one and implement it.

Proton system with a multi-leaf collimator: We were also the first group to model a proton therapy system with an unique multi-leaf collimator at the end of the beam line (the Adaptive Aperture[™], a product of Mevion Medical Systems, Inc., Littelton, USA) used to improved the sharpness of proton beams, hence decreasing the dose given laterally to healthy tissues and OARs. The development of the beam model was done parallel to the clinical implementation of this component and in close collaboration with the manufacturer, enabling the study of several features from this device and even investigate how to improve it. This model aims also to be used as an independent MC dose calculation platform with respect to the available TPS.

Furthermore, we also proved the feasibility of using this multi-leaf collimator combined with a precise imaging platform for irradiation of small-animals, a complete different field for which the system was not intended, greatly expanding its research capabilities. Pre-

clinical research is a corner stone of scientific developments in radiotherapy, from which new methodologies can be translated to clinical practice. Proton therapy is no exception and there is a need for pre-clinical experiments, however the cost of building a dedicated system is too high for most research facilities, making the option of adapting an existing clinical system very attractive. In this field, pre-clinical studies can help understand the biological impact of proton beams compared to standard radiotherapy, the impact on cell damage when using proton beam at different dose rates, or to investigate the potential benefit of combining proton therapy with immunotherapy, dose enhancers and other drugs.

Challenges and future perspectives

The translation of proton therapy from physics institutes and laboratories to clinical practice has brought numerous topics of research for the scientific community. The main goal is to assure the quality of treatment, in which the entire tumour is irradiated with the necessary dose to treat the patient, and at the same time the minimum amount of healthy tissue is irradiated with high doses.

On the other hand, particle therapy centers are considered the single most expensive specialized medical tool for cancer treatment, where treatment cost greatly exceeds the one from conventional radiotherapy. For this reason, a concern has been raised that proton therapy will be overused for common cancer for which evidence for proton therapy is still unclear, due to the potential profit it may bring for the medical institution. To decrease the cost of a proton therapy center, more compact single-room facilities have appear on the market in the last years, making its construction more affordable worldwide.

With respect to the topics investigated in this thesis, DECT potential improvement over single-energy CT might not be good enough to achieve the level of uncertainty desired in tissue segmentation and proton range prediction. Hence, other technologies have appeared as potential better alternatives, such as triple-energy CT or spectral CT. Another alternative might be the use of proton beams for imaging, called *proton CT*, which provides a direct measurement of tissue's proton stopping powers. For either case, there is a need to verify the method used by means of *in vivo* measurements of proton range, without which final validation of the methods is not achievable. These methods discussed in **Chapter 7**, are still under-development and not yet at a level of becoming part of clinical practice.

Furthermore, during the course of a treatment that can take up to seven weeks, the patient's anatomy can change drastically while the tumour can shrink/expand or move to a different location. It is for this reason necessary to do treatment adaption with the help of weekly or daily imaging. Currently, centers that do treatment adaptation, do it by recalculating the plan after seeing relevant differences on interfraction CT. However, intrafraction motion or irregularities are not measured. A future goal for treatment adaptation would be to do it online, in which the patient is positioned, the plan is partially delivered and with *in vivo* measurements the dose is verified and the plan adapted *in loco* if needed.

Target groups and social impact

The patient is the first to benefit from a more accurate proton therapy treatment. The use of large margins added around the tumour to assure full coverage and to account for all

uncertainty sources can be decreased by improving the accuracy of tissue segmentation and mass-density conversion, and by using with proper *in vivo* verification methods. Large margins imply that healthy tissue will be irradiated with a high dose, which can lead to short and long term side effects, including the growth of secondary tumours, that can have an considerable impact on the patient's quality of life and life expectancy. For this reason, proton therapy could be ideal for treating children and young adults. Many questions about the potential of proton therapy are still unanswered, for which there is an urgent need to perform clinical (and pre-clinical) trials and follow closely the patients treated with different radiotherapy modalities for many decades.

List of publications

Original articles

Brent van der Heyden¹, **Isabel P Almeida**¹, Gloria Vilches Freixas, Céline Van Beveren, Ana Vaniqui, Carmen Ares, Karin Terhaag, Daniëlle BP Eekers and Frank Verhaegen. A comparison study between single- and dual-energy CT density extraction methods for neurological proton Monte Carlo treatment planning. *submitted*.

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Isabel P Almeida¹, Guillaume Landry¹, George Dedes, Rakesh Patel, Mark Pankuch, George Coutrakon, Reinhard Schulte, Frank Verhaegen, Katia Parodi, John C Roeske. Evaluating clinical stopping power estimation from a radiotherapy dual energy CT scanners. *Acta Physica Polonica B* 2017; 48(10): 1619-1623.

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Abstracts

Ilaria Rinaldi, **Isabel P Almeida**, Gloria Vilches Freixas, Wouter van Elmpt, Frank Verhaegen Mirko Unipan, Geert Bosmans. Is single-energy CT still an up-to-date standard imaging modality in proton therapy? June 2019. Talk at the Particle Therapy Co-Operative Group (PTCOG) 58. Manchester, United Kingdom.

Isabel P Almeida, Gloria Vilches Freixas, James Cooley, Townsend Zwart, Armin Langenegger, Daniëlle BP Eekers, Frank Verhaegen, Potential benefit of using an Adaptive Aperture in treating small lesions in the brain with proton therapy. May 2018. Poster at the Particle Therapy Co-Operative Group (PTCOG) 57. Cincinnati, USA.

Isabel P Almeida, Matthias Sure, Gloria Vilches Freixas, James Cooley, Townsend Zwart, Armin Langenegger, Frank Verhaegen. Monte Carlo simulation of the Adaptive Aperture in a pencil beam scanning system. April 2018. ePoster at ESTRO 37. Barcelona, Spain.

Isabel P Almeida, Ana Vaniqui, Lotte EJR Schyns, Brent van der Heyden, James Cooley, Townsend Zwart, Armin Langenegger, Frank Verhaegen, Exploring the capabilities of a clinical proton beam with an adaptive aperture for pre-clinical research, talk at the 4th conference on small animal precision imaged-guided radiotherapy. March 13, 2018. Lisbon, Portugal.

Isabel P Almeida, Katia Parodi, Guillaume Landry, Frank Verhaegen. Cálculo de dose por simulação

¹ contributed equally

Monte Carlo para terapia com protões com base em tomografia computadorizada com dupla energia. November 7, 2017, talk at Encontro Nacional de Física Médica, Coimbra, Portugal.

* Awarded "Best oral presentation"

Isabel P Almeida, Lotte EJR Schyns, Wouter van Elmpt, George Dedes, Katia Parodi, Guillaume Landry, Frank Verhaegen. Monte Carlo dose calculations using different dual energy CT scanners for proton range verification. May 7, 2017. Talk at ESTRO, Vienna, Austria.

Isabel P Almeida, Lotte EJR Schyns, Michel Öllers, Wouter van Elmpt, Katia Parodi, Guillaume Landry, Frank Verhaegen. Proton Stopping Power Ratios derived from Twin-Beam and Dual-Source dual-energy CT scanners. September 2016. Poster at the European Network for LIGHT ion Hadron Therapy (ENLIGHT) meeting, Utrecht, the Netherlands.

Talks & lectures

Isabel P Almeida. Particle Radiotherapy. Lecture for students of the medical engineering from the Technical University of Eindhoven. February 28, 2019. Maastricht, The Netherlands.

Isabel P Almeida. Computed tomography. Lecture for students of the master in Biomedical Sciences from Maastricht University. January 28, 2019. Maastricht, The Netherlands.

Isabel P Almeida. Proton therapy in Maastricht: clinic and research. Workshop on Implementation of Proton Therapy in Portugal. November 5-6, 2018. Centre of Nuclear Sciences and Technologies, Lisbon, Portugal.

Isabel P Almeida. Dual-Energy Computed Tomography: latest findings in research. Regionale bijscholingsdag (Regional training day). October 25, 2018. Maastricht, The Netherlands.

Isabel P Almeida. Particle Radiotherapy. Lecture for students of the medical engineering from the Technical University of Eindhoven. September 27, 2018, Maastricht, The Netherlands.

Isabel P Almeida. Proton Therapy. Lecture at the University of Hasselt for students of the faculty of industrial engineering. November 28, 2017, Hasselt, Belgium.

Isabel P Almeida, Dual-energy CT for proton therapy. October 27, 2017. Talk at the 7th NCS Lustrum Symposium, Amsterdam, The Netherlands.

Isabel P Almeida. Imaging for proton Therapy. Talk at the Centre of Nuclear Sciences and Technologies. April 2017, Lisbon, Portugal.

Frank Verhaegen, **Isabel P Almeida**, Brent van der Heyden, Lotte EJR Schyns, Ana Vaniqui, Stefan J van Hoof, Patrick V Granton, Guillaume Landry, Gabriel P Fonseca, Mark Podesta. The use of imaging information in Monte Carlo simulations. First meeting on Monte Carlo Techniques for Medical Applications. October 15-18, 2017, Napoli, Italy.

Isabel P Almeida. Computed Tomography. Lecture for students of the medical engineering from the Technical University of Eindhoven. September 2016, 2017 and 2018, Maastricht, The Netherlands.

Isabel P Almeida, Frank Verhaegen, Imaging for proton therapy: See where to put the dose and if it really went there. Meeting of the regional proton referral centers. April 6, 2016, Maastricht, The Netherlands.

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Appearances in popular media

"Clinical proton system could enable small-animal studies", published on December 6th 2018 in <https://physicsworld.com/a/clinical-proton-system-could-enable-pre-clinical-studies/>

* Regarding the work of Almeida *et al.* *Br J Radiol* 2018; 91:20180446.

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Murillo, Gabriel, Louise, Planckinho and Carlos-bacon, the best nights in Maastricht were spent in your company. I will really miss those nights.

I would like to thank Isabel Teixeira, the coach of the Portuguese national team of Korfball, for her trust in me, for her continuous effort in keeping me as an option for the team, motivating me and helping me overcome the difficulties of playing korfball in different competitions. I am truly grateful Isabel, because I know you planned the preparation of the team always bearing in mind my travel arrangements, so that I could be present as much as possible, and most of all for the risk you took by never giving up on me. I also thank my friends and colleagues from the national team for their warm welcome in every period of training and competition. To the Portuguese Korfball Federation I thank for all the support, at many levels. It was more than I could ask for.

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To all my family, thank you for your love. While being here, I could see that a family knows no distance, going for a weekend escape to Porto or Hamburg was just a simple trip, where I could be spoiled with love (and food). Tio Zeca and Tia Eduarda, thank you for your support and for coming to this beautiful city to see my defense. Tio Manfred and Tia Lena, I loved that I could see you so often and that we always kept in touch. Cristina e os seus rapazes (como diz o tio Manfred) Claas, Clemens and Arne, with you I feel at home. Tia Cândida and Patrícia, you also spoil me with love and kind words boosting my ego, we are just "farinha do mesmo saco". Cláudia and Pico, there is something really special about you, you have three amazing daughters, and now Lourenço is the prince of the family, stealing the spotlight with his cuteness. Leonor, peço desculpa por geneticamente teres ficado com um feitio tão parecido com o meu, ninguém merece, pelo menos temo-nos uma à outra.

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To David, the love of my life, four years seemed extremely long, but we made it. Thank you for always being on my side, everyday. I am ready to start the next chapter of our story.

Curriculum vitae

Isabel P Almeida was born on December 13th, 1990 in Lisbon, Portugal. With a natural interest in Physics and influenced by her parents strong background in sciences, Isabel enrolled in the Physics and Technological Engineering program in the Instituto Superior Técnico (IST), Lisbon.

In 2012, Isabel attended the "2nd Particle Therapy Course" organized by ESTSeL with Dr. Georg Dietmar as main lecturer, where she realized her wish to pursue a carrier in the field of Particle Therapy. Isabel achieved her Masters degree with a thesis in positron emission mammography in a collaboration between the Laboratory of Instrumentation and Experimental Particle Physics (LIP), Lisbon, and the Institute of Nuclear Sciences Applied to Health (ICNAS), Coimbra.

In May 2015 Isabel started her PhD at Maastric Clinic, Maastricht, under the supervision of Prof. Dr. Frank Verhagen and co-supervision of Dr. Guillaume Landry from the group of Prof. Dr. Katia Parodi from Ludwig Maximilians University (LMU) in Munich. During her PhD, Isabel studied the use of dual-energy computed tomography to improve proton range prediction and tissue segmentation, and developed the Monte Carlo beam model of the Zuid-Oost Nederland Protonen Therapie Centrum (ZON-PTC), Maastricht. After finishing her PhD work, Isabel joined the proton physics team of ZON-PTC during the commissioning phase of the proton system and has been working there until the present time.