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 five 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 (right–left; 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 track the major components of intra-fraction prostate motion accurately but exhibits some limitations. The largest US RMSE was for elevational (RL) 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 the potential to improve high tracking accuracy for all motion types. It would be advisable to use US in conjunction with a small (\(\sim 2.0 \) 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.

Keywords: ultrasound, tracking, intra-fraction, prostate, hypo-fractionation

(Some figures may appear in colour only in the online journal)

1. Introduction

During radiation therapy (RT) it is known that the prostate, as delineated on computed tomography (CT) images, can undergo significant displacements (\(\sim 10 \) mm) during treatment, requiring the use of an additional treatment margin to account for this intra-fraction motion (Webb 2006, Koremman 2012). Radiation therapy of prostate 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 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 non-linear (with the ratio of fit coefficients, alpha/beta \(\sim 1.5 \)) (Fowler et al 2001, Bentzen and Ritter 2005). If the alpha/beta ratio is approximately equal to that of late responding normal tissue, a hypo-fractionated radiation treatment regime would increase the therapeutic gain of radiotherapy (Miles and Lee 2008). Unfortunately, potential benefits of hypo-fractionation may not be fully realized due to the need for large PTV margins to account for prostate motion. With increased accuracy of prostate localization (Letourneau et al 2005) and tracking (Willoughby et al 2006) comes the prospect of increasing tumour dose, reducing PTV margins (Litzenberg et al 2006) and minimizing toxicity to surrounding organs (Huang et al 2002). In turn this may help to elucidate the benefits of hypo-fractionation.

The ability to visualize the prostate in three dimensions and its position relative to 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 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 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 identification of metal fiducials via kV x-ray imaging (Jaffray et al 2002) and, more recently, using implanted electromagnetic fiducials (Willoughby et al 2006).

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

Ultrasound (US) imaging is a potential alternative method for providing high frequency positional information by contour (feature) and soft-tissue (speckle) tracking during RT (Harris et al 2007, Schlosser et al 2010, Bell et al 2012, Rubin et al 2012, Lachaine and Falco 2013). US imaging is non-ionizing and non-invasive, it provides soft-tissue definition and has the ability to provide high frame (2D) or volume 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 set-up 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 s imaging period (Lachaine and Falco 2013). TPUS imaging allows visualization 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 RT with promising results (Hsu et al 2005, Harris et al 2007, 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 RT. 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 four 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 step motors to translate the ultrasound phantom which was placed inside a 9 L water container. The motion platform was incapable of rotational motion and prostate rotational data was unavailable. Therefore only translations were considered. 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)
**Figure 1.** A trans-perineal image of prostate (coronal view) with GE RSP6-12 MHz transducer (a). Two US frames to illustrate speckle tracking: the green rectangle represents a possible 2D cross-section through a reference (kernel) volume in one ultrasound volume acquisition. The green rectangle in frame 2 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 (b). The experimental set-up of the phantom study (c) and the transducer geometry, showing trans-perineal alignment with patient axes (d).
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 (∼1540 m s⁻¹) which is comparable with human tissue (Surry et al 2004). Cellulose ultrasound scatterers (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 digitally reconstructed radiograph (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) × 5.5 cm (elevationally). 3D data were acquired by sweeping (elevationally) the linear array through an angle θ (see figure 1(d)). The central 128 elements of the probe were connected to the Diasus US system. Radio-frequency (RF) data were digitized and sampled at 66.67 MHz. The US 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 normalized correlation coefficient (3D NCC) between the reference and search volumes (Harris et al 2007). 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 NCC (ρ) values for each axis. The peak, ρmax, 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:

\[ y = (r + \text{ROC}) \sin \theta \]

\[ z = (r + \text{ROC}) \cos \theta \]
It is known that the accuracy of US displacement estimates tend to decrease due to speckle decorrelation for larger inter-volume displacements (Harris et al 2007, Bell et al 2012). This can happen for a variety of reasons. For example, large displacements are associated with large tissue strain, and strain produces a change in the spatial arrangement of ultrasound scatterers. Even in the absence of strain, however, acquisition of ultrasound echo data in polar coordinates may generate rotation of the arrangement of the scatters relative to the ultrasound beam for lateral or elevational displacements. Large displacements may also move the reference volume partially or wholly outside the search volume, resulting in partial or complete loss of correlation. 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, $\theta$, the elevational field-of-view (FOVelev) was given by:

$$\text{FOVelev} = \text{ROC} \left( \frac{\theta \pi}{180} \right),$$

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 s segment of sustained displacement (containing 3.3 mm (axial), 4.5 mm (lateral) and 0.5 mm (elevational) displacements). A sweep angle ($\theta$) of 5° and ten frames per volume gave the best trade off between FOVelev, 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 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, five 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 transmit 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 and 2 mm, respectively. The optimal reference volume used in the 3D-US speckle tracking code was 45 (axial) × 40 (lateral) × 3 (elevational) voxels. The optimal search region was (200 to 900) × (50 to 90) × 8 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 SI (axial) and ~0.05 mm AP/RL (lateral/elevational). These values were estimated based on the motor encoder outputs when returning to the same position ten 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.
Four hundred and eighty intra-fraction motion traces (at 10 Hz sample rate) from 22 patients were analysed. The system output intra-fraction centre-of-mass translations only. A MATLAB program 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 $\geq 2$ mm, $\geq 3$ mm and $\geq 5$ mm displacements and (iii) the percentage of total tracking time with $\geq 2$ mm, $\geq 3$ mm and $\geq 5$ mm displacements for each patient. Motion traces for all patients were also categorized into the following motion types:

(i) stable (i.e. displacements remain within user-specified limits i.e. $\pm 2$ mm),
(ii) transient (i.e. displacements exceed user-specified limits but return 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 generalized 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 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 give the range over which 95% of the agreement 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 $\pm 2.0$ mm indicated US could not replace fiducial markers for displacement estimation. For RL (elevational) displacements, RMSE and LOA analysis was limited to displacements of $\leq 2.0$ mm. This was justified since, within the limitations of the current probe hardware, the trade-off between FOV and volume rate meant that large RL displacements could not be tracked accurately and, additionally, RL prostate motion is small. Since such out-of-plane motion is rare, we also quantified the accuracy of 2D ultrasound tracking (2D-US):

$$\text{RMSE} = \sqrt{\frac{\sum_{t=1}^{n} (y_{\text{input}} - y_{\text{US}})^2}{n}}.$$  (4)

For prostate motion tracking analysis, the input motion data were interpolated the fiducial or US tracking points prior to calculation of RMSE. Fiducial and 2D-US tracking data was time stamped and synchronized to better than $\pm 1$ s. Temporal calibration (alignment) of input motion and tracking data was achieved by minimizing 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, which that final temporal calibration likely better than this.

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 a specified TVD value of 2.0 or 5.0 mm was reached was also assessed for each of the prostate motion traces.

### 2.5. Correlation threshold value

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 \( \rho_{\text{max}} \) value with the TVC value and if \( \rho_{\text{max}} < \text{TVC} \) 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:

\[
M_{\text{PTV}} = 2.5 \Sigma + 0.7 \sigma',
\]

where \( \Sigma \) and \( \sigma' \) 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), differences between the means 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 (FOVelev) was limited, for the present hardware, by the need to optimize volume rate for tracking dynamic...
Table 1. Comparison of kV x-ray and 3D-ultrasound tracking with known input displacements of 0.2–5 mm. The mean difference and RMSE 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) is given. The mean correlation ($\rho$) 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 (2 mm) (mm) | RMSE (5 mm) (mm) | SD (mm) | Mean $\rho$ (2 mm) | Mean $\rho$ (5 mm) |
|-----------|----------|-----------------|------------------|------------------|---------|------------------|------------------|
| 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             | 0.25             |         |                  |                  |
|           | X-ray    | 0.31            | 0.30             |                  |         |                  |                  |

(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% 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 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 from Calypso showed the largest component of prostate motion was along the AP axis. RL motion was minimal. The mean (±SD) displacement over all 480 traces was 0.0 ± 0.3, 0.0 ± 0.8 and –0.1 ± 0.3 mm for RL, SI and AP axes, respectively. The maximum displacements were 2.1 (L), 10.3 (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, ≥3 and ≥5 mm, respectively. However, some patient fractions showed large amplitude (>10 mm) unpredictable motion. Seventeen (77.3%), 19 (86.4%) and 22 (100%) patients exhibited intra-fraction displacements of <2, <3 and <5 mm for ≥95% of the total tracking time. For a threshold value of ±2 mm, 81.7% of the 480 total fractions were categorized as stable while 7.9% exhibited persistent excursions (including 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 are 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 <0.5 mm with only three exceptions.
Figure 3. Comparison of x-ray fiducial marker (FM) tracking, 3D-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 5 provides 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 and <0.4 mm, respectively. The error bars represent the uncertainty in RMSE assuming a ± 1 s error in temporal calibration between tracking data and input motion.

3.4. Correlation threshold value

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
Figure 4. Analysis of 3D-US inter-volume displacements for the lateral component of the transient motion scheme (as shown in the centre column and lowest row of figure 3) showing differences between interpolated input and 3D-US estimates.

Table 2. RMSE 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. Italic numbers indicate that the motion was not estimated by US along this axis using 2D-US.

| Motion       | RMSE (mm) | KV x-ray | 2D-US | 3D-US |
|--------------|-----------|----------|-------|-------|
|              | Axial/S-I | Lateral/A-P | Elev./R-L | All/3D | Mean ρ |
| Persistent #1| 0.74      | 0.51      | 0.14  | 0.91  | –      |
| Persistent #2| 0.10      | 0.17      | 0.18  | 0.27  | –      |
| Persistent #3| 0.08      | 0.23      | 0.15  | 0.29  | –      |
| Stable       | 0.18      | 0.12      | 0.15  | 0.26  | –      |
| Transient    | 0.13      | 0.29      | 0.18  | 0.37  | –      |
| Persistent #1| 0.17      | 0.18      | 0.17  | 0.30  | 0.967  |
| Persistent #2| 0.14      | 0.12      | 0.14  | 0.23  | 0.967  |
| Persistent #3| 0.35      | 0.37      | 0.12  | 0.52  | 0.950  |
| Stable       | 0.09      | 0.22      | 0.12  | 0.27  | 0.969  |
| Transient    | 1.47      | 5.34      | 0.65  | 5.58  | 0.967  |
| Persistent #1| 0.34      | 0.30      | 0.83  | 0.95  | 0.620  |
| Persistent #2| 0.30      | 0.22      | 0.69  | 0.78  | 0.649  |
| Persistent #3| 0.54      | 0.72      | 0.19  | 0.92  | 0.718  |
| Stable       | 0.14      | 0.52      | 0.94  | 1.08  | 0.626  |
| Transient    | 0.29      | 0.81      | 4.13  | 4.22  | 0.656  |
Figure 5. 3D-US inter-volume displacements showing the number of inter-volume displacements with differences (diff. = 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.

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 affected when incremental data points with associated inter-volume peak correlation values below TVC are set to 0.0 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 (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). A correlation threshold was also applied to axial and lateral displacement components with limited or no improvements to tracking accuracy. 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
Figure 6. 3D-Ultrasound (US) tracking accuracy for displacement thresholds of 2.0 and 5.0 mm, demonstrating the accuracy with which 3D speckle tracking can be detected when a cumulative displacement threshold has been reached. The maximum elevational displacement was less than 2.0 mm and is therefore absent. The inset figure demonstrates how the RMS error (RMSE) was calculated for a TVD = 5.0 mm example case. In this particular case the calculation of RMSE is restricted to the displacements in the time interval, t.

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 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 utilized. The margin is largely effected by elevational (RL) tracking errors.

4. Discussion

This study has investigated the use of mechanically-swept 3D ultrasound tracking of speckle intrinsic to the tissue for prostate translations with knowledge of the input motion and comparison with currently available intra-fraction imaging technology that uses surgically implanted fiducial markers. In terms of imaging rate, US is clearly advantageous (figure 3) and this advantage is expected to improve with new US technology (Bell et al 2012). For
simulated trans-perineal imaging, ultrasound tracking exhibited the lowest RMSE for SI (axial) displacement estimates. The RMSE of AP (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). The magnitude of motion along these axes can displace the prostate outside standard (∼10 mm) and hypo-fractionated (∼3–5 mm) PTV margins. Additionally, it is desirable to limit the dose to nearby 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. With knowledge of the limitations of mechanically-swept 3D probe technology, we aligned the probe to the ‘patient’ axes in what we believe to be the most sensible configuration. This alignment (i.e. mechanically focused and mechanically-swept axis aligned with RL), which arranges the direction of poorest US resolution and thus poorest displacement tracking accuracy with that of least (significant) motion, is also employed by the Elekta autoscan commercial device.

The overall spatial resolution of the CyberKnife G4 kV system was found to be ∼0.34 mm (Antypas and Pantelis 2008). The 3D-US system used in the current study had higher axial (SI) spatial resolution and comparable lateral (AP) resolution. The elevational (RL) resolution
was \( \sim 0.8 \) \text{mm}. Both systems had adequate spatial resolutions to track clinically relevant inter-image prostate displacements of 1–2 mm. The tracking accuracy of the CyberKnife G4 fiducial tracking system was reported to be 0.29\( \pm \)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. CyberKnife uses a nominal imaging interval of 30 s. Based on analysis by Xie et al (2008), this will result in 2 mm displacements in less than 5% of patient datasets. As discussed below, the x-ray imaging system is therefore likely to miss transient prostate excursions. For persistent motion types x-ray tracking RMSE was 0.43 mm (mean (3D RMSE), max.: 0.91 mm). 3D-US tracking 3D RMSE was found to be approximately a millimetre or less (mean: 0.93 mm, max.: 1.08 mm).

For RL displacements, there was a trade-off between elevational field-of-view (FOVelev), frame density and volume rate. Furthermore, the elevational resolution was limited by the small elevational acoustic aperture size and the fixed elevational mechanical focusing. One solution to all of these problems 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, 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 parallel beamforming system, 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, RL (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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{example.png}
\caption{Example of accuracy improvement in cumulative displacement when a correlation threshold (TVC) is applied to inter-volume elevational displacement estimates, shown here for the RL component of the persistent #2 prostate motion scheme (top, seen in figure 3). The correlation between consecutive ultrasound volumes is also shown (bottom).}
\end{figure}
method investigated and discussed above is one quality metric which can be used to ensure the accuracy (i.e. regularization) 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. Bell et al 2012).

Previous studies have investigated the use of ultrasound for prostate motion tracking during RT. Schlosser et al (2010) 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 function 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. Simulated 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 localization. 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 2010). 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 was larger (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 persistent excursions rather than ‘chasing’ transient excursions. Also, using a 30–60 s 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 five prostate motion traces studied was 0.964 confirming that out-of-plane prostate motion was generally not an issue if 2D tracking was to be employed.

The 3D-US system implemented in the current study could be used for gating the treatment. 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 2004). While generally smaller in magnitude than inter-fraction motion (with \( \sigma \leq 1.8^\circ \)), 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 parallelized implementation of sum absolute difference (Mehta et al 2010)),...
non-exhaustive (optimized) searching and dynamic modification of the search region based on previous inter-volume displacement estimates.

5. Conclusions

In this study, 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 than currently available x-ray tracking, which may be important for hypofractionated treatments. For simulated trans-perineal imaging, SI (axial) and AP (lateral) tracking RMSE was better than 0.81 mm in all cases. RL (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 elevational RMSE to <2.0 mm. In the future, the use of correlation to regularize tracking will require more complex methods of prediction (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 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, particularly with new (high volume rate and elevational focusing) hardware. Nevertheless, even with current mechanically-swept probes and sequential beamforming, 3D-US tracking was effective in reducing the SI and AP 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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