4D ultrasound speckle tracking of intra-fraction prostate motion: a phantom-based comparison with x-ray fiducial tracking using CyberKnife

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Abstract

This study investigates the use of a mechanically-swept 3D ultrasound (3D-US) probe for soft-tissue displacement monitoring during prostate irradiation with emphasis on quantifying the accuracy relative to CyberKnife® x-ray fiducial tracking.

An US phantom, implanted with x-ray fiducial markers was placed on a motion platform and translated in 3D using 5 real prostate motion traces acquired using the Calypso system. Motion traces were representative of all types of motion as classified by studying Calypso data for 22 patients. The phantom was imaged using a 3D swept linear-array probe (to mimic trans-perineal imaging) and, subsequently, the kV x-ray imaging system on CyberKnife. A 3D cross-correlation block matching algorithm was used to track speckle in the ultrasound data. Fiducial and US data were each compared with known phantom displacement.

Trans-perineal 3D-US imaging could track superior-inferior (SI) and anterior-posterior (AP) motion to ≤ 0.81 mm root-mean-square error (RMSE) at a 1.7 Hz volume rate. The maximum kV x-ray tracking RMSE was 0.74 mm, however the prostate motion was sampled at a significantly lower imaging rate (mean: 0.04 Hz). Initial elevational (RL) US displacement estimates showed reduced accuracy but could be improved (RMSE < 2.0 mm) using a correlation threshold in the ultrasound tracking code to remove erroneous inter-volume displacement estimates.

Mechanically-swept 3D-US can accurately track the major components of intra-fraction prostate motion accurately but exhibits some limitations. The largest US RMSE was for elevational (right-left) motion. For the AP and SI axes, accuracy was sub-millimetre. It may be feasible to track prostate motion in 2D only. 3D-US also has potential for improvement for high tracking accuracy in all circumstances. It would be advisable to use US in conjunction with a small (~ 2.0 mm) centre-of-mass displacement threshold in which case it would be possible to take full advantage of the accuracy and high imaging rate capability.

1. Introduction

During radiation therapy it is known that the prostate, as delineated on computed tomography (CT) images, can undergo significant displacements (~ 10 mm) during

2 treatment, requiring the use of an additional treatment margin to account for this intra-
fraction motion (Webb 2006, Korreman 2012). Radiation therapy (RT) of prostate
4 carcinoma is usually delivered via external mega-voltage x-ray beams. Treatment is
typically delivered using a standard 10 mm planning target volume (PTV) margin and
6 fractionation regime (e.g. 78 Gy in 2 Gy fractions) (Fowler et al. 2003). It has however
been proposed that the cell survival curve following RT for prostate cancer may be strongly
8 curved (with the ratio of fit coefficients, $\alpha/\beta \sim 1.5$) (Fowler et al. 2001, Bentzen
2005). If the α/β ratio is approximately equal to that of late responding normal
tissue, a hypo-fractionated radiation treatment regime would increase the therapeutic gain
10 of radiotherapy (Miles and Lee 2008). Unfortunately, potential benefits of hypo-
fractionation may not be fully realised due to the need for large PTV margins to account for
12 prostate motion. With increased accuracy of prostate localisation (Letourneau et al. 2004)
and tracking (Willoughby et al. 2006) comes the prospect of increasing tumour dose,
14 reducing PTV margins (Litzenberg et al. 2006) and minimising toxicity to surrounding
organs (Huang et al. 2002). In turn this may help to elucidate the benefits of hypo-
16 fractionation.

The ability to visualise the prostate in three dimensions and its position relative to
18 surrounding healthy tissues has become essential. Motion of the prostate is influenced by
a number of factors including variability in rectal activity (Roeske et al. 1995, Stillie et al.
20 2009), bladder filling (Ten haken et al. 1991) and clenching of the pelvic floor muscles
(Padhani et al. 1999). Image-guided radiotherapy for the prostate involves one of many
22 methods of identifying the location of the prostate, followed by adjustment of the treatment
fields to target the prostate. Methods of monitoring prostate position have largely relied on
24 identification of metal fiducials via kV x-ray imaging (Jaffray et al. 2002) and, more
recently, using implanted electromagnetic fiducials (Willoughby et al. 2006).

26 The CyberKnife® robotic radio-surgery system (Accuray, CA, USA) uses a robotically
mounted 6 MV linear accelerator to deliver hypo-fractionated treatments (Kilby et al. 2010).
28 A typical prostate treatment consists of a large number (~ 100) of small ($\varnothing$: 20 – 30 mm)
conformal beams. Two kV x-ray tubes and paired flat-panel detectors are used to localise
30 and track three or more gold fiducial markers implanted in the prostate. The specified
maximum imaging frequency is 0.2 Hz. A typical prostate plan requires ~ 45 minutes to
32 deliver 5 Gy per fraction, with most of the time occupied by robot positioning and fiducial
localisation (imaging). CyberKnife has shown promise in terms of superior target coverage
34 and rectum and bladder sparing when compared to prostate intensity modulated radiation
therapy (King et al. 2003). However when a mean imaging period of 30 – 60 seconds is
36 used, there will invariably be some occasions when a treatment beam misses the target
(Xie et al. 2008). Additionally, kV x-ray imaging can result in an added ionising radiation
38 dose per fraction of 0.1 – 0.6 cGy (Bujold et al. 2012). While it is recognised that the
management of imaging dose during radiation therapy is a different problem to
40 management during diagnostic imaging (Murphy et al. 2007), it is important to evaluate all
possible imaging technologies with a view to optimising the imaging frequency to improve
42 therapeutic dose conformity.

Ultrasound (US) imaging is a potential alternative method for providing high frequency
44 positional information by contour (feature) and soft-tissue (speckle) tracking during
radiation therapy (Harris et al. 2007, Schlosser et al. 2011, Lediju Bell et al. 2012, Rubin et
46 al. 2012, Lachaine and Falco 2013). US imaging is non-ionising and non-invasive, it
provides soft tissue definition and has the ability to provide high frame (2D) or volume
48 rates (3D). US also negates the need to implant fiducial markers which is an invasive

procedure with associated risks (Shinohara and Roach III 2008). US imaging has been implemented clinically for pre-treatment (inter-fraction) correction of prostate position using segmented prostate contours. The BAT® system (Best Nomos, PA, USA) uses trans-abdominal ultrasound (TAUS) imaging to provide daily corrections to inter-fraction prostate variations by comparing the prostate position with the planning CT scan contour (Lattanzi et al. 2000). The Clarity® system (Elekta, Stockholm, Sweden) provides inter-fraction setup corrections adhering to the AAPM TG154 recommendation that US guidance should use US images as reference rather than CT, by integrating US at the patient simulation stage (Molloy et al. 2011). The Clarity device, which uses a 5 MHz 3D mechanically-swept probe, is being further developed to provide intra-fraction monitoring with images acquired via the perineum (TPUS) with a 2.5 second imaging period (Lachaine and Falco 2013). TPUS imaging allows visualisation of the prostate comparable with TAUS (Terris et al. 1998). In addition, it is advantageous as it does not require the acoustic window of a full bladder, does not interfere with the radiation beam path and provides a short skin-to-prostate distance.

A number of authors have investigated the use of ultrasound speckle (soft-tissue) tracking for image guided radiation therapy with promising results (Hsu et al. 2005, Harris et al. 2007, Lediju Bell et al. 2012, Rubin et al. 2012). In the current work, we perform a phantom-based study to evaluate the accuracy of mechanically-swept 3D-US (soft-tissue) speckle tracking for intra-fraction prostate motion management during radiation therapy. The phantom, implanted with fiducial markers, was also tracked using the kV x-ray imaging system on CyberKnife for comparison. US motion tracking involved off-line correlation-based tracking of the inherent speckle pattern in the RF ultrasound image data with dynamic phantom motion generated from *in vivo* Calypso prostate motion traces. To our knowledge, no previous publication has compared US speckle tracking with known input prostate motion.

2. Materials and methods

2.1. Experimental set-up

An ultrasound phantom, implanted with Tantalum fiducials was translated in three dimensions (3D) using a motion platform to simulate realistic prostate motion. The phantom was imaged using the kV x-ray system on CyberKnife and a 3D ultrasound (US) transducer (section 2.2) positioned to mimic trans-perineal imaging (an example of which is shown in figure 1 (a)). The centre of mass of at least 4 fiducials and US speckle pattern from the phantom (figure 1 (b)) were tracked. The experimental set-up is shown in figure 1 (c).

The motion platform employed three 1.8° step motors to translate the ultrasound phantom which was placed inside a 9 L water container. The US probe was positioned such that the axial, lateral and elevational axes were aligned with the superior-inferior (SI), anterior-posterior (AP) and right-left (RL) axes, respectively. The probe was fixed in place using a mechanical articulated arm which was attached to the treatment couch. Large axial (superior-inferior) translations necessitated the use of water as a coupling material for ultrasound imaging. The ultrasound phantom was implanted with five Tantalum fiducial markers (diameter: 0.75 mm, length: 2.5 mm) to facilitate fiducial tracking using the x-ray imaging system. Fiducials were implanted under ultrasound guidance following fiducial placement requirement guidelines (Kee 2005).

Cryogel (10%), a water soluble synthetic polymer, was used to fabricate the phantom due to its long term stability and speed of sound ($\sim 1540 \text{ m s}^{-1}$) comparable with human tissue (Surry et. al 2004). Cellulose scatterer (0.25%) was added to the phantom to produce speckle. The phantom was CT scanned with 1.5 mm slice thickness at 120 kVp and maximum mAs for Cyberknife planning (MultiPlan). The planning software generated a DRR with segmented fiducials. During simulated treatment, intra-fraction motion within a specified tracking range, was automatically compensated for by the treatment manipulator. Tracking data was output to a treatment log file. For this study we selected the minimum imaging interval to provide the highest sampling of the prostate motion schemes. This resulted in a mean interval of 24.3 s between corresponding displacement data points.

2.2. Ultrasound system and 3D speckle tracking

A 3D RSP6-12 MHz probe (General Electric, CT, USA) interfaced to a Diasus US system (Dynamic Imaging) was used to acquire US data. The probe incorporates a mechanically-swept 192-element wide-band linear array transducer with a centre frequency of 7.5 MHz and bandwidth of 5.0 MHz. It contains 192 elements and has a footprint of 5 cm (laterally) x 5.5 cm (elevationally). 3D data were acquired by sweeping (elevationally) the linear array through an angle θ . The central 128 elements of the probe were connected to the Diasus US system. Radio-frequency (RF) data were digitised and sampled at 66.67 MHz. The US imaging software Stradwin (Gee et al. 2004) was used to acquire 3D RF data. While the probe's frequency may be higher than typically used for prostate imaging it was shown that, despite high attenuation at depth, it was possible to produce good quality *in vivo* trans-perineal images of the prostate (figure 1 (a)).

An in-house MATLAB (Mathworks Inc., MA, USA) 3D cross-correlation block-matching algorithm was used to track speckle incrementally in the US RF data. The code selects a reference volume or kernel in an initial ultrasound volume acquisition. A search volume of equal dimensions was selected within a user specified search region in a subsequently acquired US volume. The region was selected based on estimation of the magnitude and direction of motion. The code then calculates the 3D normalised correlation coefficient (3D NCC) between the reference and search volumes (Morsy and von Ramm 1998). The 3D NCC is calculated for all possible locations of the search volume within the search region. Finally the code calculates the peak in the 3D NCC by fitting a 1D Gaussian function to the spatial distribution of ρ values for each axis. The peak, $\rho_{\max}$, value gives an estimate of the inter-volume displacement of the tissue or phantom.

Since the probe acquires data using an angularly-swept linear array the axial, lateral and elevational displacement coordinates are given in polar coordinates of r , x and θ respectively. Conversion of cylindrical-polar to Cartesian displacements coordinates is accomplished in the axial and elevational directions by:

$$y = (r + ROC)\sin\theta \quad (1)$$

$$z = (r + ROC)\cos\theta \quad (2)$$

It is known that the accuracy of US displacement estimates decreases due to speckle decorrelation for larger inter-volume displacements. Additionally, the main aim of intra-fraction monitoring is to accurately detect small displacements before the target moves out of the planning-target-volume (PTV) margin. It was therefore important to ensure that the temporal resolution was high enough to limit the phantom motion between acquisitions (i.e

the inter-volume displacement) to a few millimetres. There is invariably a trade-off between elevational sweep angle, frame density (i.e. frames per volume), volume rate and tracking accuracy (Harris et al. 2007). For a given sweep angle, θ , the elevational field of view (FOV_{elev}) was given by:

$$FOV_{elev} = ROC(\theta \frac{\pi}{180}) \quad (3)$$

where $ROC = 78.0$ mm. The optimal sweep angle and number of frames per volume were selected by varying the sweep angle from 5° to 20° and frames per volume from 10 to 50 while imaging a 30 second segment of persistent prostate motion (containing 3.3 mm (axial), 4.5 mm (lateral) and 0.5 mm (elevational) displacements). A sweep angle (θ) of 5° and 10 frames per volume gave the best trade off between FOV_{elev} , volume rate and tracking accuracy (volume period: 0.59 s, mean correlation: 0.88 ± 0.02 , RMSE: < 0.4 mm,). The US acquisition imaging depth and width was 64.4 mm and 25.0 mm, respectively. As described below, two types of motion were evaluated: (i) step-and-shoot and (ii) dynamic. For step-and-shoot displacements, 5 US volumes were taken per displacement (section 2.3). For the dynamic (prostate) motion studies, 102 volumes of US data were acquired. A single US focus was positioned at a depth of ~ 15.0 mm in the phantom. 3D-US data was acquired by repeatedly sweeping the US transducer in a single direction. The elevational reference volume side length was varied from 2 to 7 and the resultant displacement estimate was compared with known inter-volume displacements of 1 mm and 2 mm, respectively. The optimal reference volume used in the 3D-US speckle tracking code was 45 (axial) $\times$ 40 (lateral) $\times$ 3 (elevational) voxels. The optimal search region was $(200 \text{ to } 900) \times (50 \text{ to } 90) \times 3$ in the axial (SI), lateral (AP) and elevational (RL) axis, respectively.

2.3. Input motion

2.3.1. Step-and-shoot displacements

The motion tracking capabilities of the US system were investigated with the phantom stationary and for both step-and-shoot displacements and dynamic prostate motion. The motion platform was used to translate the phantom by displacements of $0.1 - 5.0$ mm. Five US volumes and a x-ray image set were acquired at each position. This helped elucidate the intrinsic accuracy of the US transducer in the absence of motion at acquisition time and of each axis independently. The estimated precision of motion platform translation was ~ 0.1 mm superior-inferior (axial) and ~ 0.05 mm anterior-posterior / right-left (lateral / elevational). These values were estimated based on the motor encoder outputs when returning to the same position 10 times for each axis independently.

2.3.2. Prostate motion data

Prostate motion data from the Calypso electro-magnetic tracking system was used to investigate the ability of US to track dynamic tissue motion. 480 intra-fraction motion traces (sampled at 10 Hz) from 22 patients were analysed. The system output intra-fraction centre-of-mass translations only. A MATLAB code was written to calculate: (i) the maximum, mean and standard deviation in centre-of-mass displacement along each axis, (ii) the percentage of fractions with ≥ 2 mm, ≥ 3 mm and ≥ 5 mm displacements and (iii)

the percentage of total tracking time with ≥ 2 mm, ≥ 3 mm and ≥ 5 mm displacements for each patient. Motion traces for all patients were also categorised into the following motion types:

- (i) stable (*i.e. displacements remain within user-specified limits i.e. ± 2 mm*),
- (ii) transient (*i.e. displacements exceed user-specified limits but returns within limits before the end of the treatment fraction*),
- (iii) persistent excursions including continuous target drift (*i.e. displacements exceed user-specified limits and remains outside limits at end of fraction*).

Knowledge of the generalised motion along each axis aided selection of the optimum alignment of the US probe and patient axes. Since prostate motion along the AP and SI axes is the most clinically significant, it is important that these axes are tracked with the highest possible accuracy. For trans-perineal imaging, the axial axis is aligned with patient SI axis. The least accurate US axis (elevational axis) was then aligned with the patient axis exhibiting the least amount of motion (RL axis). Five Calypso motion traces, representative of all types of prostate motion, were selected and used to generate input files for the motion platform. A 60 s section of the data was used to drive the motion platform / phantom while imaging with 3D-US and the kV x-ray system.

2.4. Data analysis

Differences between fiducial marker and ultrasound displacements were analysed by calculating the root-mean-square error (RMSE) relative to the known input displacements of the motion platform for each axis (equation 4) and in 3D (by quadrature addition). Bland-Altman 95% limits of agreement (LOA) analysis was also used to determine if fiducial and 3D-US displacement estimates could be used interchangeably (Bland and Altman 1986). The LOA gives the range over which 95% of the differences between fiducial and ultrasound displacements lie. Differences between fiducial and US displacements of greater than 2.0 mm were considered to be clinically unacceptable. Therefore a LOA greater than ± 2.0 mm indicated US could not replace fiducial markers for displacement estimation. For RL (elevational) displacements, RMSE and LOA analysis was limited to displacements of ≤ 2.0 mm. This was justified since the trade-off between field-of-view and volume rate meant that large RL displacements could not be tracked accurately and, additionally, RL prostate motion is small. Since out-of-plane motion is improbable, we also quantified the accuracy of 2D ultrasound tracking (2D – US).

$$(4)$$

For prostate motion tracking analysis, the input motion data were interpolated into the fiducial or US tracking points prior to calculation of RMSE. Fiducial and 2D - US tracking data was time stamped and synchronised to within ± 1 s. Temporal calibration (alignment) of input motion and tracking data was achieved by minimising the RMSE between the input and axial 2D - US tracking data (which produced the most accurate sampling of the input data). It was estimated that a 1 s error in temporal calibration could lead to uncertainties in RMSE values of ± 0.1 mm.

Motion tracking may be used to determine if the target has reached a predetermined

displacement threshold, TVD, at which point the treatment may be paused until the target is repositioned via a couch shift (i.e. gating). Therefore the ability of US to detect when specified TVD value of 2.0 mm or 5.0 mm were also assessed for each of the prostate motion traces.

2.5. Correlation threshold value, TVC

The correlation coefficient indicates the degree of similarity between the reference volume before and after a displacement. A low correlation value is one of a number of potential metrics used to infer that the probability that the tracking code has correctly calculated the inter-volume displacement is low (Morsy and von Ramm 1999). A study was therefore conducted using the present data to determine if it was possible to use a correlation threshold to filter out inaccurate inter-volume displacement estimates and improve the tracking performance in certain situations. A correlation threshold, TVC, was retrospectively applied to the 3D-US prostate motion tracking data. This was accomplished by comparing each inter-volume peak correlation coefficient $\rho_{\max}$ value with the TVC value and if $\rho_{\max} < \text{TVC}$ then the corresponding incremental displacement estimate was excluded (i.e. set to 0.0 mm) from the cumulative (centre-of-mass) displacement estimate. The effect of applying TVC values of 0.2 – 0.8 (in 0.05 increments) was quantified by calculating RMSE between the US tracked data and motion platform input motion. This method could potentially be adapted for use with real patient data.

2.6. Planning-target-volume margins

The method of Van Herk et al. (2000) was used to determine appropriate PTV margins in both the absence and presence of US tracking. The systematic and random errors associated with input Calypso prostate motion (no intra-fraction tracking) and 3D-US tracking (intra-fraction tracking) were assessed and PTV margins calculated using:

$$M_{PTV} = 2.5\Sigma + 0.7\sigma' \quad (5)$$

where Σ and σ' represent the standard deviation and RMS of all systematic and random errors, respectively, added in quadrature. The margin calculation assumed a 2.0 mm x-ray fiducial residual set-up (inter-fraction) error (Mageras and Mechalakos 2007).

3. Results

3.1 Step-and-shoot displacements

The ability of 3D-US to estimate known phantom translations was investigated for displacements of 0 – 5 mm. The phantom was imaged while stationary to investigate the influence of noise and potential elevational positioning errors on correlation and displacement estimates. The mean correlation across five stationary US image volumes was 0.960 ± 0.003 . Table 1 lists the mean correlation (for US speckle tracking), mean differences and RMSE of phantom displacements. US displacements compared well with fiducial displacement estimates in most cases. US estimated SI (axial) and AP (lateral) displacements had lower RMSE than x-ray fiducial estimates in all cases. The US elevational field of view (FOV_{elev}) was limited by the need to optimise volume rate for

tracking dynamic (prostate) motion so there was an inability to track large (5.0 mm) inter-volume displacements. The US elevational axis suffered from the largest inter-volume decorrelation (mean: 0.558) and exhibited the largest RMSE. The maximum elevational US tracking (RMS) error was 2.24 (± 0.06) mm. For x-ray tracking, the RMSE was ≤ 0.23 (± 0.07) mm in all cases. Unlike US, there was negligible increase in RMSE when 5.0 mm displacements were included in the RMS error calculation (table 1). For displacements of up to 2 mm, the 3D RMSE was comparable for both kV x-ray (0.31) and 3D-US (0.25). When 5 mm displacements were included in the analysis the 3D RMSE increased to 2.25 mm for 3D-US tracking (largely effected by elevational tracking errors).

The 3D-US and x-ray displacement estimates were plotted against input displacements and are shown in figure 2. Linear regression analysis resulted in r values of 0.999 for axial and lateral displacement comparisons. The analysis was restricted to displacements of ≤ 2.0 mm for US elevational axis ($r = 0.996$). Bland-Altman 95% limits of agreement (LOA) was used to determine if US and fiducial displacements could be used inter-changeably, with a LOA larger than ± 2.0 mm indicating that US and fiducials could not be used inter-changeably. The LOA for axial and lateral displacements were ± 0.15 mm and ± 0.21 mm, respectively. The elevational LOA value (for displacements up to 2.0 mm) was ± 0.18 mm, which also met the criterion for agreement.

3.2. Prostate motion data analysis

Analysis of 480 intra-fraction motion traces showed the largest component of prostate motion was along the AP axis. RL motion was minimal. The mean ($\pm$ SD) displacement was 0.0 ± 0.3 mm, 0.0 ± 0.8 mm and -0.1 ± 0.3 mm for RL, SI and AP axes, respectively. The maximum displacements were 2.1 mm (L), 10.3 mm (S) and 14.2 mm (A). Prostate motion was highly patient specific and generally rare with 17.9%, 10.8% and 6.9% of the total 480 fractions exhibiting displacements of ≥ 2 mm, ≥ 3 mm and ≥ 5 mm, respectively. However, some patient fractions showed large amplitude (> 10 mm) unpredictable motion. Seventeen (77.3%), nineteen (86.4%) and twenty two (100%) patients exhibited intra-fraction displacements of < 2 mm, < 3 mm and < 5 mm for $\geq 95\%$ of the total tracking time. For a threshold value of ± 2 mm, 81.7 % of the 480 total fractions were categorised as stable while 7.9% exhibited persistent excursions or continuous drift. The remaining 10.4% showed transient excursions.

3.3. Prostate motion tracking

3D-US and x-ray fiducial tracking of prostate motion data is shown in figure 3. Qualitatively 3D-US and x-ray tracking was in good agreement with input displacements. Some notable discrepancies remained for elevational (RL) 3D-US tracking (figure 3, right column). It was also apparent that the x-ray imaging frequency was non-uniform and relatively low, with only 2 – 4 data samples per motion scheme. Table 2 quantifies the RMSE of tracking with fiducials and 2D- and 3D- US. For each axis, the tracking RMSE was < 0.5 mm with several exceptions. For x-ray tracking the RMSE was 0.25 mm (SI), 0.26 mm (AP) and 0.16 mm (RL), averaged over the five motion schemes. For 2D - US the RMSE was 0.44 mm (SI) and 1.25 mm (AP), while 3D-US RMSE was 0.32 mm (SI), 0.51 mm (AP) and 1.36 mm (RL), averaged over the five motion schemes.

The high mean correlation values (mean: 0.964) for 2D - US indicated that out-of-plane motion was not a significant issue for prostate tracking in 2D. Conversely, the lower mean

correlation values (mean: 0.648) for 3D tracking were likely influenced by decorrelation along the elevational axis. The US tracking RMSE was lowest for axial (SI) displacements. The 2D-US RMSE was largely influenced by the error in tracking prostate motion scheme #5. This scheme exhibited the largest out-of-plane (elevational) motion, therefore imaging in 3D improved the RMSE. For the remaining four motion schemes the 2D - US (mean) tracking RMSE was 0.19 mm (SI) and 0.22 mm (AP) while for 3D-US was 0.34 mm (SI), 0.44 mm (AP) and 0.66 mm (RL).

Figure 4 shows a comparison of 3D-US and input inter-volume displacements for the lateral component of the transient motion scheme. It can be seen that the 3D-US displacement estimates generally agree with input displacements to better than 0.5 mm with only three exceptions. Figure 5 provides analysis of the differences in inter-volume displacements for all five motion schemes. It was found that 98.4% of inter-volume displacements were within 0.5 mm of input values. This demonstrated that any differences between input motion and 3D-US cumulative (centre-of-mass) displacement estimates were due to very few (1.6%) tracking errors. A correlation threshold value (TVC) was investigated as one method of dealing with these errors with other potential methods presented in the discussion.

3D-US tracking could be used to monitor the target position until it has reached a predetermined displacement threshold, TVD (i.e gating the treatment). Therefore it is likely that the transient prostate motion scheme would trigger a treatment pause at some user-specified TVD value. The treatment would then resume when the prostate was repositioned within tracking limits. Figure 6 shows the RMSE as a function of TVD value for 3D-US tracking. For all motion schemes the maximum elevational (RL) displacement was 1.2 mm and therefore this axis is absent. For axial (SI) and lateral (AP) displacements, the RMSE was < 0.2 mm and < 0.4 mm, respectively. The error bars represent the uncertainty in RMSE assuming a ± 1 second error in temporal calibration between tracking data and input motion.

3.4. Correlation threshold value, TVC

For the 3D probe used in this study, tracking errors were most likely to occur along the elevational axis due to lower spatial resolution and effect of angular decorrelation. A correlation threshold was applied to the tracking data to investigate the possibility of improving the RMSE of cumulative displacement estimates. Figure 7 shows the RMS tracking error as a function of correlation threshold (TVC: 0.2 – 0.8). This shows how the RMSE for the cumulative displacement trace is effected when incremental data points with associated inter-volume peak correlation values below TVC are set =0 mm. This simple method appears to improve the 3D RMSE when the cumulative / inter-volume displacement is small (i.e. close to 0 mm) e.g. for the stable motion scheme (min. 3D RMSE for TVC = 0.8). Investigating each axis separately, for the elevational (RL) displacement component, it can be seen that the tracking RMSE improves as the correlation threshold increases. For TVC values above 0.75, the RMSE was less than 2.0 mm. A correlation threshold was also applied to axial and lateral displacement components however this did not improve tracking accuracy (i.e. For the five motion traces studied, when the correlation peak is low, an elevational inter-volume estimate = 0.0 mm is superior to displacement estimates calculated by the tracking code). Since analysis of 2D tracking results showed that axial (SI) and lateral (AP) displacements did not cause significant decorrelation (the minimum inter-volume correlation was 0.893 for all five prostate traces),

decorrelation in 3D tracking was likely due to elevational motion. Furthermore, plotting the minimum 2D peak correlation (2D tracking) against the maximum 3D elevational inter-volume displacement for the five motion schemes resulted in high Pearson correlation (-0.803) further indicating that significant decorrelation (at this volume rate) is due to out-of-plane (elevational) motion. Use of a correlation threshold will decrease the mean volume rate, however, for elevational (RL) displacements this is unlikely to be an issue as discussed below. Figure 8 shows how elevational tracking RMSE can be improved for one of the prostate motion schemes.

3.5. Planning-target-volume margins

In the absence of US tracking, the required (anisotropic) PTV margins were 3.5 mm (SI), 6.1 mm (AP) and 2.1 mm (RL). With the application of 3D-US tracking, the SI and AP PTV margins were decreased by -44.2% and -61.8% to 2.0 mm and 2.3 mm, respectively. Due to elevational tracking errors, the RL margin increased to 5.0 mm. However, by using a correlation threshold to remove erroneous inter-volume displacement estimates the RL margin could be reduced to 2.2 mm (TVC = 0.8). In the absence of tracking, an isotropic PTV margin (3D) of 7.5 mm was required. This was reduced to 6.1 mm (-18.5%) when 3D – US tracking was utilised. The margin is largely effected by elevational (RL) tracking errors.

4. Discussion

This study has investigated the use of mechanically-swept 3D ultrasound speckle tracking for prostate translations with knowledge of the input motion and comparison with currently available intra-fraction imaging technology. In terms of imaging rate, US is clearly advantageous (figure 3) and this advantage is expected to improve with new US technology (Lediju Bell et al. 2012). For simulated trans-perineal imaging, ultrasound tracking exhibited the lowest RMSE for superior-inferior (axial) displacement estimates. The RMSE of anterior-posterior (lateral) displacements was also low (< 1.0 mm) in most cases. Clinically, axial and lateral displacements are most important in terms of both displacement frequency and magnitude (Huang et al. 2002). Firstly, the magnitude of motion along these axes can displace the prostate outside standard (~ 10 mm) and hypofractionated (~ 3- 5 mm) PTV margins. Secondly, it is desirable to limit the dose to proximal organs-at-risk i.e. the bladder (which is superior) and the rectum (which is posterior). When using a swept-array probe it is important to align the most accurate displacement tracking axis with the patient axis exhibiting the most clinically significant or relevant motion.

The accuracy of the CyberKnife G4 fiducial tracking system has been reported to be 0.29 ± 0.10 mm (Antypas and Pantelis 2008). We found that the fiducial tracking RMSE was 0.22 mm (mean) for our phantom based study. It is, however, important to note that the accuracy in tracking and beam targeting is highly dependent on the imaging frequency. As discussed below, the x-ray imaging system is likely to miss transient prostate excursions. For continuous target drift and persistent motion types x-ray tracking RMSE was 0.43 mm (mean (3D RMSE), max.: 0.91 mm). 3D – US tracking 3D RMSE was also found to be approximately a millimetre or less (mean: 0.93 mm, max.: 1.08 mm).

For right-left displacements, there was a trade-off between elevational field-of-view (FOV_{elev}), frame density and volume rate. One solution to this problem would be the use of

a 2D matrix array transducer which can acquire high resolution volumetric data at very high imaging rates without the need to sweep the transducer array along the elevational axis (Byram et al. 2010, Lediju Bell et al. 2012). In the current study it was also shown that the application of a simple correlation threshold to elevational (inter-volume) displacement estimates could improve the cumulative (centre-of-mass) displacement tracking. While this would reduce the effective mean volume rate this could also in the future be recovered using a high-volume rate 2D matrix transducer, which itself would improve correlation and tracking accuracy because inter-volume displacements would be smaller. In addition, and as relevant to the present mechanically-swept 3D-US, right-left (elevational) prostate motion generally involves low frequency, small magnitude displacements (Huang et al. 2002). An analysis of 3D-US inter-volume displacement estimates (figure 5) showed that discrepancies between input and 3D-US cumulative displacements (figure 3) was due to very few ($< 2\%$) large (> 0.5 mm) differences. The correlation threshold method investigated and discussed above is one quality metric which can be used to ensure the accuracy (i.e. regularisation) of tracking data. Other methods could rely on analysis of temporal behaviour (e.g. filtering based on analysis of population motion characteristics) or spatial behaviour of the tissue or phantom (e.g. Lediju Bell et al. 2012).

Previous studies have investigated the use of ultrasound for prostate motion tracking during radiation therapy. Schlosser et al. (2011) demonstrated the feasibility of using a telerobotic-based ultrasound imaging device. The system used correlation based tracking of trans-abdominal 2D – US data. A drop in the peak of the correlation coefficient was used as an indicator of potential rotations and out-of-plane motion. It was reported that in-plane (AP/SI) prostate translations, rotations and out-of-plane (RL) translations could be detected before they exceeded 2.5 mm, 5° and 2.8 mm, respectively (at the 95% confidence level). Rubin et al. (2012) evaluated 2D - US speckle tracking of prostate motion which was simulated by rocking the transducer on the perineum. Angular displacement of the prostate was found to be within 1.1° of that measured by manual tracking on B-mode images. These studies demonstrated the feasibility of 2D tracking of *in vivo* prostate motion. The current study has extended this to 3D tracking with known phantom prostate-derived motion.

It is arguable whether 3D tracking is required for prostate motion. Our analysis of 480 Calypso-tracked patient fractions showed RL intra-fraction motion was small (S.D.: 0.3 mm, max.: 2.1 mm). Li et al. (2008) studied the dosimetric consequences of intra-fraction prostate motion and found that although significant motion can be observed in individual fractions, the dosimetric impact is insignificant during a typical course of therapy when PTV margins of ≥ 2 mm are used with pre-treatment localisation. It may therefore be feasible to track the prostate in 2D (using a 2.0 mm RL margin) reverting to 3D only when the inter-volume peak correlation drops below a specified threshold value (Schlosser et al. 2011). This would also allow tracking at a much higher imaging rate (frame rate). The RMSE of 2D - US tracking was investigated and found to be < 0.5 mm for the stable and persistent prostate motion traces studied (table 2). While the RMSE of tracking the transient motion trace increased (table 2), it is argued here and elsewhere (Lachaine and Falco 2013) that clinical use of prostate motion tracking is generally concerned with compensating for drifts and persistent excursions rather than “chasing” transient excursions. Also, using a 30 – 60 second imaging period, it is likely that the CyberKnife imaging system could “miss” a transient excursion (Xie et al. 2008). Furthermore, the mean correlation for all 5 prostate motion traces studied was 0.964 confirming that out-of-plane prostate motion was generally not an issue.

The 3D-US system implemented in the current study could also be used for gating the treatment (Schlosser et al. 2011). The ability to treat prostate patients using very small margins and displacement thresholds has previously been investigated using the Calypso electromagnetic tracking system (Tropper et al. 2009). We have shown that 3D-US can accurately detect SI and AP displacement thresholds (TVD) of 2.0 and 5.0 mm (< 0.2 mm and < 0.4 mm RMSE) for the five selected motion traces (figure 6). A tracking threshold of 2.0 mm could be used to treat patients with a 2.5 mm margin accounting for residual tracking errors. When a threshold value is detected, a treatment pause could be triggered. A correlation threshold could be applied to the elevational axis to improve RL displacement detection. The current study has not addressed intra-fraction prostate rotation (Aubry et al. 2003). While generally smaller in magnitude ($\sigma \leq 1.8^\circ$) than inter-fraction motion, it may be important to account for rotation when considering the use of extremely small PTV margins or displacement thresholds. Finally, the tracking algorithm needs to operate in real-time. In the current study all ultrasound speckle-tracking was performed retrospectively and offline. Methods of increasing tracking speed could include using a faster method of block-matching (e.g. a parallelised implementation of sum absolute difference (Mehta et al. 2010)) and dynamic modification of the search region based on previous inter-volume displacement estimates.

5. Conclusions

3D-ultrasound (US) speckle tracking has, in general, shown low RMSE (< 0.5 mm) for intra-fraction prostate translation monitoring when compared to known phantom motion and kV x-ray fiducial tracking. US has a significantly higher imaging rate which may be important for hypo-fractionated treatments. For simulated trans-perineal imaging, superior-inferior (axial) and anterior-posterior (lateral) tracking RMSE was better than 0.81 mm in all cases. Right-left (elevational) tracking suffered from some erroneous results however, when inter-volume displacements are small, it was found that application of a speckle tracking correlation threshold could reduce the RMSE to < 2.0 mm. In the future, use of correlation values to regularise tracking will require more complex methods of extrapolation or weighted curve fitting of the displacement data to improve results for all motion types. The largest US RMSE was for a high magnitude transient excursion. For continuous target drift and persistent motion types – which would likely have the largest dosimetric impact – the RMSE was sub-millimetre. 3D-US has potential for improvement for high tracking accuracy in all circumstances. 3D-US tracking was effective in reducing the superior-inferior and anterior-posterior treatment margins and detecting relevant centre-of-mass displacement thresholds. This phantom-based study has shown that 3D-US potentially has the accuracy needed to track prostate motion. It may be feasible to track the prostate in 2D only. It would be insightful to study the ability of 2D/3D-US speckle tracking to accurately monitor *in vivo* motion of the prostate and account for prostate rotations.

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Figure 1. Trans-perineal image of prostate (coronal view) with GE RSP6-12 MHz transducer (a). The green rectangle represents a possible reference (kernel) volume in one ultrasound volume acquisition. The green rectangle in frame two is the best estimate of the position of the initial reference volume in a subsequent US volume after a cross-correlation search within the blue rectangular region. Experimental set-up of phantom study (b) and transducer geometry showing trans-perineal alignment with patient axes (c).

Figure 2. Comparison of x-ray and 3D – ultrasound (US) estimated displacements with motion platform input displacements. The error bars give the standard deviation in displacement across the reference volume for the ultrasound displacement estimate and three measurements for x-ray fiducial marker estimates.

**note the different ordinate scales*

Figure 3. Comparison of x-ray fiducial marker (FM) tracking, 3D – ultrasound (US) speckle tracking and input prostate motion schemes (from Calypso). The error bars give the standard deviation in FM displacement estimates. Each row gives the axial, lateral and elevational tracking of motion schemes 1 – 5 (as quantified in table 2).

Figure 4. Analysis of 3D-US inter-volume displacements for lateral component of transient motion scheme showing differences between interpolated input and 3D-US estimates.

Figure 5. Analysis of 3D-US inter-volume displacements showing the number of inter-volume displacements with differences (3D-US – input) of 0.0 to ± 0.5 mm, ± 0.5 to ± 1.0 mm, ± 1.0 mm to ± 1.5 mm and ± 1.5 mm to ± 2.0 mm, for each of the five motion schemes.

Figure 6. 3D-Ultrasound (US) tracking accuracy for displacement thresholds of 2.0 mm and 5.0 mm demonstrating the accuracy with which 3D speckle tracking can detect when a cumulative displacement threshold has been reached. The inset figure demonstrates how the RMS error was calculated for a TVD = 5.0 mm example case.

Figure 7. 3D-Ultrasound (US) tracking RMS error as a function of correlation threshold (TVC) for axial (a), lateral (b) elevational (c) and 3D (d) estimates of prostate motion traces. The 3D estimates RMSE have been normalised to one using the RMSE for original motion trace with no correlation threshold applied. Therefore a RMSE of less than one implies the corresponding correlation threshold value improves the RMSE. (circle: drift, square: persist. #1, diamond: persist. #2, triangle: stable, triangle left: transient). Linear regression lines to help guide the reader.

Figure 8. Example of accuracy improvement in cumulative displacement when a correlation threshold (TVC) is applied to inter-volume elevational displacement estimates. Shown here for the right-left component of the persistent #1 prostate motion scheme (top). The correlation between consecutive ultrasound volumes is also shown (bottom).

Table 1. Comparison of kV x-ray and 3D-ultrasound tracking with known input displacements of 0.2 – 5 mm. Mean difference and root-mean-square error for displacements in the range of 0.2 – 2.0 mm and 0.2 – 5.0 mm for each of the three major axis and 3D (axes combined). The mean correlation (ρ) across the reference volume for the ultrasound tracking estimates and standard deviation for three x-ray measurements is also listed.

Direction	Modality	Mean diff. [mm]	RMSE (2mm) [mm]	RMSE (5mm) [mm]	SD [mm]	Mean ρ (2mm)	Mean ρ (5mm)
Axial / S-I	US	-0.15	0.14	0.15	-	0.831	0.766
	X-ray	0.22	0.23	0.22	0.03	-	-
Lateral / A-P	US	-0.15	0.12	0.17	-	0.744	0.685
	X-ray	-0.17	0.17	0.17	0.03	-	-
Elevation / R-L	US	-0.14	0.17	2.24	-	0.558	0.447
	X-ray	-0.12	0.13	0.12	0.07	-	-
All / 3D	US		0.25	2.25			
	X-ray		0.31	0.30			

Table 2. Root-mean-square errors for kV tracking and ultrasound 2D (axial and lateral frames only) and 3D incremental tracking of prostate motion traces. The mean correlation across the tracked ultrasound volume is also listed.

	Motion		RMSE [mm]			Mean ρ
		<i>Axial / S-I</i>	<i>Lateral / A-P</i>	<i>Elev. / R-L</i>	<i>All / 3D</i>	
			KV x-ray			
1	Con. drift	0.74	0.51	0.14	0.91	-
2	Persistent #1	0.10	0.17	0.18	0.27	-
3	Persistent #2	0.08	0.23	0.15	0.29	-
4	Stable	0.18	0.12	0.15	0.26	-
5	Transient	0.13	0.29	0.18	0.37	-
			2D - US			
1	Con. drift	0.17	0.18	0.17	0.30	0.967
2	Persistent #1	0.14	0.12	0.14	0.23	0.967
3	Persistent #2	0.35	0.37	0.12	0.52	0.950
4	Stable	0.09	0.22	0.12	0.27	0.969
5	Transient	1.47	5.34	0.65	5.58	0.967
			3D - US			
1	Con. drift	0.34	0.30	0.83	0.95	0.620
2	Persistent #1	0.30	0.22	0.69	0.78	0.649
3	Persistent #2	0.54	0.72	0.19	0.92	0.718
4	Stable	0.14	0.52	0.94	1.08	0.626
5	Transient	0.29	0.81	4.13	4.22	0.656