Motion compensation for 4D PET/CT
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Citation for published version (APA):
Kruis, M. F. (2014). Motion compensation for 4D PET/CT
Chapter 1

Introduction

Radiation therapy (RT) is, besides surgery and chemotherapy, one of the most important curative treatment modalities the treatment of cancer. The aim of RT is to kill all tumour cells by inflicting irreversible DNA damage by means of ionizing radiation. Most often, a linear accelerator is used to deliver this radiation.

Over the last two decades, RT has become much more precise. The development of techniques like multileaf collimators has made it possible to more precisely apply a prescribed dose to the tumour and to avoid undesired irradiation of normal surrounding structures [1]. Furthermore, target areas and organs at risk (OARs) can be defined more precisely by advanced imaging modalities like X-ray computed tomography (CT) [2], single-photon emission computed tomography (SPECT) [3], magnetic resonance imaging (MRI) [4] and positron emission tomography (PET) [5, 6]. This allows for better prediction of toxicity and differentiation between areas with different biological characteristics within the tumour. Imaging modalities incorporated into the RT delivery machine finally made it possible to visualize the patient anatomy prior and during treatment and guide the dose delivery. Image-Guided RT (IGRT) by means of Cone-beam CT (CB-CT) has become a standard treatment strategy [7] and accelerators combined with an online MRI scanner are currently being developed [8].

1.1 PET/CT imaging

The main imaging modality used in RT planning is CT [9]. CT provides information about the patient's anatomy, which can be used to delineate structures of interest (i.e. tumour mass and OARs), and since CT measures the local electron density, it is also used to estimate the attenuation of the radiation beam in the patient [10]. The delineation and dose-estimation are used to design a treatment plan that aims to satisfy dose constraints that are stipulated by a radiation oncologist.

CT provides a good visualisation of the patient's anatomy. However, the soft-tissue contrast is limited and CT normally does not provide functional information. Therefore, other imaging modalities, such as MRI and PET, are a valuable addition to iden-
PET imaging relies on positron emitting radiotracers. After intravenous injection, the radiotracer is distributed to specific parts of the body, depending on its pharmacodynamic properties. An often used tracer is $^{18}$F-Fluorodeoxyglucose (FDG). Since FDG is very similar to glucose, it has a tendency to accumulate in the metabolic active regions within the body, such as tumours, as well as the brain [13]. A positron emitted from $^{18}$F annihilates with an electron, resulting in two photons moving in opposite directions. These photons are detected using scintillating crystal detectors placed in a ring around the patient, and by pairing coinciding photons their source can be localized on a line of response (LOR). The LORs are combined and reconstructed into a 3D map of the tracer distribution. The majority of the photons are however absorbed or scattered by the body, resul-
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...the signal. To correct for this, an electron density map is required. In older systems, a Germanium-68 transmission scan was used to measure the attenuation [14].

Most contemporary PET systems are integrated with a CT scanner [15]. The registered CT data provides a visualisation of the anatomy of the patient, which aids the localisation of the detected tracer activity. The CT is also used to construct the attenuation map [16]. It is important that the patient is scanned in the same position during both the PET and the CT acquisition. An offset will hamper localisation of PET activity on the anatomy as revealed by the CT data and will cause incorrect attenuation correction [17–25].

PET is in principle a quantitative imaging modality. Local tracer uptake is often expressed in a standardised uptake value (SUV), which expresses the tracer uptake, corrected for the total amount of injected radiotracer, time between injection and measurement, and patient weight [26], lean body weight [27] or body surface [28]. There are however many factors that compromise the accuracy of quantitative PET measurements, such as imperfections in the scanner calibration, differences in radiotracer administration and respiratory motion [26]. These factors make SUV measurements inaccurate and therefore SUV differences between measurements are only considered significant in clinical practice if they are larger than 25% [29].

1.2 Dose painting

Studies have suggested that not all parts of the tumour are equally radiosensitive [30, 31]. With PET information, the dose can be distributed to match the local radiosensitivity, instead of applying a homogeneous dose to the entire tumour [32–34]. The technique of shaping the dose to local functional properties is christened “dose painting” [35].

There are roughly two dose painting approaches [36]. In dose painting by contours, regions within the tumour are delineated to which a dose is prescribed that differs from the rest of the tumour [5]. For dose painting by numbers [37, 38], the local prescribed dose is directly linked to the locally measured SUV.

It is obvious that quantitative properties of PET imaging are of more importance for dose painting than when PET data is solely used for the detection of tumours. Differences in PET values will directly lead to differences in dose distributions. It is therefore important to make the PET measurements as quantitative as possible.

1.3 Respiratory motion

During respiration, air is breathed in and out of the lungs to exchange carbon dioxide for oxygen in the blood. Two mechanisms can propel human respiration; chest and...
abdominal breathing. The chest moves on average between 3 to 5 mm during tidal breathing [39], while the diaphragm moves on average 13 mm [40, 41]. Respiratory motion of the tissues varies considerably within the lungs. The top hardly moves, while much more respiratory motion can be found near the diaphragm. Respiration causes pulmonary tumours to move 4 mm on average in cranial-caudal direction [42]. Since the liver closely follows the motion of the diaphragm, tumours in the liver typically experience considerably more motion than lung tumours [41, 43].

Figure 1.2: A sagittal patient example of an inhale (a) and exhale (b) CT. It is visible that most motion occurs around the diaphragm.

1.4 Respiratory motion effects

Respiratory motion hinders PET and CT image acquisition. CT is a fast scanning technique, acquiring multiple slices per second. Therefore, individual slices are little affected by respiratory motion. However, to obtain a 3D volume, multiple slices need to be scanned. In helical CT scanners, individual slices are consecutively obtained. Since not all slices are acquired simultaneous, each slice will be in an arbitrary phase of the respiratory cycle, which causes distortions. It is possible to eliminate respiratory induced motion artefacts by taking a breath-hold CT scan in about 5 to 10 seconds [44]. Respiratory motion causes different artefacts in PET than in CT. Since PET imaging takes around 2 minutes per bed position, the detected PET signal is blurred over the trajectory of many respiratory cycles [45, 46]. Due to the long acquisition time that
is required, breath-hold scanning is not an option for PET. This motion blur will diffuse the measured uptake, making organs and tumours less visible and making SUV measurements dependent on the patient-individual breathing motion. This compromises the quantification of the PET signal.

1.5 4D imaging

A way to deal with respiratory motion during imaging is to acquire respiration correlated 4D instead of 3D data [45, 47]. In this way, respiration artefacts can be reduced, while the 4D data also provides information about the respiratory motion, which can be incorporated in RT planning.

4D CT data is created by acquiring an oversampled dataset, in which every slice location is scanned for the duration of at least an entire respiratory cycle, while the respiration is monitored by a respiratory sensor. By sorting the image data into a number of bins according to the respiratory signal, a 4th dimension can be created [48, 49]. To obtain 4D PET data, all detected coincidences are binned according to the simultaneously acquired respiratory signal and for every bin a separate 3D reconstruction is made [45]. The individual reconstructions are then combined into a 4D PET dataset.

4D PET/CT imaging will lead to sharper images with fewer artefacts. Apart from improving the individual images, the position of the anatomy in the individual PET frames will correspond better with the position in the corresponding CT frames, compared to 3D PET/CT. Since a position offset between the two modalities introduces artefacts in the attenuation corrected PET data, it is likely that 3D PET/CT will be compromised by attenuation uncertainties [17–25]. 4D imaging will probably reduce these uncertainties.

1.5.1 Binning artefacts

Although 4D imaging reduces respiratory artefacts, there are still residual artefacts limiting the image quality. Since the respiration varies between cycles, binning of 4D data is not a trivial task [50, 51]. The most commonly applied binning techniques are phase and amplitude binning [50, 52]. For phase binning, usually the end-inhale moment is detected in the respiratory signal to identify individual respiratory cycles [53]. Each respiratory cycle is subsequently divided into time bins. For amplitude binning the data are assigned bins directly according to the magnitude of the respiratory signal [54]. Both phase and amplitude binning require a predictive correlation between the respiratory signal and the internal motion during the respiration.
Amplitude binning is more robust to deal with irregular breathing than phase binning [50, 52, 54, 55]. Amplitude binning is however not very suitable for RT planning, since individual bins do not represent the same amount of time. The average position in an amplitude binned 4D dataset therefore does not represent the true average position [56].

1.5.2 Signal-To-Noise Ratio

Treatment planning (target delineation and dose optimization) is usually performed on 3D data. For this purpose, one 3D frame could be chosen from the 4D dataset [57]. Analysing the individual frames of the 4D PET dataset, will also yield results which are little affected by motion artefacts. The individual frames will, however, be constructed with a subset of the data, leading to a poor signal-to-noise ratio (SNR). For comparison of measures like the maximum SUV in the tumour (SUV\text{max}) between datasets, it is however important to maintain a good SNR [46, 58]. It is known that a decrease of SNR is associated with a higher SUV\text{max} (for instance, for a 2-minute acquisitions SUV\text{max} is about 18% higher than a 15-minute acquisition, according to Lodge et al. [59]. In order to obtain a SNR similar to a normal 3D scan, more signal is needed. For CT scanning, this means an increase of imaging dose [23]. For PET imaging increase of the FDG dose is often not possible due to the noise equivalent count rate [60] and the cost of the tracer, which means that the only way to increase the amount of detected counts is to increase the acquisition time [61, 62]. Since PET acquisition is already rather time consuming (a normal whole body 3D PET/CT protocol takes about 30 minutes) an increase in the duration of the protocol is not desirable, which might explain why 4D PET imaging has not yet become widely used in clinical practice.

1.6 Motion Compensation

Instead of using an individual 4D frame from treatment planning, it is also possible to combine all the signal into one 3D image, in which the effect of motion on the signal has been compensated. One way to achieve this, for CT data, is to register the different frames of the 4D CT dataset to each other and average them [63]. In this manner, artefacts are averaged out and the SNR is improved, without increasing dose. Similar methods have also been developed for 4D PET data [64, 65]. However, 4D PET data does not provide much anatomical information, especially when the images have low SNR. It is therefore difficult to create a respiratory motion model from
4D PET data only. Most contemporary PET scanners are however combined with a CT scanner. Since the intra-fractional variability of motion during the acquisition is expected to be small (1.6mm according to Rit et al [66]), a motion model created from the 4D CT data is likely useable for motion compensation of the 4D PET data. Most of the registration methods that are used to extract a motion model from the 4D CT data have been developed for thoracic data. Respiratory motion is however also present (and often even larger [40, 41]) in abdominal organs, like the liver, stomach and kidneys. It would therefore be worthwhile to investigate the usability of these registration methods for motion compensation of 4D abdominal data.

1.7 Objectives of this thesis

The objective of this work is to improve quantitative PET imaging for organs that move due to respiration, while maintaining a short acquisition time. To achieve this, we developed a clinical platform for the motion compensation of 4D PET-CT data. We have tested our methods and quantified the effects of motion compensation for patients with lung and liver tumours.

In chapter 2 we describe a method to create a motion compensated Mid-Position (MidP) PET scan from 4D PET/CT data. We have tested this method on phantom data and 27 lung cancer patients and have quantified the blurring effects of respiratory motion on the PET images.

Since 4D attenuation correction leads to better attenuation agreement between the PET and CT frames, we also expect improved attenuation correction in MidP PET data, compared to standard 3D PET data. In chapter 3 we have quantified these differences in a clinical dataset of 32 lung cancer patients.

Our motion compensation techniques have initially been developed and tested for pulmonary PET/CT data. However, since respiratory motion is typically larger for liver lesions than for pulmonary lesions, the potential benefit of motion compensation is larger for the liver. The performance of the proposed registration method can, however, be compromised by the increased motion and the limited CT contrast in the liver. In chapter 4, we therefore test the performance of our motion compensation method in liver cancer patients. In chapter 5, we apply our CT-based motion compensation technique on 4D PET data of liver patients.

When patients do not breathe regularly, severe artefacts can appear in 4D CT data. These artefacts degrade the quality of the motion model, which will have an effect on the quality of the treatment plan and PET motion compensation. In chapter 6, we investigate how we can apply amplitude binned 4D data into the RT treatment planning process, in order to improve the quality of 4D CT motion model. Furthermore,
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we have developed a method to detect potential artefacts at an early stage in the image acquisition process.

In the final chapter of this thesis, we discuss the results of chapters 2 to 6 and reflect on the consequences for quantitative PET measurements and clinical RT.