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Motion representation in 4DCBCT

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Short title: Motion representation in 4DCBCT

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4D cone beam CT-measured target motion underrepresents actual motion

Short title: Motion representation in 4DCBCT
Summary
Daily four-dimensional cone beam CT (4DCBCT) provides pre-treatment tumor motion information. We compared the real-time centroid motion of electromagnetic beacons (“target”) in the lung with 4DCBCT measurements using two different reconstruction algorithms in combination with internal or external respiratory signals. Our results show that target motion is generally underrepresented in the 4DCBCT scans, and that there is no significant difference between the motion measured in 4DCBCT scans reconstructed using different algorithms and respiratory signals.
Abstract

Purpose
4D cone-beam CT (4DCBCT) facilitates verification of lung tumor motion before each treatment fraction and enables accurate patient setup in lung stereotactic ablative body radiation therapy (SABR). This work aims to quantify the real-time motion represented in 4DCBCT, depending on the reconstruction algorithm and the respiratory signal utilized for reconstruction.

Methods and Materials
Eight lung cancer patients were implanted with electromagnetic Calypso beacons in airways close to the tumor, enabling real-time motion measurements. 4DCBCT scans were reconstructed from projections for treatment setup CBCT for 1-2 fractions of 8 patients with the Feldkamp-Davis-Kress (FDK) or the prior image constrained compressed sensing (PICCS) method and internal real-time Calypso beacon trajectories or an external respiratory signal (bellows belt). The real-time beacon centroid (“target”) motion was compared to beacon centroid positions segmented in the 4DCBCT reconstructions. We tested the hypotheses that 1) the actual target motion was accurately represented in the reconstructions and 2) the reconstruction/respiratory signal combinations performed similarly in the representation of the real-time motion.

Results
On average the target motion was significantly underrepresented and exceeded the 4DCBCT motion for 48%, 25% and 40% of the time in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions respectively. The average underrepresentation for the LR, SI and AP direction was 1.7mm, 4.2mm and 2.5mm, respectively. No difference could be shown between the reconstruction algorithms or respiratory signals in LR direction (FDK vs. PICCS: p=0.47, Calypso vs. bellows: p=0.19), SI direction (FDK vs. PICCS: p=0.49, Calypso vs. bellows: p=0.22) and AP direction (FDK vs. PICCS: p=0.62, Calypso vs. bellows: p=0.34).

Conclusions
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The 4DCBCT scans all underrepresented the real-time target motion. The selection of the reconstruction algorithm and respiratory signal for the 4DCBCT reconstruction does not have an impact on the reconstructed motion range.
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Introduction

Lung stereotactic ablative body radiotherapy (SABR) treatment planning typically relies on motion estimation from four-dimensional (4D) computed tomography (CT). However, the motion estimation from one 4DCT scan represents a snapshot in time. Shah et al. (2013) showed that the lung tumor motion of a patient due to respiration can vary substantially from breath-to-breath and from day-to-day [1]. The major challenges for optimal motion and target estimation are tumor motion exceeding the measured motion from planning 4DCT and motion artefacts resulting from irregular breathing during CT acquisition. [2–5]. An accurate motion measurement and treatment setup are crucial for SABR, where high doses to small, moving targets are delivered in very few fractions [6,7]. The current practice for managing uncertainty in motion and target estimation is to utilize sufficient population-based margins, combined with either an internal target volume (ITV) or a mid-ventilation-based approach, and perform treatment setup based on a (3D) cone beam CT (CBCT) scan [8,9].

Pioneered by Sonke et al., a 4D reconstruction of the cone-beam CT (4DCBCT) [10] found its way into clinical practice through integration in commercially available imaging systems. 4DCBCT facilitates verification of tumor motion before each treatment fraction and thus a reduction of geometrical uncertainties for improved accuracy in patient setup. Purdie et al. showed that discrepancies in motion ranges of up to 10mm can be observed between the 4DCT scan for treatment planning and a 4DCBCT at the time of treatment [11].

4DCBCT averages many images acquired over 1-4 minutes into typically 10 discrete motion bins based on a respiratory signal. This averaging process suggests that the actual motion during the 4DCBCT acquisition period is larger than that measured from the 4DCBCT scan. However, this difference has yet to be quantified.

Previous studies either examined different reconstruction algorithms and compared the results to a reference 4DCBCT [12], or used markers in the lung to quantify the motion underrepresentation for Feldkamp-Davis-Kress (FDK) reconstructions [13], usually suffering from poor image quality [14]. There is currently no data in the literature that quantifies the motion underrepresentation for iterative reconstructions in a patient study by comparing to real-time motion data.
Iterative reconstructions, like the prior image constrained compressed sensing (PICCS) method [15] and the associated improvements in image quality will play a major role in future lung SABR treatments. Thus, an investigation of the motion underrepresentation in a patient study with a real-time motion signal for comparison is of great clinical interest.

In the absence of an internal marker signal for respiratory binning, various external surrogates like infrared markers placed on the abdomen or respiratory belts can be utilized. Respiratory belts are widely used for binning in 4DCT imaging and provide a convenient external respiratory signal for binning in 4DCBCT reconstruction, but the imperfect correlation between internal target motion and motion of the external respiratory signal used for triggering the 4D reconstruction can lead to a reduced accuracy of the motion representation. Thus, a quantification of resulting uncertainties is important for a clinical use. Extracting the diaphragm position from the projection images has proven to be another robust method for binning [10,11], but was not possible for all our patients as the diaphragm was not within the imaging field of view for upper lobe tumors.

We performed 4DCBCT motion range measurements using two reconstruction algorithms (FDK and PICCS) in combination with internal (Calypso beacons) or external (bellows belt) respiratory signals. Firstly, we determined the accuracy of the 4DCBCT measurements using the real-time beacon centroid (“target”) motion as the ground truth and secondly, we compared the performance of the 4DCBCT algorithm/respiratory signal combinations. Additionally, this work aims to provide an estimation of the motion underrepresentation component for margin calculations for clinical applications.

**Material and Methods**

**Patients**

Eight patients were treated within the XXX study (XXX) and were implanted with three Calypso lung transponder beacons (Varian Medical Systems, Palo Alto) close to their tumor, one week prior to treatment simulation (Table 1).
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Treatment planning

The 4DCT scan for treatment planning was performed with the patients free breathing and positioned in a BodyFix BlueBAG (Elekta, Stockholm, Sweden) system. Depending on the location of the tumor, the patients were simulated and treated in either supine or prone position to allow the beacons to be within detectable distance from the panel positioned above the patient (<19 cm beacon to panel). One patient was treated in lateral decubitus position and excluded from the analysis, because truncation artefacts in the reconstructions, resulting from the setup rendered the images unsuitable for analysis.

The 4DCT scans and pre-treatment fluoroscopy were reviewed to quantify the surrogacy error between the beacon centroid motion and target motion. In two patients, one of the beacons was excluded from tracking to keep the surrogacy error below 3 mm (Table 1) [16,17].

The treatment was delivered as a 2-arc Volumetric Modulated Arc Therapy. The Gross Tumor Volume (GTV)-to-Planning Tumor Volume (PTV) margin was 5mm for all patients and accounted among other uncertainties for the surrogacy error between the tumor and Calypso beacons utilized for tracking. The patients received either 48Gy in 4 fractions or 50Gy in 5 fractions. The prescription isodose surface was chosen such that 100% of the GTV received no less than 100% of the dose and at least 97% of the PTV received the prescription dose.

In-room imaging

Before each treatment fraction a half-fan, full rotation CBCT scan was performed for setup verification with the standard 60s acquisition protocol (680 projections) on a Varian Trilogy linear accelerator (Varian Medical Systems, Palo Alto). At the same time the Calypso system recorded the real-time motion signal of the implanted beacons (Figure 1). In addition, the patients' breathing signals were recorded with a bellows belt (Philips Medical Systems, Cleveland, OH). Respiratory phases for both Calypso and bellows signals were calculated retrospectively such that end inhale was assigned 0% phase, end exhale was assigned 50%, and phase values in between end inhale and end exhale were linearly interpolated.
Ground truth motion

As described in the report of AAPM Task Group 101, the linear accelerator’s image-guidance systems are often not able to deliver the real-time position of a soft-tissue tumor. The implantation of markers in the vicinity of the tumor in combination with x-ray imaging or electromagnetic tracking are well accepted approaches to overcome this obstacle [18]. For this study, goal of the implantation procedure was to place the beacons such that the tumor was at or near the centroid of the beacons. The real-time motion was measured by the Calypso system as the motion of the centroid position of 2-3 electromagnetic Calypso beacons, which can be localized with sub-mm accuracy [19,20], and was defined as the ground truth “target” motion when later comparing it to the reconstructed motion ranges of the same beacons.

4D CBCT image reconstruction

4DCBCT scans were reconstructed from the projections of the treatment setup CBCT for fractions of eight patients (=1-2 fractions per patient), where both the raw imaging data (CBCT projection images) and respiratory signal data (Calypso and bellows) were available. Every fraction that had a complete data set was included. For each fraction, 4D reconstructions from the same CBCT projections were performed using the

- FDK method [21] and
- the iterative PICCS method [15].

The PICCS method utilizes total-variation minimization and a prior image similarity constraint to reduce noise and streaking artefacts when reconstructing based on undersampled data. For this reason, 3D FDK volumetric data sets were reconstructed in addition and utilized as the prior image. For both FDK and PICCS, 4D reconstructions were performed using phase-based binning based on two different respiratory signals:

- the centroid of the internal Calypso motion trajectories in the SI direction (“internal motion”) or
- the bellows belt signal (“external respiratory signal”)
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with an image spacing of 1x1x1mm³. Phase-based binning was used instead of amplitude-based binning to avoid large maximum angular gaps and interbin image quality variations due to baseline shifts in the respiratory signal when reconstructing from sparse data [14]. The prior weighting factor for the PICCS reconstructions was chosen to be 0.5 as suggested by Chen et al. [15].

4DCBCT motion range measurement

The Calypso beacons were segmented for the 10 phases of all the 4DCBCT scans in 3DSlicer (v4.5.0-1) and their position in each phase determined. The windowing for the segmentation was optimized for the beacon visualization as shown in Figure S1. The beacon centroid motion with respect to the end exhale reference phase was then calculated. Subsequently, the reconstructed motion ranges from the 4DCBCT scans were compared to the real-time target motion during image acquisition.

Statistical analysis

The differences between the motion ranges from the 4DCBCT scans and the real-time target motion were computed. For the real-time target measurements, the range was calculated as the mean ± 2 standard deviations (SDs) = 4SDs or ≈ 95% of the motion, to limit the effect of extreme values. The motion ranges used in the statistical analysis are reported in Table 2 however the figures show the full target motion ranges (minimum and maximum values). The mean difference, standard deviation and maximum deviation for each reconstruction combination and direction were calculated. ANOVA, followed by pairwise comparisons using the Dunnett’s test, was performed in Prism 7 (GraphPad, Inc) to test whether the real-time motion ranges were similar to the 4DCBCT motion ranges. Motion ranges in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions were analyzed separately. The data were matched for fractions in the statistical testing and the significance level for the p-value was 0.05.

Two-way ANOVA testing, followed by pairwise comparison using the Tukey’s test, was performed on the motion ranges in the reconstructed 4DCBCT scans to identify a possible impact of the reconstruction algorithm (FDK, PICCS) or respiratory signal (Calypso, bellows) on the obtained motion ranges. Motion ranges in the LR, SI and
AP directions were analyzed separately. Again, the data were matched for fractions in the statistical testing and the significance level for the p-value was 0.05. The hypothesis for testing was that there is no difference between the reconstruction algorithms and the respiratory signals for binning.

In addition, the percentage of time during CBCT image acquisition, where the true target motion was larger than the reconstructed motion ranges in the 4DCBCT images was evaluated.

**Results**

All 4DCBCT reconstruction methods failed to represent the full target motion range. The measured reconstructed motion ranges were substantially smaller than the real-time target motion (4SDs) during CBCT acquisition as shown in Table 2. The only exception was patient 7, fx 3, where a larger motion was seen in the 4DCBCT scans in the SI direction. The difference was <1 mm, and was likely due to the segmentation uncertainty limited by the reconstruction voxel size of 1 mm. In Figure 2 the full real-time target motion distribution is shown in comparison to the reconstructed ranges in the 4DCBCT scans for the SI direction.

The maximum deviation between the real-time target motion (4SDs) and the 4DCBCT motion ranges was 6.9mm in the LR direction, 19.1mm in the SI direction and 12.5mm in the AP direction. The largest mean deviation between the real-time target motion and the represented motion in the 4DCBCT scans was found in the direction of the largest real-time motion, the SI direction, with a motion underrepresentation of on average 4.2mm. The average underrepresentation in the LR direction (1.7mm) and AP direction (2.5mm) was smaller.

Testing the first hypothesis, that the real-time target motion is accurately represented in the 4DCBCT scans, we found a significant motion underrepresentation in the 4DCBCT scans compared to the real-time target motion for all directions (LR: p=<0.0001, SI: p=0.0003, AP: p=0.002), and therefore reject the null hypothesis (pairwise comparisons in Figure S2).

For some patients, the different reconstruction combinations led to a substantial variation in the measured motion in 4DCBCT scans, as shown in Figure 3A for
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patient 2, fraction 4. Patient 5, fraction 1, shown in Figure 3B, was the patient with the largest real-time target SI motion of 31.4mm (4SDs), which led to a more consistent motion representation in the reconstructions in all directions. In general, the motion range in the reconstructed images was the most consistent with the real-time target motion ranges in the SI direction.

Two-way ANOVA testing for the second hypothesis did not show any impact of the reconstruction algorithm or respiratory signal on the motion ranges measured in the reconstructed 4DCBCT scans in the LR direction (FDK vs. PICCS: p=0.47, Calypso vs. bellows: p=0.19), SI direction (FDK vs. PICCS: p=0.49, Calypso vs. bellows: p=0.22) and AP direction (FDK vs. PICCS: p=0.62, Calypso vs. bellows: p=0.34). Thus, the hypothesis that there is no difference between the different reconstruction combinations cannot be rejected.

The 4DCBCT scanning methods produced very similar average motion ranges within each direction. All methods showed a higher average motion range in the SI direction compared with the LR and AP directions (Table 2).

The mean variation in the motion ranges between the different reconstruction combinations was $0.33\pm0.53$mm in the LR direction, $0.27\pm0.29$mm in the SI direction and $0.49\pm0.73$mm in the AP direction.

The percentage of time when the real-time target motion exceeded the measured reconstructed motion range from the 4DCBCT scans is shown in Table 3. In the LR direction the real-time motion exceeded the reconstructed motion range for 48±16% of the time. The real-time motion exceeded the 4DCBCT motion range for the least time in the SI direction (on average 25±15%) followed by the AP direction (40±17%). This is visualized in more detail in Figure S3, where the percentage of time when the real-time target motion exceeded the measured reconstructed motion range from the 4DCBCT scans is shown as a function of motion larger than the reconstructed motion for all directions.

Discussion

Despite being based on the same projection image data, the different 4DCBCT reconstruction combinations led to some variation of measured motion ranges
although this did not reach statistical significance (as shown for patient 2, fx 4 in Figure 3). The variation was especially pronounced for patient 4, fx 1 shown in Table 2, where the SI motion was not the dominant motion. The reconstructed Calypso motion trajectories were the most consistent for patient 5 and patient 8 (fx2), where the SI motion was predominant and larger than for the other patients (Figures 2-3 and Table 2).

The real-time target motion was generally underrepresented in the 4DCBCT scans, due to an averaging within the motion bins, and sudden motion peaks (like the cough of patient 5 in fx 1) and breathing irregularities were not picked up in the reconstructions, as a result of the averaging over 10.5-25 breaths/min (Table 1). We could not observe any patterns for motion underrepresentation depending on large (lower lobe) or small motion (upper lobe) or motion in LR/AP direction being larger than motion in SI direction. This could be due to the sample size being somewhat limited. Figure S3 shows, however, that motion in inferior direction was the most underrepresented, potentially caused by the inspiration phase being shorter than the expiration phase [22] and end-exhale being more stable [23]. This finding is in agreement with the data presented by Iramina et al. for reconstruction with FDK [13]. Figure S3 can be used as a tool to estimate the non-isotropic motion underrepresentation in 4DCBCT scans for clinical applications. However, one limitation of our study is that the data in this work all originates from a 60s-acquisition protocol and we did not look into the quantitative effects of 4DCBCT acquisition time on motion estimation. The results could be different when using different protocols of longer acquisition times.

While the reconstruction algorithm did not have an impact on the motion representation, the image quality of the PICCS reconstruction, qualitatively determined through visual inspection, was superior to the FDK reconstruction, with image noise and streaking artefacts being substantially reduced (Figure S1, Video S4). However, the contrast of the Calypso beacons in the FDK reconstruction was superior to the PICCS reconstruction. Overall, the appearance of the PICCS 4DCBCTs was slightly blurry, which is a common problem of reconstruction algorithms that utilize total-variation minimization to reduce noise and artefacts.
Based on the image quality, the PICCS reconstruction is to be favored over the FDK reconstruction (Video S4). The computation time for a 10-phase 4D PICCS reconstruction was roughly ten minutes, compared to only one minute for a 10-phase 4D FDK reconstruction (NVIDIA Quadro M5000 Graphics Processing Unit).

Yuasa et al. investigated the accuracy of motion trajectory measurement depending on the gantry speed during CBCT acquisition in a phantom study and observed a loss of accuracy for high gantry speeds of 4-6º/s as used in this study [24]. Image acquisition at slower gantry speeds and a larger number of projections could potentially improve the accuracy of the motion representation in 4DCBCT scans. However, Dang et al. simulated 60s 4DCBCT scans of patients by reducing the number of projections (to 33-38 per bin) and could only observe maximal differences <1.2mm for PICCS reconstructions compared to the original 4-6min scans [12].

Vergalasova et al. concluded that the ITV in (3D)CBCT scans gets underestimated in inferior direction because of the relatively short inspiration phase, but used the motion range from 4DCBCT scan as the reference [22]. We could show that this reference suffers from a motion underrepresentation as well.

In contrast to Iramina et al., who reported on the accuracy of target motion trajectories in dual-source 4DCBCT scans and concluded that amplitude-based binning lead to superior results in terms of an accurate motion representation [13], our study utilized phase-based binning for both Calypso and bellows to avoid large maximum angular gaps and interbin image quality variation due to baseline shifts in the respiratory signal [14], due to an observed drift of the bellows signal and sparse projection data (60s scan). In addition, we present iterative PICCS reconstructions and our results for the maximum errors observed for both FDK and PICCS reconstructions are comparable to their data [13].

In this study, the range of Calypso beacon centroid motion in the 4DCBCT reconstructions was investigated and not the tumor motion directly. We used beacons as an objective measure in order not to introduce additional uncertainties for the tumor delineation in undersampled 4DCBCT scans [25] or CBCT projection images. Our 4DCBCT and real-time target motion measurements were consistently performed on the centroid motion of the Calypso beacons and due to their close
vicinity to the tumor we can assume this as representative for the effects of reconstruction on motion underrepresentation for reconstructed tumor motion. The surrogacy error between tumor and beacon centroid motion was investigated in a separate study by Hardcastle et al. [16,17], and needs to be added to the motion underrepresentation error when using markers/beacons for tumor tracking [26]. There is also a small uncertainty when segmenting the beacons in the reconstructed 4DCBCT scans. Iramina et al. report a marker segmentation error of 0.29 mm for manual beacon segmentation at the same voxel size of 1x1x1 mm$^3$ [13].

Finally, the uncertainties from a 4DCBCT scan need to be put into perspective. As extensively studied by van Herk [27,28], respiratory motion leads to blurring of the dose distribution close to a Gaussian approximation and can be treated as a component of the random error of the size of 0.36 times the amplitude of the motion for amplitudes $<1$ cm. For larger amplitudes, the effect on the dose distribution is asymmetrical and the additional margin for respiration in each direction is a linear function of the motion amplitude ($0.25 \times$ amplitude to $0.45 \times$ amplitude) depending also on the isodose level prescription. Hence, the motion underrepresentation in the 4DCBCT scans does not directly translate into a margin, but will need to be scaled down with one of these recipes depending on the motion amplitude. An accurate treatment setup, however, is crucial, because a setup error is of a systematic nature in a stereotactic setting with only few fractions. For this purpose, the 4DCBCT is a valuable tool providing more information than a blurry 3DCBCT [22].

A further consideration is that the motion during the irradiation can exceed the motion during setup imaging [1]. Additionally, modulated delivery techniques, like IMRT and VMAT, in combination with extreme hypofractionation and flattening filter free beams can lead to hot and cold spots in the dose distribution [29,30]. These uncertainties should be either considered when choosing margins during the treatment planning process, or should be mitigated with robust treatment planning [31] or real-time treatment adaptation [32].

Conclusions
The 4DCBCT scans all underrepresented the real-time target motion. The selection of the reconstruction algorithm and respiratory signal for the 4DCBCT reconstruction does not have an impact on the reconstructed motion range.
References


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**Figures**

**Figure 1.** Workflow for the 4DCBCT reconstruction and comparison of the 4DCBCT motion ranges with the Calypso motion.

**Figure 2.** Real-time target motion distribution and reconstructed 4DCBCT motion ranges for FDK Calypso, FDK bellows, PICCS Calypso and PICCS bellows (boxes and vertical guidance lines) in the superior-inferior (SI) direction. A different scale was used for patient 5 and patient 8 as a result of larger motion than for the other patients.

**Figure 3.** Motion observed from reconstructed 4D CBCT scans (bold) compared with the measured real-time target motion during the scan with Calypso (light). A) The reconstructed motion trajectories in the 4DCBCT scans are rather inconsistent for small motion ranges. B) For larger motion in the SI direction, the reconstructed motion trajectories in the 4DCBCT scans are more consistent. The outlying real-time motion for patient 5, fx1 (lower right corner) shows a cough at the end of the CBCT scan.

**Table 1.** Patient characteristics. Gross tumor volume (GTV), tumor location: left lower lobe (LLL), left upper lobe (LUL), right lower lobe (RLL).

**Table 2.** Reconstructed motion ranges (max-min) for FDK Calypso (FC), FDK bellows (FB), PICCS Calypso (PC) and PICCS bellows (PB) in comparison to the real-time target motion (TM) ranges (4 standard deviations ≈ 95% of the motion) in mm in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions. (Pat=patient, Fx=fraction)

**Table 3.** Percentage of time (mean and standard deviation) when the real-time target motion exceeded the measured reconstructed motion ranges for FDK Calypso, FDK bellows, PICCS Calypso and PICCS bellows in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions for all patients.
Table 1. Patient characteristics. Gross tumor volume (GTV), tumor location: left lower lobe (LLL), left upper lobe (LUL), right lower lobe (RLL).

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Table 2. Reconstructed motion ranges (max-min) for FDK Calypso (FC), FDK bellows (FB), PICCS Calypso (PC) and PICCS bellows (PB) in comparison to the real-time target motion (TM) ranges (4 standard deviations ≈ 95% of the motion) in mm in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions. (Pat=patient, Fx=fraction)

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<tr>
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<td>1.2</td>
<td>1.6</td>
<td>1.3</td>
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Table 3. Percentage of time (mean and standard deviation) when the real-time target motion exceeded the measured reconstructed motion ranges for FDK Calypso, FDK bellows, PICCS Calypso and PICCS bellows in the left-right (LR), superior-inferior (SI) and anterior-posterior (AP) directions for all patients.

<table>
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<tr>
<th>Motion direction</th>
<th>Time of exceeding motion [%]</th>
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<td>AP Stdv</td>
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