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

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Link to publication

Download date: 29 May. 2022

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 comercially 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 [ρ_e,Z_{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 ($\alpha CT_{low} + (1 - \alpha) CT_{high}$), 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 ± 0.023 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 where 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 x 10 cm^2 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 mm^3 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-coefficientsf or 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 difference 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:

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