Motion compensation for 4D PET/CT
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Chapter 2

PET Motion Compensation for Radiation Therapy Using a CT-Based Mid-Position Motion Model: Methodology and Clinical Evaluation

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**Abstract**

**Purpose:** Four-dimensional positron emission tomography (4D PET) imaging of the thorax produces sharper images with reduced motion artifacts. Current radiation therapy planning systems, however, do not facilitate 4D plan optimization. When images are acquired in a 2-minute time slot, the signal-to-noise ratio of each 4D frame is low, compromising image quality. The purpose of this study was to implement and evaluate the construction of mid-position 3D PET scans, with motion compensation using a 4D computed tomography (CT)-derived motion model.

**Materials and Methods:** All voxels of 4D PET were registered to the time-averaged position by using a motion model derived from the 4D CT frames. After the registration the scans were summed, resulting in a motion-compensated 3D mid-position PET scan. The method was tested with a phantom dataset as well as data from 27 lung cancer patients.

**Results:** PET motion compensation using a CT-based motion model improved image quality of both phantoms and patients in terms of increased maximum SUV (SUV$_{max}$) values and decreased apparent volumes. In homogenous phantom data, a strong relationship was found between the amplitude-to-diameter ratio and the effects of the method. In heterogeneous patient data, the effect correlated better with the motion amplitude. In case of large amplitudes, motion compensation may increase SUV$_{max}$ up to 25% and reduce the diameter of the 50% SUV$_{max}$ volume by 10%.

**Conclusion:** 4D CT-based motion-compensated mid-position PET scans provide improved quantitative data in terms of uptake values and volumes at the time-averaged position, thereby facilitating more accurate radiation therapy treatment planning of pulmonary lesions.
2.1 Introduction

External beam radiation therapy, often combined with concurrent chemotherapy, is the primary treatment for patients with inoperable lung cancer. Although many improvements in radiation therapy planning and delivery have been realised, survival rates are still poor. The incidence of local recurrences is high, and dose escalation is hampered by pulmonary toxicity [67].

Local recurrences have been related to the uptake of $^{18}$F-labeled fluorodeoxyglucose (FDG) in the tumour prior to radiation therapy [68]. Therefore, instead of applying a homogeneous dose, studies are being performed on the use of positron-emission tomography (PET) to modulate the dose distribution within the primary tumour [5, 69, 70]. The aim of this so-called PET boosting or "dose painting" is to increase the dose in parts of the tumour with higher standardised uptake values (SUV).

Dose painting of SUV puts a higher demand on both numeric and geometric accuracy of the 3-dimensional (3D) SUV distribution and its registration with the planning computed tomography (CT) scan. A major cause of image deterioration and CT misregistration during acquisition of PET data is respiratory motion. The peak-to-peak amplitude of a lung tumour can exceed 20 mm [42]. This motion blurs the PET signal over the motion trajectory, increasing the apparent tumour volume and decreasing the maximum SUV values and thereby reducing visibility of small lesions. The blurring will also obscure any inhomogeneous uptake within the tumour [61].

The acquisition time of a PET scan, in our case 2 minutes per bed position, makes breathhold PET scans impossible. Time-resolved imaging mitigates the effects of respiration motion by binning the PET signal according to a respiratory signal to produce a 4D PET dataset. The signal-to-noise (SNR) drops considerably with each extra reconstructed 4D frame [61], because each bin contains only a fraction of the detected annihilation events.

To increase the SNR, the duration of the 4D acquisitions could be extended. However, PET acquisition is already time consuming; so for us, this is not an attractive option. Increasing the applied amount of radio tracer is also not desirable, considering the noise-equivalent counting rate and the increase in radiation dose and costs.

Instead of increasing the amount of counts, a motion-compensated 3D dataset could be created. Several attempts to achieve this goal have been performed. These methods can be divided into 2 groups.

The first group of techniques repositions lines of response in the raw list data according to a motion model before performing image reconstruction. Because most reconstruction algorithms are nonlinear [58], these methods will give the best SNR. However, full deformable registration of list-mode data is usually not performed because conventional PET reconstruction algorithms are designed for straight lines of response. Therefore many methods apply affine motion compensation to the list-mode data [71]. Furthermore, attenuation correction is difficult because attenuation
characteristics are scrambled by the motion compensation. The effect of respiration specific attenuation correction could be substantial near the diaphragm [20]. Rosario et al. [25] however found that these effects are often negligible for lung tumours.

A simpler approach is to perform motion compensation with reconstructed 4D PET data [64]. The separate frames are registered and averaged. The advantage is that a deformable motion model may be used and respiration specific attenuation correction can be applied. Furthermore, because no list-mode data are needed and most commercial PET scanners are capable of 4D imaging, the method would be applicable to data from all vendors.

For compensation, an adequate motion model is necessary. Bai et al. [64] used a motion model derived from the PET data for this purpose. PET data in general provide little anatomical detail. Furthermore, given our 2-minute 4D PET acquisition, motion detection in 4D PET data is difficult. The resulting low SNR decreases visibility of motion and increases the chance of coregistration of noise, resulting in an amplification of noise after averaging.

Because most contemporary PET scanners are combined with a CT scanner, we used a motion model based on 4D CT data instead of a motion model derived from PET data. Motion detection in pulmonary 4D CT scans has been investigated extensively and provides good results. Similar to the method described by Wolthaus et al. [63], we created a 3D mid-position (MidP) PET dataset, to be used alongside a MidP CT in the RT planning process.

Our aim was to assess and compensate for motion-induced blurring in PET imaging of the thorax. A registration motion model was calculated using 4D CT according to the method developed by Wolthaus et al. [63]. Using this motion model, we created a motion-compensated 3D MidP PET/CT from 4D PET/CT data, which was acquired in the same time as normal 3D PET/CT data.

2.2 Materials and Methods

2.2.1 Acquisition settings

Data were acquired with a combined PET/CT scanner (Gemini TF; Philips Medical Systems, Cleveland, OH). The reconstruction voxel size of the PET data was $4 \times 4 \times 4$ mm, while the voxel size of the CT data was $1 \times 1 \times 3$ mm. The 4D PET/CT data were reconstructed in 10 phases, and the attenuation in each frame of the 4D PET data was corrected with the corresponding 4D CT frame. The acquisition time of the 4D PET was kept the same as that used for 3D PET: 2 minutes per bed position.
2.2.2 Phantom experiments
Phantom experiments were performed with a respiratory phantom (Dynamic Thorax Phantom; CIRS, Norfolk, VA). We removed the attenuation material and mounted 4 spheres (diameters of 34 mm, 31 mm, 16 mm, and 12 mm) filled with a clinically relevant solution of $^{18}$F-labeled fluorodeoxyglucose (FDG) on the phantom ($\sim 50$ kBq/mL). Unfortunately, the phantom did not allow the use of background activity. These spheres moved in a sinusoidal pattern along the craniocaudal direction with a variety of amplitudes, ranging up to 40 mm. The range of amplitudes was chosen such that the range of ratios between amplitude and diameter of the sphere was comparable for all measurements. The period was kept at 4 seconds for all measurements.

2.2.3 Patient data
Between 2010 and 2013, 27 patients with a diagnosis of lung cancer underwent a 4D PET and 4D CT scan after written informed consent was acquired. At 1 hour before PET scanning, 190 MBq of FDG was administered to the patient. All patients were candidates for radical (chemo-)radiation therapy. One patient was rescanned 1 year after radiation therapy for response assessment. For 2 patients, respiration was monitored using a thermocouple (Type T, copper-constantan, S-CC-UO-7/1; Volenc, Hradec Králové, Czech Republic) inserted into an oxygen mask [63]. The other 25 patients were scanned using a bellows belt (Interactive Breath-hold Control System; Mayo Clinic / Medspira, Minneapolis, MN).

2.2.4 Motion registration on CT
Respiratory motion was detected in the 4D CT datasets by using the method developed by Wolthaus et al. [63]. The exhale frame was chosen from the dataset to function as a reference to which all others were registered, using a phase-based optical flow method [72].

After registration, the 4D deformation vector field (DVF) provided the deformation of each frame toward the reference. However, this frame is not the most representative position of the body during the respiration. Therefore, the local average displacement over the breathing cycle was subtracted, such that the average displacement in each voxel was zero. This average position is called the mid-position [63].

2.2.5 Mid-position PET
Each 4D PET scan was deformed using the corresponding inverse of the 4D MidP DVF derived from the 4D CT. For the interpolation of the deformation and the voxel values, third-order b-splines were used to reduce loss of information. Subsequently, the average voxel values over all frames were calculated, yielding the MidP PET scan.
2.2.6 Image Quality

We compared the motion-compensated MidP PET scan to the uncompensated frame average of the 4D PET scan. We will refer to this averaged scan as the 3D PET scan, as it simulates a regular 3D PET scan.

The lesions were selected manually. In an ongoing PET boost study [5], the boost volume is automatically created by thresholding to 50% of the SUV$_{max}$. We used this threshold to automatically delineate a boost volume. In this boost volume, we calculated the average SUV value (SUV$_{mean}$) and the effective diameter (D), defined as

$$D = 2 \sqrt[3]{\frac{3V}{4\pi}}$$  \hspace{1cm} (2.1)

where V is the volume of the boost area. Park et al [46] suggested that the effects of motion in PET data are dependent on the amplitude and the diameter of a tumour. We therefore investigated the amplitude-to-diameter ratio (A/D) and the diameter alone and the effects of motion compensation. Finally, in the patient data, we investigated the relationship between the position of the tumour in the lung, the amplitude, and the SUV$_{max}$.

2.3 Results

2.3.1 Phantom experiments

In fig. 2.1, the difference between the compensated and uncompensated scans in terms of SUV$_{max}$, effective diameter of the 50% SUV$_{max}$ region, and SUV$_{mean}$ in this region are shown. PET slices through the center of the sphere are shown (fig. 2.1(d)). We performed a second-order fitting through the measurements, describing the relationship between A/D and these effects. The coefficients of determination ($R^2$) of these fittings were 0.96, 0.86, and 0.95, for $\Delta$SUV$_{max}$, $\Delta$Diameter, and $\Delta$SUV$_{mean}$ respectively. For fittings based on the amplitude alone, we found $R^2$ values of 0.58, 0.45, and 0.72 respectively.

2.3.2 Patient data

4D PET/CT scans were acquired from 27 patients, of whom 1 patient was scanned twice. The 2 scans of this patient were analyzed separately, resulting in a total of 28 scans. In most (19 scans), only 1 tumour was visible; in 8 scans, 2 lesions were present; and in 1 case, 4 separate lesions could be detected. Together, this summed to a total of 39 lesions. On average, these lesions moved with a peak-to-peak amplitude of 5.7 mm, ranging from 1.4 mm to 14.7 mm. The mean apparent size of these boost...
Figure 2.1: Changes in SUV\textsubscript{max} (a), effective diameter of 50% SUV\textsubscript{max} region (b) and SUV\textsubscript{mean} (c) in this region. Coefficients of determination (R\textsuperscript{2}) of the 3 fittings were 0.995, 0.855, and 0.954, respectively. Dotted line represents 95% confidence intervals. Visualization of the phantom measurements containing the static 3D CT, static 3D PET (0 cm), 3D PET of a dynamic measurement (2 cm), and a motion-compensated 3D PET of this dynamic measurement (2 cm) (d). Black curves illustrate automatic segmentation based on the 50% SUV\textsubscript{max} threshold, and white horizontal lines indicate differences between extents of this delineation in the direction of the motion.
volume, based on a threshold of 50% of the SUV\textsubscript{max} on the uncompensated 3D PET scan, was 13.5 cm\textsuperscript{3} (range, 0.7 to 76.2 cm\textsuperscript{3}).

Visual inspection showed no differences between PET and CT registration for 4D and MidP scans. This suggests that the breathing motions for both modalities were sufficiently similar. In fig. 2.2, a sagittal slice of a patient dataset is shown, demonstrating that motion compensation results in sharper images, while the SNR level remains high. Because the images are sharper, the uptake heterogeneity within the tumour is better visible.

Figure 2.2: PET-CT data of a dorsally located lung tumour. This tumour was moving with a peak-to-peak amplitude of 1.5 cm. Top row shows frame 0 of the 4D CT (a) and PET (b) data, and segments of the 10 PET frames (c). Bottom row shows the motion-compensated MidP CT (d), uncompensated PET (e), and motion-compensated MidP PET scan (f). The averaged scans possess less noise. The tumour appears smaller and more heterogeneous in the compensated PET scan (50% SUV\textsubscript{max} region is 26% smaller and SUV\textsubscript{max} is 25% higher).

Compared to the uncompensated 3D PET scans, the SUV\textsubscript{max} showed an average increase of 4.5% (range, -6.5% to 25.3%) in the 3D MidP PET scans. The volume of the lesion with an SUV value larger than 50% of the SUV\textsubscript{max} decreased on average by 5.3% (range, -13.3% to 25.9%). Within this volume, the SUV\textsubscript{mean} increased by 4.6% (range, -7.4% to 26.0%). All these changes were significant (P<.001) according to a paired Student t test.
Motion compensation for 4D lung PET/CT

Similar to relationships among the phantom measurements, we investigated the relationship between A/D and the increase of $SUV_{max}$, changes in effective diameter of the boost volume (threshold of 50% $SUV_{max}$), and $SUV_{mean}$ in this segmentation (figs. 2.3(a) to 2.3(c)). The fitting of these data was poor; therefore, we also investigated the relationship between the amplitude alone and the motion compensation effects (figs. 2.3(d) to 2.3(f)). The correlation with the diameter alone was better than that of A/D in the patient data.

![Figure 2.3: Plots of the changes of SUV<sub>max</sub>, effective diameter of the boost volume, and SUV<sub>mean</sub> relative to A/D ((a) (b) (c)), and amplitude ((d) (e) (f)), with linear fitting and 95% confidence intervals. Individual volumes are illustrated by the size of the circles.](image)

Finally, we scored the lesions according to their position in the thorax in three groups. Seven lesions were located in the mediastinum or outside the lungs (eg, the thoracic wall) and were not analyzed. The other lesions were divided between the upper lobes (16) and the middle and lower lobes (16) (fig. 2.4). A significant difference (Wilcoxon rank sum test) in amplitude was found between the 2 groups ($P<.019$). Between these
2 groups we measured a borderline significant difference ($P=.048$) in gain in $\text{SUV}_{\text{max}}$ after motion compensation.

Figure 2.4: Boxplots displaying the relationship between tumour location and amplitude and $\Delta \text{SUV}_{\text{max}}$. There were significant differences between the amplitude of tumours in the upper lobe and those in the lower and middle lobes, coinciding with a significant difference in $\text{SUV}_{\text{max}}$.

2.4 Discussion

We describe a method to construct a motion-compensated 3D PET scan at the time-averaged position by using a 4D CT-derived motion model and demonstrate improved quantitative uptake values and volumes. The underlying 4D PET scans were acquired in the same time as normal clinical 3D PET scans facilitating an efficient workflow.

Our phantom data suggest a strong correlation between the amplitude-to-diameter ratio and motion compensation effects. Park et al. [46] have demonstrated that target size and motion amplitude have a combined effect on 3D PET measurements. However, they moved the phantom with only 2 different amplitudes. We have tried to quantify the relationship between tumour size and motion and the effects of motion compensation by testing a range of sizes and amplitudes. Park et al. [46] found that the recovery coefficient of a sphere with a diameter of 2.0 cm decreases from 83% (static) to 78% and 58% with 1.0 and 2.0 cm amplitudes, respectively. This means that for ratios of 0.5 and 1.0, they found an increase of 6.4% and 43.1% respectively. This is in accordance with our results, as shown in fig. 2.1(a).

Bai et al. [64] described and tested a similar method with pulmonary phantom data. They extracted the motion model directly from the 4D PET data. Prior to this study, we tried to extract motion patterns directly from some of our clinical 4D PET scans. These results were very unsatisfactory. The short acquisition time led to low SNR,
and therefore we were not able to extract proper motion models. We believe that a CT-based motion model from a combined scanner is a good surrogate. Because the PET and CT acquisition were performed on the same machine, only intrafractional motion is expected (approximately 1.6 mm) [66].

In the clinical data, the predictive value of the amplitude alone was much stronger than in the phantom results. A likely explanation for this discrepancy is that the phantom spheres were homogeneous, while tumours are typically not. In fact, the smallest size of a homogeneous region should be considered, which is difficult to do.

In contrast to the phantom data, background activity was present in the clinical data, possibly reducing the absolute effect of motion compensation on $SUV_{max}$ and threshold volume. Furthermore, the spheres in the phantom data were moving in a perfectly regular pattern, while some variation is expected in patients [66]. This may cause artefacts, especially in CT, and differences in breathing dynamics during the PET and CT scans. In 1 patient, a major artefact at the location of the tumour led to a substantial decrease in $SUV_{max}$ (7.4%) and an increase in effective diameter (3.9%). For three other lesions, we found an increase of the effective diameter of more than 2%. However, these lesions were relatively small (0.9 cc, 1.1 cc, and 2.2 cc), suggesting a possible partial volume effect. In these cases, one could choose to use the uncompensated data.

We repositioned the motion-compensated PET data to the mid-position [63], minimizing systematic errors for radiation therapy treatment planning. Note that the mid-position is not necessarily an actual snapshot of the 4D respiratory cycle. However, the mid-position should correspond best with the position of the original 3D PET, because it is the average position over the respiration. This also makes the data, in combination with 3D MidP CT, ideal for radiation therapy treatment planning.

Differences in the size of the 50% $SUV_{max}$ boost volume show the potential value of the method within a radiation therapy setting. Differences in effective diameter of the boost volume can be as large as 9.5%, in which case the difference in boost volume was actually 23.9%. In this case, the use of motion-compensated PET data for "dose painting by contours" [5] will have direct effect on the dose distribution. The effect of motion compensation on "dose painting by number" is less clear. The potential clinical relevance of motion compensation for such planning methods should be investigated.

However, many lung tumours hardly move. In the clinical dataset, we showed that the need for motion compensation depends mainly on the motion amplitude and to a much lesser extend the size of the lesion. We found that tumours moving with an amplitude smaller than 5 mm hardly show effects, while clear effects become apparent for tumours moving with an amplitude of more than 10 mm. In a radiation therapy setting, the amplitude is usually unknown, but because respiratory motion is instigated by the diaphragm, proximity to the diaphragm increases respiratory mo-
Our data suggest that our method is mainly clinically relevant for tumours positioned in the lower quadrant of the lung. However, the method described also has great potential for abdominal tumours, which on average, have an amplitude of 13 mm [74]. Additionally, the background activity is much higher in abdominal organs, decreasing the visibility of lesions, and therefore needing high data sharpness.

### 2.5 Conclusions

Using a CT-based motion model, we were able to reconstruct a motion-compensated MidP PET scan from rapidly acquired 4D PET data. The motion compensation corrects for the effects of respiratory motion of tumours, such as considerable blurring of the SUV values in PET scans, which influences the appearance of tumour and boost volumes. The effects of motion compensation depend mainly on the amplitude and, thus, the location of the tumour and to a much lesser extend to its size. Compared to a normal 3D PET scan, the lesion in the corrected scans had higher SUV values and smaller 50% SUV$_{max}$ volumes. These differences change the volumes used in PET boost studies. The clinical impact of PET motion compensation on dose distributions when by numbers is applied, needs to be investigated in a planning study.

### 2.6 Acknowledgments

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