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

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Chapter 4

Registration accuracy and image quality of time averaged mid-position CT scans for liver SBRT

This chapter has been published as:
Abstract

Purpose: The purpose was to validate the accuracy of motion models derived from deformable registration from four-dimensional computed tomography (4DCT) and breath-hold contrast enhanced computed tomography (BHCCT) scans for liver SBRT. Additionally, the image quality of the time averaged mid-position (MidP) CT constructed using the detected motion model was assessed.

Materials and methods: 4DCT and BHCCT liver scans of 11 patients were acquired with 1 or 2 fiducial markers. Using parametric sampling the markers were digitally removed. Phase-based optical flow was used to register the 4D frames and the BHCCT, and create MidP data. We compared the deformable registration of the markerless scans with the actual displacement of the markers to assess registration accuracy. The noise levels of the MidP scans were compared to those of the 4DCT and BHCCT data.

Results: We found an average misregistration of 1.8 mm (±0.5 mm). The constructed MidPCT scan contained around three times less noise than the original 4D scan. The residual error between the MidPCT and the BHCCT was 3.0 mm (±0.9 mm).

Conclusions: High precision deformable image registration of 4DCT and BHCCT liver cancer patients was achieved and used to create motion compensated MidPCT scans, with increased contrast-to-noise (CNR) levels. This improved visualisation of tumours and anatomy, facilitates radiotherapy treatment planning.
4.1 Introduction

The radiotherapy (RT) of liver cancer is challenging due to large respiratory motion and high radio-sensitivity of the organ. Recent developments, like image guided RT (IGRT) and stereotactic body RT (SBRT) have made more precise focal dose delivery possible. This potentially reduces the risk of radiation-induced liver disease (RILD), improving treatment possibilities [84].

Since the liver is located directly under the diaphragm, it exhibits large respiratory motion. The average displacement is 13 mm, but can reach up to 50 mm [41], requiring robust respiratory management during radiotherapy. Four-dimensional computed tomography (4DCT) data provides information on the breathing dynamics. By data registration a motion model can be derived and used to define treatment margins, and derive a 3D planning CT from the 4DCT data.

Many deformable registration methods have been described for, and tested on pulmonary 4DCT data. However, registration of the liver on 4DCT has been investigated to a much lesser extent [85].

It is tempting to use the methods developed for the lung on the liver. However, these methods might not be readily applicable. Absence of contrast on liver CT data complicates registration and makes it more reliant on outer contours than inner structure. Therefore Brock et al. [86] used contours to detect organ motion and deformation. However, research shows that image based deformable registration of the liver is possible [85, 87].

We applied the registration method developed by Wolthaus et al. [63] for 4D lung CT data on 4D liver CT data. The extracted motion was used to derive a time averaged mid-position (MidP) scan. Since contrast timing is very difficult in 4DCT, a separate 3D breath-hold contrast enhanced CT (BHCCT) scan was acquired and registered to the derived MidP scan.

Since liver structures are hardly visible on 4DCT without contrast agents, anatomical landmarks could not be used to investigate the registration accuracy. We therefore used fiducial markers to assess the registration accuracy by digitally removing the markers and comparing the registration of the original dataset with the registration of the data without the markers.

4.2 Materials and Methods

4.2.1 Patients

Eleven patients that were scheduled for liver SBRT between 2009 and 2011 and received 1 or 2 markers in the liver, were included. These fiducial markers (O-twist, 3 mm, 18 g, BIP gbh, Germany) were placed in close proximity of the target lesion by a
radiologist under CT or ultrasound guidance, facilitating image guidance with cone-beam CT (CBCT) during SBRT [88]. All individual markers were manually delineated in all phases and analysed separately.

4.2.2 CT data

The CT data were acquired on a multi-slice scanner (24-slice Somatom Sensation Open, Siemens, Forchheim, Germany) and reconstructed on a voxel size of 1 mm by 1 mm, with slices of 3 mm thick. A 4D scan was acquired without contrast agent, since contrast timing is difficult in a 4D scan [89]. The 4D data was constructed by sorting an oversampled helical scan in 10 phases according to a respiratory signal detected by a thermocouple (Type T, Volenec, Czech Republic) in an oxygen mask [63]. The pitch and rotation time of the acquisition protocol were tailored to the patient respiratory frequency to obtain adequate sampling. This protocol was validated on 4DCT phantom data with large amplitudes and was accurate within 2 mm (data not shown). Additionally, a 3D exhale breath-hold CT scan was acquired with the use of intravenous contrast (iohexol). The average exposure was 75 mAs/slice (range 64-95) per slice for the 4DCT and 83.4 mAs/slice (61-105) for the BHCCT.

4.2.3 Deformable registration

The registration method has been described by Wolthaus et al [63]. In short, before registration a quadrature filter was applied, to extract the phase signal. The phase image describes transitions between bright and dark. After filtering, the data were registered to a reference frame using an optical flow registration method. The exhale frame was chosen as a reference, because in this frame the respiratory velocity is typically the smallest and thus contains the fewest breathing artefacts. The local motion was stored in a 4D Deformation Vector Field (DVF).

4.2.4 Mid-position CT

We transformed the DVFs to the time average position instead of the position of the reference frame. We call this average position, the Mid-Position (MidP). All frames were deformed to the MidP DVF. From these frames, we calculated the median of the coinciding voxels of the individual frames during the respiration, resulting in a high quality 3D MidPCT scan [63]. Note that due to hysteresis the MidP is not necessarily a physically achievable situation. However, since systematic errors are minimised in the MidP scan, it is best suited for RT treatment planning in combination with suitable margins [90] in case no gating, tracking or breathhold is used. Moreover, the MidP scan provides a density grid for dose calculation yielding results close to a full 4D scan [91].
4.2.5 Registration of BHCCT to MidPCT

The BHCCT scans had to be registered to the MidP. The absence of contrast agent during the 4D scans, caused intensity differences between the BHCCT and MidP scans. To make the scans compatible for the registration method, the contrast was removed digitally.

The contrast agent concentrates in the vasculature and the well perfused organs, which normally have intensities of around 30-60 Hounsfield Units (HU). The agent increases these densities up to 200 HU. IV contrast does hardly distribute into fat (∼-84 HU) and bone (∼700 HU), and therefore their intensities do not change. In order to normalise the CT scans, we selected voxels with HU between 0 and 250 and replaced these values with 0 in both scans. We subsequently added a small amount of Gaussian noise (σ = 1 HU), since the registration algorithm performs better on non-homogeneous data. We also applied a minor homogeneous smoothing kernel (3 mm × 3 mm × 9 mm) to eliminate sharp transitions. After normalisation, the scans were compatible and registered using the same method as was used for the 4D phases.

4.2.6 Marker removal

The markers were manually identified. A region of interest was placed generously to encompass the majority of streak artefacts, and replaced by a generalised 3D version of the non-parametric sampling method proposed by Efros and Leung [92]. It uses a sample space in a representative part of the liver without markers, from where voxels were selected to iteratively replace voxels at the border of the mask. The neighbourhood around the bordering voxel to be replaced was compared to the sample space, to find the region with the lowest sum of squared differences. The voxel at the centre of this region was used to replace the masked voxel. A graphical illustration of this process is given in fig. 4.1.

4.2.7 Registration analyses

To quantify the registration accuracy within the liver, we removed the markers and computed the Euclidian distance between the local deformable registration of the markerless data and the marker displacement. The manual marker delineation was used to find the average displacement in the deformable registration. The centre of mass displacement of the marker region that had a density larger than 300 HU was used as golden standard.

We subsequently compared the deformable and rigid registrations of the original data with the deformable registration results of the markerless data. Finally we investigated the accuracy of the registration of the BHCCT to the MidPCT. To evaluate the influence of the digital erasing process on the local deformable registration, we also replaced a region in the centre of the liver where no markers were present with
a synthetic texture and calculated deformable registration difference. To evaluate noise differences between the 4DCT scan, the BHCCT scan and the MidP scan, we calculated the standard deviation of the CT values in a part of the liver without tumours or major vessels.

4.3 Results

The average peak-to-peak marker amplitude was around 17 mm (see table 4.1). On average we masked a volume of 17 cc ($\pm$ 8 cc) per marker. The original marker location was hardly visible after masking the marker (figs. 4.2(a) and 4.2(b)). However, when streak artefacts were present in the data, these may have remained visible (figs. 4.2(d)}
Registration accuracy of 4D liver CT

and 4.2(e)). After marker masking we performed all registrations. In the resulting MidPCT data, no streak artefacts were visible.

**Table 4.1:** An overview and comparison of the registration results. It provides per registration, the amplitudes of the registration and the average Euclidean distance between the motion of the centre of mass of the marker and the deformable registration of the original data at the region around the marker.

<table>
<thead>
<tr>
<th>Amplitude (mm)</th>
<th>Δ with motion of centre of mass of markers (mm)</th>
<th>Δ with def. reg. with markers (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>CC</td>
</tr>
<tr>
<td>Motion of centre of mass of markers</td>
<td>2.5 (±1.6)</td>
<td>17.2 (±7.4)</td>
</tr>
<tr>
<td>Def. reg. 4DCT with markers</td>
<td>3.0 (±2.4)</td>
<td>16.8 (±7.1)</td>
</tr>
<tr>
<td>Def. reg. 4DCT without markers</td>
<td>3.8 (±2.5)</td>
<td>17.0 (±7.3)</td>
</tr>
<tr>
<td>Def. reg. BH CT and MidP without markers</td>
<td>1.0 (±1.0)</td>
<td>4.0 (±1.7)</td>
</tr>
<tr>
<td>Def. reg. 4DCT at reference location, away from markers</td>
<td>7.1 (±2.9)</td>
<td>15.8 (±5.4)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ± = standard dev.; LR = left–right; CC = cranial–caudal; AP = anterior–posterior.

We measured the influence of the masking process by replacing a part of the liver, away from the tumour and visible structures. The registration difference between the original and masked data in this area can also be found in table 4.1.

Using the deformable registration we constructed MidPCT scans. The standard deviation in the liver in this scan was 11.1 HU (range 8.1-14.8), while in the original 4DCT the standard deviation was 31.54 HU (18.2-54.9) and in the BH CT 20.3 HU (18.0-23.9). The decrease in noise between the 4DCT and the MidPCT improved the CNR and thereby the vasculature and tumour visibility (see fig. 4.3).

We removed the markers and normalised both the MidP scans and the BH CCT scans. An example of this normalisation is given in fig. 4.4. Then, we registered the results to each other (see table 4.1). Visual comparison of the location of the vasculature on the BH CCT scans and the MidP scans revealed that these vessels were positioned correctly.
4.4 Discussion

We tested a phase-based optical flow method for the registration and MidP construction of 4D liver CTs. Between the 4DCT phases, we found an average registration error of 1.8 mm. With the registered 4DCT we were able to reconstruct respiration averaged mid-position CT scans, with decreased noise levels. The registration accuracy of the MidP scan with the BHCCT scan was 3.0 mm. These results are consistent with the MIDRAS [85] study in which this methodology was tested on one hepatic 4DCT dataset.

To remove the markers, we used a three dimensional implementation of non-parametric sampling. This method was chosen since it can restore local surrounding structure, by mimicking similar structures from a sampling space. It is commonly used for 2D texture synthesis, since it does not require many parameters and provides good results [92]. To our knowledge this is the first time it was used for biomedical 3D textures synthesis.

The resulting artificial structure looks natural. Original marker locations were hardly visible and only minor streak artefacts remained. Since artefacts were not local and
Figure 4.3: In the original 4DCT data ((a) and (d)) the vasculature and the tumours are poorly visible due to a high level of noise. In the MidPCT ((b) and (e)) the noise has decreased considerably, leading to better visibility of structures. In the two right figures ((c) and (f)) we see registered BHCCT data.

their locations were not continuous between the phases, we were convinced that these remaining artefacts would not aid the registration method. The fact that we did not see the remaining artefacts back on the MidP scans, supports this assumption.

Although liver motion can be reduced significantly by abdominal compression [93], residual motion will always persist. Therefore, even with abdominal compression, precise knowledge on the respiratory motion remains important.

Liu et al [87] found Euclidean distance errors in their phantom study between 2.0 mm and 3.8 mm. Piper et al [94] report average registration errors of 3.7 mm, and the MIDRAS study [85] reports errors between 1.8 mm and 8.2 mm. Our average registration error of 1.8 mm seems to be decent, especially since no contrast agent was used in the 4D data. The registration error was somewhat larger for the registration between the MidPCT and the BHCCT (3.0 mm). This can be explained by the loss of structural information after normalisation.

The use of masked markers as references is a strong measuring tool, but does not give many measuring points per patients. Therefore it does not provide a strong vol-
Figure 4.4: Examples of BHCCT (a) and MidPCT data (b). In (c) and (d) we see the results of the normalisation.

umetric model verification. It would therefore be interesting to include more patients in the future, to increase the statistical power.

The MidPCT has superior CNR over the original 4DCT, due to a decrease of noise. The increase was similar to the findings of Wang et al [95]. This improved the visibility of the vasculature and the tumours. In the case of a simultaneously acquired PET-CT, the MidPCT is likely of added value. Rosario et al. [25] demonstrated that a mid-ventilation CT can be used to accompany PET for attenuation correction as well as localisation. We hypothesise that a mid-position CT will lead to even better results due to its improved image quality and geometrical correspondence to the average position. The DVF}s could also be used to compensate for motion and reduce respiration related artefacts in 4D PET [77] and CBCT scans [96].
4.5 Conclusion

Image based motion registration of liver 4DCT data without markers can be achieved with a precision well within the voxel size. The registration can be used to create a 3D MidPCT scan, which possesses superior CNR to the original 4DCT scan. We also showed that these 4D datasets could be registered to a BHCCT, facilitating the use of using these scans for planning purposes of stereotactic irradiation.