A TECHNICAL AND CLINICAL ASSESSMENT OF STEREOTACTIC REGISTRATION TECHNIQUES TO IMPROVE MRI GUIDED NEEDLE NAVIGATION IN PROSTATE CANCER TARGETING

by

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A thesis submitted in conformity with the requirements for the degree of Master of Health Science
Institute of Biomaterials and Biomedical Engineering
University of Toronto

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ABSTRACT

Prostate cancer is prevalent among men and one of the few cancer sites where local therapies currently target the entire organ instead of tumour. MRI holds promise in accurately depicting regions of cancer burden within the prostate gland and guiding tumour-targeted diagnostics and therapeutics. The clinical performance of a novel stereotactic MRI-guided needle navigation system for prostate cancer targeting was evaluated. Mean absolute in-plane stereotactic needle-targeting error for 10 patients was 2.2 mm and mean absolute depth error was 6.5 mm, highlighting a need to improve technical accuracy of the system. Consequently, alternative stereotactic registration techniques were investigated. Metrics of performance were in-plane stereotactic needle-targeting error, depth error, and registration time. A Z-shaped fiducial motif using automated registration performed best in phantom experiments with an in-plane error of 2.0 mm and depth error of 1.0 mm. These results will guide further software and hardware development to improve clinical performance.
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<tr>
<td>ABS</td>
<td>Acrylonitrile Butadiene Styrene</td>
</tr>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>A/P</td>
<td>Anterior/Posterior</td>
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<td>BPH</td>
<td>Benign Prostatic Hyperplasia</td>
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<td>BRW</td>
<td>Brown-Roberts-Wells</td>
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<td>BW</td>
<td>Bandwidth</td>
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<tr>
<td>CNC</td>
<td>Computer Numerical Control</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DCE</td>
<td>Dynamic Contrast-Enhanced</td>
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<td>DOF</td>
<td>Degrees-of-Freedom</td>
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<tr>
<td>DRE</td>
<td>Digital Rectal Examination</td>
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<td>DWI</td>
<td>Diffusion-Weighted Imaging</td>
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<td>ERC</td>
<td>Endorectal Coil</td>
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<td>FOV</td>
<td>Field of View</td>
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<td>FSE</td>
<td>Fast Spin Echo</td>
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<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MRSI</td>
<td>Magnetic Resonance Spectroscopic Imaging</td>
</tr>
<tr>
<td>MS</td>
<td>Multi-Slice</td>
</tr>
<tr>
<td>NEX</td>
<td>Number of Excitations</td>
</tr>
<tr>
<td>PMH</td>
<td>Princess Margaret Hospital</td>
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<tr>
<td>PPA</td>
<td>Pelvic Phased Array</td>
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PSA: Prostate-Specific Antigen
RF: Radiofrequency
R/L: Right/Left
SE: Spin Echo
SNR: Signal-to-Noise Ratio
SS: Single-Slice
SSFP: Steady-State Free Precession
TE: Echo Time
TR: Repeat Time
TRUS: Transrectal Ultrasound
US: Ultrasound
CHAPTER 1

1 INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer among men today and is the sixth deadliest cancer in men worldwide [1]. As a result there are a variety of screening, diagnosis, staging, and treatment options available for patients with prostate cancer. Specifically, methods involving the use of magnetic resonance imaging (MRI) have in particular shown promise and merit increasing attention. This thesis focuses on the subject of MRI-guided needle navigation in prostate cancer targeting.

1.1 THESIS OBJECTIVE

The objective of this thesis was to investigate techniques aimed at improving the needle-targeting accuracy and time efficiency of MRI-guided procedures for prostate cancer targeting. The goal was to enhance the navigation system by testing various fiducial marker schemes and stereotactic registration techniques, which affect the accuracy of registration between the device coordinate system and the MRI coordinate system.

1.2 RESEARCH METHODS

First, the clinical performance of a novel navigation system was analyzed. Needle targeting data was collected from several biopsy patients enrolled in a prospective clinical trial. Next, alternative stereotactic registration techniques were investigated in phantom experiments and compared with the current clinical method. Different configurations of fiducial markers were tested using a commercial prostate phantom and biopsy needles. Performance was assessed by metrics such as in-plane stereotactic needle targeting accuracy, depth targeting accuracy, and total time required for imaging and stereotactic registration.

1.3 THESIS ROADMAP

Chapter 2 of this thesis is an introductory chapter that considers pertinent background information regarding the prostate gland, prostate cancer, prostate cancer screening, diagnosis, staging, and treatment, as well as the motivation for interventional MRI and current state of the art. Chapter 3 reports on the technical development and clinical performance of a novel needle navigation system for MRI-guided prostate interventions currently being investigated at Princess Margaret Hospital, Toronto, Canada. First the navigation system hardware is described followed
by an overview of the workflow of the clinical procedure. The results and critical evaluation of
the clinical performance follow. The ensuing chapter is guided by the findings of the analysis of
the clinical MRI-guided needle navigation system. Chapter 4 details the phantom experiments
designed and carried out to improve upon the limitations of the clinical navigation system. The
resulting needle targeting accuracy is discussed for each method tested. The best solution is
also recommended. The final chapter summarizes the research that was carried out and the
results that were achieved, provides a clinical recommendation, and considers potential future
directions for research.
CHAPTER 2

2 BACKGROUND

2.1 PROSTATE ANATOMY

The prostate is a small, soft gland similar in size to a walnut and is located inferior to the bladder and anterior to the rectum with the urethra running directly through it [2]. Sitting superiorly of the prostate are the seminal vesicles, two small glands that secrete nearly 60% of the substances contained in semen [2]. Running alongside and attached to the lateral sides of the prostate are the nerves that control erectile function [2]. The prostate is composed of glands surrounded by the capsule, which is a dense layer of fibromuscular stroma and fat, and the glands are lined by cells that produce secretions [3]. The prostate is divided into three internal zones: the peripheral zone, transition zone, and central zone [4]. The peripheral zone is located in the posterior part of the prostate near the rectum and contains the bulk of the glandular elements in the prostate and is also the region where most prostate cancer occurs [4]. The transition zone is next to the urethra and after the age of 40 begins to enlarge, eventually becoming the largest zone of the prostate [4]. The central zone is involved in the connection of seminal vesicles to the prostate and holds most of the remaining glands of the prostate [4]. The prostate has three main functions: produce a thin, clear fluid for semen that helps move sperm; produce the protein prostate-specific antigen (PSA) that is added to semen; and its muscle fibres help control urine flow [4].

2.2 PROSTATE CANCER

In the United States there will be an estimated 186,320 new cases of prostate cancer diagnosed in the year 2008 alone [3]. It is estimated that 1 in 6 men in the U.S. will be diagnosed with prostate cancer during their lifetime and 1 in 35 will die from prostate cancer [3]. The Prostate Research Foundation of Canada states that prostate cancer is the most common cancer among Canadian men and will afflict 1 in 7 in their lifetimes, about 24,700 men in 2008 alone and 1 in 27 will die from it, about 4,300 in 2008 [5]. The strongest risk factor for prostate cancer is age with close to 70% of prostate cancers found in men older than 65 years of age [3]. Prostate cancer occurs when the cells in the prostate replicate uncontrollably, generally resulting in one or several tumours in the prostate [6]. Prostate cancer is usually asymptomatic until more advanced stages when patients may present with obstructive symptoms like difficulty urinating
Research has revealed that 70% of prostate cancers develop in the peripheral zone, 20% occur in the transition zone, and the remaining 10% originate in the central zone [8]. If left untreated prostate cancer may spread to other regions of the body, common areas being the bones and lymph nodes, producing secondary tumours or metastases and significantly reducing the chances for survival [6]. The American Joint Committee for Cancer (AJCC) classifies prostate cancer according to the tumour (T), lymph node involvement (N), and distant metastases (M) [3].

2.3 Standard Prostate Cancer Screening and Diagnosis

Prostate cancer is typically diagnosed by identifying patients with elevated serum prostate-specific antigen (PSA) levels or a palpable lesion on digital rectal examination (DRE) [3]. In the case of a PSA test, the higher the serum PSA concentration the more likely the presence of prostate cancer [9], although benign prostatic hyperplasia (BPH) also elevates PSA levels [7]. However, the test is not perfect so several other methods can be utilized to improve the accuracy of PSA measurement such as PSA ratio (ratio of free to total PSA), PSA velocity (how quickly PSA levels rise over time), PSA doubling time (time it takes for PSA value to double) [9], and PSA density (accounting for total gland volume) [7]. With respect to DRE, a normal prostate feels smooth and firm whereas a cancerous prostate may feel hard and irregular [10]. However, small lesions may not be felt during a DRE so it is normally performed along with a PSA test [10]. Transrectal ultrasound (TRUS) can be used to acquire information about the size and shape of the prostate and is occasionally able to identify a hypoechoic lesion in the peripheral zone that appears as a dark area [3]. Other techniques using TRUS include colour Doppler imaging that is capable of detecting areas of increased blood flow and ultrasound microbubbles that are used experimentally to find hypervascular sites [3].

The next step in screening if PSA is high and DRE feels abnormal is to do a systematic biopsy of the prostate, usually under the guidance of TRUS to ensure biopsies are taken from all parts of the prostate [3]. Nevertheless, despite the best efforts to visualize a tumour with TRUS, even multiple systematic biopsies may miss the tumour in some patients leading to a false negative [3]. This is distressing to the patient and physician for two reasons, firstly the patient will likely need to get another biopsy, which carries certain risks as always, but there is also the psychological effect of the patient and physician not knowing for certain whether there is cancer or not and this has lead to many patients being over treated [7]. Studies have shown, however, that MRI guided biopsy of the prostate may have a higher sensitivity for detecting prostate cancer compared to DRE and TRUS guided biopsy [11, 12].
2.4 Magnetic Resonance Imaging of Prostate Cancer

The excellent soft tissue contrast of MRI makes it ideal for providing high-resolution, anatomically detailed images of the prostate gland. The use of an endorectal coil combined with a pelvic phased-array coil for MRI of the prostate delivers optimal image resolution and more precise staging of prostate cancer [8]. The diagnostic image sequence generally recommended for the prostate is high-resolution T2-weighted fast spin echo (FSE) images [8]. Prostate cancer in the peripheral zone is seen as an area of low signal intensity compared to the higher signal intensity of normal tissue when using a T2-weighted image sequence [8]. However, low signal intensity in the peripheral zone may also be indicative of benign conditions such as haemorrhage, prostatitis, hyperplastic nodules, and previous radiation and hormonal therapies [8]. Detecting tumours in the central zone is even more challenging because normal tissue has low signal intensity in T2-weighted images just like cancerous tissue so the shape and contour of the anatomy must be examined rather than signal intensity [8]. It is important to recognize that the transition zone is not regularly sampled by standard biopsy techniques. As such, there is a need to explore adjunctive MRI acquisition techniques that will improve the diagnostic performance of MRI both in the peripheral zone and the central gland.

Another promising MRI technique for locating prostate tumours is called dynamic contrast-enhanced (DCE) MRI. Due to the increased microvessel density and permeability of a tumour, DCE MRI shows greater uptake of the injected contrast agent in the tumour in contrast to the uptake in normal tissue [8]. Also, magnetic resonance spectroscopic imaging (MRSI) offers non-invasive measurement of tissue metabolism [8]. MRSI exploits the ability of nuclei of different metabolites to be excited by different frequencies of RF pulses in the presence of a magnetic field, resulting in a map of signal intensity in relation to frequency and spatial location [8]. Prostate cancer has been shown to demonstrate an elevated ratio of choline plus creatine to citrate [8]. Diffusion-weighted imaging (DWI) is yet another MRI technique sensitive to the structure of biological tissue at the microscopic level [13]. In prostate cancer, normal glandular tissue is disrupted and supplanted by aggregated cancer cells, which restricts the diffusion of water molecules compared to normal tissue and results in a reduced apparent diffusion coefficient (ADC) [14]. DWI is limited by poor spatial resolution and the potential for image distortion caused by post-biopsy haemorrhage [14]. Advantages of DWI include short acquisition time and high contrast between tumour and normal tissue, which significantly improves tumour localization when combined with T2-weighted imaging [14].

MRI, therefore, offers non-invasive assessment of anatomic, physiologic, and metabolic characteristics of prostate cancer which may lead to accurate detection, localization, disease
characterization and staging [8]. MRI may also be useful for treatment planning, biopsy guidance, and guidance of focal therapies. Depicting the boundaries of cancer-bearing regions remains challenging however, and the subject of ongoing research.

2.5 MRI GUIDED PROSTATE BIOPSY

The MRI operating environment poses many challenges for interactive biopsy guidance because of geometric constraints as well as the presence of a strong magnetic field and radiofrequency pulses. Instruments in the MRI suite may be subjected to strong magnetic forces and torque, radiofrequency heating, or induced voltages, adversely affecting patient and operator safety [15]. Radiofrequency pulses emitted during image acquisition may cause implanted devices to malfunction or may induce current in electrocardiographic (ECG) leads and metallic implants resulting in burns [15]. In addition, instruments used for interventions may cause significant artifacts that result in distorted images with the degree of distortion depending on several factors such as the type, size, and orientation of the main magnetic field, the imaging sequence used, and the frequency-encoding direction [15]. Therefore, the materials used in an interventional system must be carefully selected to be MRI safe (does not harm patient) and MRI compatible (does not adversely affect image quality) [15]. Materials suitable for use in the MRI environment include titanium, nickel, aluminum, plastics, and ceramics [15]. Another challenge posed by the MRI environment is that there is limited access to the patient while in the imaging position.

One method of dealing with this problem is using TRUS to guide the needle and registering the real-time ultrasound images with previously acquired diagnostic MR images [16]. The main advantage of this method is that it integrates offline MR without fundamentally changing standard workflow with TRUS-guided needle biopsy, eliminating the cost, throughput, and equipment compatibility issues associated with interventions inside the MRI suite [16]. However, an additional visit to the hospital is required for the MRI scan prior to biopsy. Some other disadvantages include the lack of robust and accurate algorithms for real-time deformable registration of the US images with MRI as well as the variability in the degree of TRUS transducer insertion, angle of insertion, and pressure on the rectal wall and prostate causing prostate deformation [16], all of which compromise anatomic needle targeting accuracy. The value of directly registering MR images to TRUS, as opposed to simply visualizing MR images on a separate workstation, remains to be demonstrated.

There are a number of research groups doing prostate interventions in the MRI suite allowing biopsy and needle guidance/verification with up-to-date MR images, but using a different
approach than the group at PMH (1.5T MRI, supine patient position, transperineal needle insertion, manual needle insertion). Some advantages of using a 1.5T MRI scanner are the ability to use advanced imaging techniques such as MR spectroscopy, DCE-MRI, and diffusion-weighted imaging that assist in tumour localization as well as the fact that it can be a shared resource used for diagnostic imaging and interventions making it a less costly investment compared to an open scanner with a lower field strength and lower SNR [17]. The supine position is generally preferred because it has been shown to have less patient motion and to be more comfortable for the patient [18]. The needle is inserted via the transperineal route because the risk of sepsis is lower [19]. Transperineal access also allows more effective and selective sampling of the prostate peripheral zone and easier sampling of the anterior zone compared to transrectal biopsy [20].

One research group used an approach differing from the PMH method in that the needle insertion route was transrectal and the needle guide position was directly applied to the prostate target while deforming the gland [21]. Other MR guided biopsy procedures use different patient positions such as the prone position [22] and the left lateral decubitus position [23]. Another MR guided approach uses a robotic system for guiding and inserting the needle inside the bore of the scanner. The robotic systems use various patient positions and both the transrectal and transperineal approach for needle insertion [24, 25]. While these systems are able to take advantage of robotic consistency and use real-time MR imaging during guidance, they are more expensive and complex to design, build, and maintain. Needle targeting accuracy also needs to be reported for biopsies on humans for comparison to the other manual need insertion techniques [25, 26].

2.6 PROSTATE CANCER TREATMENT

Standard care options for the treatment of localized prostate cancer include active surveillance (watchful waiting), external beam radiation therapy, radical prostatectomy, transperineal brachytherapy, and androgen-deprivation therapy, with the choice of therapy (or combination of therapies) depending on the disease stage [1]. The most common side effect of localized prostate cancer treatment, regardless of modality, is erectile dysfunction [1]. Bladder and bowel function can also be impaired after therapy depending on the modality used. These treatment complications may have a long-term adverse effect on the patient’s quality of life and so treatment options must be carefully weighed. This is especially true considering that prostate cancer often progresses slowly and a large number of men live for many years after initial diagnosis, with or without receiving treatment [1].
This highlights the importance of correct disease staging in order to optimize the selection of treatment. Moreover, local therapies for prostate cancer currently target the entire organ rather than the specific tumour sites. MRI and MRI-guided biopsy are ideally suited for early, accurate prostate cancer detection and staging, as well as for tumour-targeted therapies. The outcomes of many localized non-invasive treatments such as transperineal brachytherapy and external beam radiation therapy may possibly benefit from online MRI guidance as treatment becomes more tailored to sub-regions of cancer burden and virulence within the prostate gland [1].

2.7 Techniques for Needle Navigation under MRI Guidance

The simplest and the most commonly used technique for MRI guidance is the free-hand technique [27]. A skin entry point is located using an MRI visible marker, the needle is advanced toward the target, fast sequential image slices are acquired centered on the needle position, and the needle trajectory is verified and adjusted according to what is observed in the images [27]. This method is highly dependent on the skill of the operator and may become time consuming if the needle trajectory must be adjusted multiple times.

Another popular method, particularly in MRI-guided breast biopsy, is frame-based stereotaxy [27]. A rigid stereotactic device is registered to the MRI coordinate system and is used to calculate the coordinates of the target and a fixed needle trajectory is calculated to reach the target [27]. This method does not allow for compensation of intraprocedural tissue deformations and shifts like the free-hand technique [27]. A related method is called frameless stereotaxy, which combines a stereotactic approach with the ability to have unlimited trajectories [27]. The stereotactic approach to prostate needle navigation has been favoured by the group at Princess Margaret Hospital principally due to extensive experience in ultrasound-guided transperineal stereotactic brachytherapy. In general, the prostate gland exhibits minimal motion due to breathing and/or peristalsis while the patient is immobilized in the dorsal lithotomy position, especially when an imaging device is placed in the rectum. Stability of the target tissue in reference to the stereotactic coordinate system can be further enhanced with anaesthesia. However, limitations of the stereotactic approach include deformations and displacements of the prostate gland with needle insertion and patients moving their pelvis in discomfort during protracted procedures. These latter issues are largely outside the scope of the work presented here. Nonetheless, a more efficient approach to stereotactic definition would allow repeated device registrations to be performed through the course of a procedure to adapt to bulk motions of the patient and device relative to the reference MRI coordinate system.
Defining stereotactic space for navigation can be achieved through various techniques. Optically linked stereotaxy is a technique based on actively coupling the imaging scan plane to the orientation of the interventional device using optical technologies such as light emitting diodes (LED’s) or reflective balls which are visible to a camera system [27]. The camera system must first be calibrated to the image coordinate system and then the spatial orientation of the device can be continuously updated [27]. This method may suffer from line-of-sight issues, meaning the optical markers must always be visible to the camera system. A related technique is called non-optical stereotaxy or active tracking and is based on the same concept as optically linked stereotaxy but does not use light or stereotactic cameras [27]. Rather, this technique generally requires a custom software interface that registers the coordinate system of the imager with active fiducial markers that are tuned to the resonant frequency of the scanner [27]. These active fiducial markers are mounted to the biopsy needle or other interventional devices and do not suffer from line-of-sight issues [27]. Another technique uses imaging to identify the location of passive fiducial markers. The fiducial markers are composed of an MRI visible material and rigidly attached to the stereotactic device. Volumetric MR images of the stereotactic device are acquired, the passive fiducial markers are segmented in the images, and then the device position in MRI coordinates is determined [24]. This is the technique preferred by the group at Princess Margaret Hospital because it avoids the complexity of active fiducials and the line-of-sight issues associated with optical stereotaxy. Some disadvantages of this method are the time required for volumetric imaging and identifying the fiducial marker position.

2.8 CONCLUSION
Prostate cancer is affecting an increasing number of men throughout the world. Left untreated, prostate cancer has the potential to spread. Therefore, early and accurate diagnosis is important for determining the proper course of action. MRI has been shown to possess great potential in prostate cancer diagnosis and staging. MRI guided biopsy has the potential to supplement current techniques such as testing PSA level, digital rectal examination, and TRUS guided biopsy when inconclusive. MRI guided biopsy is only a valuable tool if navigation to tumour sites is accurate. Thus the motivation for this thesis to study the accuracy of a novel approach to MRI guided needle navigation. The analysis of that navigation system may yield areas for improvement which will be tested with known stereotactic registration techniques with the goal of improving MRI guided prostate cancer targeting.
CHAPTER 3

3  CLINICAL PERFORMANCE OF AN MRI GUIDED NEEDLE NAVIGATION SYSTEM FOR PROSTATE CANCER TARGETING

3.1 INTRODUCTION

MRI has an increasingly important role in prostate cancer imaging and staging because it is more accurate than CT, ultrasound, and DRE [8]. Studies have shown that MRI performed significantly better than DRE in the detection of cancer in the apex, mid gland, and base of the prostate and significantly better than TRUS-guided biopsy in the mid gland and base [8]. In addition, MRI is capable of detecting tumour in the transition zone, which DRE and TRUS-guided biopsy cannot [8]. MRI of the prostate, particularly when carried out at 1.5T with an ERC and pelvic phased array (PPA) coil, provides high-resolution images with sufficient anatomical detail and soft tissue contrast to be useful in prostate cancer staging and the determination of extraprostatic disease [28]. DCE imaging, DWI, and MRSI are valuable adjuncts for differentiating between healthy and cancerous tissue and when superimposed on anatomic images allow for localization of tumour-bearing tissues [28].

MRI indeed holds much promise in accurately depicting the regions of cancer burden within the prostate gland and mandates further refinement and validation, especially when applied to defining the boundaries of cancer-bearing regions and guiding therapies accordingly. To achieve this task, accurate MRI voxel-to-tissue co-localization is required. Online MRI needle guidance systems with accurate and responsive navigation may help better define cancer features on MRI and enable tumour-targeted diagnostics and therapeutics. This chapter reports on the technical development and clinical performance of a stereotactic needle navigation system for MRI-guided prostate interventions being investigated at Princess Margaret Hospital, Toronto, Canada.

The navigation system is a fundamental component of image guided prostate cancer targeting. Figure 1 illustrates the feedback relationships designed to improve prostate cancer targeting accuracy of the navigation system. This thesis specifically focuses on improving stereotactic targeting accuracy. First, the navigation system hardware is described. Then an overview is
given of the workflow of the clinical procedure taking place at Princess Margaret Hospital. Results and discussion of the clinical performance follow.

Figure 1 - Illustration of the feedback relationships designed to improve targeting accuracy of the navigation system. General MRI features of prostate cancer (nodular area of hypointensity on T2 weighted images, low apparent diffusion coefficient, elevated choline relative to citrate, and intense and rapid contrast enhancement and washout visualized here in the right peripheral zone) are used to identify suspicious imaging targets for biopsy (red target). 3D needle verification images are used to assess and improve the stereotactic performance of the navigation system by comparing the actual needle location (dark signal void) to that intended (red target) in stereotactic space. These images, in conjunction with deformable image registration, can also provide metrics of anatomic needle targeting accuracy. This data can be used to create needle deformation models that could be incorporated into the navigation system for improved needle targeting. Most importantly, 3D needle/tissue verification images and deformable image registration enable accurate voxel-to-tissue co-localization that will validate and help refine quantitative MRI parameters diagnostic of cancer burden and biological virulence, thereby improving imaging target accuracy.

3.2 METHODS

3.2.1 NAVIGATION SYSTEM HARDWARE
The navigation system utilized a dedicated MRI table assembly (Sentinelle Medical, Toronto, ON) that offered the physician access to the perineum. The table, shown in Figure 2, also featured adjustable stirrups to support the patient’s legs as well as an adjustable arm which connects to a stereotactic transperineal template system. The stereotactic transperineal
template system contained four embedded fiducial registration markers that were visible on MRI when filled with an aqueous gel named Surgilube® (Fougera, Melville, NY). Three markers were located in the stereotactic needle localization template and the fourth was contained in the endorectal sheath. The stereotactic needle localization template contained a grid-like arrangement of 1.65 mm diameter holes (16 gauge) spaced 4 mm apart and attached directly to the adjustable arm of the MRI table. The three fiducial markers in the needle template were 3 mm in diameter and formed a triangle around the needle guidance holes. The endorectal sheath contained a 2 mm square channel along its length that served as the fourth fiducial marker and the sheath also supported the endorectal imaging coil. The needle template and endorectal sheath were assembled together such that the template and sheath were perpendicular and the axis of the sheath fiducial marker was parallel to the axis of the needle holes as shown in Figure 3c. The accuracy of the navigation system was dependent on this geometric relationship between the assembled components. The procedure also used 16 gauge MRI safe titanium coaxial needles and 18 gauge MRI safe titanium, fully automatic biopsy guns (Invivo, Germany).

Figure 2 - Dedicated MRI table providing physician with access to the perineum. The patient lies down on the table in the partial dorsal lithotomy position with the hips flexed, the knees bent, and the feet placed in the adjustable stirrups with pads and straps. The stereotactic transperineal template system was attached to the table via an adjustable arm.
3.2.2 Procedure Workflow

The MRI-guided procedure was performed in a closed bore 1.5T cylindrical MRI scanner to guide biopsy needles via the transperineal route into the prostate gland of a patient lying down on an MRI table in the partial dorsal lithotomy position. Inside the magnet room the patient was placed on the custom table, which was docked with the scanner, in the partial dorsal lithotomy position with the hips flexed, the knees bent, and the feet placed in adjustable stirrups. Anaesthesia was then administered using conscious sedation. Next, the localization template, endorectal sheath, and endorectal coil were assembled together and inserted into the patient’s rectum, and applied centered against the perineum. The assembly was then secured to the table via the adjustable arm and final preparations were made for imaging. This included immobilization of the pelvis using a belt-like device secured to the table.

Following a fast three-plane localization scan, the position of the device was adjusted to center on the prostate anatomy. After confirmation of appropriate device positioning, multiparametric diagnostic imaging of the prostate gland ensued. The imaging protocol included: T2-weighted fast spin echo (FSE) for the anatomy (TE = 96.0 ms, TR = 4300 ms, BW = 20.83, FOV = 14.0 cm, slice thickness = 3.0 mm, frequency = 320, phase = 256, frequency direction = A/P, NEX = 3.0); diffusion weighted imaging (DWI, TE = minimum, TR = 6000 ms, FOV = 16.0 cm, slice thickness = 6.0 mm, frequency = 128, phase = 256, frequency direction = A/P, NEX = 10, B value = 600); spectroscopy (GE’s PROSE: PROstate Spectroscopy and imaging Examination, TE = 130.0 ms, TR = 1000.0 ms, FOV = 12.0 cm, slice thickness = 39.0 mm, slice spacing = 7.5 mm, frequency = 16, phase = 8, frequency direction = R/L, NEX = 1.0); and dynamic contrast enhanced imaging (DCE, Flip Angle = 20, TE = Minimum, BW = 62.5, FOV = 18.0 cm, slice thickness = 6.0 mm, frequency = 256, phase = 128, frequency direction = R/L, NEX = 0.5, slice
per location = 60). Figure 4 shows the appearance of prostate cancer (a, b, c) and needle voids (d) using this imaging protocol.

Figure 4 – Appearance of prostate cancer on MRI (red box). (A) nodular area of hypointensity on T2-weighted image, (B) low apparent diffusion coefficient, (C) intense and rapid contrast enhancement, (D) needle verification image with two biopsy needles inserted, one in the non-suspicious lobe (patient right) and another in the suspicious (patient left, red box) lobe of the prostate gland. Needle voids are visible as circular hypointensities (arrows).

T2-weighted fast spin echo images were also used for stereotactic registration of the device. The endorectal sheath fiducial marker was visible in these images. Next, the needle localization template was imaged using a fast 3D steady-state free precession sequence (GE’s 3D FIESTA: Fast Imaging Employing STeady-state Acquisition, Flip Angle = 35, TE = minimum, BW = 62.5, FOV = 20.0 cm, slice thickness = 3.0 mm, frequency = 256, phase = 192, frequency direction = R/L, NEX = 4.0). The remaining three fiducial markers were visible in these images. Figure 5 demonstrates how the fiducial markers appeared on MRI. The next step was registration of the stereotactic system to the MRI coordinate system.
Figure 5 - MR images with the four fiducial registration markers circled in red. (A) An axial T2-weighted fast spin echo image slice through the endorectal sheath showing the fiducial marker circled in red situated in the rectum with the seminal vesicles above. (B) An axial 3D SSFP image slice through the needle localization template showing all three fiducial markers circled in red surrounding the grid-like arrangement of needle guidance holes.

Using the navigation software, Aegis (Sentinelle Medical), an operator manually selected the center of the fiducial markers in the images of the stereotactic system. The vector representing the needle axis was calculated by selecting the center of the endorectal sheath fiducial marker in two axial images of the prostate that were as far apart as possible. The targeting software automatically reformatted all of the images to be perpendicular to this axis. Next, using the images of the needle template, two additional vectors were determined using the three fiducial markers to define the plane at the surface of the needle template containing the needle holes. The targeting software used this information to compute the registration between MRI coordinates and stereotactic needle template coordinates. Figure 6 shows a screen capture of the registration procedure in the needle navigation software, Aegis.
Biopsy targets were identified after imaging and registration of the stereotactic system was completed. Needle targets were selected to be along the prospective needle path. The targeting software computed and displayed the required needle hole and depth to reach each target, as shown in Figure 7. The MRI table and patient were translated partially out of the scanner bore to allow the physician access to the needle template and the biopsy needles were inserted. First the coaxial needle was used to puncture the skin and was inserted into the prostate. The inner stylet was removed and the outer cannula remained in place to serve as a guide for the biopsy gun. The biopsy gun was a spring-loaded double shooting gun. During the first firing the stylet specimen notch rapidly penetrated the tissue. The second firing rapidly propelled the outer cannula over the stylet specimen notch, cutting and capturing the tissue specimen. After needle insertion and firing, the table and patient were translated back into the scanner isocenter for 3D needle verification imaging to assess needle placement accuracy (2D, T2-weighted FSE image sequence, TE = 90.0 ms, TR = 2117.0 ms, BW = 20.83, FOV = 14.0 cm, slice thickness = 3.0 mm, frequency = 320, phase = 224, frequency direction = A/P, NEX = 2.0). This procedure must
be repeated for each needle target, for a minimum of six targets. After the procedure the patient was removed from the scanner room to recover.

![Figure 7 – Needle navigation software output. Once registration of the stereotactic system was completed, the targeting software computed the required needle hole grid coordinate and depth to reach each target.](image)

3.2.3 **CLINICAL PERFORMANCE ASSESSMENT**

Clinical performance of the navigation system was tested in patients prospectively enrolled on a clinical trial approved by the institutional research ethics board. The needle void to stereotactic coordinate targeting error was analyzed as in-plane needle targeting error and depth error. The in-plane stereotactic targeting accuracy was calculated by finding the distance between the actual needle and the intended target location in MRI coordinates. The actual needle location was recorded as the center of the signal void visible in the needle verification images. The needle depth error was measured as the number of 3 mm slices between the actual needle tip and the depth calculated by the needle targeting software. This method of assessing depth error was to some extent not ideal because of the image resolution, but the clinical tolerance for depth error was higher since the length of the biopsy core (1.5 cm) was nearly 10 times the diameter of the biopsy core. Also, the markings on the needle were at 1 cm intervals which ultimately limited the accuracy of manual needle insertion depth. The clinical needle insertion depth error produced a negative value to indicate the needle did not reach the intended target depth and a positive value to indicate the needle surpassed the intended target depth. The extent and nature of stereotactic device motion during the biopsy procedure was also measured. In-plane motion of the stereotactic needle template was measured by tracking the position of the endorectal sheath fiducial marker in each needle verification image volume. In-plane hardware motion was measured by comparing the position of the endorectal sheath
fiducial marker in the original diagnostic image set with the position in each needle verification image in MRI coordinates. This produced a 2D translation vector.

3.2.4 **INTERVENTIONS APPLIED TO IMPROVE CLINICAL PERFORMANCE**

Early clinical observations and analysis of the targeting accuracy drew attention to possible hardware, software, and workflow issues with the clinical navigation system. Several interventions were applied to improve the clinical performance of the navigation system. First, the consistent posterior bias of the in-plane errors was of concern (results to follow). The first hypothesis tested was that the endorectal component of the device (and associated fiducial marker) was not perfectly perpendicular to the template and/or not perfectly straight along its entire length due to pressure applied to the device. To investigate the source of stereotactic targeting errors in the anterior-posterior plane, the endorectal sheath was physically measured. Measurements were undertaken by a trained machinist using a specialized measurement probe attached to a modern CNC machine. Measurements were acquired at regular intervals along the length of the fiducial marker channel of the endorectal sheath since any deflection in this region may affect stereotactic registration accuracy. The endorectal sheath was positioned under the CNC probe and clamped into place. The CNC probe would automatically lower and contact the endorectal sheath to obtain an estimate of its position. Then the probe would retract and once again descend toward the endorectal sheath very slowly until just touching the endorectal sheath surface. This ensured the measurement probe did not contribute significantly to deflection of the endorectal sheath.

To address possible problems in calculating the needle targeting depth and to deal with problems visualizing the needle template fiducial markers, the needle targeting software and registration methodology were altered. Originally, registration required identifying the three needle template fiducial markers in the most inferior image slice of the needle template. Early observations showed that the fiducial markers were not always visible in that particular image slice. Using the incorrect image slice could result in depth targeting errors. The registration method and software were updated to first independently identify the most superior surface of the needle template and then identify the three needle template fiducial markers in any image slice.

A potential workflow issue that affected the accuracy of needle targeting analysis was addressed with the introduction of a new record keeping form. The purpose of the new form was for improved tracking of targeting changes incorporated during the clinical procedure in the magnet room. Any changes with respect to needle targeting introduced on-the-fly in the magnet
room were required to be recorded on the new form. This ensured that all changes were able to be accounted for while performing clinical needle-targeting analysis post-procedure. Other interventions included the introduction of longer biopsy needles in order to reach tumour targets located more superiorly as well as increasing the patient’s level of sedation to reduce intra-procedural movement.

3.3 RESULTS
12 patients were enrolled over one year on a prospective clinical trial for MRI-guided prostate biopsy between March 2008 and February 2009. Needle targeting data was available for analysis from 10 patients, as data was lost for two patients.

3.3.1 IN-PLANE ERROR
The mean absolute in-plane stereotactic needle-targeting error was 2.2 mm with standard deviation 0.7 mm. If each needle target was treated as an independent variable then the mean absolute in-plane error for all needle targets was 2.2 mm with standard deviation 1.2 mm. The in-plane error was distributed randomly in the right to left direction but a small posterior systematic bias of the in-plane errors of 1 mm was observed. The in-plane error in the R/L direction passed the one-sample z-test with 95% confidence interval of -0.5 mm to 0.8 mm and with the null hypothesis being a standard normal distribution (0 mean and standard deviation of 1). The in-plane error in the A/P direction failed the z-test with 95% confidence interval of 0.3 mm to 1.5 mm, indicating the small posterior in-plane error bias was likely statistically significant. Figure 8d shows that the absolute in-plane error was overall decreasing with time.
Figure 8 – (A) In-plane error with global mean. The blue markers represent the in-plane error for each biopsy needle and the red square is the global mean in-plane error with standard deviation indicated by the red error bars. The dashed green box represents the clinical objective in-plane error of 2 mm. The global mean in-plane error in this figure shows a systemic posterior error bias of about 1 mm. (B) Mean in-plane error for each patient. Each blue marker represents the mean in-plane error for each patient. The red marker is the global mean error with the red bars indicating the standard deviation. (C) Absolute in-plane error. The mean absolute in-plane error was 2.2 mm with standard deviation 1.2 mm. The normalized counts represents the percentage of needle insertions within a given error range. (D) Mean absolute in-plane error for each patient over time with error bars indicating standard deviation. The trend in mean absolute in-plane error is overall improving over time. Interventions applied to improve performance are indicated by the red arrows. The new endorectal sheath was used starting with patient #5 and the level of sedation was increased. Improved record keeping commenced with patient #6. Updated needle targeting software with a new stereotactic registration technique was used for patient #10.
3.3.2 **In-Plane Stereotactic Hardware Movement**

The mean absolute hardware movement was 1.2 mm with standard deviation of 1.9 mm because one patient (patient #2) had a mean motion of 6.2 mm. Not including that patient, the mean absolute hardware movement was 0.6 mm with standard deviation 0.3 mm.

![Graph A](image1)
![Graph B](image2)
![Graph C](image3)

Figure 9 – Stereotactic Device In-Plane Motion. (A) Each data point represents the mean in-plane motion of the endorectal sheath fiducial marker from its position in the original diagnostic image volume. The bars represent the standard deviation. Patient #2 had a large motion in the posterior direction. (B) Zoomed view of in-plane hardware motion excluding patient #2. The hardware generally moved posteriorly and to the right. The motion was not significant, less than 1 mm in all cases excluding patient #2. (C) Mean absolute stereotactic device in-plane motion for each patient over time with standard deviation indicated by the error bars. Excluding patient #2, the mean absolute in-plane motion was 0.6 mm with standard deviation 0.3 mm. The level of anaesthesia was increased beginning with patient #5.
3.3.3 Depth Error
For all needle targets the mean absolute depth error was 6.5 mm with standard deviation 4.7 mm. The mean depth error exhibited a bias in the inferior direction.

Figure 10 – Top: Absolute depth error. Slice thickness was 3 mm. The normalized counts represents the percentage of needle insertions within a given error range. Bottom: Mean depth error for each patient. The clinical needle insertion depth error produced a negative value to indicate the needle did not reach the intended target depth and a positive value indicated the needle surpassed the intended target depth. Each data point represents the mean depth error for each patient and is meant to display the trend in depth error over time. There was a systematic inferior error bias for depth targeting. Changes to workflow are indicated by the large red arrows. Longer needles were used starting with patient #5 and the level of sedation increased. Improved record keeping commenced with patient #6. The correct image slice was used for stereotactic registration from patient #8 onwards. An updated version of the needle targeting software with a new stereotactic registration technique was used for patient #10.
3.3.4 **INTERVENTIONS TO IMPROVE NEEDLE TARGETING**
Physical measurements of the endorectal sheath revealed that some warping and bending had taken place over time which may have been due to the cleaning and sterilization process. Thus the Z-axis or needle-axis fiducial calculation was no longer correct. Figure 11 shows the extent of the endorectal sheath deformation. Assuming an average needle target depth of 115 mm, the endorectal sheath deformation could produce a posterior targeting error of 1.6 to 1.9 mm.

![Figure 11 - Endorectal sheath deflection. Measurements were taken along the center of the endorectal sheath starting from the end closest to the needle template and moving towards the tip.](image)

As a solution, a new endorectal sheath was manufactured and a new quality assurance procedure was implemented to monitor the physical geometric integrity of the hardware. Furthermore, the sterilization procedure was altered from autoclaving to gas sterilization performed at a lower temperature. Two new endorectal sheaths were constructed by the machine shop. One sheath was clinically used starting with patient #5 while the other was kept as a control.
3.4 DISCUSSION

3.4.1 IN-PLANE ERROR
Patient #2 exhibited the largest in-plane error, as well as the largest device motion. Device motion was reduced with improved anaesthesia, which also improved stereotactic needle targeting accuracy. Thus, for the remainder of biopsy procedures, device motion was negligible. The remaining targeting inaccuracies were relatively small, random, and could be the result of needle deflection [26]. However, the results continue to point to a small posterior bias in needle targeting as seen in Figure 8. This suggested there was a systematic error with the navigation system, either hardware or software related, or a combination of both. Even after replacing the warped endorectal sheath from patient #5 onward there was still a small posterior bias. It was possible then that the angle between the endorectal sheath fiducial and needle template was less than 90 degrees when inserted into the patient. Further testing as suggested in section 3.4.3 should be carried out to verify this hypothesis. Although beyond the scope of this thesis, a systematic posterior deflection of the biopsy needle by the target tissues may be an alternative hypothesis to explain the small posterior error bias.

3.4.2 DEPTH ERROR
The depth error was particularly large for patient #2. This patient experienced back discomfort during the procedure which resulted in several large movements that moved the stereotactic device and so the needle insertion depth accuracy was severely affected in MRI coordinates. The depth error was also larger for patient #5. New, longer biopsy needles were used for the first time during this session so unfamiliarity with these needles was hypothesized as a possible source of error. Targeting was also changed on-the-fly, or in the magnet room prior to needle insertion, during this session and these changes may not have been correctly reflected in the MRI coordinates during data analysis leading to a larger than normal depth error. The new record keeping form was subsequently introduced to track any changes in needle targets made in the magnet room. Depth error steadily improved for patient #6 through patient #9. Patient #10 was the first procedure to use the updated version of the needle targeting software, Aegis 2.0. Although changes in this version of the software were designed to improve depth error, the depth error was worse than the previous patient. This may have been due to unfamiliarity with the new software. Patient #12 also had a larger depth error. Initially the updated version of the needle targeting software was used during this session but an unexpected glitch resulted in switching to the original version of the software. Likely this unexpected switch contributed to a larger depth error. It was also discovered that the incorrect image slice of the needle template was being used for stereotactic registration from patient #4 to patient #7. The most superior
image slice (closest to patient) was being used when it should have been the most inferior slice. This could have potentially been an error of 12 mm. However, the effect was minimal because in some cases there was only one image slice with all three fiducial markers visible, usually located in the center of the needle template. In other cases there were only two or three image slices appropriate for registration that were located more inferiorly. Therefore, only a single needle target’s depth error required correction and only by a single image slice since the needle verification images had a slice thickness of 3 mm. This situation highlights why the needle depth error was consistently negative (i.e. needle did not reach the intended target depth) since the image slice being used for registration was always located more superiorly than the targeting software was expecting by some value, \( \varepsilon \). Thus the depth to insert the needle was calculated from the most inferior surface of the needle template but the target was actually located \( \varepsilon \) mm in the superior direction in MRI coordinates.

3.4.3 Hardware Intervention
The small but consistent posterior bias observed in the in-plane error during early analysis lead to an investigation into the geometric integrity of the stereotactic hardware. Measurements revealed the endorectal sheath was not perfectly straight along its entire length and a new sheath was manufactured and used clinically starting with patient #5. However, the in-plane error results did not improve after this intervention as demonstrated in Figure 8. An alternative hypothesis to consider was that perhaps the angle between the endorectal sheath and the needle template was less than 90 degrees after being inserted into the patient’s rectum. Future work to test this hypothesis may include additional imaging during the biopsy procedure to fully visualize the endorectal sheath fiducial marker and the needle template and then calculating the angle between the endorectal sheath and the needle template surface. To test if the systematic posterior error bias was due to the intrinsic geometric distortion of MRI, the aforementioned testing procedure could be repeated using CT by changing the fiducial marker material. Another hypothesis to consider, which was beyond the scope of this thesis, was that the consistent posterior bias was due to needle deflection caused by needle/tissue interactions. Needle deflection during the biopsy procedure could be investigated by imaging the entire needle path.

3.4.4 Software Intervention
Another problem observed during biopsy procedures involved an inability to visualize all of the fiducial markers in the required imaging slice, namely the most inferior slice at the surface of the needle template. This may have been due to difficulties in prescribing the image plane perfectly parallel to the device, volume averaging at the surface given a 1 mm slice thickness, lower SNR at the surface where little water content was present, or inadequate filling of the fiducial space
with MR visible gel. All of these factors were hypothesised to contribute to the depth inaccuracies observed. This problem was addressed by changing the registration method such that the superior surface of the needle template would be identified independently. Then the three needle template fiducial markers could be identified in any image slice to define the X and Y axes. This change was implemented in an updated version of the clinical needle targeting software named Aegis 2.0 and was first used on patient #10. This new version of the targeting software also introduced a new diagram displaying the biopsy needle markings and the coaxial needle. This feature was designed to aid the physician with depth determination because the biopsy needle, which had markings every 1 cm, was inserted into the coaxial needle that did not have any depth markings and created difficulty in gauging the insertion depth. Since needle targeting data using the new version of the needle targeting software was only available for a single patient it was not clear whether the depth targeting accuracy had been improved significantly.

3.5 CONCLUSION
A system for MRI-guided needle navigation in prostate cancer targeting had been developed and showed promise in early clinical evaluations of technical performance. Overall, the mean absolute in-plane needle targeting error was 2.2 mm and the mean absolute depth error was 6.5 mm. Prospective problems and issues with the system hardware and registration methodology were detected and corrective measures were taken to improve technical performance. Motion of the system hardware was identified as a major contributing factor toward needle targeting error. The problem of device motion and its adverse effect on needle targeting accuracy was largely solved with increased anaesthesia. However, it would be preferable to have a system that is responsive to motion, thus allowing a reduction in the level of anaesthesia required for accurate tumour targeting. The combination of accurate registration and management of device motion would be expected to enhance the technical performance of the clinical navigation system.

Ongoing developments include testing of several new arrangements of fiducial registration markers, automated registration schemes, and an imaging method to capture and adapt to motion of the prostate prior to needle insertion. The testing of new fiducial registration schemes will be discussed in the following chapter. Analysis of the needle navigation system revealed that the magnitude of the depth error and inferior error bias was also of particular concern as well as the small posterior bias in the in-plane needle to MRI coordinate targeting error. These issues will be addressed by the alternative registration schemes in the following chapter. Another issue was user inconsistency and time required for manual registration. These issues may be addressed by automated, rather than manual, registration schemes.
CHAPTER 4

4 A TECHNICAL ASSESSMENT OF STEREOTACTIC REGISTRATION TECHNIQUES TO IMPROVE MRI GUIDED NEEDLE NAVIGATION IN PROSTATE CANCER TARGETING

4.1 INTRODUCTION
Analysis of the clinical performance of the navigation system in Chapter 3 identified a number of issues regarding stereotactic targeting. Specifically, the magnitude of the depth error, the small posterior and larger inferior systematic bias, the user errors in registration, and the time required for manual registration were identified as problems that may benefit from technical improvements of stereotactic registration. Consequently, there was an evident need to investigate alternative stereotactic registration techniques capable of addressing the issues identified with the navigation system. To that end several registration techniques and motifs of fiducial markers were examined. In particular the objective was to investigate methods that would improve the depth error as well as eliminate user errors and reduce registration time through automated techniques. This study was restricted to image-based passive fiducial registration techniques to draw upon experience with the clinical navigation system and to avoid the complexity of active fiducials and the line-of-sight issues associated with optical stereotaxy.

4.2 REGISTRATION METHODS

4.2.1 METHOD #1 – CLINICAL METHOD
This method was described in detail in Chapter 3 and served as the gold standard reference upon which system performance was compared. In this method the orientation of each of the three planes and the location of the stereotactic device were manually and independently defined on the volumetric MR images. To summarize, four fiducial markers were required for stereotactic registration. Figure 3 in Chapter 3 depicted the hardware used clinically that housed all the fiducial markers. Figure 5 in Chapter 3 showed how the markers appeared on MR images. Three markers were located in the needle template itself and were cylinders of 3.175 mm diameter and 12.7 mm in length parallel to the needle holes\(^1\). The fourth marker was

\(^1\) This specific geometry was for the clinical needle template. However, for experimental testing a custom needle template was built to accommodate a different fiducial marker material as well as the fiducial motifs of the other experimental methods. The needle holes in this custom needle template were still spaced 4 mm apart in a grid-like pattern but the diameter of the holes was 1.02 mm (for 18 gauge needles).
located in the endorectal sheath and was a channel 63.5 mm in length with a square cross-section of 2.3 mm. At least two axial slices through the endorectal sheath fiducial marker were required for registration. The fiducial marker appeared in the T2-weighted diagnostic images of the prostate. Two image slices that were as far apart as possible were chosen for registration and the center of the marker was manually selected by the user in the needle targeting software. The vector between these two slices defined the needle axis in MRI coordinates and all images were reformatted to be normal to this vector. A 3D volume of the needle template was also acquired. The superior surface of the needle template, which was pressed against the perineum of the patient, was identified as a reference in the newest version of the needle targeting software. Then the centers of each of the three remaining fiducial markers were identified to define the plane normal to the needle axis. The original version of the needle targeting software, which was used for testing, required identifying the three markers in the slice at the most inferior surface of the needle template, the surface where the needles were inserted. This surface was marked with an MRI visible gel to be accurate for depth calculations and to be equivalent to the new method implemented in the updated version of the targeting software. The registration was completed manually by a trained operator using the needle targeting software and required six minutes on average clinically. This number included the time for manually identifying the endorectal sheath fiducial marker in two image slices, prescribing the image slice planes and volumetric imaging of the needle template (which was carried out by the MRI operator while the first two fiducial markers were being identified), and manually identifying the three needle template fiducial markers.

4.2.2 METHOD #2 – Z-SHAPED FIDUCIAL MOTIF

The first additional method being investigated used three Z-shaped fiducial motifs, two motifs were parallel to each other and the third was positioned between the parallel motifs, perpendicular to them. Each Z-shaped motif had three fiducial markers, two that formed the top and bottom lines of the Z-shape were parallel and 50 mm apart, the third diagonal marker was at an angle of 45 degrees to the parallel markers. Figure 12 shows a 3D model of the Z-shaped fiducial motifs. This stereotactic registration frame was essentially a miniaturized Brown-Roberts-Wells (BRW) frame that was rigidly attached to the needle template instead of being fixed to the patient [29]. The Z-shaped fiducial motifs have been shown to exhibit favourable error characteristics, accuracy, and reliability in a large angular range using CT [29]. A single axial or cross sectional image slice was required for registration. The axial image contained nine fiducial marks, three from each Z pattern. The distances between the three marks from each motif were used to determine the coordinates along the diagonal marker of the Z pattern where the image slice intersects. Once the location of intersection with the image plane of all three
middle markers was known in fiducial coordinates and MRI coordinates, the centroid of the triangular plane they created was calculated in both coordinate systems. The normal to this plane was calculated using two vectors found from the three known points. Another vector was determined by calculating the cross product of the normal vector with one of the known vectors to form three perpendicular vectors in each coordinate system. These three orthogonal vectors along with the centroids were used to calculate the transformation matrix between the needle and MRI coordinate systems directly [30]. This method was very desirable for registration because it only required one axial image slice with all markers visible that could be obtained rapidly for a full six degrees-of-freedom (DOF) registration and produced a closed form solution.

Figure 12 – 3D model of the Z-shaped fiducial motifs. Two motifs are parallel to each other and the third is positioned between the parallel motifs, perpendicular to them. Each Z-shaped motif has three fiducial markers, two that form the top and bottom lines of the Z-shape that are parallel and 50 mm apart, the third diagonal marker is at an angle of 45 degrees to the parallel markers.

For this method two imaging protocols were investigated, a single-slice protocol and a multi-slice protocol. For the multi-slice protocol, the coordinates of the corresponding three points were determined in each image slice in both the needle and MRI coordinate systems. The 6-DOF transformation matrix was calculated using the three corresponding points from each slice with Horn’s method for absolute orientation using quaternions [31]. Horn’s method finds the transformation between corresponding points in two coordinate systems using a closed-form
solution for the least-squares problem of absolute orientation [31]. A MATLAB implementation of Horn’s method was obtained free from the online file exchange on the MathWorks™ website. The iterative closest point (ICP) algorithm was also investigated as a possible alternative to find the transformation matrix and had results similar to Horn’s method but was ultimately not used in the final implementation. In keeping with the results obtained by [29] the hypothesis was that the performance of the multi-slice protocol will be marginally better than the single slice protocol.

Both the single-slice and multi-slice Z-shaped motifs registration methods were automated. A MATLAB program was developed to automatically locate the fiducial markers in an axial image and compute the transformation matrix. Simple binary thresholding was used to segment the image since the fiducial markers appeared as ellipses of high signal intensity. Next, any areas of high signal intensity that were too large or too small to be the fiducial markers were filtered out of the image. The remaining high signal intensity objects were considered fiducial markers. Originally, their center of mass or centroid was calculated to approximate the center of the fiducial mark. A new center finding method was implemented which attempted to fit a circle of the same size as the fiducial markers to the areas of high signal intensity in the image with the pixel of best fit being the center. This method appeared to deal with small air bubbles or distortions of the fiducial marker cross-section better than the center of mass method. These center coordinates were used to calculate all possible two-point line segments in the image. The lines were defined in a parameter space, the parameters being the angle the line makes with the X-axis and the orthogonal distance from the line to the origin. Next, each two-point line segment was tested to see if it could form a three-point line segment with another potential marker’s center point. Since the fiducial markers lie in a straight line that was exactly 50 mm long it was possible to enforce specific criteria to be met by each potential three-point line segment so that only lines using the center points making up the fiducial markers were found. After all possible three point line segments were found, the algorithm searched for lines that were parallel and a specific distance apart. This pair represented the left and right Z patterns. Finally, the perpendicular Z pattern was found by searching for a line that was perpendicular to the parallel pair and positioned above and between the parallel pair. These constraints provided a very robust method for finding only the markers making up the fiducial patterns. Figure 13 (top) shows the output from MATLAB with the correct nine markers selected. The automated registration algorithm was also re-written in C# and incorporated into the clinical targeting software (Aegis) as an add-on or plug-in, the output is shown in Figure 13 (bottom). However, a pop-up textbox only displays the transformation matrix; the add-on remains to be fully integrated into the targeting software.
Figure 13 - Automated registration of Z-shaped motifs. Top: MATLAB output. The coordinates of the marker centers, marked in red, were used to calculate the 6-DOF transformation matrix between MRI coordinates and needle template coordinates. Bottom: Aegis output. The centers of the correct markers were found but the transformation matrix was only displayed in a pop-up textbox.
4.2.3 Method #3 – Three Orthogonal Line Fiducials

The third method utilized three orthogonal line markers fixed to the needle template. A 3D model is shown in Figure 14. In this case the markers corresponded to the X, Y, and Z axes of the needle template. The center of each marker was found in each image slice for all three directions (axial, sagittal, and coronal) and these points were used to define three 3D lines in MRI coordinates. The point of intersection was then calculated. The point of intersection and the equations of the lines in the needle coordinate system were already known. Corresponding points along the 3D lines were determined in each coordinate system and Horn’s method was used to find the transformation matrix. Registration for this method was completed in a semi-automated fashion using MATLAB. The user was required to define a bounding box with the mouse in one axial, one sagittal, and one coronal image to ensure the correct fiducial marker was being used. The centers of the fiducial markers and transformation matrix were found automatically, the output is shown in Figure 15. The centers of the fiducial markers had to be selected manually using the higher resolution images due to unresolved issues with reformatting the imaging volume in MATLAB. However, once the centers were selected in the high resolution images the transformation matrix was computed in the same manner as the semi-automated method.

Figure 14 – 3D model of three orthogonal line markers.
A new stereotactic needle template was required in order to avoid interference with the clinical template had to be dissolved in a solvent bath to seal the surfaces.

MATLAB output from semi-automated registration of three orthogonal line markers. The user defined a bounding box with the mouse in one axial, one sagittal, and one coronal image to ensure the correct fiducial marker was being used. The centers of the fiducial markers, circled in red, and transformation matrix were found automatically. (A) X-axis line marker in sagittal slice, (B) Y-axis line marker in coronal slice, (C) Z-axis marker in axial slice.

4.2.4 FIDUCIAL MARKER MATERIAL
Various materials for the fiducial patterns were considered for phantom experimentation. The first fiducial marker tested consisted of nine cylindrical channels 3.175 mm in diameter drilled into an older version of the needle template and filled with a copper sulphate solution. The second fiducial material tested consisted of channels with a square cross section of 3.175 mm per side filled with an aqueous gel called Surgilube®. The third fiducial material tested was MR-SPOTS® with Radiance® (Beekley, Bristol, CT), generally referred to as Beekley markers, which were 7 mm in diameter and 30 mm in length. The Beekley markers were chosen as the fiducial material to use for phantom testing because they were more suitable for repeated imaging sessions of long duration compared to the copper sulphate solution and aqueous gel. In addition, the Beekley markers exhibited suitable signal intensity and yielded an increased number of image slices suitable for stereotactic registration compared to the other fiducial materials.

4.2.5 STEREOTACTIC NEEDLE TEMPLATE
A new stereotactic needle template was required in order to avoid interference with the clinical biopsy procedure. The new needle template was designed to be capable of holding a wider Z pattern than the clinical needle template. This new needle template was built using a rapid prototyper. The rapid prototyper used a porous polycarbonate as the material so the needle template had to be dissolved in a solvent bath to seal the surfaces. This process slightly altered
the dimensions of the needle template by about 0.1 – 0.2 mm along the length of the fiducial markers. The alterations for all markers were measured and a correction applied in the registration software but the results were not impacted because the alterations were equal on either side of the needle template and the origin of the needle coordinate system was located in between the Z-shaped motifs. The needle template was designed to have interchangeable fiducial patterns so that if the pattern design were to change, only three small pieces would need to be produced instead of an entire new needle template. Figure 16 shows the newly designed needle template with three Beekley markers in each interchangeable fiducial pattern holder to form one Z-shaped motif.

![Newly designed needle template](image16.png)

Figure 16 – Newly designed needle template. (A) 3D model shown with one interchangeable fiducial pattern holder attached that is filled with three Beekley markers to form one Z-shaped motif. (B) Actual needle template with all Beekley markers attached. 30 mm length Beekley markers are shown. This needle template was built using a rapid prototyping machine at Princess Margaret Hospital.

4.2.6 **IMAGING PROTOCOL**

In MRI, the MR signal may exhibit spatial variation across the imaging volume referred to as image intensity non-uniformity. Intensity non-uniformity and the resulting geometric distortion may be caused by scanner hardware such as the transmit and receive radiofrequency (RF) coils
having spatial sensitivity, the gradient coils deviating from expected linear behaviour (gradient non-linearity), and the inhomogeneity of the magnetic field created by the main magnet [32]. Geometric distortion from inhomogeneity of the main magnetic field would be expected to be small in modern superconducting scanners with advanced shimming technologies [32]. The intensity non-uniformity is normally measured using a bulky water-filled phantom to act as a homogeneous signal source and analyzing selected image slices [32]. However, the goal of this thesis was not to test the absolute accuracy of various stereotactic registration techniques. Rather, the goal of the experiments in this thesis was to directly compare the performance of different stereotactic registration techniques in a setting closely mimicking the clinical environment. Therefore, characterization of the image intensity non-uniformity was not performed because each registration method was tested with the same image sequences and fiducial marker material. In addition, geometric distortion has been shown to be small when imaging within 20 cm of the scanner isocenter [33, 34]. However, various MR image sequences are affected differently by the presence of local magnetic field inhomogeneities that leads to signal loss and geometric distortion [35].

Any magnetic field variation beyond the applied gradient that is present during frequency encoding causes spins to be spatially encoded at the wrong position and is referred to as image distortion [35]. Image distortion effects during frequency encoding are identical for gradient echo and spin echo images (shifted image and shearing effect) but irregular field variations generally have a greater impact on gradient echo images [35]. Another artifact called echo shifting pertains only to gradient echo imaging and leads to signal loss and an additional phase in the image [35]. For experimentation, a spin echo image sequence was considered because the 90 degree pulse followed by at least one 180 degree pulse helps to minimize the field inhomogeneity effects, thus lowering geometric distortion. Disadvantages include reduced echo amplitude resulting in lower SNR as well as the longer acquisition time. Gradient echo sequences were considered because of high SNR and fast acquisition times, even for 3D imaging. A disadvantage was the increased sensitivity to field inhomogeneities leading to geometric distortion. No attempt was made to optimize the imaging parameters during sequence selection as this was beyond the scope of this thesis. Instead, sequences already in use clinically for stereotactic registration at Princess Margaret Hospital were used for experimentation.

Two sequences were chosen for testing stereotactic targeting accuracy based on the suitability of the images produced for automated image processing (i.e. high signal intensity, absence of susceptibility artifact from air bubbles). The imaging protocol with the highest spatial resolution
was a T2 weighted fast spin echo pulse sequence. The T2-weighted FSE sequence was chosen because it had low geometric distortion, high spatial resolution, and sufficient SNR for phantom testing. This sequence was referred to as the High Resolution sequence in the targeting accuracy results. The other sequence chosen was a 2D spin echo single shot localizer sequence because of the fast acquisition time and it had sufficient SNR for phantom testing. This sequence was referred to as the Low Resolution sequence in the targeting accuracy results. The 2D spin echo single shot sequence had the lowest spatial resolution but the fastest image acquisition time. Images were acquired in all three planes with this sequence for use with method #3’s semi-automated registration routine. This pulse sequence also required a larger field-of-view (FOV) to increase the SNR and signal intensity of the fiducial markers. Figure 17 shows the needle template imaged with a variety of pulse sequences and with different fiducial marker materials.

Figure 17 – MR images of the needle template using different imaging sequences and fiducial marker materials. (A) T2-weighted (2D FSE) images with Beekley markers, (B) 3D fast relaxation FSE with Beekley markers, (C) 3D steady-state free precession (SSFP) with Beekley markers, (D) 2D spin echo single shot with Beekley markers, (E) 3D SSFP with copper sulphate solution, (F) 3D SSFP with aqueous gel. The Beekley markers appeared best in the FSE images but the 3D SSFP sequence highlighted the presence of tiny air bubbles. However, the 3D SSFP sequence worked well with the gel and copper sulphate solution.

The sequences for the prostate phantom volume and needle verification were the same as the sequences used clinically, both of which are T2-weighted FSE pulse sequences. Table 1 gives a summary of the imaging protocol used for phantom testing.
Table 1 - Summary of imaging protocol used for testing phantom needle targeting accuracy.

<table>
<thead>
<tr>
<th>High Resolution Needle Template Stereotactic Registration Image Sequence</th>
<th>Low Resolution Needle Template Stereotactic Registration Image Sequence</th>
<th>Endorectal Sheath Fiducial Marker Registration Sequence&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Needle Verification Image Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse Sequence</td>
<td>2D FSE</td>
<td>2D SE single shot</td>
<td>2D FSE</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>96.0</td>
<td>80.0</td>
<td>96.0</td>
</tr>
<tr>
<td>TR (ms)</td>
<td>4417.0</td>
<td>854.4</td>
<td>3467.0</td>
</tr>
<tr>
<td>BW</td>
<td>20.83</td>
<td>83.33</td>
<td>20.83</td>
</tr>
<tr>
<td>FOV</td>
<td>16 cm</td>
<td>32 cm</td>
<td>16 cm</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>2 mm</td>
<td>2 mm</td>
<td>3 mm</td>
</tr>
<tr>
<td>No. of Slices</td>
<td>20</td>
<td>116&lt;sup&gt;3&lt;/sup&gt;</td>
<td>18</td>
</tr>
<tr>
<td>Scan Time</td>
<td>2:26 minutes</td>
<td>1:40 minutes</td>
<td>1:58 minutes</td>
</tr>
<tr>
<td>Frequency</td>
<td>256</td>
<td>256</td>
<td>256</td>
</tr>
<tr>
<td>Phase</td>
<td>256</td>
<td>128</td>
<td>256</td>
</tr>
<tr>
<td>Frequency Direction</td>
<td>R → L</td>
<td>Unswap</td>
<td>R → L</td>
</tr>
<tr>
<td>Other</td>
<td>NEX = 2, echo train length = 16</td>
<td>Phase FOV = 1.0</td>
<td>NEX = 2, echo train length = 16</td>
</tr>
</tbody>
</table>

4.3 PHANTOM NEEDLE TARGETING ACCURACY

4.3.1 NEEDLE TARGETING ACCURACY METHODS

In-plane needle targeting accuracy was the main metric for comparing the performance of each registration method. Needle targeting accuracy was tested by inserting needles (18 gauge MRI-safe biopsy guns) into the commercial prostate phantom (CIRS Inc., Norfolk, VA) through specific holes in the needle template to a particular depth. The coordinates of the needle were thus known in the fiducial or needle coordinate system. The MRI coordinates of the needle tip were found by using the last image slice where the needle void was visible and recording the coordinates of the center of that signal void in the needle verification images. The method used to evaluate the in-plane targeting accuracy involved using the known fiducial coordinates of the needle tip and the inverse transformation matrix to calculate the predicted MRI coordinates of the needle tip. The distance between the actual needle tip in MRI coordinates and the predicted needle position in MRI coordinates was the in-plane needle targeting error. Another performance metric was the depth error which was calculated as the distance from the actual needle tip to the predicted needle tip in MRI coordinates, except for the depth error of the clinical needle targeting software, method #1. One of the outputs from the clinical needle targeting software was the depth to insert the needle such that the target will be at the center of the biopsy core. The needle has depth markings at 1 cm intervals along its length for the

<sup>2</sup>This sequence was only required for method #1 to image the endorectal sheath fiducial marker.

<sup>3</sup>22 axial slices, 47 sagittal slices, and 47 coronal slices.
physician to reference. The needle tip is 5.5 mm from the needle targeting software’s output value so the depth error was calculated as the distance between the actual needle insertion depth in fiducial coordinates and the pre-firing depth from the clinical needle targeting software plus 5.5 mm. The other metric for performance was the time required for registration, which included the time for processing the images, either manually or automatically, to identify the fiducial markers as well as the time required for imaging the needle template.

4.3.2 Needle Targeting Accuracy Experiments
In total, 23 needles were inserted into the prostate phantom and imaged. The testing procedure was designed to mimic the clinical situation. The needles were inserted to depths of 104 to 144 mm, with mean insertion depth of 127 mm. In Experiment #1, a set of registration images were obtained and then five needles were inserted and imaged one by one in one session. This was repeated during a second session for a second registration image set and five needles (Experiment #2). A third session and third registration image set was collected for four more needles (Experiment #3) and five vitamin E capsules (Experiment #5). The final session (Experiment #4) and final nine needles were tested in a way that would mimic re-registration after patient movement. Registration images would be acquired and then a single needle inserted and imaged. Then the phantom was moved and the process repeated for each needle. The needle template and phantom were moved 1 mm and 5 mm along the Z-axis or needle axis, 1 mm and 5 mm along the X-axis or right-to-left direction, and rotated 1 degree and 5 degrees about the X-axis. The five vitamin E capsules were attached to the surface of the phantom at locations known in the fiducial coordinate system. These targets were visible in a T1 weighted image of the phantom. The vitamin E capsules were used to test shallow target depths. The depths ranged from 72 to 75 mm, the mean depth was 74 mm. The error was calculated in the same manner as the needle targets. Figure 18 shows the distribution of needle holes in the needle template that were used to test the different registration methods and the needle targeting accuracy.
Figure 18 - Needle holes used to test the needle targeting accuracy of the different registration methods (red circles). Needle holes were chosen from all areas of the needle template (green circles) where puncture of the needle phantom was possible.

4.3.3 Hardware for Testing Needle Targeting Accuracy

In order for the phantom needle targeting experiments to be accurate it was necessary that the needle template, phantom, and other components did not move relative to each other or in MRI space during imaging and multiple translations in and out of the scanner for needle insertion. Therefore several custom components were designed to hold the transperineal template system and prostate phantom in place during experiments. The assembly of components was designed to attach to another assembly which was designed to attach rigidly to the MRI table. The entire system was made from various plastics (acrylic, acetal/delrin, a polycarbonate-ABS blend, and nylon) to ensure image quality was not affected. The main component that was used to rigidly hold the needle template and phantom in place is shown in Figure 19. This assembly was able to attach to two other assemblies that allowed controlled movements and which attached to a base assembly that rigidly attached to the MRI table.
Figure 19 – Assembly of plastic components (grey) used to rigidly hold the needle template (black) and prostate phantom (blue) in place during needle targeting accuracy tests. All components were custom built by the machine shop except for the prostate phantom and the nylon screws.

4.4 RESULTS

4.4.1 IN-PLANE ERROR
The top pane of the figure below demonstrates that stereotactic registration using the low resolution image sequence performed the same and in some cases better than the high resolution image sequence. The bottom pane of the figure below shows the distribution of the in-plane errors using the low resolution image sequences for each method side-by-side for comparison. Method #1, the clinical method, has a larger proportion of data points in the right and posterior quadrant. Method #2, the Z-shaped fiducial motif, appears to have the expected distribution (normal distribution) of data points centered about 0. Method #3, the three orthogonal line markers, has a larger proportion of data points in the left quadrants.
Figure 20 – (A) Overall in-plane error for each stereotactic registration method. Each blue point represents the mean in-plane error using the high resolution pulse sequence with the blue bars indicating the standard deviation. Each cyan point represents the mean in-plane error using the low resolution pulse sequence with the cyan bars indicating the standard deviation. The dashed red box represents the clinical objective in-plane error of 2 mm. Method #1 exhibits an error bias toward the right and posterior. Method #2 has a slight posterior bias using the low resolution image sequence but not with the high resolution image sequence. Method #3 exhibits an error bias to the left. (B) In-plane error for each stereotactic registration method using low resolution pulse sequences. Each point represents the distance between the MRI coordinate of the actual needle tip minus the predicted MRI coordinate of the needle tip in the plane of the needle tip. The dashed red box represents the clinical objective in-plane error of 2 mm.
4.4.2 **Absolute In-Plane Error**

The figures below show the histograms of the absolute in-plane error for each method side-by-side for comparison. The normalized frequency represents the percentage of error values belonging to each error range.

Figure 21 – Comparison of absolute in-plane error for each method using the high resolution image sequence (top) and low resolution image sequence (bottom). In method #2, SS stands for single-slice, MS stands for multi-slice.
4.4.3 **Absolute Depth Error**

The figure below shows the histograms of the absolute depth error for each method side-by-side for comparison. The normalized frequency represents the percentage of error values belonging to each error range. The largest depth errors for method #1 occurred during experiment #4 when the needle template and phantom were rotated about the X-axis (right to left direction) by 5 degrees. The high resolution image sequence had the better depth error performance, except for method #1 which performed better with the low resolution image sequence.

![Absolute Depth Error: using high resolution images](image)

![Absolute Depth Error: using low resolution images](image)

*Figure 22 - Comparison of absolute depth error for each method using the high resolution image sequence (top) and low resolution image sequence (bottom). In method #2, SS stands for single-slice, MS stands for multi-slice.*
4.4.4 SUMMARY OF RESULTS
Method #1 required 3:00 minutes for registration and imaging of the needle template using the low resolution image sequence. The time required by the low resolution sequence was less than 30 seconds since only the axial image slices were required for this registration method. The time required for imaging the needle template was included in the total time because selection of the endorectal sheath fiducial marker was completed during the imaging of the needle template. The high resolution sequence required 5:00 minutes for stereotactic registration because of a longer acquisition time.

Method #2, both single-slice and multi-slice, required 30 seconds for registration and imaging of the needle template using the low resolution image sequence. The time required by the low resolution sequence was less than 30 seconds since only the axial image slices were required for this registration method. The time required was essentially the time for imaging the needle template because the automated algorithm was extremely fast. The high resolution image sequence required 2:30 minutes.

Method #3 required 2:30 minutes for registration and imaging of the needle template using the low resolution image sequence. The bulk of the time required was for defining the bounding box around the markers in each plane using the semi-automated algorithm in MATLAB. Using the high resolution image sequence required 6:00 minutes because the center of the line markers had to be manually selected after reformatting the images from axial to sagittal to coronal.

Table 2 gives a summary of the results obtained with each method using the low resolution imaging sequence.

Table 2 – Summary of results using the low resolution imaging sequence. In method #2, SS stands for single-slice, MS stands for multi-slice.

<table>
<thead>
<tr>
<th>Method: Low Resolution</th>
<th>Absolute In-Plane Error</th>
<th>Absolute Depth Error</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Error</td>
<td>Std. Dev.</td>
<td>Error</td>
</tr>
<tr>
<td>Method #1</td>
<td>2.3 mm</td>
<td>1.3 mm</td>
<td>1.4 mm</td>
</tr>
<tr>
<td>Method #2: SS</td>
<td>2.0 mm</td>
<td>0.9 mm</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Method #2: MS</td>
<td>2.0 mm</td>
<td>0.9 mm</td>
<td>1.0 mm</td>
</tr>
<tr>
<td>Method #3</td>
<td>2.2 mm</td>
<td>1.0 mm</td>
<td>1.7 mm</td>
</tr>
</tbody>
</table>

4.5 DISCUSSION

4.5.1 METHOD #1
This method had the highest in-plane error of all methods compared. There was a very evident bias of the in-plane errors using both the high and low resolution imaging sequences, about 1.0 – 1.5 mm toward patient right and about 1.0 mm in the posterior direction. The magnitude of the
bias in the posterior direction was very similar to the systematic bias observed clinically. This may suggest a systematic error in the needle targeting software and this particular stereotactic registration method. The in-plane error bias to the right observed in phantom testing was of concern. There was no significant right error bias observed clinically. It was possible that the hardware used for phantom experimentation introduced the bias in the direction of patient right. However, there was no obvious hardware deflection observed during experimentation. At an average depth of 125 mm, a bias of 1.5 mm toward patient right was the result of a 0.7 degree deflection from normal. This finding illustrates the sensitivity of method #1 to imprecise hardware geometry. However, due to the imprecise hardware geometry, these results may not truly reflect the accuracy of method #1. The depth error for this method was also of concern. The results show that the method used by the clinical needle targeting software to calculate the depth error was sound when the scan plane was parallel to the surface of the needle template. The largest depth errors occurred during experiment #4 when the needle template and phantom were rotated about the X-axis (right to left direction) by 5 degrees. Although the software reformatted the images to be normal to the endorectal sheath fiducial there may be some error in this process when the angle was large resulting in a larger depth error. The clinical depth error of the needle targeting software was significantly worse due to the increased sources of error that may be encountered during the biopsy procedure. The time required for registration was the highest because the user must manually place the mouse cursor over the center of each fiducial marker in two separate image volumes. The time required for registration was shorter than what was measured clinically because the fiducial marker size was smaller in the clinical needle template requiring greater attention when trying to select the center. In addition, two separate registration sessions were performed for this method in order to determine the effect of the variability in choosing the center of the fiducial marker. The largest difference observed in the in-plane error was only 0.7 mm along either direction. The variability during the clinical procedure, however, would be greater since the fiducial marker size was smaller. There may also be variability from one user to another, which was a key advantage to using automated registration. The time required for this method could be reduced if an automated registration scheme were developed. The user would need to select the appropriate images of the endorectal sheath fiducial, mark the most superior surface of the needle template, and select an image of the needle template. Finding the centers of the markers would be accomplished automatically.

4.5.2 Method #2
The method using the Z-shaped fiducial motif had the lowest in-plane error as well as the lowest depth error. The depth error was particularly good using the high resolution image sequence.
This method was expected to have the best depth error because it does not depend on the user identifying a particular image slice or single landmark because the depth was encoded into the fiducial pattern. The depth error was not significantly affected by changing the orientation of the needle template during experiment #4 either showing that it was an accurate registration method in orientations likely to be encountered clinically. The method using the Z-shaped motif was also the fastest because of the fully automated registration algorithm. The registration procedure did not significantly add to the time required for imaging the needle template which was a desirable feature if registration must be repeated due to patient or hardware movement. The in-plane error distribution was also the best observed. The in-plane error appeared to have a small left error bias using the high resolution sequence and a small posterior error bias using the low resolution images. A possible source of error resulting in these small error biases was the dimensions of the hardware not being exactly to specifications after the needle template was placed in the solvent bath. Error in finding the fiducial marker center is likely the greatest contributor to in-plane error, particularly the diagonal markers since they produce an ellipse rather than a circle in the images. Using multiple image slices through the needle template for registration did not result in a significant improvement over using only a single slice, the averages were identical. However, there was also no significant benefit from using only a single image slice since the difference in the time required was negligible for processing the images. Also, under normal circumstances the time required for imaging was the same since multiple image slices were acquired anyways in order to guarantee an image slice appropriate for stereotactic registration (i.e. all fiducial markers visible). Using a single-slice would be of benefit if registration had to be repeated due to motion. However, there would exist the risk that the single image slice acquired does not contain all of the fiducial markers, in which case imaging would have to be repeated. Therefore, it would be better to acquire multiple image slices. However, whether all of the images were used for registration or not did not significantly impact the targeting accuracy. The fact that the results for single and multiple image slices were so similar gives confidence that using only a single-slice for registration was valid.

4.5.3 METHOD #3
This method also had good in-plane error. However, there appeared to be a significant left error bias, particularly for deeper targets. The vitamin E capsules (Experiment #5) were the shallowest targets and exhibited the smallest in-plane error. It was expected that this method could suffer from angular errors which were more pronounced for deeper targets. This angular error could be improved by using two sets of orthogonal fiducial motifs on opposite sides of the needle template and averaging their direction vectors together. The depth error was better for the high resolution images compared to the low resolution images. The depth error was mainly
due to the error in calculating the point of intersection of the three 3D lines created by the fiducial markers. The depth error was less than the slice thickness for the high and low resolution image sequences which would be the expected maximum depth error. However, the depth error of the low resolution sequence is greater possibly due to an increased error in calculating the centers of the fiducial markers in each slice or from using axial, sagittal, and coronal slices instead of a single reformatted volume. The time required for registration using the low resolution sequence was less because it was a semi-automated procedure, only requiring a few mouse clicks from the user to define a bounding box around the fiducial marker of interest. The registration time was much greater for the high resolution images because the mouse cursor had to be positioned over the center of each marker at opposite ends of the marker and manually entered into the computer. This was not the intended registration procedure but problems were encountered with reformatting the image volume in MATLAB that could not be resolved in a timely manner.

4.5.4 REQUIREMENTS FOR CLINICAL TRANSLATION
The technical performance of the Z-shaped motifs was the best observed. However, several minor changes would be required in order for this fiducial motif to be translated into the clinic. The hardware requirements for this method were not as favourable when compared to the other methods because more fiducial markers were required. However, the number of markers required may be reduced to seven instead of nine if two of the parallel markers are shared. This geometry has been implemented by [30]. In addition, the needle template designed for testing was larger than the clinical needle template to accommodate the Z-shaped fiducials with Beekley markers. However, the size of the clinical needle template should not be increased substantially. Therefore, an alternative design would be required to fit the seven fiducial rods into the clinical needle template. The automated registration add-on for the clinical needle targeting software (Aegis) developed during experimentation could be quickly incorporated into the targeting software with minimal changes. Then the Z-shaped motifs would be ready for clinical translation.

4.6 CONCLUSION
Three alternative registration techniques and motifs of fiducial registration markers were investigated to address the shortcomings identified in the current clinical navigation system. The goal was to introduce automated registration methods, methods with fiducial marker motifs contained entirely in the needle template, and methods with improved depth error. The performance of these alternative methods was compared to the performance of the current navigation system subjected to the same phantom tests. The metrics of performance were in-
plane MRI to needle coordinate targeting error, MRI to needle coordinate targeting depth error, and the length of time required for registration including the time required for imaging of the needle template. Method #2, the Z-shaped motif, had the best in-plane targeting accuracy which was the most important performance metric because the length of the biopsy core was nearly ten times the diameter of the biopsy core. The best depth accuracy and time performance belonged to method #2 as well. This method also utilized a robust, automated registration algorithm which was preferable to manual registration in terms of speed and repeatability, especially when registration must be repeated due to motion. Method #1 and method #3 suffered from angular errors which resulted in a significant bias of the in-plane error. However, the time performance of methods #1 and #3 could be improved by developing automated registration.
CHAPTER 5

5 CONCLUSION

Prostate cancer is afflicting an increasing number of men around the world. The excellent soft tissue contrast of MRI coupled with advanced techniques such as dynamic contrast enhanced imaging and magnetic resonance spectroscopic imaging are ideally suited for supplementing existing non-invasive screening techniques. MRI-guided biopsy has also been shown to be a promising method for detecting prostate cancer better than digital rectal examination and transrectal ultrasound guided biopsy. At Princess Margaret Hospital an MRI-guided needle navigation system for prostate cancer targeting has been developed and shows promise in early clinical evaluations of technical performance. The mean in-plane coordinate needle-targeting error for 10 patients analyzed to date was 2.2 mm with standard deviation 1.2 mm. The mean absolute depth error was 6.5 mm with standard deviation 4.7 mm. Several vulnerabilities with the system hardware and registration methodology were discovered during analysis and corrective measures were taken to improve clinical performance.

In order to address the weaknesses identified in the current clinical navigation system it was deemed meaningful to investigate three alternative registration techniques and motifs of fiducial registration markers. The goal was to introduce automated registration methods, methods with fiducial marker motifs contained entirely in the needle template, and methods with improved depth error. The performance of these alternative methods was compared to the performance of the current navigation system subjected to the same phantom tests. The metrics of performance were in-plane MRI to needle coordinate targeting error, MRI to needle coordinate targeting depth error, and the length of time required for registration including the time required for imaging of the needle template. Method #2, the Z-shaped motifs, had the best in-plane targeting accuracy with a mean absolute in-plane error of 2.0 mm using low resolution images, 2.1 mm using high resolution images. The best depth accuracy and time performance were also observed with method #2, the Z-shaped motifs. The mean absolute depth error was 1.0 mm using the low resolution images and 0.8 mm using the high resolution images. These methods also utilized a robust, automated registration algorithm which is preferable to manual registration in terms of speed and repeatability.

Therefore, it is the recommendation of this thesis that the Z-shaped fiducial motifs, method #2, be adopted for MRI-guided needle navigation. These fiducial motifs and the automated
registration method had the best in-plane needle targeting accuracy, the best depth targeting accuracy, and the time required for registration was the lowest due to the automated registration algorithm.

The main source of clinical needle targeting error was patient and hardware movement prior to increasing the level of anaesthesia. It would be preferable to use less anaesthetic. If device movement can be accounted for prior to needle insertion then the clinical performance of the MRI guided needle navigation system will be improved without the need for increased anaesthesia. An ongoing development for the navigation system includes an imaging method to capture and adapt to motion of the stereotactic device prior to needle insertion, which is still being validated in phantom tests. This motion correction method could be used effectively with the Z-shaped motif since registration requires a single, quick image slice. The navigation system and all the lessons learned during its development may be beneficially applied to all focal therapies on the prostate in the future, particularly brachytherapy.
REFERENCES


