The accuracy and precision of Kilovoltage Intrafraction Monitoring (KIM) six degree-of-freedom prostate motion measurements during patient treatments

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Running head: Accuracy & precision of 6DoF KIM motion

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Introduction

Widely available kilovoltage imaging systems, using marker-based [1-6] and markerless technology [7-12] are being actively developed and are moving into clinical practice. One technology that has been clinically implemented using a linear-accelerator gantry-mounted imaging system is kilovoltage intrafraction monitoring (KIM) [13,14],; which measures the 3D tumor positions in real-time from 2D projections of the implanted fiducial markers acquired by a single kV imager based on a probability distribution function. wWith the most recent step being the clinical implementation of real-time six-degree of freedom (6DoF) target motion monitoring, in which both the target translation and rotation are being measured in real-time [15].

Management of intrafraction tumor motion is particularly important for non-uniform dose prescription or the use of boost volumes in hypofractionation, which are postulated to be superior for prostate cancer treatment compared to 3D conformal radiotherapy [16-18]. There is increasing evidence to demonstrate the importance of accounting for translational and rotational (6DoF) tumor motion during prostate radiotherapy [19-24]. The magnitude of rotational motion during radiotherapy has been quantified for lung, liver and prostate cancer patients [20,25-27]. Ignoring the rotational motion was shown to result in a significant underdosing effect even if the translational tumor motion was properly managed [19]. Appropriate management of the rotational tumor motion can improve the accuracy of the tumor positional estimates [25] and further reduce the treatment margins by 4-6 mm, while maintaining target coverage given the controllability of rotation motion within 1° [23].

With the clinical introduction of a real-time six degrees-of-freedom (6DoF) tumor motion monitoring system [15], an obvious question is how accurate and precise are the translation and rotational measurements. To answer this question, we performed a quantitative analysis of the clinical accuracy and precision of the KIM six degree-of-freedom prostate motion measurements based on the in-treatment kV and MV imaging data collected from 377 fractions of 14 patients. The real-time 6DoF KIM measurements were compared against the concurrent ground truth motion derived from kV/MV triangulation.

Methods and Materials

Clinical trial data

In this ethics-approved clinical trial (NCT01742403), Kilovoltage Intrafraction Monitoring (KIM) was used to monitor the 6DoF prostate tumor motion in real-time and to trigger a gating event where the treatment beam was paused and the couch position was adjusted to compensate for the prostate motion when it exceeded the threshold (3-mm/5-seconds for standard dose fractions and 2-mm/5-seconds for SBRT fractions).

The real-time 6DoF tumor motion information was recorded for 14 patients (age range 62 to 85, median of 78.5). The maximum hip width, which influences the marker visibility, for these patients ranged from 32.3 to 39.6 cm with the median of 36.4 cm. Out of a total of 403 treatment fractions, o~~ with a total of 403 fractions.The mwas O~~nly 377 fractions were available for analysis due to missing and/or incomplete acquisition of the MV images which are required for the ground truth. Of the 377 fractions, 7 were 15-Gy SBRT fractions (BOOSTER trial, NCT02004223) and 370 2-Gy fractions.

Real-time measured 6DoF prostate tumor motion

The focus of this study was on the accuracy and precision of the KIM 6DoF system. A large amount of prostate 6DoF motion was measured, and the motion from 14 patients (377 fractions) is summarized in supplementary table 1~~ and~~. It should be noted that as a 3-mm translation motion gating threshold (2-mm for SBRT) was used, that the translational motion was less than would have been observed if no intrafraction correction strategy was in place. In addition, t~~t~~wo interesting examples of 6DoF prostate motion trajectories ~~with large intrafractional rotation motion~~ are shown in supplementary figure 1, where a large intrafractional rotation motion of > 10° was present whilst the translation motion was relatively small within the gating threshold~~.~~, which demonstrates the importance of real-time guidance of tumor motion in 6DoF. ~~It should be noted that as a 3-mm translation motion gating threshold (2-mm for SBRT) was used, that the translational motion was less than would have been observed if no intrafraction correction strategy was in place.~~

Evaluating the accuracy and precision 6DoF motion measurements

Figure 1 shows the workflow of the analysis for the accuracy and precision of real-time acquired 6DoF KIM prostate motion. Six parameters describing three translations and three rotations about the left-right (*LR*), superior-inferior (*SI*) and anterior-posterior (*AP*) axes were used to represent the rigid transformation in 6 DoF, and these are denoted as T_{LR}, T_{SI}, T_{AP}, R_{LR}, R_{SI}, R_{AP}, respectively. In each treatment, kV and MV images were simultaneously acquired at 10 Hz. Real-time 6DoF target motion, relative to its position in the planning CT scan was estimated from the successive kV images using KIM. Concurrently acquired MV frames were collected and saved for post-treatment kV/MV triangulation analysis to derive the ground-truth motion.

We previously developed a procedure to derive 6DoF motion information from kV/MV triangulated 3D markers' positions [28] given all three markers 3D positions are available. These kV/MV triangulation derived 6DoF motion estimates served as the ground truth.

Due to the low contrast of MV images and marker occlusions by MLC leaves in VMAT, marker segmentation in MV images was challenging. The predicted marker positions on the MV images were obtained using a two-step semi-automated procedure (i) forward projecting the temporally-synchronized 3D KIM marker position onto the MV imager; and (ii) using an MV marker detection algorithm. Figure 2 shows temporally synchronized kV and MV images with the segmented marker positions. The automatic kV marker segmentation from the real-time KIM measurements was used in the kV/MV triangulation. The segmentation quality was visually inspected and corrected if necessary on each image to limit the influence of the segmentation errors from KIM propagate into the ground-truth motion estimates.

As the KIM and the ground truth 6DoF prostate motion derived from kV/MV triangulation are concurrent and directly comparable, the real-time 6 DoF KIM prostate motion measurement accuracy and precision was calculated in each DoF as the mean and standard deviation (s.d.) of the differences, respectively. Further analysis was undertaken on the relationship between the KIM 6DoF accuracy and (i) the gantry angle; and (ii) the magnitude of the motion. The Pearson correlation coefficient (ρ) between the actual motion (ground-truth) and the KIM measured motion was computed in each DoF.

Results

Ground truth 6DoF motion from kV/MV triangulation

kV/MV image frames from the 377 fractions from 14 patients were used for triangulation. 15,739 kV and MV frames were obtained where all three markers were visible and successfully segmented. The data spanned approximately 10% of the entire treatment time.

The accuracy and precision of 6DoF KIM

The accuracy and precision of 6DoF KIM motion estimates are listed in Table 1. The accuracy of the rotational motion measurements of the entire collection of the data (upper rows) in each axis was comparable to within 0.2° whilst the highest precision of rotation motion (to within ±0.5°) was found in *AP*, followed by *LR* (±1.0°) and *SI* (±1.3°) axes. Translational motion was most accurate and precise in *SI* direction (-0.1 ± 0.2 mm) and the other two directions had analogous accuracy and precision of 0.0 ± 0.5 mm. Relatively large minimum and maximum values are found in R_{LR} and R_{SI} for rotations, and T_{AP} for translations. The vast majority of these values are the result of measurement noise, which is evident in the 5th and 95th percentiles. Relatively large errors (>3.4° for rotation and >1.2 mm for translation) were present in 2% of the analysed data. Based on this table, overall R_{SI} and T_{AP} are the least accurate degrees of freedom for rotational and translational measurements, respectively. The distribution of the differences between KIM and ground truth is shown in Figure 3, clearly demonstrating that T_{SI} and R_{SI} were the most precise translation and least precise rotation motion, respectively. None of these differences were normally distributed based on the Kolmogorov-Smirnov test.

Table 1 also lists the results of the same analysis of the data divided into two treatment types: (i) Standard fractions (mid rows); and (ii) SBRT fractions (lower rows). A previous study showed that longer treatment duration degraded the accuracy of KIM motion measurements in simulations [29], which is not evident in the results of the current study. In all DoF, the standard and SBRT treatments exhibited comparable accuracy and precision, as well as 5th and 95th percentiles, except R_{SI} in which showed a smaller range of 5th, 95th percentiles for SBRT fractions. The difference in findings may have been caused by the considerably smaller datasets in the SBRT fractions (7 fractions) compared to standard fractions (370 fractions), requiring a further analysis upon the collection of more data.

Figure 4 shows the overall accuracy and precision of the KIM motion as a function of gantry angle. A slight dependency in the accuracy and precision of KIM-measured rotational motion was found which varied from ~0° to ±2° as the gantry angle ranging from -140° to +140° (Varian IEC 601-2 scale) where a reduction in both accuracy and precision was found at lateral gantry angles (±90°) for rotations in *LR* and *SI* directions, which is expected as both R_{LR} and R_{SI} rely on T_{AP}, which is the least accurate DoF at the lateral gantry angles. Although the translational motion was all within ±1 mm, sinusoidal variations in the accuracy depending on the gantry angle were visible. This could be attributed to (i) inherent dependencies of the accuracy of translational motion estimates with KIM on gantry angle where the T_{SI} is always resolved, hence the most accurate whilst the accuracies of T_{LR} and T_{AP} alternate depending on the gantry angle i.e. T_{LR} is most accurate at gantry angle of ±90° and T_{AP} is most accurate at gantry angle of 0°; and (ii) small residual misalignment (≤ ±0.5 mm) in the positions of the isocenter between kV and MV imagers after applying the correction factor based on Winston-Lutz test [30]. Although the effect of this residual misalignment in the isocenter position is visible in the data, the magnitude was within the tolerance (≤1.0 mm) recommended by Task Group 142 [31].

The magnitude of KIM-measured motion is plotted against the actual ground-truth motion in Figure 5, which shows that there is no dependency of the accuracy and precision of real-time KIM measured 6DoF motion on the magnitude of the actual motion. The Pearson correlation coefficients (ρ) were calculated for each DoF and showed there were very strong correlations (all ≥0.88) between the KIM and ground-truth motion. This result implies that the KIM provided the 6DoF motion estimates that are sufficiently accurate and precise for the entire motion ranges of clinical relevance, retrospectively ensuring that the gating events were correctly issued.

Discussion

This study reports the accuracy and precision of the real-time estimated intrafractional 6DoF tumor motion, measured across 14 prostate cancer patients during VMAT treatments from the prospective ethics-approved clinical trial (NCT01742403) of KIM. The results demonstrate that the 6DoF prostate tumor motion can be measured with an accuracy±precision of 0.2±1.3° and 0.0±0.5 mm for rotations and translations, respectively. For the first patient (5 fractions) enrolled in a separate study, the Stereotactic Prostate Adaptive Radiotherapy Utilising Kilovoltage Intrafraction Monitoring (SPARK) trial (TROG 15.01, NCT02397317), the accuracy and precision of the real-time 6DoF prostate motion measured using KIM were reported to be within 4° and one millimeter for rotational and translational prostate motion, respectively [15]. The differences in the quantified accuracy and precision are attributed to significantly lower number of data points used in the SPARK trial (n = 18) compared to this study (n = 15,739).

The accuracy and precision of the 6DoF KIM motion measurements were performed by comparing against the corresponding ground-truth motion derived from kV/MV triangulation. This study provided a method to evaluate the accuracy of the intrafractional 6DoF target motion for post-treatment quality control and better understanding of the limits in the accuracy and precision of the measured target motion using KIM. All of these are of clinical significance in moving towards real-time 6DoF tumor motion adaptive radiotherapy. As both kV and MV imagers are standard on conventional cancer radiotherapy systems, kV/MV triangulation enables the routine post-treatment evaluation of the KIM accuracy and could be deployed in parallel with the KIM algorithm. The limitation of using kV/MV triangulation as the ground truth for KIM is that the kV system is used for both methods and there is a common marker segmentation task, the accuracy of which is limited by systematic uncertainties in the kV system e.g. finite pixel size and isocenter alignment. Therefore, the KIM errors originating from these sources may not be detected. To reduce the likelihood of this problem, the kV system should be part of a comprehensive quality assurance program, for example that described in AAPM Task Group 142 [31].

Although overall accuracy and precision of 6DoF KIM seem promising, outliers with relatively large errors (of up to 15° and 5 mm) are also present in the data. These outliers appear to have been resulted from errors in kV segmentation or 2D to 3D conversion, which only occurred for limited time (≈ 0.2% of the treatment time). Despite the fact that these outliers did not affect the quality of the treatment delivery in this study as (i) these erroneous outliers only affected short period of time that were much shorter than the gating threshold of 5s, and (ii) treatment adaptation was only carried out as the means of manual couch shifts, tThese large errors require further investigation and refinement of the current implementation of the KIM method particularly prior to automating simultaneous 6DoF treatment adaptation.

The accuracy of the motion measurements varied to within ±1.5° and ±0.7 mm, and the precision varied within ±2.0° and ±0.5 mm for the gantry angle ranging from -140° to +140°. Based on the spread of the data and the calculated ρ values (Figure 5), KIM translations are again most accurate in the *SI* direction (which is always resolved in kV) and least accurate in the *LR* direction, which is only crudely estimated to be equal to the KIM estimated mean position for prostate KIM by not optimizing the *LR* translation for prostate [32]. Consequently, KIM rotations are assumed to be most accurate around the *LR* axis (which relies on *SI* and *AP* translations) and least accurate around the *SI* axis (which relies on *LR* and *AP* motion).

The ground-truth 6DoF motion was derived from kV/MV triangulation using a closed-form least squares method [33]. Although this method provides accurate and concurrent measurements of the three implanted markers, it required all three markers 3D triangulated positions. Due to the modulated treatment field, the ground-truth motion was available on only ≈10% of the entire treatment data. This is an indication that MV-based localization techniques will only provide 6DoF motion measurements for around 10% of the treatment time depending on the degree of the treatment field modulation, as compared to tracking nearly 100% of the entire treatment with the kV-based localization technique, such as KIM.

This limited number of ground-truth 6DoF motion was to an extent overcome by including multiple patients and fractions. However, we currently have limited data for high dose SBRT fractions (only 7 fractions), which has much longer treatment duration to standard fractions and requires more accurate pose measurements during the treatment.

Previously, we have quantified the accuracy and precision of the real-time 6DoF KIM motion measurements for dynamic prostate and lung tumor motion traces, using a phantom [28]. In this study, we found the 6DoF KIM had sub-mm accuracy and precision for translation motion estimates, and sub-degree and 1.3° accuracy and precision for rotation motion estimates. The degraded accuracy and precision for patient data compared to the phantom study could be attributed to an increase in measurement uncertainty in the marker segmentation due to much less signal-to-noise ratio in kV and MV images for patient data compared to the phantom.

Li *et al.* showed that dosimetric discrepancies caused by prostate rotation were more significant than those caused by translational intrafractional motion, and significant reduction in the treatment margin may be enabled if the rotation motion can be controlled to within 1° [23]. Based on this study, the 6DoF KIM may be able to provide the real-time rotational and translational tumor motion measurements with the accuracy and precision required to achieve this level of clinical significance. In particular, achieving clinically required accuracy and precision together with the use of the commonly available gantry mounted kV imager for the 6DoF KIM method could enable a streamlined and cost-effective pathway for the broader dissemination of the technology for widespread patient use. Current plans are to expand the clinical application of KIM in more cancer centers and treating more sites, particularly tumors in the thorax and abdomen where motion is a significant problem.

Although accurate real-time 6DoF intrafractional tumor motion monitoring is enabled using KIM, it should be noted that there are some limitations associated with these measurements, including (i) it imposes extra imaging dose to patients (≈ 15 mSv for standard treatment from [34]), (ii) it measures surrogate motion (implanted markers), not actual tumor motion, and (iii) the tumor is approximated as rigid body and it does not account for the deformation. Furthermore, although the current study only included VMAT treatments, the KIM method can also be utilized for conformal and IMRT treatments [35], which will need to be clinically tested. These limitations present opportunities for further research and development into real-time kilovoltage-guided radiotherapy.

Conclusions

This study quantitatively assessed the accuracy and precision of real-time 6DoF prostate motion measured during treatment using the KIM method. The results showed that the accuracy and precision are within 0.2° and 1.3° for rotations and 0.1 mm and 0.5 mm for translations, respectively, with slight gantry angle dependence and no motion magnitude dependence. As KIM only requires a single x-ray imager, which is available on most modern cancer radiotherapy devices, there is potential for widespread adoption of this technology.

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Conflict of Interest

Authors Poulsen and Keall are inventors of a patent that has been licensed to Varian Medical Systems and Nano-X Pty Ltd by Stanford University, and authors O'Brien, Poulsen and Keall are inventors of an additional unlicensed patent.

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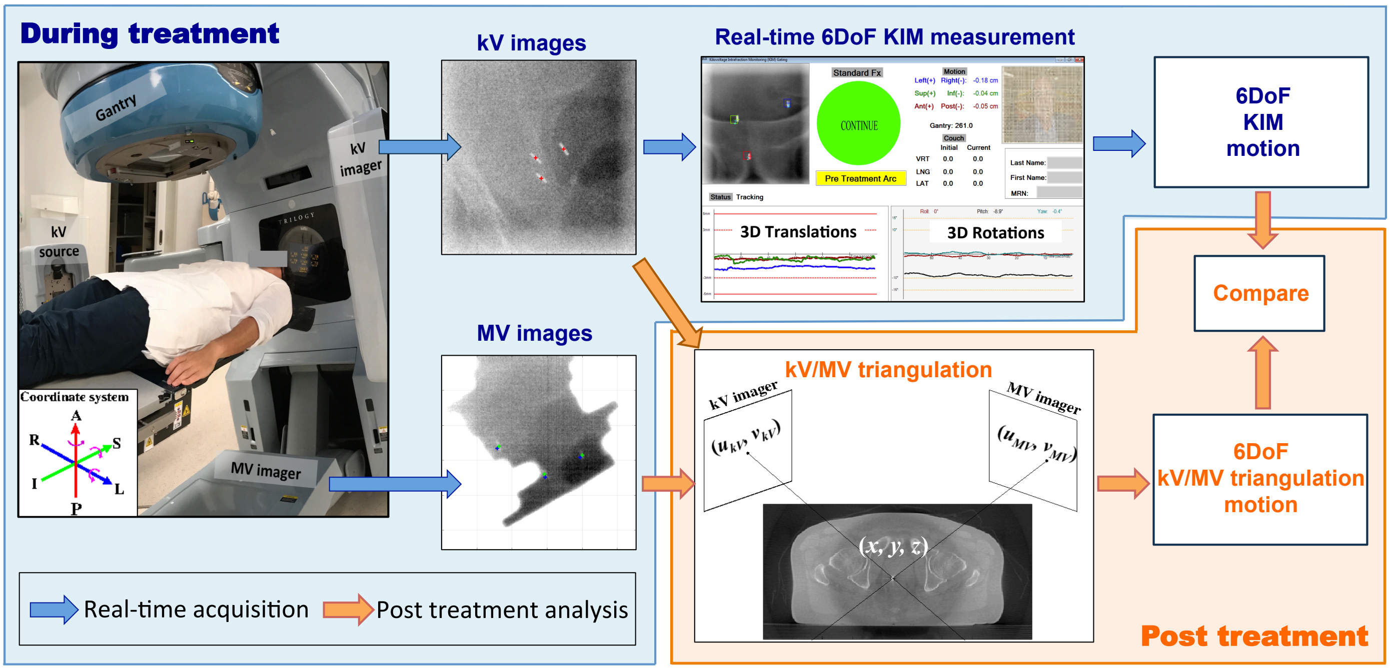
Table

Table 1 Accuracy (mean), precision (s.d.), 5th, 95th percentiles, minimum and maximum differences between 6DoF KIM and the corresponding ground-truth motion.

		Rotation (°)			Translation (mm)		
		LR	*SI*	*AP*	*LR*	*SI*	*AP*
All fractions (n = 377)	Accuracy ± precision	-0.2 ± 1.0	0.0 ± 1.3	-0.1 ± 0.5	0.0 ± 0.5	-0.1 ± 0.2	0.0 ± 0.5
	[5th, 95th]	[-1.7, 1.2]	[-2.1, 2.1]	[-0.9, 0.8]	[-0.7, 0.7]	[-0.4, 0.3]	[-0.6, 0.8]
	[Min, Max]	[-14.7, 15.5]	[-7.5, 7.9]	[-3.9, 3.3]	[-1.8, 2.0]	[-1.4, 1.5]	[-4.9, 2.3]
Standard fractions (n = 370)	Accuracy ± precision	-0.2 ± 0.9	0.0 ± 1.3	-0.0 ± 0.5	0.0 ± 0.5	-0.1 ± 0.2	0.0 ± 0.5
	[5th, 95th]	[-1.7, 1.2]	[-2.2, 2.1]	[-0.9, 0.8]	[-0.7, 0.7]	[-0.4, 0.3]	[-0.6, 0.8]
	[Min, Max]	[-14.7, 7.8]	[-7.5, 7.9]	[-3.9, 3.3]	[-1.8, 2.0]	[-1.4, 1.5]	[-4.9, 2.3]
SBRT fractions (n = 7)	Accuracy ± precision	-0.2 ± 1.7	0.0 ± 1.0	-0.1 ± 0.5	0.0 ± 0.4	-0.1 ± 0.2	-0.0 ± 0.5
	[5th, 95th]	[-1.9, 1.2]	[-1.5, 1.6]	[-0.9, 0.6]	[-0.7, 0.7]	[-0.4, 0.3]	[-0.7, 0.8]
	[Min, Max]	[-9.2, 15.5]	[-4.9, 6.8]	[-2.0, 2.4]	[-0.9, 1.0]	[-0.9, 0.6]	[-2.2, 2.0]

Figure1



During treatment
Gantry
kV imager
kV source
MV imager
Coordinate system
A
R
S
I
L
P
kV images
MV images
Real-time 6DoF KIM measurement
CONTINUE
Pre Treatment Arc
3D Translations
3D Rotations
6DoF
KIM
motion
Compare
kV/MV triangulation
kV imager
MV imager
(u_{kV}, v_{kV})
(u_{MV}, v_{MV})
(x, y, z)
6DoF
kV/MV triangulation
motion
Real-time acquisition
Post treatment analysis
Post treatment

Figure2

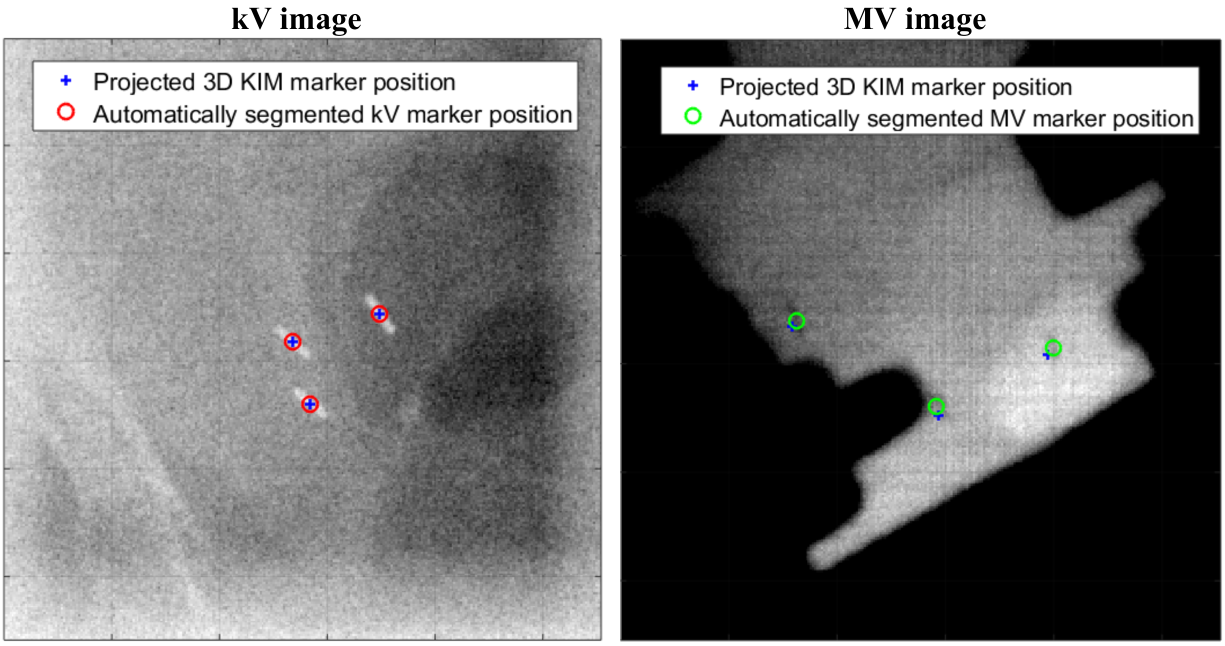
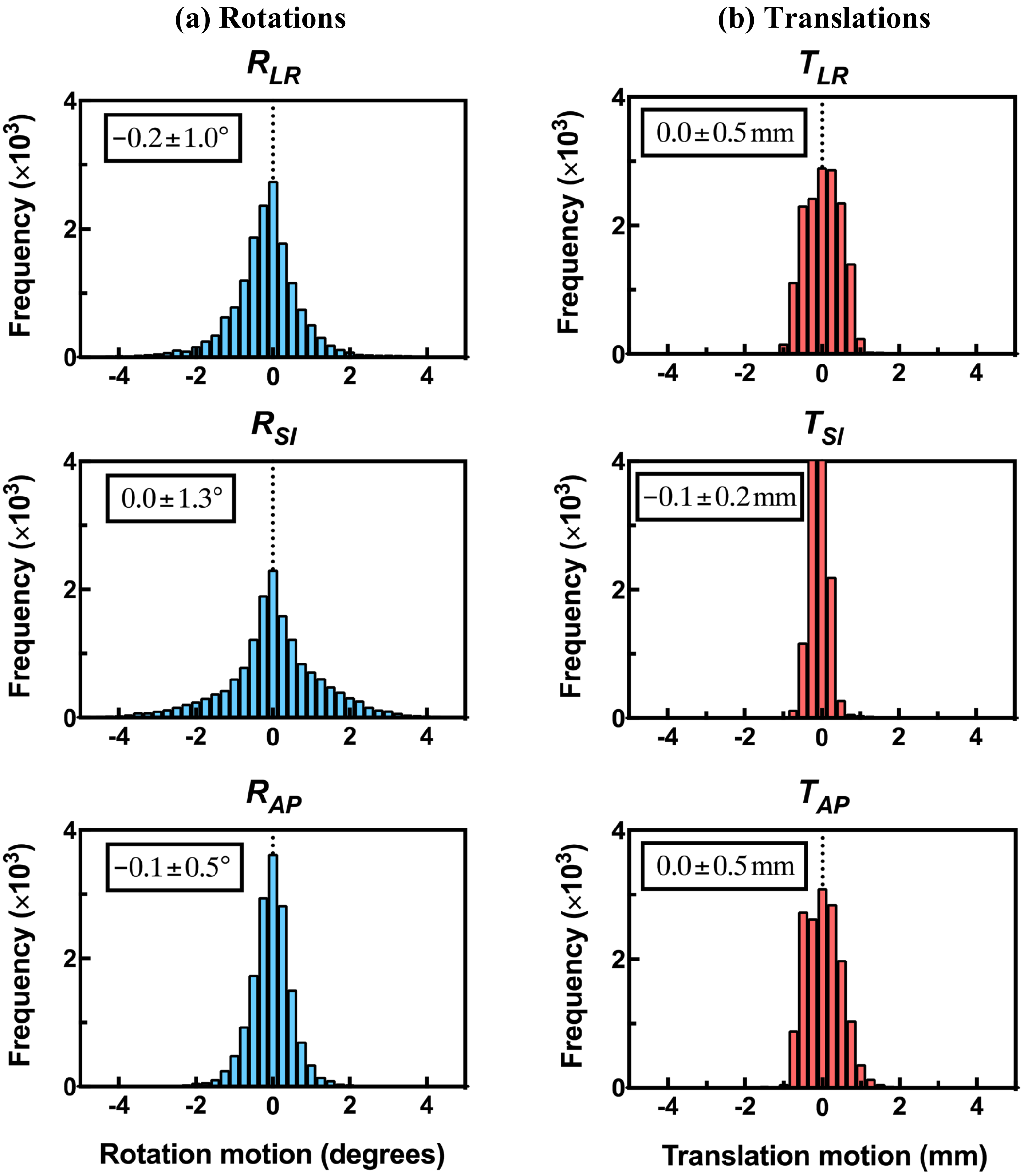

kV image
Projected 3D KIM marker position
Automatically segmented kV marker position
MV image
Projected 3D KIM marker position
Automatically segmented MV marker position

Figure3



(a) Rotations
(b) Translations
R_{LR}
$-0.2 \pm 1.0°$
T_{LR}
0.0 ± 0.5 mm
R_{SI}
$0.0 \pm 1.3°$
T_{SI}
-0.1 ± 0.2 mm
R_{AP}
$-0.1 \pm 0.5°$
T_{AP}
0.0 ± 0.5 mm
Frequency ($\times 10^3$)
0
2
4
-4
-2
0
2
4
Rotation motion (degrees)
Translation motion (mm)

Figure4

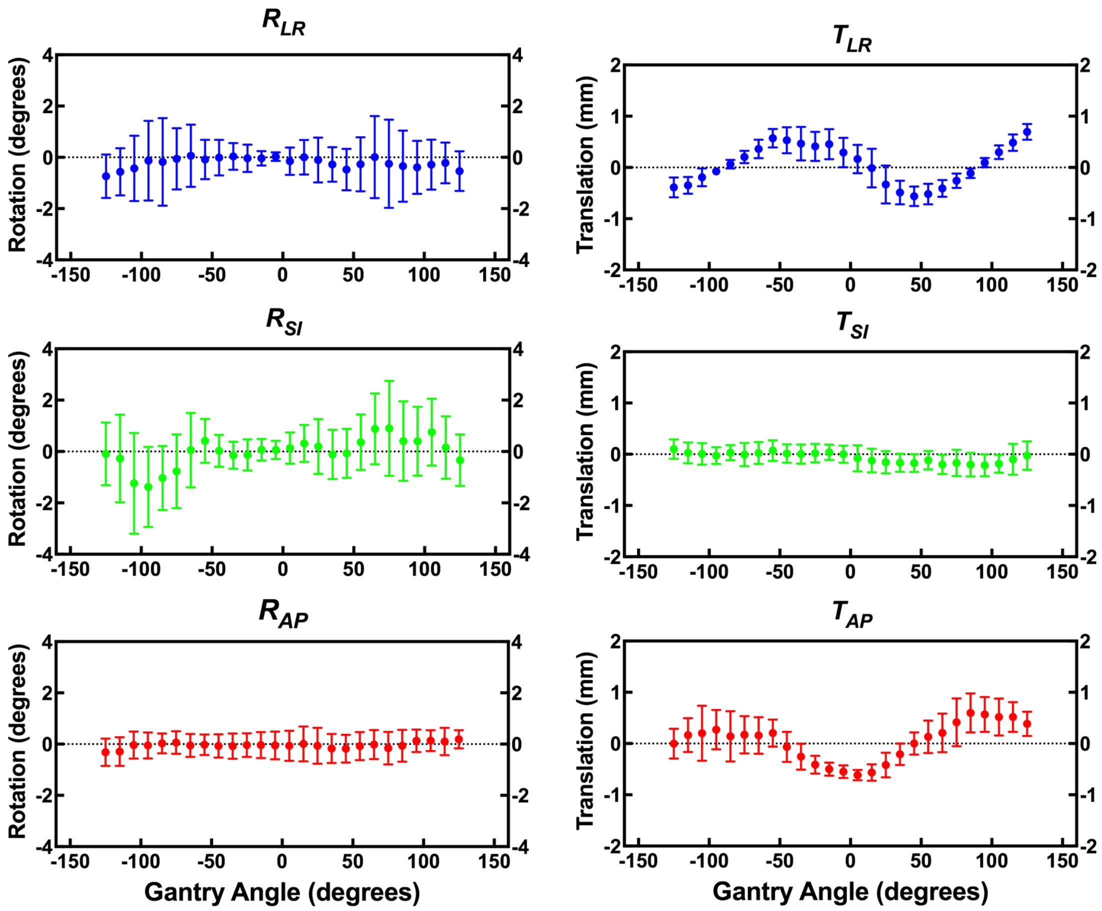
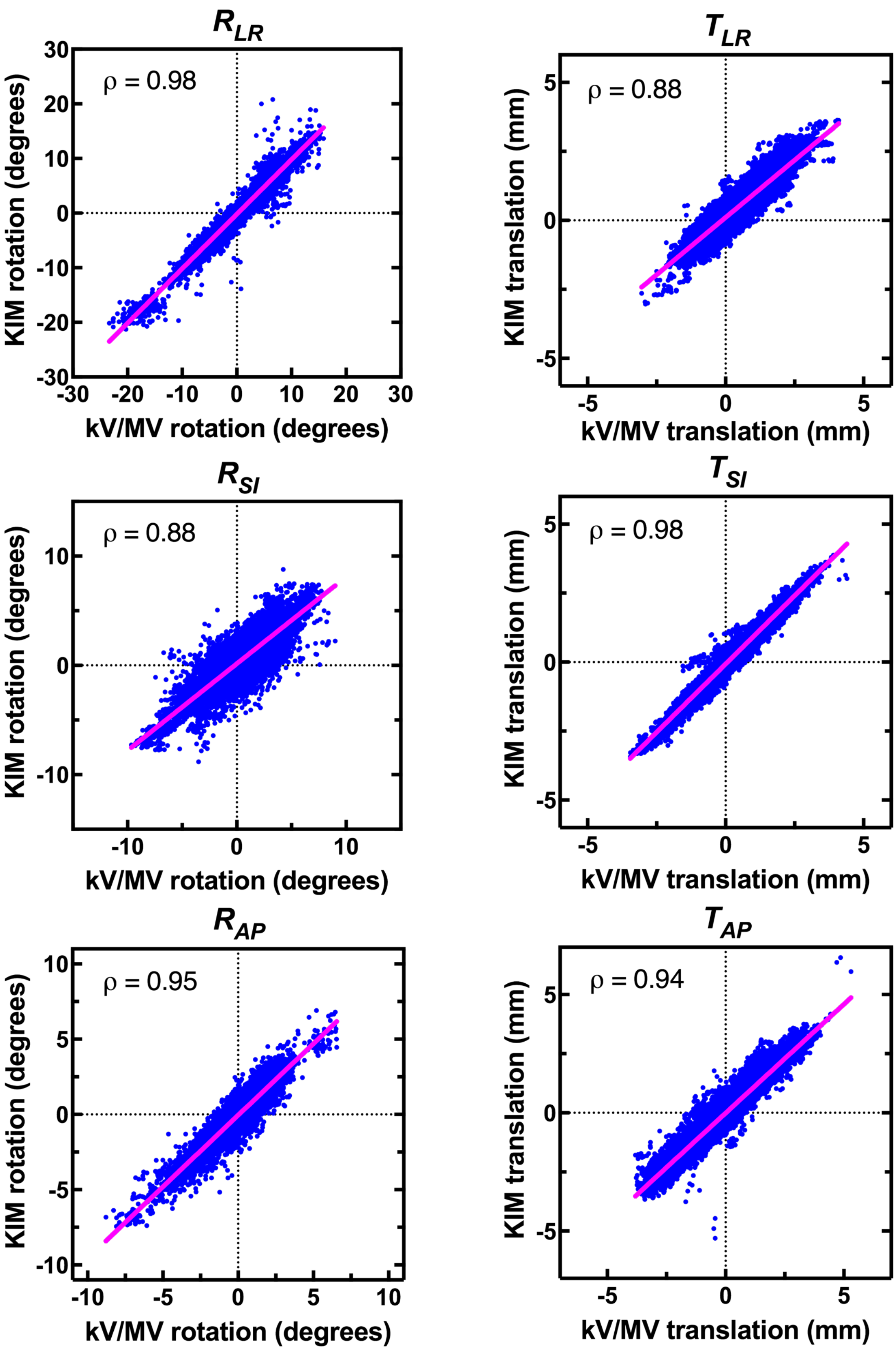


Figure 4 Accuracy (mean) and precision (error bars, 1 s.d.) of 6DoF KIM motion as a function of gantry angle.

Figure5



R_{LR}
ρ = 0.98
KIM rotation (degrees)
kV/MV rotation (degrees)
30
20
10
0
-10
-20
-30
-30 -20 -10 0 10 20 30
T_{LR}
ρ = 0.88
KIM translation (mm)
kV/MV translation (mm)
5
0
-5
-5 0 5
R_{SI}
ρ = 0.88
KIM rotation (degrees)
kV/MV rotation (degrees)
10
0
-10
-10 0 10
T_{SI}
ρ = 0.98
KIM translation (mm)
kV/MV translation (mm)
5
0
-5
-5 0 5
R_{AP}
ρ = 0.95
KIM rotation (degrees)
kV/MV rotation (degrees)
10
5
0
-5
-10
-10 -5 0 5 10
T_{AP}
ρ = 0.94
KIM translation (mm)
kV/MV translation (mm)
5
0
-5
-5 0 5