Honorable Mention Poster Award

Intra-operative Localization of Brachytherapy Implants Using Intensity-based Registration

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ABSTRACT

In prostate brachytherapy, a transrectal ultrasound (TRUS) will show the prostate boundary but not all the implanted seeds, while fluoroscopy will show all the seeds clearly but not the boundary. We propose an intensity-based registration between TRUS images and the implant reconstructed from fluoroscopy as a means of achieving accurate intra-operative dosimetry. The TRUS images are first filtered and compounded, and then registered to the fluoroscopy model via mutual information. A training phantom was implanted with 48 seeds and imaged. Various ultrasound filtering techniques were analyzed, and the best results were achieved with the Bayesian combination of adaptive thresholding, phase congruency, and compensation for the non-uniform ultrasound beam profile in the elevation and lateral directions. The average registration error between corresponding seeds relative to the ground truth was 0.78 mm. The effect of false positives and false negatives in ultrasound were investigated by masking true seeds in the fluoroscopy volume or adding false seeds. The registration error remained below 1.01 mm when the false positive rate was 31%, and 0.96 mm when the false negative rate was 31%. This fully automated method delivers excellent registration accuracy and robustness in phantom studies, and promises to demonstrate clinically adequate performance on human data as well.

Keywords: Prostate brachytherapy, Ultrasound, Fluoroscopy, Registration.

1. INTRODUCTION

Prostate cancer continues to be the most commonly diagnosed cancer and the second leading cause of cancer death among men in the western hemisphere. In the U.S. alone, there are about 220,000 new cases diagnosed each year.[1] Brachytherapy has emerged as one of the definitive treatment option for early stage prostate cancer. The procedure entails permanent implantation of radioactive pellets (called seeds) into the prostate to eradicate the cancer with ionizing radiation while sparing healthy tissues. Faulty needle and seed placement often cause an insufficient dose to the cancer and/or inadvertent irradiation of the rectum, urethra or bladder. The former causes failure of treatment while the latter results in adverse side effects like rectal ulceration, incontinence and painful urination. The ability to perform dosimetry optimization during the procedure could change the standard of care in brachytherapy, but such functionality is not available today and it is unfortunate that implants are currently performed without an explicit dosimetry evaluation in the operating room.

Generally, dosimetric analysis requires precise localization of the implanted seeds in relation to the prostate and surrounding anatomy. Brachytherapy is predominantly performed with transrectal ultrasound (TRUS) guidance that provides adequate real-time visualization of the prostate but not of the implanted seeds. Despite significant efforts, localization of seeds directly from TRUS has not been clinically practical or robust. C-arm

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fluoroscopy is often used for gross visual assessment of the implant, in fact accurate reconstruction of seeds from fluoroscopy has recently become possible,[2–5] but fluoroscopy cannot show the prostate itself. In special operating rooms, CT imaging[6] or cone beam CT[7] imaging is available as an alternative. Because the shortcomings of TRUS and X-ray offset each other, quantitative dosimetry could be performed via spatial registration of the two.

In order to register TRUS and fluoroscopy, Zaider *et al.*[8] suggested affixing radio-opaque fiducials to the TRUS probe, thereby permanently altering standard clinical equipment. Jain *et al.*[2] proposed precision machined fiducial structure calibrated to the needle guide template. Gong *et al.*[9] used needle tips as fiducials for the registration. For a variety of reasons specific to the brachytherapy workflow, fiducial-based approaches are not sufficiently reliable or clinically practical. Su *et al.* and and Tutar *et al.* suggested point-based registration between seeds segmented and reconstructed in both fluoroscopy and TRUS.[3,4] The generally poor quality of TRUS (due to noise, speckle, acoustic decoupling, calcifications masquerading as seeds, shadowing, multiple reflections, etc.) makes seed segmentation prone to error, causing instable registration performance. In contrast to prior art, we propose intensity-based registration. Generally, mutual information (MI) tends not to work between ultrasound and X-ray tomography, mostly because the anatomical structures are embedded in low contrast environment with little distinctive information. But implanting the prostate with seeds changes the situation advantageously. While TRUS remains noisy and hampered by artifacts, the seeds in both modalities seem to carry enough distinctive information for MI to prevail. Interestingly, despite the availability of technical capability, our previous report of using intensity-based registration appears to be the first one in the literature.[10] The apparent straightforwardness of our approach, however, should not detract from the investment of effort needed to make a workable clinical tool. Here, we present the results of a detailed experimental analysis conducted in a controlled laboratory environment on training phantoms using the proposed approach.

2. METHODS

In essence, we propose to filter the TRUS and X-ray data, reconstruct them to volumes, and apply mutual information (MI) based multi-modal registration. The overall framework is shown in Figure 1. We assume the CT/Fluoro reconstruction to be pre-created in one of several ways. In rare cases, intra-operative CT is available.[6] Cone beam tomography reconstruction can be applied with specialized tables and advanced fluoroscopy units.[7] Discrete shot fluoroscopy allows for both tomosynthesis producing a coarse tomographic volume[5] and segmentation-based seed matching yielding a cloud of seeds (i.e. binary volume).[2] We can handle all of these flavors.

CT Filtering: As seeds are prominent in CT and fluoroscopy, we only clip a region of interest and use window-level scaling to create an 8-bit CT and optional thresholding to binarized the images. There is not significant difference between 8-bit CT and binary-CT as seeds dominate the scene anyway.

Ultrasound Filtering: We tested and compared various filters on TRUS to suppress artifacts and enhance seed-like regions without explicit segmentation. The baseline for comparison is no filtering (*US-0*). *US-1* is a noise reduction filter based on two successive thresholdings followed by removal of regions whose area is smaller than that of a typical seed. The threshold values are obtained based on the average intensity of the pixels. *US-2* is a phase congruency filter. Previously, Hacihaliloglu *et al.* used phase congruency (PCON) for detecting bone edges in ultrasound.[11] PCON evaluates features based on phase rather than amplitude information. Since it gives a measure of significance for each point invariant to image brightness or contrast, a constant and uniform threshold can be applied to extract feature points from the phase information.[12] We calculate the PCON at each pixel of each image in order to measure phase symmetry. The more symmetrical the phase of a region is, the more likely it is to be a seed. The measure of symmetry is calculated as the weighted average resulting from even and odd symmetry filters. In this paper, we used the MATLAB® implementation of PCON from Kovesi*. The beam profile filter (*US-3*) accounts for the finite thickness of the ultrasound beam and the focusing in the elevational and lateral directions, which make fidelity across the image nonuniform.[13] In our experiment, the number of focal points in the lateral plane was set to two. We give more weight to the regions near the focal

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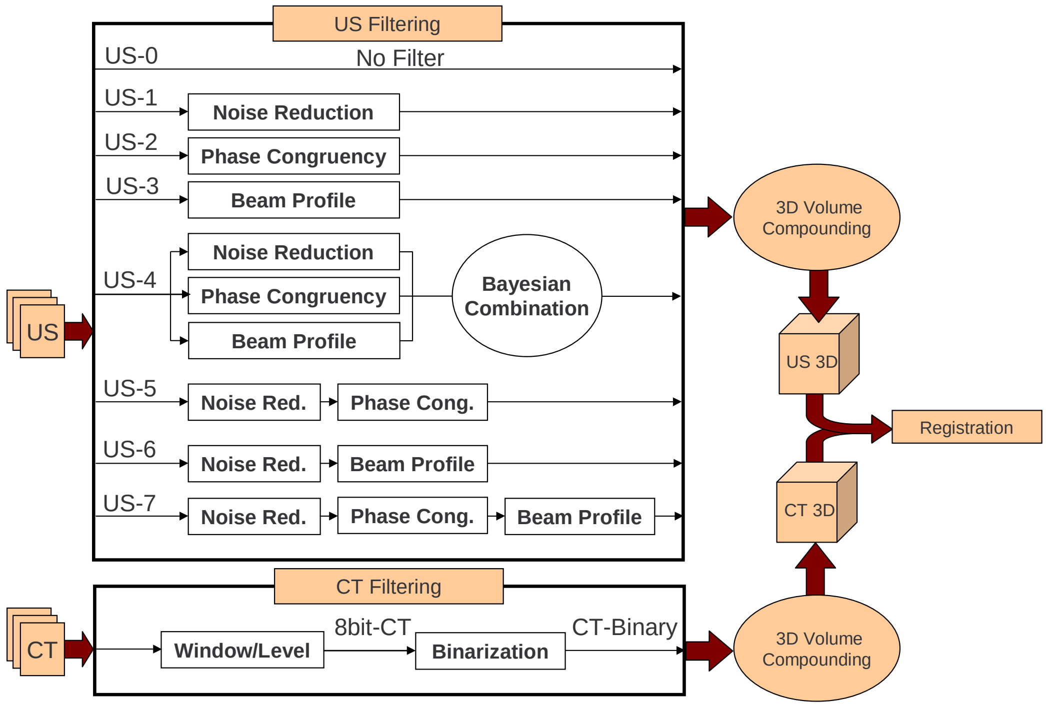


Figure 1. Intensity-based registration framework. TRUS frames are processed by one of seven filters. CT frames are scaled and binarized. Volumes are compounded and supplied to the MI registration engine.

points and less to the the ends of the image where the beam is less accurate. In *US-4*, we combine parallel noise reduction, phase congruency and beam profile filters in a Bayesian model, where each filter independently estimates "seedness" and their results are combined as in Scepanovic *et al.*[14] In *US-5* noise reduction is followed by phase congruency. In *US-6*, noise reduction is followed by beam profile filtering. Finally, in *US-7* we cascade noise reduction, phase congruency, and beam profile filtering.

Registration: TRUS and fluoroscopy are performed almost concurrently. After TRUS, the probe is retracted from the rectum, so as not to block seeds during fluoroscopy, causing the prostate to sag usually without apparent deformation. Thus, rigid MI registration should suffice, and we have an accurate initial guess for the registration. Consistent patient positioning allows for estimating the main symmetry axes of the prostate, and alignment of the gravity centers of the TRUS and CT/fluoro volumes yields accurate guess for translation.[2]

Ground Truth Data: Figure 2 shows our experimental ground truth phantom setup. We assume that the process and notations are familiar from basic surgical navigation literature. We made a realistic implant in a phantom (CIRS, Norfolk, VA) with 48 seeds, arranged a set of 1 mm CT fiducials on the container box, and acquired a CT volume with 0.3 mm pixel size and 0.6 mm slice thickness. We carefully segmented the six fiducials attached to the walls of the phantom. The CT fiducials were also localized with a calibrated pointer (Traxtal Inc., Toronto, ON) and Certus optical tracker (NDI, Waterloo, ON) with respect to the DRB coordinate on the phantom. Finally, we transformed the positions of seeds segmented in CT images to the TRUS coordinate system, thereby defining the ground truth for the registration. In order to maximize registration and tracking accuracy, the fiducials and tracking bodies were arranged so that their centroids fell close to the center of the prostate.

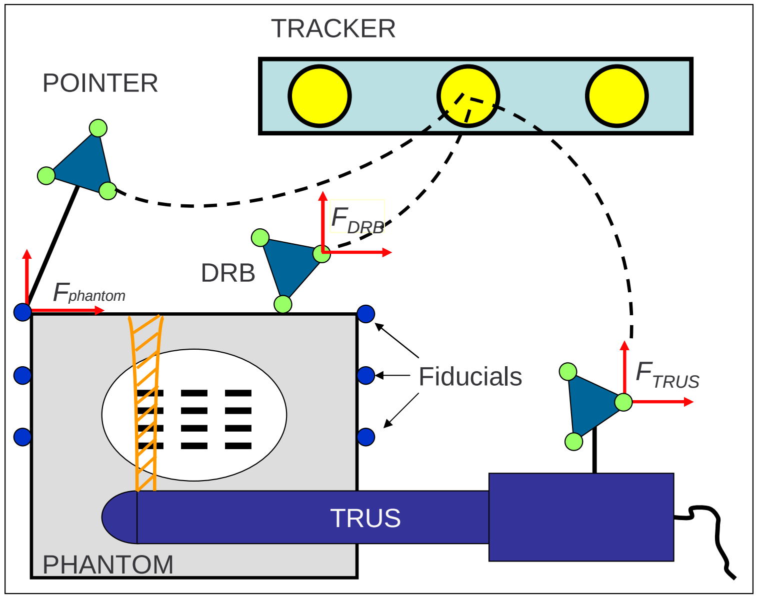


Figure 2. Coordinate transformations in Ground Truth Phantom. Calibrated pointer is used to register the CT fiducials to the dynamic reference body (DRB). The TRUS probe is tracked relative to the DRB.

3. RESULTS AND DISCUSSION

Perturbation was applied to the TRUS volume (i.e. moving image) and the registration was performed to bring the TRUS volume back to coincidence with the CT volume. The effects of various TRUS pre-processing filters, described in Figure 1, were tested extensively. In testing each filter, 100 registrations were accomplished starting from 100 different initial misalignments, randomly chosen from the range of ±15 degrees for three-axis rotation and ±5 mm for Cartesian translation. The mean registration error and STD of the seeds were calculated from the difference between true and estimated seed positions, obtained from the ground truth and the registration, respectively. This measure served as target registration error (TRE). Registration was marked as a "failure" if TRE after the registration was above 2 mm. All registrations were performed using Mattes mutual information method[15] implemented in ITK 3.4[†]. We ran a set of registrations between TRUS and the 8-bit CT and another set between TRUS and binarized CT. As seeds dominate the scene inside the prostate and window-level scaling yields a near binary volume, the performances of the binary and the 8-bit filters were almost identical (Table 1). Nonetheless, binarization was included to be compatible with all X-ray reconstruction techniques.

[†]National Library of Medicine, Insight Toolkit, http://www.kitware.com

Methods	CT-8bit		CT-Binary	
	$Mean \pm Std$ mm	% of Failure	$Mean \pm Std$ mm	% of Failure
US-0	1.03 ± 046	4	1.16 ± 0.40	15
US-1	0.82 ± 0.31	1	0.95 ± 0.38	7
US-2	0.73 ± 0.25	0	0.76 ± 0.33	2
US-3	0.72 ± 0.34	0	0.92 ± 0.43	11
US-4	0.72 ± 0.31	0	0.78 ± 0.31	1
US-5	0.88 ± 0.40	1	0.86 ± 0.32	4
US-6	0.76 ± 0.35	0	0.86 ± 0.36	4
US-7	0.77 ± 0.35	1	0.86 ± 0.34	6

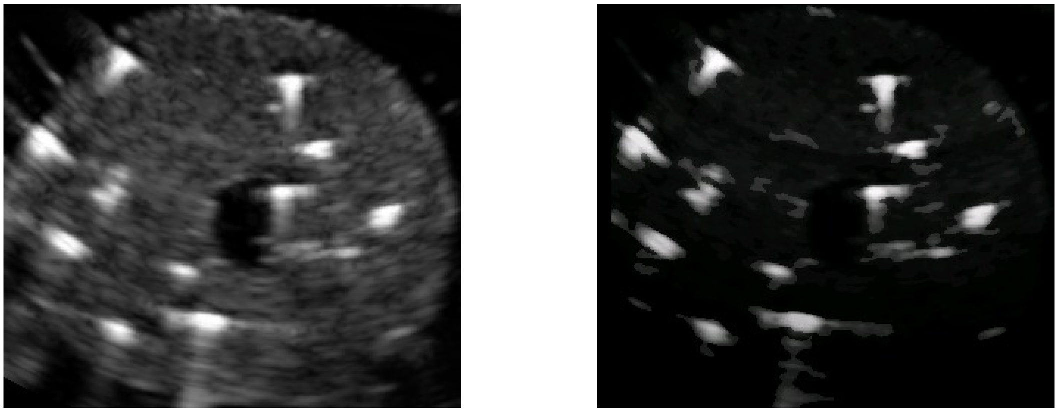
Table 1. US images are preprocessed using one of the methods (US0 to US7), CT volume is compounded by either 8-bit or binary images. For each chosen CT and US volume, registration is run 100 times using different random initial misalignments. Mean and standard deviation of TRE and the failure rate per each trial are reported.

All methods (excluding *US-0* which is non-processed US data) gave a mean seed registration error less than 1 mm which is well below the clinically acceptable threshold (the diameters of implant needles and seeds are about 2 mm and 1 mm, respectively.)

In all of the cases the registration results for 8-bit CT outperforms the results of CT-binary and this was predictable since the US data is in gray scale and mutual information also needs intensity information for better estimating the transform parameters. Therefore, existing gray scales in the 8-bit CT data helps the registration to find the final transformation with better accuracy. Comparing the results, in both cases (8-bit and binary), the TRE and failure rate are the worst for the non-processed US volume (*US-0*), with 1.03 mm mean TRE and 4% failure rate for 8-bit CT and 1.16 mm mean TRE with15% failure rate for CT-binary. The best filter for both 8-bit CT and CT-binary is *US-4* which is the parallel Bayesian combination of noise reduction, phase congruency and beam profile filters. It has 0.72 mm mean TRE with zero failure for 8-bit CT and 0.78 mm mean TRE with 1% failure for CT-binary. Accordingly, mean TRE has significantly decreased for both cases ($P < 0.05$) relative to *US-0*. *US-2* which is the phase congruency filter, also yielded very good results for both 8-bit and binary data. Although its mean TRE is slightly less than that of *US-4* for the binary data ($P = 0.34 > 0.05$), but the failure rate for *US-4* is smaller. However, the rest of the processing filters showed acceptable registrations results. It could be interesting to know which of the filters made the greatest contribution if being applied to the patient data which is a question presently being investigated.
Figure 3 shows the result of applying (*US-4*) to a TRUS image and Figure 4 shows an overlay view of two data sets (the US volume and the 3D seed model) using the registration results.

In US images, human prostates tend to present with false positive appearances such as double reflections and calcifications. Furthermore, US is suboptimal in term of showing all of the seeds. Therefore, there are some seeds in the fluoroscopy model that do not have any corresponding points in the US data, creating false negatives. These false positive and false negative are simulated by manipulating the CT volume. In the CT volume, we simulated false positives by masking seeds, and false negatives by duplicating the gray levels of a randomly chosen seed to a random location within the prostate boundary. We ran our Bayesian filter (*US-4*) and compared the results to the baseline of *US-0*. Up to 15 seeds (31%) in the CT volume were masked out for false positive or added for false negative. For each trial, the masked seeds or added seeds were picked randomly, repeated 100 times. We ran the registration only for binary CT since it is compatible with all X-ray reconstruction techniques (Table 2). Robustness to false positives and false negatives shows significant improvement over the baseline. For up to 31% false positives, we received 10% failure rate for *US-4* with 1.01 mm TRE, while almost 51% of all registrations failed with the baseline filter. For false negative analysis, we received 8% failure rate for *US-4* in the worst case with 0.96 mm TRE, while almost 41% of all registrations failed with the baseline filter. In these tests, the use of a parallel Bayesian TRUS filter paid off generously.

The *US-4* filter took approximately 17 seconds per image and each registration took 1.5 minutes using an Intel Core2, 2.4 GHz, dual-core computer. Most modern brachytherapy units have an optically encoded probe



(a) (b)

Figure 3. US processing, (a) a non-processed US image, (b) a processed US image with US-4: Bayesian combination of noise reduction, phase congruency and beam profile filters

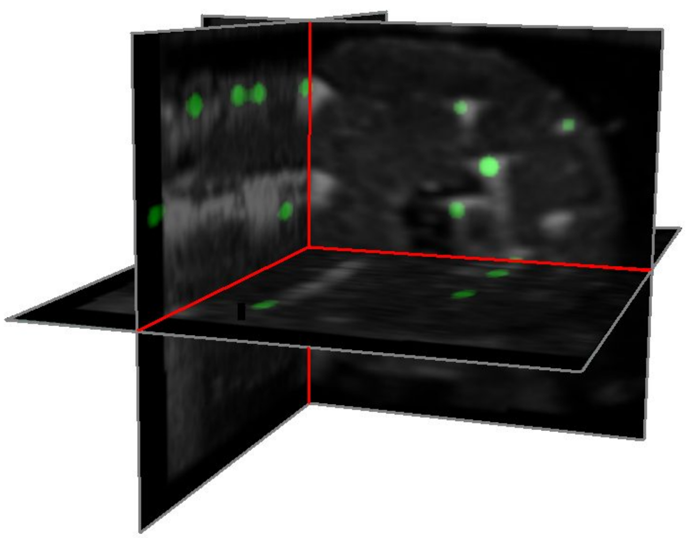


Figure 4. Overlay view of US volume and binarized CT volume. The green spots show the implanted seeds segmented from the CT data.

FP%	US-4		US-0		FN%	US-4		US-0	
	Mean ± Std mm	*% of Failure*	*Mean ± Std mm*	*% of Failure*		*Mean ± Std mm*	*% of Failure*	*Mean ± Std mm*	*% of Failure*
2%	0.94 ± 0.32	4%	1.16 ± 0.42	12%	2%	0.83 ± 0.37	2%	1.04 ± 0.40	15%
6%	0.83 ± 0.34	0	1.29 ± 0.43	24%	6%	0.84 ± 0.29	1%	1.06 ± 0.44	27%
13%	0.85 ± 0.34	1%	1.29 ± 0.41	28%	13%	0.90 ± 0.39	3%	1.31 ± 0.45	30%
17%	0.77 ± 0.34	3%	1.38 ± 0.31	49%	17%	0.88 ± 0.38	5%	1.13 ± 0.44	27%
20%	1.09 ± 0.37	6%	1.21 ± 0.44	30%	20%	0.82 ± 0.33	7%	1.26 ± 0.47	23%
27%	0.87 ± 0.34	2%	1.15 ± 0.42	33%	27%	0.96 ± 0.40	3%	1.31 ± 0.39	37%
31%	1.01 ± 0.36	10%	1.45 ± 0.42	51%	31%	0.96 ± 0.34	8%	1.33 ± 0.52	41%

Table 2. False Positive (FP) and False Negative (FN) evaluation of the proposed method (US-4) in comparison to the non-processed US volume. For each FP and FN percentage, registration is run 100 times. Mean and standard deviation of TRE as well as the failure rate are reported. CT volume is compounded by binary images.

stepper that makes it possible to collect TRUS slices that overlap in the elevation direction. This feature will allow us to compound very dense and jitter-free TRUS volumes, especially on units where RF ultrasound data is available in addition to conventional B-mode images. Also, prior to the registration, it seems more logical to apply 3D filtering to the reconstructed data, rather than to apply 2D filtering before 3D reconstruction. This will be investigated in follow-up work.

4. SUMMARY

In summary, intensity based registration between TRUS and CT/fluoroscopy imaging of prostate implants was found to be excellent in phantom studies: TRE was consistently below clinical threshold, capture range was significantly larger than the initial guess guaranteed by the clinical workflow, robustness was excellent to both false positive and false negative seed appearances, and temporal performance was adequate. The system is ready for testing on actual patent data. Regulatory approval for human subject research has been obtained, and trials are currently underway.

5. NOVELTY AND ORIGINALITY

In this paper we present a detailed experimental analysis of the intensity-based for solving the localization problem of brachytherapy seeds. The fundamentals of the method with limited results were published earlier by our team.[10] This work is not being, or has not been, submitted for publication or presentation elsewhere.

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