TARGET LOCALIZATION IN
MRI-guided PROSTATE BIOPSY

by

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Abstract

Prostate cancer is a worldwide health concern for men. Needle biopsy is the most definitive form of cancer diagnosis. Target-specific biopsies can be performed under magnetic resonance imaging (MRI) guidance. However, needle placements are often inaccurate due to intra-operative prostate motion and the lack of motion compensation techniques. As a result, malignant tumors can be missed, which in turn will lead to an increased number of repeated biopsies and delaying of treatment. To increase the needle targeting accuracy, intra-operative prostate motion and deformation need to be studied so that motion compensation techniques can be developed accordingly.

This thesis intends to make three main contributions:

1. A comprehensive survey of the state-of-art in image-guided prostate needle placement interventions.

2. Retrospective clinical accuracy validation of a MRI-guided robotic prostate biopsy system that was used in the U.S. National Cancer Institute for over 6 years. A 3D-3D registration algorithm consists of an initial two-step rigid alignment followed by a B-spline deformable transform was developed to align the pre- and post-needle insertion images. A total of 90 biopsies from 24 patients were studied. The mean target displacement, needle placement error, and clinical biopsy error were 5.2, 2.5, and 4.3 mm, respectively.
3. Development of a multi-slice-to-volume registration for intra-operative target localization. The algorithm aligns the planning volume with three orthogonal image slices of the prostate acquired immediately before needle insertion. It consists of a rigid registration followed by a deformable step using only the prostate region. The algorithm was validated on 14 clinical images sets from Brigham and Women’s Hospital in Boston, Massachusetts. All registration errors were well below the radius of a clinically significant tumour (5 mm), and are considered clinically acceptable.

The results show that there was a substantial amount of biopsy error caused by prostate motion and deformation during MRI-guided biopsy. This error can be reduced by using quantitative imaging techniques for prostate registration and motion compensation. In particular, the multi-slice-to-volume registration algorithm demonstrated the feasibility of intra-operative target localization and motion compensation; which in turn may improve the quality of MRI-guided prostate interventions.
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Statement of Originality

I hereby declare that the materials and results in this thesis are original and have not been published elsewhere, except where indicated by specific references.
Contents

Abstract i

Acknowledgments iii

Statement of Originality v

Contents vi

List of Tables ix

List of Figures xi

Chapter 1: Introduction 1

1.1 Motivation ........................................ 3
1.2 Objective ........................................ 3
1.3 Contributions ..................................... 4
1.4 Thesis Outline ................................... 5

Chapter 2: Background 6

2.1 Image Guidance Modalities ....................... 6
  2.1.1 Ultrasound Guidance .......................... 7
  2.1.2 MRI Guidance ................................ 13
  2.1.3 CT Guidance .................................. 14
2.2 Needle Puncture Trajectory ....................... 15
  2.2.1 Transrectal Access ......................... 16
  2.2.2 Transperineal Access ......................... 18
  2.2.3 Transgluteal and Transischiorectal Access .... 18

Chapter 3: Prostate Motion and Deformation Upon Needle Insertion 20

3.1 Patient-Induced Prostate Motion ................ 21
3.2 Transrectal Procedures ......................... 23
3.3 Transperineal Procedures ....................... 25
6.1.2 Accuracy Analysis in MRI-guided Robotic Prostate Biopsy . . 81
6.1.3 Target Localization in MRI-guided Transperineal Prostate Biopsy using Multi-Slice-to-Volume Registration . . . . . . . . . . 81
6.2 Future Work . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . 82

Bibliography 84
## List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Registration parameters of different TRUS and MRI fusion methods</td>
<td>32</td>
</tr>
<tr>
<td>3.2</td>
<td>Deformable registration results of MR prostate images [9]</td>
<td>35</td>
</tr>
<tr>
<td>4.1</td>
<td>Data statistics for accessing biopsy accuracy</td>
<td>52</td>
</tr>
<tr>
<td>5.1</td>
<td>Registration validation experiments summary</td>
<td>67</td>
</tr>
<tr>
<td>5.2</td>
<td>Summary of execution time statistics for multi-slice-to-volume registraion with clinical images</td>
<td>69</td>
</tr>
<tr>
<td>5.3</td>
<td>Gradient descent optimizer parameters for the rigid registration step.</td>
<td>69</td>
</tr>
<tr>
<td>5.4</td>
<td>L-BFGS-B optimizer parameters for the deformable registration step.</td>
<td>70</td>
</tr>
<tr>
<td>5.5</td>
<td>TRE statistics for Experiment 1a: multi-slice-to-volume rigid registraion between the planning volume and simulated intra-operative orthogonal image slices. The simulated images were undistorted (no deformation was applied)</td>
<td>70</td>
</tr>
<tr>
<td>5.6</td>
<td>TRE statistics for Experiment 1b: multi-slice-to-volume deformable registraion between the planning volume and simulated intra-operative orthogonal image slices</td>
<td>71</td>
</tr>
<tr>
<td>5.7</td>
<td>TRE statistics for Experiment 2a: multi-slice-to-volume rigid registraion between the planning volume and clinical intra-operative orthogonal image slices</td>
<td>73</td>
</tr>
</tbody>
</table>
5.8 TRE statistics for Experiment 2b: multi-slice-to-volume deformable registration between the planning volume and clinical intra-operative orthogonal image slices
## List of Figures

1.1 a) Anatomy of the male pelvis, including the prostate gland (prostate-cancer.ca). b) Zones of the prostate gland (pathologyoutlines.com).  

2.1 Anatomical planes (mevislab.de).  

2.2 a) End-fire TRUS probe and an example of the image it produces. (hitachi-medical-systems.co.uk). b) 3D TRUS image acquisition using the end-fire probe and its sample image (intechopen.com).  

2.3 a) Side-fire (bi-plane) TRUS probe and examples of transverse (middle) and sagittal (right) images that it produces. (hitachi-medical-systems.co.uk). b) 3D TRUS image acquisition using the side-fire probe and its sample image (intechopen.com).  

2.4 a) Illustration of a 2D TRUS-guided prostate biopsy (cancer.gov) with an end-fire probe and a sample image (bkmed.com). b) A example of the 12-core biopsy protocol in the coronal plane of the prostate [4].  

2.5 a) TRUS-guided LDR prostate brachytherapy using a side-fire probe (duooxfordshire.org.uk). b) Top: Sagittal view of the prostate before seed implantation. Bottom: Transverse view of the prostate after seed implantation (bkmed.com).
2.6 a) TRUS-guided HDR prostate brachytherapy using a side-fire probe (intechopen.com). b) Transverse image of the prostate post-needle insertion [46].

2.7 a) Example of a MRI-guided biopsy setup [89]. b) A sample MR image of the prostate in transverse plane [89].

2.8 a) Example of a MRI-guided LDR brachytherapy setup [100]. b) Example of a MRI-guided HDR brachytherapy setup [57].

2.9 A sample CT scan of the prostate (aboutcancer.com).

2.10 a) Transrectal access path (radiographics.rsna.org). b) Transperineal access path (duo.oxfordshire.org.uk). c) Transgluteal access path [116] (transverse MRI with visible needle path). d) Transischiorectal access path [48] (transverse CT image with visible needle path).


3.1 Standard anatomical directions used in human anatomy (thesebonesofmine.wordpress.com).

3.2 a) MR image of the prostate without endorectal imaging coil. b) MR image of the prostate with an air-inflated endorectal imaging coil [64]. c) MR image of the prostate with a special endorectal imaging coil on the sheath.

3.3 Prostate deformation caused by ultrasound probe positioning during brachytherapy.
3.4 a) Parallel stabilization needle configuration. b) Oblique stabilization needle configuration.

3.5 a) Different types of stabilization needles. Top: needle with hook extended. Middle: needle with hook retracted. Bottom: diamond tip needle [71]. b) Clinical image of the inserted oblique stabilization needles [27].

4.1 The APT-MRI robotic biopsy device system used in NCI [51].

4.2 Workflow of the three-stage registration algorithm between the pre- and post-needle insertion volumes using mutual information.

4.3 Illustration of the prostate dislocation during needle insertion and the parameters used in biopsy accuracy analysis.

4.4 The decomposition of target displacement into parallel and orthogonal component.

4.5 Prostate contour overlays before (left) and after (right) the automatic registration.

4.6 Left: Histograms of target displacement (top), needle placement errors (middle), and biopsy errors (bottom) of the 90 biopsies. Right: Transverse (top), sagittal (middle), and coronal (bottom) view of the prostate target displacement. '*' and '.' represent biopsies on the left and right prostate lobes, respectively.
5.1 Clinical workflow of the image acquisitions during MRI-guided prostate biopsy. The solid lines indicate the standard biopsy procedure, and the dashed lines represent the additional orthogonal image slice acquisition specific to our study. The grey box is the motion compensation registration method we propose to incorporate.

5.2 Workflow of the multi-slice-to-volume registration between the pre-operative planning volume and intra-operative image slices.

5.3 The arrangement of 5 ground truth points chosen on the prostate.

5.4 Examples of clinical image prostate contour overlay in the transverse plane. Each of the three images are copies of the same fixed image overlaid with the contours from the moving image a) before registration, b) after rigid registration, c) after deformable registration.

5.5 TREs for Experiment 1a: the 55 multi-slice-to-volume rigid registrations using simulated images. The simulated images were undistorted (no deformation was applied). A random initial transform of ±20 mm translation and ±10° rotation along each axis were set to the registrations. The distance between the initial target and the ground truth target was defined as the initial misalignment.

5.6 TREs for Experiment 1b: the 11 multi-slice-to-volume deformable registrations using simulated images. The simulated images were warped ±5 mm based on two sets of manually defined points using Landwrap landmark deformable registration in 3D Slicer.

5.7 Examples of prostate contour overlay on the simulated fixed transverse image slice a) before registration, b) after deformable registration.
5.8 TREs for Experiment 2a: the 70 multi-slice-to-volume rigid registrations using clinical images. A random initial transform of ± 20 mm translation and ± 10° rotation along each axis were set to the registrations. The distance between the initial target and the ground truth target was defined as the initial misalignment.

5.9 TREs for Experiment 2b: the 14 multi-slice-to-volume deformable registrations using clinical images. The image volumes were warped ± 5 mm based on two sets of manually defined points using Landwrap landmark deformable registration in 3D Slicer.

5.10 Experiment 3: Histogram of the target reconstruction distances between multi-slice-to-volume and volume-to-volume registration.
Chapter 1

Introduction

The prostate is a walnut sized exocrine gland of the male reproductive system. It is located in front of the rectum, just below the bladder, and surrounds the urethra (Figure 1.1). Prostate cancer is a major health concern for men in developed countries. In 2012, there were an estimated 241,740 new cases and 28,170 deaths of this disease in the United States (U.S.), making it the most commonly diagnosed cancer and the second most common cause of cancer death for American men [85].

The two most common screening methods for prostate cancer are prostate-specific antigen (PSA) test and digital rectal exam (DRE). The existence of a tumour maybe suspected when there is an increased level of PSA (usually >4 ng/ml [14]) or abnormal prostate hardness and lumpiness during a DRE. However, PSA has high sensitivity but low specificity, and results from DRE are often subjective, inconsistent and inconclusive. Therefore, needle biopsy is often recommended to determine the existence and extent of cancer based on histological analysis. Each year, approximately 1.5 million prostate biopsies are performed in the U.S. and one positive case is found in every 6 to 8 biopsies. Out of these cancer cases, 1 in 7 patients will die from it [80]. The relatively low positive case and death to biopsy ratio suggests that there is an
Figure 1.1: a) Anatomy of the male pelvis, including the prostate gland (prostate-cancer.ca). b) Zones of the prostate gland (pathologyoutlines.com).

over biopsy for prostate cancer. This could be a result of the high sensitivity but inconclusive results from PSA testing and DRE [103], thus adding another complexity dimension to the management of prostate cancer.

There are several ways of treating prostate cancer depending on the stage of cancer and the overall condition of the patient. Early stage cancer can be treated by prostatectomy, external beam radiation therapy (EBRT), and brachytherapy, while later stages can be treated with a combination of EBRT and hormone or chemotherapy. Other experimental treatment options include high intensity focused ultrasound [55], cryotherapy [78] and photodynamic therapy [105].

This thesis focuses on prostate biopsy and other needle placement procedures for prostate cancer treatment under image guidance.
1.1 Motivation

The prostate is a soft tissue organ attached only by connective tissues. Therefore, needle insertions can be complex when the targeted tissue moves and deforms due to a combination of mechanical forces exerted by the biopsy device and patient motion. Unfortunately, contemporary standard procedures do not account for these intra-procedural motions or changes to organ geometry. Inaccurate needle placement often leads to failure of the procedure and/or complications, such as excessive tissue damage and bleeding. In order for needle-based interventions to be safe and effective, it is important to understand the prostate behaviour upon needle insertion and incorporate motion compensation methods into the current clinical protocol to increase needle placement accuracy.

1.2 Objective

The overall objective of this thesis is to study the intra-operative prostate motion and deformation upon needle insertion and to develop a motion compensation method for improving the needle targeting accuracy under magnetic resonance imaging (MRI) guidance. More specifically, this thesis proposes to:

- Survey the current image-guided prostate needle placement interventions with emphasis on prostate motion and deformation upon needle insertion

- Retrospectively evaluate the clinical accuracy of a MRI-guided robotic prostate biopsy system that was used in the U.S. National Cancer Institute (NCI) for over 6 years
1.3. CONTRIBUTIONS

- Develop a registration algorithm for intra-operative target localization and motion compensation in MRI-guided prostate biopsy

1.3 Contributions

This thesis intends to make three main contributions:

1. A comprehensive survey of the state-of-art in image-guided prostate needle placement interventions was conducted. This includes reports on intra-operative prostate motion and deformation as well as motion compensation methods that have been used clinically. This work is presently in preparation for journal submission.

2. A three-stage 3D-3D registration algorithm was developed to validate the clinical accuracy of a MRI-guided robotic prostate biopsy system from the U.S. NCI. Quantitative evaluations of the system and a detailed prostate motion analysis based on 90 biopsies from 24 patients were reported. This work was published in Xu et al. IJCARS 2013.

3. A multi-slice-to-volume registration was developed for intra-operative target localization and motion compensation in MRI-guided prostate biopsy. It was validated on clinical images from Brigham and Womens Hospital (BWH) in Boston, Massachusetts. All registration errors and execution times based on 14 MR biopsies images of 10 patients were clinically acceptable. This work was submitted to IEEE TBME as Xu et al. and is currently under review.
1.4 Thesis Outline

The remainder of this thesis is organized as follows:

Chapter 2 reviews the current prostate needle placement procedures for the diagnosis and treatment of prostate cancer.

Chapter 3 reviews studies on intra-operative prostate motion and deformation upon needle insertion and image registration methods aimed to improve the accuracy of needle placement.

Chapter 4 presents a 3D-3D registration algorithm developed for accuracy validation of a MRI-guided biopsy system used at the National Cancer Institute (NCI), as well as the image-based prostate motion analysis.

Chapter 5 introduces a multi-slice-to-volume registration for intra-operative motion compensation and its validation on clinical MR images from Brigham and Women’s Hospital (BWH).

Finally, Chapter 6 summarizes and concludes the work done for this thesis and outlines directions for future research.
Chapter 2

Background

This chapter introduces the different types of image guidance modalities and needle puncture trajectories used in needle placement procedures for prostate cancer diagnosis and treatment.

2.1 Image Guidance Modalities

Two-dimensional (2D) transrectal ultrasound (TRUS) is currently the standard imaging modality for guiding prostate needle placement procedures due to its low cost, ease-of-use, and real-time imaging capabilities. However, magnetic resonance imaging (MRI) has superior soft tissue image quality, and it has emerged as an alternative tool for guidance. Although computed tomography (CT) or fluoroscopy are commonly used in radiation treatment planning, it is rarely used as an image guidance modality for prostate needle placements due to its limited ability to image soft tissues. The following sections explore the pros and cons of each imaging modality for prostate interventions.
2.1. IMAGE GUIDANCE MODALITIES

2.1.1 Ultrasound Guidance

The two most commonly used transrectal ultrasound probes for image guidance are the end-fire and side-fire probes. The end-fire probe (Figure 2.2) contains a curved array at the tip, and is typically used for transrectal biopsy. The side-fire probe (Figure 2.3) has longitudinal transducers, allowing imaging in the sagittal and transverse (Figure 2.1) plane (bi-plane). It is ideal for transperineal procedures, including brachytherapy.

For 2D TRUS-guided prostate biopsy, the ultrasound probe is equipped with a needle guide that ensures the puncture trajectory lies in the image plane. It is held and inserted into the patient’s rectum by the physician to image and to gain access to the prostate (Figure 2.4 a). Ultrasound images do not show prostate morphology.
or carcinomas. In addition, artifacts can also be present due to calcifications within the prostate. Therefore, contemporary TRUS-guided biopsy uses a grid sampling approach, obtaining around 6 (hence "sextant biopsy") to 18 tissue samples from upper, mid, and lower areas of the left and right sides to obtain a representative sampling of the gland and determine the degree and extent of cancer [14] (Figure 2.4 b).

Many problems are associated with the aforementioned non-exhaustive systematic search method for an unknown target. First, the pressure from the transducer probe while imaging causes dynamic prostate deformation throughout the procedure (Figure 2.4 a), which can lead to inaccurate needle placement. The location of biopsy is also
2.1. IMAGE GUIDANCE MODALITIES

Figure 2.3: a) Side-fire (bi-plane) TRUS probe and examples of transverse (middle) and sagittal (right) images that it produces. (hitachi-medical-systems.co.uk). b) 3D TRUS image acquisition using the side-fire probe and its sample image (intechopen.com).

Figure 2.4: a) Illustration of a 2D TRUS-guided prostate biopsy (cancer.gov) with an end-fire probe and a sample image (bkmed.com). b) A example of the 12-core biopsy protocol in the coronal plane of the prostate [4].
lost after the procedure, making precise re-biopsy of the same region of the prostate
difficult or impossible. TRUS-guided biopsy provides a significant number of false-
negatives and its detection rate is only about 20-40% [94] [52]. Wefer et al. [106]
have also shown that TRUS misses cancer in at least 20% of the cases. A more recent
study by Mozer et al. [61] reported that only 63% of planned targets were reached
under 2D TRUS guidance. Such observations have been seen with no major changes
for about a decade [95] [96]. Cancers have been routinely missed, resulting in a large
number of repeat biopsy cases [107].

To improve the standard 2D TRUS-guided biopsy, Bax et al. [5] and Natarajan
et al. [62] developed a 3D ultrasound-guided (Figure 2.3 b) biopsy tracking and
targeting device. Systematic biopsy (Figure 2.4 b) under 3D guidance was completed
successfully in 180 out of 218 patients. Doppler imaging was also used to determine
possible cancerous regions based on the amount of blood flow within the prostate
prior to biopsy. Cho et al. [11] reported a sensitivity, specificity and accuracy of 80%,
84%, and 82%, respectively, based on 39 patients. Frauscher et al. [28] found Doppler
targeted biopsy detected as many cancers as systematic biopsy with fewer than half
of biopsy cores in 230 patients, while Taverna et al. [93] reported no significant
improvement in detection rate with 300 patients. Takahashi et al. [91] concluded
that Doppler-directed biopsy does not identify cancer with sufficient accuracy to omit
systematic biopsy. Finally, to exploit the features of multiple imaging modalities,
ultrasound and MR imaging have been fused together for biopsy guidance [83] [42]
[13] [62] [97].
TRUS is also the standard imaging modality for brachytherapy, a commonly practiced localized treatment of prostate cancer. Low-dose-rate (LDR) brachytherapy involves permanent placement of radioactive seeds (Iodine-125) into the prostate via catheters inserted through the perineum using template guidance (Figure 2.5). Radiation is delivered directly from within the gland while sparing surrounding critical organs [76]. However, similar to biopsy, using the TRUS probe as an imaging tool causes distortions to the prostate and affects the accuracy of needle placement. Furthermore, the implanted seeds are difficult to localize in ultrasound images due to speckles. As a result, the dose distribution is usually calculated based on implanted catheter position rather than seed position. This is a major drawback since loose seeds can move within the prostate during or after needle retraction, resulting in suboptimal dosimetry [72]. Other groups have incorporated fluoroscopy [86], CT [30] and cone-beam computed tomography (CBCT) [108] into the standard ultrasound procedure for better seed visualization and allowing for dynamic intra-procedural dosimetry.

TRUS-guided high-dose-rate (HDR) brachytherapy (Figure 2.6 b) is similar to LDR, except a higher radiation dose rate is delivered and the radiation sources (Iridium-192) are removed at the end of the treatment session. In HDR, the catheters that contain the radioactive seeds remain in place throughout the procedure, whereas in LDR, catheters are retracted after seed deposition and the seeds may migrate within the prostate.
2.1. IMAGE GUIDANCE MODALITIES

Figure 2.5: a) TRUS-guided LDR prostate brachytherapy using a side-fire probe (duoxfordshire.org.uk). b) Top: Sagittal view of the prostate before seed implantation. Bottom: Transverse view of the prostate after seed implantation (bkmed.com).

Figure 2.6: a) TRUS-guided HDR prostate brachytherapy using a side-fire probe (in-techopen.com). b) Transverse image of the prostate post-needle insertion [46].
2.1. IMAGE GUIDANCE MODALITIES

2.1.2 MRI Guidance

MRI provides an alternative approach for image guidance. Its high soft tissue contrast provides clear visualization of the prostate and its anatomical substructures. This allows suspicious lesions to be identified for target specific biopsies (Figure 2.7). Several groups have shown that the sensitivity of MRI-guided biopsy exceeds that of the TRUS-guided system [32] [36] [3]. Estimates of the sensitivity of MRI for the detection of prostate cancer using T2-weighted sequences and endorectal coils vary from 60% to 96% [47]. The MRI scanner has strong magnetic fields and confined physical space; therefore needle insertion may benefit from robotic assistance. Numerous biopsy systems were developed for this purpose [73]. Furthermore, metabolic information from MR spectroscopy [2], dynamic contrast enhanced (DCE) MRI [88], and diffusion weighted imaging (DWI)[41] have also emerged for better biopsy target selection.

Figure 2.7: a) Example of a MRI-guided biopsy setup [89]. b) A sample MR image of the prostate in transverse plane [89].
In addition to biopsy, MRI has been used for guiding LDR brachytherapy \([15] [37] [100]\) (Figure 2.8 a). Due to limited access inside the MR scanner, van Gellekom \textit{et al.} [33] developed a single needle method in which a needle is inserted into the prostate multiple times at different angles instead of the standard multi-parallel approach. Other groups have also used MRI for treatment planning during HDR brachytherapy \([12] [57] [74]\) (Figure 2.8 b).

Despite the positive aspects, MRI has not been widely adopted for prostate interventions due to its limited availability and high cost. Nonetheless, it plays an important part in research and remains as an alternative for patients that are not suitable for TRUS procedures or have rising PSA levels but repeated negative TRUS-guided biopsy results.

### 2.1.3 CT Guidance

Computed tomography (CT) (Figure 2.9) is not a common imaging modality for guiding needle insertions into the prostate because the organ anatomy is not sufficiently
2.2 NEEDLE PUNCTURE TRAJECTORY

Figure 2.9: A sample CT scan of the prostate (aboutcancer.com).

defined in its images [29]. However, it is an option for patients with large prostates or who are not suitable for transrectal imaging due to prior rectal surgery. Molloy et al. [60] used CT guidance for brachytherapy. Koutrouvelis et al. [48] [49] performed both 3D CT-guided biopsy and brachytherapy on over 100 patients.

2.2 Needle Puncture Trajectory

There are four ways to access the prostate with needles: transrectally, transperineally, transgluteally, and transischiorectally (Figure 2.10). The transrectal approach has the shortest puncture path and is ideal for biopsy. However, due to infection concerns, treatment procedures that require more extensive needle placements are done transperineally. The transgluteal and transischiorectal methods are rare and can be performed on patients with prior rectal surgery. The following sections provide a more detailed description for each of these methods.
2.2. NEEDLE PUNCTURE TRAJECTORY

Figure 2.10: a) Transrectal access path (radiographics.rsna.org). b) Transperineal access path (duooxfordshire.org.uk). c) Transgluteal access path [116] (transverse MRI with visible needle path). d) Transischiorectal access path [48] (transverse CT image with visible needle path).

2.2.1 Transrectal Access

The transrectal approach (Figure 2.10 a) is generally used for biopsy, the definitive form of diagnosis for prostate cancer. The biopsy needle (usually 18 Gauge) contains a notch in the distal region and an external sheath that slides over the needle. During tissue acquisition, the needle enters the targeted region of the prostate and the sheath closes onto a tissue sample, which is contained in the notch of the needle. Since
2.2. NEEDLE PUNCTURE TRAJECTORY

commonly used biopsy needles have cores about 12 to 15 mm long [14], the insertion depth is a less important factor compared to the transverse needle displacement.

Due to the short puncture path of the transrectal approach, biopsies can be performed with no or local anaesthesia and is normally well tolerated by patients [14]. The left lateral decubitus position (Figure 2.11) is most commonly used for the procedure but some groups have also used prone [89] and supine [20] [21] positions for transrectal biopsies.

In addition to biopsy, Susil et al. [89] performed fiducial (gold marker) placement transrectally via needles with the patients in prone position (Figure 2.11). Fiducials are sometimes needed in external beam radiation therapy (EBRT) for patient position verification and are often used as reference landmarks for validating image registration accuracy.

Figure 2.11: Patient positions for prostate needle placement procedures. a) Supine (paramedicine.com). b) Prone (paramedicine.com). c) Lithotomy (hopkinsarthritis.org). d) Left lateral decubitus (www2.aofoundation.org).
2.2. NEEDLE PUNCTURE TRAJECTORY

2.2.2 Transperineal Access

Treatment procedures such as LDR and HDR brachytherapy, which involves a large number of needle insertions, are commonly performed transperineally (Figure 2.10 b) with the patient in lithotomy position (Figure 2.11). Disinfection of the perineal region and lumbar or full anaesthesia is required.

Biopsies have also been performed transperineally with the patient in lithotomy position [16] [35] [8] [66]. The transperineal method is capable of obtaining more tissue volume from the peripheral zone (PZ), where most of cancer (70%) tends to occur [94]. It has been theoretically demonstrated that of the tissue extracted transperineally, 98.5% can be from the PZ, whereas only 64.9% of transrectally sampled tissue are from the PZ [59]. However, the transperineal approach requires a much longer needle path, which increases tissue damage and risks of needle deflection. Based on a study of 414 patients, Huo et al. [40] reported an average sensitivity and specificity of 48% and 84.1%, respectively, for cancer detection using this approach. There was a significant decrease in sensitivity for larger prostates.

Furthermore, fiducial placement can be performed transperineally under TRUS-guidance similar to the brachytherapy setup. Van den Bosch et al. [100] demonstrated the feasibility of the procedure under MRI-guidance and robotic assistance with the patient in lithotomy position.

2.2.3 Transgluteal and Transischiorectal Access

For patients with prior rectal surgery, the transgluteal (Figure 2.10 c) approach can be used. Zangos et al. [116] carried out biopsies with the patients in prone position. A large insertion depth is required for this method, but it was mentioned that this
2.2. NEEDLE PUNCTURE TRAJECTORY

...technique provides superior results for biopsying the apex part of the prostate and it minimizes injuries to the bladder, bowel loops, and iliac vessels.

...The transischiorectal approach (Figure 2.10 d) was used in CT-guided biopsy [48] and brachytherapy [60] [48] [49] with the patients in prone position.
Chapter 3

Prostate Motion and Deformation Upon Needle Insertion

Over the past decade, methods for improving standard image-guided diagnosis and treatment of prostate cancer have received significant attention in the research community. However, only a fraction of these have been evaluated in clinical practice. Numerous systems and algorithms that were developed remained in academia, away from the operating room. Since the end goal of such projects is to improve the quality of current patient care, clinical compatibility and trial outcomes therefore have the utmost importance. It would be beneficial to extract the proposed methods that have made into the operating room from the large pool of prostate imaging literature. The objective of this chapter is to survey recent literature on the state-of-art in clinical image-guided prostate needle placement procedures with emphasis on prostate motion and deformation upon needle insertion.
3.1 Patient-Induced Prostate Motion

Reports from external beam radiation therapy (EBRT) show the amount of intra-procedural prostate motion that already exists without needle insertions or the usage of transrectal imaging probes. Wallner et al. reported the primary prostate motion in the absence of needle insertion is in the anterior-posterior direction (Figure 3.1). Vargas et al. [102] studied prostate motion in 7 patients during a 4-minute Cine-MRI. Prostate motion was found to be dependent on time, patient position, and rectal filling. More motion was observed in the second half of the experiment compared to the first half. Furthermore, the prostate moved more in prone position than supine. Van Herk et al. [101] also found larger prostate motion in prone position than supine position based on 11 patients during radiotherapy. Dinkel et al. [18] reported respiratory-induced mean prostate displacement of 43 patients in cranial-caudal (Figure 3.1) and anterior-posterior direction to be $2.7 \pm 1.9$ mm and $1.8 \pm 1$ mm, respectively, using dynamic MRI. In 69% of the subjects, breathing-related prostate movements were found to be less than 3 mm.

In addition to the motion that occurs naturally, image-guided needle insertions further deforms the prostate. The accuracy of needle placement procedures is affected by a combination of the following:

- Pressure induced by the transrectal imaging probe [44] [4]
- Tissue motion and deformation during needle insertion and tissue acquisition [112] [82]
- Needle bending and deflection during insertion [8]
- Time delay between imaging and needle insertion [89] [102]
3.1. PATIENT-INDUCED PROSTATE MOTION

![Standard anatomical directions used in human anatomy](thesebonesofmine.wordpress.com)

- Reactionary patient motion due to discomfort (leg motion, clenching of pelvic floor muscles, pelvis movement) [112] [63]

- Unintentional patient motion (breathing, rectum activity, bladder filling) [63]

The extent of these motions also depends on patient position and varies from patient to patient. Observations have shown that the maximum prostate deformation upon needle insertion occurs during capsular penetration stage of the prostate [58].

Considering these factors, needle placements still need to be sufficiently accurate to hit the targeted tissue in order for the procedures to be effective. The clinical significance of a tumor is dependent on many factors such as its size, location, and Gleason score. For the purpose of this thesis, we define a clinically significant tumor to be one with a volume of 0.5 cm$^3$ or greater [69], which corresponds to a spherical tumour with a radius of approximately 5 mm. Although tumour shapes can be irregular, this sets an upper limit for needle targeting accuracy. To improve the accuracy
of needle placements, prostate behaviour upon needle insertions need to be studied. The rest of this chapter discusses prostate motion and deformation during transrectal and transperineal needle placement procedures as well as methods attempted to reduce these affects.

3.2 Transrectal Procedures

During transrectal procedures, the prostate shape and position are affected by the presence of imaging probe in the rectum and forces from the needle insertion. In addition, for TRUS-guided procedures, the probe exerts varying pressure on the rectum and prostate while imaging, whereas in MRI-guided procedures, there is time delay between imaging and needle insertion. The following reviews prostate dislocation and deformation under both TRUS and MRI guidance.

Majority of the prostate motion and deformation in TRUS-guided biopsy are caused by the imaging probe (Figure 2.10 a). The prostate moves and deforms as a result of the probe placement inside the rectum and the varying pressure it exerts on the prostate while imaging. It was found that the prostate dislocation is predominately along the transducer probe axis and the majority of the deformation occurs in the peripheral zone (PZ) (Figure 1.1 b) [44].

For motion due to needle insertion in TRUS-guided biopsy, De Silva et al. [82] performed non-rigid registration on data from 9 patients and observed that the mean dislocation as a consequence of needle insertion and tissue acquisition alone is only 0.4 mm. The majority of this occurred lateral to the needle, away from the center of the prostate, and at the needle’s piercing point at the prostate boundary.

The presence of endorectal imaging coil used in MRI-guided transrectal biopsies
3.2. TRANSRECTAL PROCEDURES

Figure 3.2: a) MR image of the prostate without endorectal imaging coil. b) MR image of the prostate with an air-inflated endorectal imaging coil [64]. c) MR image of the prostate with a special endorectal imaging coil on the sheath.

also deforms the prostate (Figure 3.2). However, the coil should ideally be stable after its initial placement and therefore decoupling prostate motions from itself [51]. An exception to this is the device developed by Elhawary et al. [19], where the probe containing the coil is able to move transrectally. In addition, Beyersdorf et al. [6] performed biopsy with an in-vivo device that only used a surface body coil instead of an endorectal probe. Apart from imaging probe issues, there is a long time gap between image acquisition and needle insertion [89], during which prostate motion can occur.

To quantify prostate motion during biopsy under MRI guidance, Xu et al. [109] performed a validation study on an MRI-guided robotic biopsy system developed by Krieger et al. [51]. The paper uses an intensity-based two-step rigid registration followed by a deformable refinement between the pre- and post-needle insertion image volumes to capture prostate motion during the procedure. It was observed that the mean tissue displacement of 90 biopsies was 5.2 mm. The results show that even
though robotic needle placement was accurate, the dislocation of the intended target can still lead to a mean biopsy error of 4.3 mm. To determine whether this movement is related to the needle insertion direction, the displacement was decomposed into two components: one parallel and one orthogonal to the needle vector. It was found that the two were not significantly different from each other.

3.3 Transperineal Procedures

Transperineal prostate procedures are generally performed with the patient under general or lumbar anaesthesia, therefore patient motion in this case is reduced. However, prostate deformation is still present due to needle insertions and tissue acquisitions. In addition, this approach still requires the presence of an imaging probe for prostate visualization, which deforms the anatomy and displaces the prostate. The following discusses effects of transperineal needle insertions on prostate motion and deformation.

Regarding the effects of needle insertion during TRUS-guided LDR brachytherapy, Stone et al. [87] found significant gland deformation and displacement in 19 patients. The medium movement in cranial-caudal, lateral, and anterior-posterior direction was 15 mm, 1.9 mm and 2.6 mm, respectively. Wallner et al. [104] reported up to 10 mm of lateral and cephalad motion for needle insertion during ultrasound and fluoroscopy-guided LDR brachytherapy. Furthermore, anterior displacement occurs when posteriorly placed needles strike the posterior surface tangentially. Lagerburg et al. [53] have shown significant prostate rotation upon needle insertion in the coronal plane using 3D ultrasound. The maximum rotation was 13.8° with a significant correlation between the place of insertion and rotation. In the sagittal plane, the
maximum rotation was 10.2°. Furthermore, only rotation in the coronal plane could be predicted and reduced by the use of locking needles.

The insertion depth of the TRUS probe need to be adjusted to image the prostate from its base to apex during brachytherapy, and therefore deforming the prostate (Figure 3.3). Different types of MRI endorectal imaging coil can also induce various deformations of the prostate. Kim et al. [45] reported that inflatable coils may cause larger distortions (4.1 \( \pm \) 3 mm) in the anterior-posterior direction than rigid coils (1.2 \( \pm \) 2.2 mm).

Intra-operative prostate motion during transperineal MRI-guided prostate biopsy was quantified by Fedorov et al.. Based on 538 images from 40 patients, it was found that the mean prostate centroid motion was 8.7 mm (range: 0.2-34.7 mm).

3.4 Prostate Motion and Deformation Reduction

There are several methods used in clinical practice to reduce prostate motion. However, none of them is capable of completely eliminating motion or deformation. This section lists these motion reduction techniques.
3.4. PROSTATE MOTION AND DEFORMATION REDUCTION

Figure 3.4: a) Parallel stabilization needle configuration. b) Oblique stabilization needle configuration.

3.4.1 Stabilization Needles

Bilateral stabilization (Figure 3.4 and 3.5) needles are sometimes used in brachytherapy to reduce prostate motion, especially in the transverse plane, in order to have more precise seed placement and dose distribution. The stabilizing needles are inserted into the outer left and right side of the prostate prior to therapy and remain throughout the procedure to provide rigidity and support to the organ. However, Taschereau et al. [92] found no effect of parallel stabilization needles in reducing seed misplacement by comparing the results from 10 experimental and 20 control patients.

Feygelman et al. [26] discovered an improved treatment quality using three instead of two stabilizing needles to secure the prostate. Dattoli et al. [17] inserted the stabilizing needles obliquely into the prostate of a patient and the maximum lateral displacement decreased from about 10 mm to 0.2 mm. The motion in cranial-caudal direction also became negligible. In a more recent study, Podder et al. [71] observed 25 brachytherapy patients and found about 24% and 15% reductions in prostate movement when using two 17G and 18G stabilization needles, respectively. Further phantom study by the same group revealed that the oblique configuration of needles
3.4. PROSTATE MOTION AND DEFORMATION REDUCTION

Figure 3.5: a) Different types of stabilization needles. Top: needle with hook extended. Middle: needle with hook retracted. Bottom: diamond tip needle [71]. b) Clinical image of the inserted oblique stabilization needles [27].

was more effective than the parallel configuration, and hooked needles provided more stabilization compared to regular brachytherapy needles [71].

3.4.2 Needle Sizes

Regarding needle sizes, Podder et al. [70] reported a lower insertion force and velocity for 18G needles compared to 17G based on data from 20 brachytherapy patients. Therefore, 18G needles cause less prostate deformation during procedure. However, 17G needles are used for patients with harder prostate due to prior therapies. Some transverse forces were observed on the needles, which were due to the combined effects of lateral forces exerted by the movement of internal organs, heterogeneity of tissues,
presence of template, pre-bending of the needle, and lateral movement of the surgeon’s hand.

3.4.3 Robotic Needle Drivers

Lagerburg et al. [54] developed a new tapping needle insertion method to reduce tissue motion. Prostate displacement due to needle insertion was measured using ultrasound images on video record in 30 patients. A total of 32 needles were manually pushed into the prostate and 29 were tapped with a prototype robotic system. The mean prostate motion in cranial-caudal direction was significantly less when the needle was pushed (5.6 mm) than when the needle was tapped (0.9 mm) into the prostate. Other robotic needle drivers with rotation, oscillation, translation, tapping, or a combination of these techniques have also been proposed but not clinically tested.

3.4.4 Imaging Probe Modification

To address the prostate deformation problem caused by pressure from transrectal imaging probes, devices were built to decouple the probe motion from that of the prostate. Bax et al. [5] developed a passive mechanical arm to provide 3D ultrasound image reconstruction by rotational scanning without distorting the prostate. Clinical trial results from 3 patients have shown in-plane prostate displacements of less than 1 mm during the biopsy procedure. In MRI-guided procedures, Krieger et al. [51] designed a protective sheath to physically separate robot end-effector motion from the prostate.
3.5. INTRA-PROCEDURAL IMAGE REGISTRATION

3.5 Intra-procedural Image Registration

The above findings suggest that pre-treatment images alone may not be sufficiently reliable for accurate needle placement. It is useful to integrate pre- and intra-procedural data to improve the overall targeting accuracy. Although many groups have proposed methods to address the problem, we mainly focus on the ones that have been used in clinical practice. A few other methods that are part of ongoing clinical trials which specifically concentrate on dealing with intra-procedural prostate motion during needle placement are briefly mentioned.

3.5.1 Image fusion between TRUS and MRI

TRUS has real-time imaging capabilities but poor image quality while MRI has superior soft tissue contrast but slow image acquisition speed. Therefore by combining the two, advantages from both imaging modalities can be exploited.

For transrectal biopsy guidance, Xu et al. [114] presented a system that fuses real-time 2D TRUS images with pre-acquired 3D MRI. Singh et al. [83], Pinto et al. [68], and Kadoury et al. [42] all demonstrated the feasibility of this system and showed an increased positive biopsy rate on a cohort of 101 patients. The system uses electromagnetic tracking and intra-procedural image registration to superimpose the MRI data onto the US images. It was shown that the overlap of prostate in MRI and US images was $71 \pm 18\%$ without motion compensation and $90 \pm 7\%$ after motion compensation. Similarly, Cool et al. [13] fused MRI and TRUS by a surface-based non-linear registration incorporating thin-plate splines to provide real-time overlays of suspicious MR lesions onto 3D TRUS. Results of the initial clinical study involving 25 patients demonstrated a significantly higher rate of positive biopsy
cores and a higher Gleason score cancer grading compared to the standard 12-core sextant biopsy. Natarajan et al. [62] incorporated pre-procedural MRI with DCE and DWI for biopsy target selection prior to the fusion with real-time ultrasound. The fusion algorithm consists of segmentation, rigid alignment via anatomical landmarks, surface registration, and elastic interpolation. A 33% positive biopsy rate was found in 47 patients compared to only 7% in systematic biopsy.

Kaplan et al. [43] performed targeted transperineal biopsy in 2 patients by fusing intra-procedural TRUS with pre-procedural MRI. A 3D affine transformation was performed on 6 manually chosen corresponding fiducials on the ultrasound and MR images. The computation took less than 1 second to complete and 7 out of 8 biopsies were found to be positive.

In brachytherapy, Reynier et al. [75] fused real-time ultrasound and pre-procedural MR data of 11 patients during intra-procedural dosimetry planning. The fusion was accomplished by a two-stage surface-based registration, with an initial rigid step followed by elastic registration. Patient trials have shown that this method improves TRUS image segmentation, especially in the apex and base of the prostate, which is important in treatment planning.

Table 3.1 summaries the registration parameters of all ultrasound to MRI fusion methods mentioned in this section.

The following methods concentrate on dealing with intra-procedural prostate motion during needle placement. They have not yet been integrated into clinical practice, but they are all part of ongoing clinical research projects and have been validated on retrospective patient images with promising results.
### 3.5. INTRA-PROCEDURAL IMAGE REGISTRATION

Table 3.1: Registration parameters of different TRUS and MRI fusion methods

<table>
<thead>
<tr>
<th>Author</th>
<th>Application</th>
<th>Similarity Metric</th>
<th>Optimizer</th>
<th>Transform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu [114]</td>
<td>transrectal biopsy</td>
<td>SSD</td>
<td>Gaussian Newton</td>
<td>rigid</td>
</tr>
<tr>
<td>Cool [13]</td>
<td>transrectal biopsy</td>
<td>MI</td>
<td>na</td>
<td>rigid and thin-plate spline</td>
</tr>
<tr>
<td>Natarajan [62]</td>
<td>transrectal biopsy</td>
<td>na</td>
<td>na</td>
<td>rigid and elastic</td>
</tr>
<tr>
<td>Kaplan [43]</td>
<td>transperineal biopsy</td>
<td>SSD</td>
<td>simulated annealing</td>
<td>affine</td>
</tr>
<tr>
<td>Reynier [75]</td>
<td>brachytherapy</td>
<td>SSD variation</td>
<td>Levenberg Marquardt</td>
<td>rigid and elastic</td>
</tr>
</tbody>
</table>

*Abbreviations: SSD = sum of square distance; MI = mutual information; na = not available.*

#### 3.5.2 Ultrasound Image Registration

To improve the targeting accuracy in standard 2D ultrasound guidance, De Silva *et al.* [81] proposed an intensity-based (normalized cross correlation) prostate tracking technique that rigidly registers real-time 2D images with a pre-acquired 3D reference volume. The method was validated using 33 manually identified intrinsic fiducials in 8 subjects and the target registration error was found to be 1.9 mm. Similarly, Baumann *et al.* [4] used a 2D-3D registration approach capable of deformation estimation. It solves the patient motion problem with an a priori model of rectal probe kinematics, and prostate deformations are estimated with rigid and elastic registrations. Correlation coefficient and correlation ratio were used as the similarity metrics for rigid and deformation registration, respectively. The accuracy was evaluated to be $0.8 \pm 0.5$ mm using manually segmented fiducials from 40 patients.

Registration accuracy is affected by the type of method used. Karnik *et al.* [44]
evaluated prostate surface- and image-based 3D-to-3D TRUS registration by measuring the target registration error (TRE) of manually marked, corresponding, intrinsic fiducials in the whole gland and PZ. The study found that image-based registration method yields significantly lower error than the surface-based approach. Since the central region of the PZ moves upward and the lateral lobes bulge downward in response to probe pressure, the PZ had an increased error anisotropy compared to the whole gland.

A comparison between rigid and elastic ultrasound image registration was carried out by Baumann et al. [4] to evaluate the clinical relevance of deformation estimation. It was found that elastic registration improved TRE of rigid registration about at least one third. However, the gland is barely deformed in majority of the volumes that were analyzed. Only about 20% to 30% of volumes have strong deformations that can be observed and reduced with elastic registration. There was also a computation time increase of three to four folds for elastic registration in order to reduce the risk of a missing target by only 10%.

3.5.3 MR Image Registration

To address the prostate motion problem that occurs due to time delay between MRI acquisition and actual needle biopsy, Tadayyon et al. [90] proposed an intra-procedural multi-slice-to-volume registration to compensate for the change. Three orthogonal intra-procedural slices are acquired in the approximate center of the prostate and are registered to a high-resolution target planning volume using mutual information (MI).

Fei et al. [24] investigated the difference between rigid and deformable registration
3.5. **INTRA-PROCEDURAL IMAGE REGISTRATION**

in MR images. The rigid registration uses MI and correlation coefficient as similarity measures at different resolutions. The non-rigid registration is based on independent optimization of many interactively placed control points using MI and thin plate spline transformation. More than 100 registration experiments with 17 MR volume pairs were performed. Both visual and numerical evaluation confirmed that non-rigid registration consistently worked better than rigid body. In addition, results showed that <180 strategically placed points were sufficient to capture the features of prostate deformation. Tadayyon *et al.* [90] also concluded that non-rigid registrations of MRI yield more accurate results, but rigid tracking was sufficient enough in capturing majority of the motion during intervention.

Another study by Brock *et al.* [9] accessed the accuracy, reproducibility and computational performance of different deformable image registration algorithms on MR prostate images. Based on results provided by three different institutions using the same data set, it was found that the linear elastic finite element analysis method achieved the best results but took the longest time to perform. The results are summarized in Table 3.2.

It is worth mentioning that there are extensive research focusing on the registrations between clinical data and prostate models for motion or deformation prediction. These include statistical shape [38], finite element [7], and statistical motion [39] models. Some groups also focus on the registration of pre- and intra-procedural images [65], while others fuse clinical data with histopathology images to identify cancerous regions [56]. However, these methods are not necessarily specific to dealing with intra-procedural prostate motion during needle placement and none have been implemented clinically.
### 3.6 SUMMARY

#### Table 3.2: Deformable registration results of MR prostate images [9]

<table>
<thead>
<tr>
<th>Method</th>
<th>Demons: active force and multi-resolution</th>
<th>Thin plate spline</th>
<th>Linear elastic FEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>0.75-2.3</td>
<td>0.12-5</td>
<td>1.2-22</td>
</tr>
<tr>
<td>Similarity Metric</td>
<td>SSD</td>
<td>surface matching</td>
<td>contour matching</td>
</tr>
<tr>
<td>AVG MAG</td>
<td>7.4 mm</td>
<td>4.3 mm</td>
<td>2.3 mm</td>
</tr>
<tr>
<td>ABS AVG LR</td>
<td>6.2 mm</td>
<td>3.1 mm</td>
<td>2.0 mm</td>
</tr>
<tr>
<td>ABS AVG AP</td>
<td>0.5 mm</td>
<td>3.7 mm</td>
<td>2.0 mm</td>
</tr>
<tr>
<td>ABS AVG SI</td>
<td>1.0 mm</td>
<td>3.2 mm</td>
<td>0.4 mm</td>
</tr>
</tbody>
</table>

*Abbreviations: FEA = finite element analysis; SSD = sum of square distance; AVG = average; MAG = magnitude; ABS = absolute; LR = left-right; AP = anterior-posterior; SI = superior-inferior.*

#### 3.6 Summary

Overall, findings of image-guided needle placement procedures for prostate cancer have shown that there is substantial prostate dislocation and deformation intraoperatively. However, current standard ultrasound-guided procedures do not account for these changes, which result in inaccurate needle placements. Although some studies have been done to improve the basic clinical protocols, ultrasound is still limited in its image quality. In addition, the varying probe pressure exerted on the prostate while imaging makes it difficult to quantify, model, and predict intra-procedural prostate position.

Recent research have moved onto MRI for solutions to these problems. Even though MRI have been used with and without ultrasound in guiding needles into the prostate, it is still at its early stages of research since many questions remain unsolved. Very few studies have quantified prostate motion and deformation for MRI-guided interventions. This information can provide a basis for statistical analysis or modelling and then be used as a reference to predict intra-procedural prostate location upon
needle insertion. Once the prostate movement is predictable, motion compensation
techniques such as tracking and registration between pre and intra-procedural images
can be developed and integrated into the operating room to improve needle targeting
accuracy. In general, algorithms that work well are usually more computationally
expensive. Therefore, knowing how much accuracy can be sacrificed for computation
speed in real time procedures is important.

Another challenge is to find validation methods to test the accuracy and robust-
ness of these intra-procedural registration algorithms. The prostate does not contain
anatomical landmarks such as bones to be used for registration evaluation. As a
result, contours are often used as an assessment. Contouring of the prostate can be
subjective, inconsistent, and difficult especially at the apex and base of the gland.
The question of how accurate the contours need to be for validation or even registra-
tion purposes is still open to discussion. In conclusion, a lot of work has been done in
prostate cancer research over the past decade, yet there is still a lot more that need
to be done in the next decade.
Chapter 4

Accuracy Analysis in MRI-guided Robotic Prostate Biopsy

The material in this chapter has been published as Xu et al. in the International Journal of Computer Assisted Radiology and Surgery (IJCARS) [109]. Preliminary studies of this work were also published in Medical Image Computing and Computer Assisted Intervention (MICCAI) [112], Third Hamlyn Symposium on Medical Robotics [111], Medical Physics [113], and SPIE Medical Imaging 2010 [110], where I was the first author.

4.1 Overview

Purpose: To assess retrospectively the clinical accuracy of an MRI-guided robotic prostate biopsy system that has been used in the U.S. National Cancer Institute for over six years.

Methods: Series of 2D transverse volumetric MR image slices of the prostate both pre (high-resolution T2-weighted) and post (low-resolution) needle insertions were used to evaluate biopsy accuracy. A three-stage registration algorithm consisting
of an initial two-step rigid registration followed by a B-spline deformable alignment was developed to capture prostate motion during biopsy. The target displacement (distance between planned and actual biopsy target), needle placement error (distance from planned biopsy target to needle trajectory), and biopsy error (distance from actual biopsy target to needle trajectory) were calculated as accuracy assessment.

Results: A total of 90 biopsies from 24 patients were studied. The registrations were validated by checking prostate contour alignment using image overlay, and the results were accurate to within 2 mm. The mean target displacement, needle placement error, and clinical biopsy error were 5.2 mm, 2.5 mm, and 4.3 mm, respectively.

Conclusion: The biopsy error reported suggests that quantitative imaging techniques for prostate registration and motion compensation may improve prostate biopsy targeting accuracy.

4.2 Introduction

The superior soft tissue imaging quality of MRI provides clear visualization of the prostate along with its substructures, such as the peripheral zone, where most of cancer occurs [94]. It allows suspicious lesions to be identified so that target specific biopsies can be performed at these sites. MRI-guided biopsy can be performed on patients who have had prior negative outcomes from TRUS-guided biopsy but persistent cancer symptoms such as high levels of prostate specific antigen (PSA). Patients with previously diagnosed cancer can also use MRI guidance for re-biopsying the tumor site to detect if there are any cancer reoccurrence. Due to the limited physical space in conventional closed-bore scanners and the length of the procedure, robotic assistance is often required. Numerous MRI-compatible biopsy systems were developed
4.2. INTRODUCTION

The Access to Prostate Tissue under MRI (APT-MRI) system has been used at the U.S. National Cancer Institute (NCI) for over six years [51] [50] (Figure 4.1). The robot is fixated to the patient table and the end that contains the imaging probe with a built-in needle guide is placed inside the patient transrectally. The device is then calibrated to scanner coordinate system, and diagnostic scans are taken. Next, it is remotely controlled to set the desired needle position and angle for a specific biopsy target. The needle is then advanced into the prostate transrectally through the needle guide to acquire tissue samples for histological analysis.

The prostate movement upon needle insertion can be extremely complex since it can deform and dislocate independently from surrounding structures. In addition, patient movement due to discomfort can further complicate the problem. The current system does not take into consideration of these factors, yet the biopsies still need to be sufficiently accurate to hit the intended target in order not to miss the suspected cancerous tissue. This paper reports a retrospective quantitative evaluation of the biopsy accuracy for the APT-MRI robotic biopsy system. In addition, a detailed prostate motion analysis during biopsy is also provided.
4.2. INTRODUCTION

4.2.1 Related Works

Prostate motion and deformation upon needle insertion have only been studied by a few groups using MR images. Some common approaches include tracking a number of manually identified anatomical landmarks [43] or using surface contours to align the prostate [37] [75]. The accuracy of these feature-based methods depends heavily on the user segmentation, which can be inconsistent especially at the apex and base of the prostate gland. Some groups applied biomechanical models to study the organ geometry and boundary constraints [10] [1] [58], while others chose image-based methods such as rigid or deformable registration using mutual information and correlation coefficient [65] [25]. Biomechanical models also require segmentation and knowledge of material properties, which can be difficult and time consuming. Thus, image-based rigid and deformable registration would be the most suitable for our case. However, due to huge variability in the image quality from the large dataset provided by the NCI, none of the existing method mentioned is capable of accurately determining the transformation between our image pairs with short computation time and little manual interference. We developed an algorithm designed to capture the majority of prostate motion during APT-MRI-guided transrectal biopsy for most of our patient data.

A preliminary study was previously done by our group [112]. This version presents results from a larger data set and includes several major improvements to the original registration framework. These include: image pre-processing, deformable registration and accuracy validation on all dataset instead of a randomly selected small subset, validation using ground truth, more in depth statistical analysis, and major decrease in the amount of manual work.
4.3 Methods

4.3.1 Data Acquisition

The MR images were collected from the U.S. NCI over a period of six years. Although there were variations in the clinical protocol, the following steps were common to all trials. First, a series of 2D high-resolution T2 transverse volumetric image slices covering the whole prostate were acquired with the patient in prone or supine position inside the MRI scanner. From this pre-needle insertion volume, the clinicians select the biopsy target locations in right-anterior-superior (RAS) coordinates, where the origin is approximately the center of the prostate. Once the biopsy target locations are chosen, the APT-MRI device was used to place the biopsy needle transrectally into the prostate to acquire tissue samples. While the needle is still in place, another set of 2D transverse volumetric image slices were obtained to confirm needle placement.

There was an at least 10-minute gap between the diagnostic targeting image acquisition and the biopsy needle confirmation image, during which prostate and patient movement may have occurred. Therefore, to obtain the actual biopsy target location, image registration between the pre and post needle insertion volumes need to be performed to account for rigid motion and deformation during the procedure. The resulting transformation from the registration can then be applied to the planned biopsy target to locate its coordinates in the post needle insertion volume.

4.3.2 Image Registration

Developing a registration algorithm to capture the prostate motion and deformation for the majority of the images in the dataset was a difficult task. The images were collected over the past 6 years from different clinical trials, using different imaging
protocols on different scanners, by different clinicians, with several versions of the APT-MRI device. Therefore, there are large variations among the images, including resolution, artifacts etc. In addition, the complex prostate movement and deformation due to needle insertion along with patient motion during the procedure further complicate the task. The extent of these motions and deformations also varies from patient to patient. Nonetheless, a computation method that is suitable for most of the cases is needed for retrospective biopsy accuracy analysis. The rest of this section describes our implementation details.

The data used for registration and biopsy accuracy evaluation are the sets of 2D transverse volumetric image slices of the prostate pre and post needle insertion. The MR images were first pre-processed to decrease intensity non-uniformity in homogeneous tissue regions using N4ITK (Nicks N3 Insight Toolkit) implementation for MRI bias field correction [99]. This method does not require expert supervision, user interaction or training, and only has a few user-defined parameters. The two most important parameters are bias full width at half maximum (BWHM) and noise. BWHM defines the Gaussian that estimates the bias field, and noise specifies the Wiener filter used for field estimation. By experimentation, it was found that BWHM at 0.5 and noise at 0.01 worked the best for most of our clinical images. The remaining few images had better results with a noise of 0.1. Other parameters had a much smaller influence on the bias correction results.

After pre-processing, a three-stage volume-to-volume registration procedure was developed using ITK [115] to determine the transformation between the pre and post needle insertion volumes. This captures the prostate movement, including both dislocation and deformation during biopsy (Figure 4.2). The procedure starts with
4.3. METHODS

a simple rigid registration of the entire image volume to compensate for prostate motion in coherence with the biopsy device and patient. Next, another rigid step was performed using only the prostate as the region of interest (ROI) to correct for residual decoupled prostate motion. Finally, a B-spline deformable registration with a grid size of $5 \times 5 \times 5$ was used to fine-tune the alignment and to adjust for tissue deformation that occurred during the procedure. The whole registration process is fully automatic after the initial user selection of the rectangular prism prostate ROI on the fixed image by specifying the starting position and size.

Due to the aforementioned large differences in our images, mutual information was chosen to be the similarity metric. The mutual information metric has a distinctive property that it does not require a known mapping function between the intensities of different images, but only assume the existence of a probabilistic relationship. Mutual information ($I$) is the amount of information that one can obtain about a random variable ($X$) by observing another random variable ($Y$). The random variables in this case are the image intensities. Mutual information can be expressed by the following equations:

$$I(X, Y) = H(X) + H(Y) - H(X, Y) \quad (4.1)$$

$$I(X, Y) = H(X) - H(X|Y) = H(Y) - H(Y|X) \quad (4.2)$$

$$I(x, y) = \sum_{y \in Y} \sum_{x \in X} p(x, y) \log \left( \frac{p(x, y)}{p(x)p(y)} \right) \quad (4.3)$$

where $H(X)$ and $H(Y)$ are the marginal entropies of $X$ and $Y$ respectively, and $H(X, Y)$ is their joint entropy. $H(X|Y)$ is the conditional entropy of $X$ given $Y$, and $H(Y|X)$ is the conditional entropy of $Y$ given $X$. The joint probability density of
Figure 4.2: Workflow of the three-stage registration algorithm between the pre- and post-needle insertion volumes using mutual information.

$\mathbf{X}, \mathbf{Y}$ is denoted as $p(x, y)$, and the marginal probability densities are $p(x)$ and $p(y)$.

Furthermore, our implementation involved a variant of the gradient descent optimizer for versor rigid 3D transform, and a L-BFGS-B (Limited-memory Broyden-Fletcher-Goldfarb-Shannon with simple bounds) optimizer for the deformable component.

### 4.3.3 Registration Validation

In the clinical MR images, the exact correspondence of the prostate anatomy cannot be identified easily. In addition, prostate movement can be decoupled from surrounding organs and bony structures. Therefore, typical validation methods such as using landmarks to evaluate the registration accuracy are not applicable in our case. To validate our registration algorithm, we first generated simulated image volumes by applying known transformations (ground truth) to an existing image volume. The ground truth values were chosen based on observations of prostate dislocation from
the images and prior expert knowledge. It was found that a range of ± 20 mm translation and ± 10° rotation along each of the three axes was large enough to cover majority of the prostate motion during biopsy. The target displacement differences between the ground truths and recovered transformations generated by the algorithm from registering simulated volumes with the original volume was calculated.

We then proceeded to validate the algorithm on actual clinical image pairs by performing image overlays and evaluating the prostate contour alignment between the resulting volumes with its corresponding fixed volume. The contours were also confirmed with the radiologists involved in this study. This process was done in 3D Slicer [67], a free open source software package for visualization and image analysis. All of the images in the dataset were verified for its registration accuracy based on the image overlay method. If the maximum contour misalignment (measured using the RAS physical space feature in 3D Slicer) after the proposed three-stage registration is over 2 mm, then manual registrations were performed. We set the 2 mm standard for registration accuracy because the MR image spacing of the slices is 3 mm, and therefore it can ensure the correct alignment of the image slices within the volumes.

4.3.4 Biopsy Accuracy Analysis

To evaluate quantitatively and analyze the biopsy accuracy, we defined and studied the following three terms (Figure 4.3):

- **Target displacement**: the distance between planned (pre-needle insertion) and actual (post-needle insertion) biopsy target. The actual target location was obtained by applying the transformation from the registration algorithm to the planned target (therefore it is dependent on the registration accuracy). To
determine whether this dislocation is the same as the needle insertion direction, the displacement was decomposed into two components: one parallel and one orthogonal to the needle vector (Figure 4.4). A Wilcoxon signed rank test (non-parametric test for paired samples) was conducted to see whether target movement in the needle direction was significantly higher than the orthogonal direction.

- **Needle placement error**: the distance from the planned biopsy target to the biopsy needle trajectory line. This distance indicates how much the robot had missed the intended target, assuming no prostate motion during the biopsy procedure. The needle trajectory line was obtained using two needle tip coordinates from the post-insertion volume. Commonly used titanium needles are not directly visible in MRI, but they generate an artifact in the immediate neighborhood of the needle. Therefore, the true needle position may differ from the artifact position. However, in this particular case, the needle artifact errors are significantly smaller than the errors due to patient motion and tissue deformation [77].

- **Biopsy error**: the distance from the actual biopsy target to the needle trajectory line. This is the most relevant metric for assessing biopsy accuracy, since the length of the tissue core excised by the needle is about 20 mm long; hence target movement orthogonal to the needle trajectory is of our main concern. To further study the orthogonal component of the displacement, it was separated into RAS coordinates and principle component analysis (PCA) was performed on the data.
4.3. METHODS

Figure 4.3: Illustration of the prostate dislocation during needle insertion and the parameters used in biopsy accuracy analysis.

Figure 4.4: The decomposition of target displacement into parallel and orthogonal component.
4.4 Results

4.4.1 Registration Accuracy

The patient data selection for this study simply requires available planning and needle confirmation image volumes along with the corresponding planned biopsy target coordinates. A total of 90 image sets from 24 patients were studied.

The accuracy of the registration procedure was studied in order to provide a bound on biopsy accuracy evaluation. Images from 5 randomly selected patients were each transformed by a different ground truth. The target displacement differences between all of the ground truth and the recovered transformations from the algorithm were less than 1.0 mm, which demonstrates the correctness of the method to recover prostate dislocation using simulated images. The actual clinical image pairs are quite different from the simulated images since they were acquired with different imaging sequences. Therefore, further testings with simulated images are not necessary.

The registration results from all 90 clinical image pairs were validated using the previously discussed image overlay approach. Majority of the images registered well (accurate to within 2 mm based on contour evaluations), and only a small subset (22%) were over the 2 mm error. The inaccuracy from the automatic registration was mainly due to poor image quality, such as the existence of large glares around the endorectal coil that the bias correction was not able to recover. After manual adjustments for these images, all registrations were accurate to within 2 mm. In this study, all of the contour alignments were verified by the same person. However, it is important to note that there are some intra-observer variability in prostate contouring [84]. Figure 4.5 shows an example of the prostate contour overlay before and after the automatic registration. The signed rank test has shown that the results from rigid
4.4. RESULTS

Figure 4.5: Prostate contour overlays before (left) and after (right) the automatic registration.

and deformable registrations were significantly different ($p = 4.6 \times 10^{-4}$). However, rigid registrations recovered the majority (88%) of the target displacement.

As part of our validation process, we also manually registered the rectum and pubic bone from some of the images separately to verify if patient and robotic device motion were different from that of the prostate. We chose to estimate patient motion by measuring the displacement of the pubic bone, and robotic motion by the displacement of the rectum, since it contains the endorectal imaging probe of the biopsy device. We found that the prostate motion was different from its surrounding structures, and it was more similar to the bone motion than the rectum motion. This confirmed our assumption that prostate motion does differ from its surrounding structures even though it can be affected by them, and this should be taken into consideration when performing registration.
4.4. RESULTS

4.4.2 Biopsy Accuracy

The mean, range, and standard deviation for target displacement, needle placement error, and biopsy error are summarized in Table 4.1. The histograms of these measurements for all 90 biopsies are shown in Figure 4.6 a-c. Furthermore, target displacements in RAS coordinates are plotted in Figure 4.6 d-f. Lilliefors normality tests (for unknown distribution mean and variance of small samples) were conducted and it was found that none of the target displacements, needle placement errors, and biopsy errors are normally distributed.

The parallel (mean 3.1 mm) and orthogonal (mean 3.6 mm) component of the displacement to the needle trajectory was computed and found to be not statistically different ($p = 0.3$) from one another, based on a signed rank test. For the parallel component, only 32% of the targets moved toward the needle insertion direction (mean 2.8 mm), and the rest 68% went in the opposite direction (mean 3.3 mm). Since the biopsy tissue core is about 20 mm in length, it was still able to excise the tissue that had displaced in the direction that is parallel to the needle. A PCA was performed on the orthogonal component in RAS coordinates. The resulting first two principal components ([1, 0.1, -0.1] and [-0.2, 0.9, -0.4]) accounted for 96% of the data variance.

To study the effect of patient movement on biopsy accuracy, 22 biopsies that contained lateral patient motion (determined by visual inspection of the displacement of rectum and pubic bone in 3D Slicer) greater than 5 mm were grouped separately. Motions larger than 5 mm were suspected to be caused by involuntary patient movements such as pelvis movement or reflexive muscle clenching due to discomfort, which is in nature different from prostate dislocation and deformation caused by the needle.
Figure 4.6: Left: Histograms of target displacement (top), needle placement errors (middle), and biopsy errors (bottom) of the 90 biopsies. Right: Transverse (top), sagittal (middle), and coronal (bottom) view of the prostate target displacement. '*' and '.' represent biopsies on the left and right prostate lobes, respectively.
Table 4.1: Data statistics for accessing biopsy accuracy

<table>
<thead>
<tr>
<th></th>
<th>Target Displacement (mm)</th>
<th>Needle Placement Error (mm)</th>
<th>Biopsy Error (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.2</td>
<td>2.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Range</td>
<td>0.9-18</td>
<td>0.1-10.7</td>
<td>0.2-12</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>3.5</td>
<td>1.6</td>
<td>2.9</td>
</tr>
</tbody>
</table>

* Biopsies without the patient movement >5 mm group. ** Biopsies only for patient movement >5 mm group.

The results for these 22 biopsies alone and the rest of the 68 biopsies are listed in Table 4.1. The large patient motion caused a 2.1 mm increase in the mean biopsy error. Biopsies performed at the left and right side of the prostate were also analyzed separately. Results show that 43% of right biopsies had a prostate displacement towards right, and 61% of left biopsies had displacement toward left. This is because the clinicians may have introduced a systematic bias by always using the beveled tip needles in the same orientation.

4.5 Discussion

The results from our three-stage registration algorithm allowed for quantitative evaluation of the targeting accuracy for the APT-MRI system as well as prostate motion analysis during biopsy. A clinically significant tumor has a minimum volume of 0.5 cm$^3$ [69], which corresponds to a sphere with a radius of approximately 5 mm. Therefore, the maximum error should be less than 5 mm to not miss the targeted region. The targeting accuracy of the APT-MRI system is considered to be acceptable, since the mean of its needle placement error is 2.5 mm (Table 4.1). This implies that the
robotic device was accurate enough to place the needle at the intended biopsy target assuming no prostate movement during the procedure. However, the prostate did dislocate and deform upon needle insertion. Based on the 90 biopsy cases used in this study, the mean prostate displacement was over 5 mm. This resulted in a mean biopsy error of 4.3 mm. Furthermore, 28% of the biopsies have an error greater than 5 mm, and this error is higher for cases with large patient motion (Table 4.1). To monitor for gross and sudden changes to the prostate location due to patient motion, real-time tracking by plane-to-volume registrations can be used [90].

The biopsy needle was inserted approximately in the superior-anterior direction towards the prostate. However, statistical test indicated that only half of the prostate dislocation was in this direction. The majority of the variance from the other half can be captured by the first two eigenvectors from PCA of the orthogonal component of the displacement. This implies that the component of prostate dislocations that caused the majority of the biopsy errors can be defined by a plane with vectors [1, 0.1, -0.1] and [-0.2, 0.9, -0.4]. It is important to note that the biopsy needles have a beveled tip, which can also have an effect on the biopsy target dislocation.

The separate registrations of prostate, rectum, and pubic bone indicated that the prostate was capable of moving independently of its surrounding structures. This confirms with our assumption, and further validates our muti-step registration approach that uses both the entire image and only the prostate as ROI. The reason why its movement was more similar to the pubic bone may be due to the transrectal robotic device limiting rectum movement when the patient moves. The registration results also have shown that even though the majority of prostate motion during biopsy is
rigid, there was also a significant amount of deformation caused by the needle insertion process. Therefore, to track the precise target location during biopsy, deformable registration is recommended in addition to rigid registration.

In conclusion, a retrospective accuracy analysis of an MRI-guided robotic prostate biopsy system [51] [50] was performed on 90 image sets by using a three-stage registration procedure to capture prostate motion during biopsy. The volumetric and soft tissue imaging capabilities of MRI enabled us to identify the needle location in relation to the prostate anatomy. In addition, the registration results allowed for quantitative characterization of prostate dislocation and deformation during transrectal biopsy. It was found that majority of the prostate motion during the procedure were rigid, but there were also a significant amount of deformation during the process. Furthermore, the prostate moved differently from its surrounding structures. The exact amount of this motion and deformation cannot be determined without fiducials or finer volume images. However, even taking into account of the imperfections of our validation framework, the results demonstrate that there is a substantial amount of biopsy errors that should not be ignored. Further research on prostate motion and deformation upon needle insertion should be conducted to facilitate the development of motion compensation techniques, which can be incorporated into the clinical protocol to increase biopsy accuracy.
Chapter 5

Target Localization in MRI-guided Transperineal Prostate Biopsy using Multi-Slice-to-Volume Registration

At the time of writing this thesis, this chapter was prepared for journal submission.

5.1 Overview

Prostate needle biopsy is a commonly performed procedure since it is the most definitive form of cancer diagnosis. Magnetic resonance imaging (MRI) allows target-specific biopsies to be performed. However, needle placements are often inaccurate due to intra-operative prostate motion and the lack of motion compensation techniques.

Purpose: To detect and determine the extent of tissue dislocation during an MRI-guided biopsy so that the needle insertion plan can be adjusted accordingly.

Method: A multi-slice-to-volume registration algorithm was developed to align the pre-operative planning image volume with three intra-operative orthogonal image slices of the prostate acquired immediately before needle insertion. The algorithm
consists of an initial rigid transformation followed by a deformable step.

Results: A total of 14 image sets from 10 patients were studied. Based on prostate contour alignment, the registrations were accurate to within 2 mm.

Conclusion: This algorithm can be used to increase the needle targeting accuracy by alerting the clinician if the biopsy target has moved significantly prior to needle insertion. The proposed method demonstrated feasibility of intra-operative target localization and motion compensation for MRI-guided prostate biopsy.

5.2 Introduction

Current clinical biopsy protocols do not take into consideration of possible intra-operative prostate motion and deformation during the procedure due to both patient movement and mechanical forces exerted by the biopsy system. The prostate is a soft tissue organ attached only by connective tissues. Therefore, it can shift, rotate, and deform differently from the surrounding structures. Biomechanical modeling of the organ behaviour during biopsy is extremely complex since its parameters and material properties can vary between patients. Our previous study [22] found a mean prostate centroid motion of 8.7 mm (range: 0.2-34.7 mm) during MRI-guided transperineal biopsies based on 538 images. Xu et al. [109] reported a mean prostate displacement of 5.2 mm (range: 0.9-18 mm) for 90 needle insertions in MRI-guided transrectal biopsy, and 28% of the biopsy errors exceeded 5 mm, which corresponds to the radius of a clinically significant tumor (0.5 cc) [69].

Intra-operative prostate motion and deformation can cause inaccurate needle placement during biopsy [109]. As a result, malignant tumors can be missed, which in turn will lead to an increased number of repeated biopsies and delaying of treatment.
Therefore, it is important to incorporate motion tracking techniques into the clinical procedure in order to improve the overall needle targeting accuracy.

The ultimate goal would be to track both the intended biopsy target and the needle in real-time. However, as the first step, we focus on estimating the target position and developing a motion detection method to warn the clinician if there is large dislocation of the intended biopsy target prior to needle insertion. If possible, the clinician can then adjust the needle insertion plan to compensate for this motion. Otherwise, a new planning scan can be acquired, and the insertion plan can be made based on this new image. Such methods need to be integrated into imaging protocols available on any regular MRI scanner. Since volumetric MRI (multi-slice 2D imaging series) acquisition typically takes around a minute, methods that require multiple of these image series to locate the biopsy targets are not ideal. As an alternative, intermittent acquisition of only a few image slices can be used to obtain the required information of a full image volume. This process takes considerably less time, since a single image slice can usually be obtained in only a few seconds.

5.2.1 Related Works

There are numerous methods developed for tracking the prostate during biopsy. However, most of these methods use ultrasound images or focus on ultrasound and MRI fusion. In the context of MR image-based prostate registration using multiple image slices, there are three closely relevant papers by Fei et al. [23], Gill et al. [34], and Tadayyon et al. [90].

Fei et al. developed a single-slice-to-volume rigid registration algorithm for radio-frequency thermal ablation of prostate cancer. The pre-operative image volumes and
intra-operative image slices in transverse, sagittal, and coronal planes were acquired from 3 volunteers using a conventional 1.5T scanner and a clinical 0.2T C-arm open MRI scanner, respectively. The image slices from each volunteer were individually registered to the corresponding MRI volumes. A total of 450 registrations were performed and it was found that images in the transverse orientation produced the best results based on comparison with volume-to-volume registration. The algorithm used two similarity metrics and featured a multi-resolution approach with an automatic restart. The restart applied a random perturbation to the last transformation parameters found by the registration in order to escape the potential local optima of the cost function.

Gill et al. addressed the problem of local extremes and the inefficiency in Fei’s optimization. The need for restarting the registration was eliminated by using a multi-resolution registration based on a region of interest. Due to insufficient information from a single transverse image slice, Gill’s implementation incorporated a simulated sagittal slice centered at the prostate to improve the registration result.

Both studies mentioned above do not take into consideration of prostate deformation, which is a known issue during biopsy. Tadayyon et al. proposed a non-rigid method to account for prostate deformation in addition to rigid motion. The algorithm can handle multiple image slices with different orientations all at once without using the multi-resolution scheme. Simulated intra-operative image slices were pasted into an empty volume (sparse volume construction) and 3D-to-3D image-based registration were performed. The study showed that three image slices in the transverse, sagittal, and coronal plane were sufficient enough to be used for image registration purposes. It is important to note that this exploratory study only used simulated
image slices based on the high resolution image volume. Real clinical intra-operative image slices can be quite different to these simulated images since a different imaging protocol is often used. Furthermore, the mean execution time for the registrations was over 16 minutes, which is not clinically practical.

This chapter reports a multi-slice-to-volume deformable registration method that aligns the pre-operative planning image volume with three intra-operative orthogonal image slices acquired immediately before needle insertion. The method was tested on clinical images provided by Brigham and Women’s Hospital (BWH) in Boston, MA, United States. We present several major improvements to Tadayyon’s work. These include:

- Method validation on actual clinical data instead of just simulated images
- Ability to handle image slices in any orientation rather than just transverse, sagittal, and coronal
- Elimination of the sparse volume construction step, and register the image slices directly to the planning volume without any resampling
- Improved method validation techniques
- Region of interest is no longer needed in the rigid step
- Incorporation of image pre-processing for MRI bias field correction

The remainder of this paper presents the detailed methodology and validation of our multi-slice-volume registration using clinical images from MRI-guided transperineal prostate biopsy.
5.3 Methods

The objective is to detect cases where large intra-operative motion is present prior to needle insertion so that either modifications of the original biopsy plan can be made (compensating for the motion) or re-acquisition of the planning volume can be performed to compensate for the target dislocation. By registering the intra-operative orthogonal image slices with the pre-operative planning volume, the existence of prostate motion and deformation can be determined.

5.3.1 Image Acquisition

A custom setup and software was developed at BWH to perform MRI-guided transperineal biopsy without moving the patient out of the scanner [98]. The setup consists of a specially designed tabletop and a needle guiding template that gives clinicians access to the perineum of the patient at the imaging position.

The remainder of this section describes the portion of the clinical protocol that is relevant to the acquisition of the images used in this study. First, the patients were sedated and immobilized on the table top with velcro wraps. Then they were placed into a wide bore Siemens Magnetom Verio 3T scanner in supine position, and a 4-minute T2-weighted multi-slice 2D transverse imaging series covering the whole prostate gland were taken with the turbo spin-echo (TSE) sequence. This was used as the pre-operative planning volume where potential biopsy targets in scanner coordinate system were selected by the clinicians. Immediately before the needle insertion, a quick 18-second scan of 3 orthogonal image slices in the transverse, sagittal, and coronal plane were collected at approximate center of the prostate with half-Fourier acquisition single-shot turbo spin-echo (HASTE) localizer sequence. The
clinicians then proceeded with the needle placement. Finally, another multi-slice transverse T2-weighted sequence (1-minute scan) were acquired with the needles in place to confirm its placement. Figure 5.1 illustrates the overall clinical workflow.

The process starting from the initial acquisition of the pre-operative planning volume to the final needle confirmation image takes an average of 90 minutes. During this time, intra-operative motion of the prostate may occur. If this motion is large, then the biopsy target locations that were chosen based on the pre-operative planning volume would no longer be valid.
5.3. METHODS

5.3.2 Image Registration

The images used in the multi-slice-to-volume registration were the pre-operative planning T2-weighted volume (multi-slice 2D transverse image series) and the intra-operative orthogonal image slices. All images were first pre-processed to correct for nonuniform intensity caused by field inhomogeneities. Since the biopsy procedure at BWH did not include the use of an endorectal coil, the pre-processing step does not have a large effect on their images. However, this step is included in the algorithm so that it can be applied to a broader range of images which are taken with the endorectal probe. N4ITK (Nicks N3 Insight Toolkit) implementation for MRI bias field correction [99] was used because it does not require expert supervision, user interaction, or training, and only has a few user-defined parameters. The two most important parameters are bias full width at half maximum (BWHM) and noise. BWHM defines the Gaussian that estimates the bias field, and noise specifies the Wiener filter used for field estimation. Values of 0.5 for BWHM and 0.01 for noise were found to work the best with our clinical images.

After bias field correction, a multi-slice-to-volume registration algorithm (Figure 5.2) was developed using ITK [115] to determine the transformation between the pre-operative planning volume (\(V\)) and intra-operative orthogonal image slices (\(S\)) acquired just prior to needle insertion. The fixed and moving images of the registration were \(S\) and \(V\), respectively. Due to imaging protocol differences, the same tissue structures have different intensities on the fixed and moving images. Therefore, mutual information was chosen as the metric for evaluating image alignment instead of metrics such as cross correlation that uses direct comparison of pixel intensities. Since each of the three orthogonal image slices needs to be registered to the planning
5.3. METHODS

volume, the mutual information metric was modified so that it calculates the sum of these three metrics.

The algorithm consists of an initial rigid registration using the entire image to correct for gross prostate motion in coherence with the device and patient. To recover tissue deformation, a B-spline deformable registration with grid size of $5 \times 5 \times 5$ was performed using only the prostate as the region of interest. The B-spline transform is able to represent a typical prostate deformation. In addition, it is fast to compute, and the number of grid points and its maximum dislocation can be used to keep the deformation field under control during registration. A gradient descent optimizer was implemented for the versor rigid 3D transform, and an L-BFGS-B (Limited-memory Broyden-Fletcher-Goldfarb-Shannon with simple bounds) optimizer was used for the deformable component. The detailed workflow is shown in Figure 5.2. The entire process is fully automatic after the initial user selection of the rectangular prism prostate ROI on the fixed image by specifying the starting position and size. One of the main implementation challenges was to tune a set of registration parameters that would work the best for our imaging sequence. These parameters were chosen based on both speed and accuracy of the registration result.

5.3.3 Registration Validation

Experiment 1 - Simulated Images

To validate the accuracy of rigid registration, we first simulated intra-operative orthogonal image slices from the pre-operative planning volume. Three empty image slices in transverse, sagittal, and coronal plane were created, and the pixel information from the planning volume were resampled into the slices. These simulated images
Figure 5.2: Workflow of the multi-slice-to-volume registration between the pre-operative planning volume and intra-operative image slices.

were then registered back to the planning volume with a random initial transform that was set to a range of \( \pm 20 \) mm translation and \( \pm 10^\circ \) rotation along each of the three axes. If the rigid registration works properly, it should correct for this initial misalignment and produce a transformation matrix that is close to the identity. Five points in the center, left, right, top, and bottom of the prostate (Figure 5.3) were chosen on the fixed images, and its target registration error (TRE) were calculated. The TRE was defined as the distance between one of the chosen points and its reconstructed point. The process was repeated 5 times for each of the 11 planning images we have, and all of the TREs with its corresponding initial misalignment were recorded.
The accuracy of deformable registration was also tested using simulated intra-operative orthogonal image slices. We selected two corresponding sets of five points on the planning volume. The second set of points were randomly displaced $\pm 5$ mm in plane from the first set. A Landwarp landmark deformable registration by Plastimatch was performed in 3D Slicer [67], a free open source software package for visualization and image analysis. The planning volume was warped based on the displacements of the two point sets using thin-plate spline transform and radial basis functions [79]. The reason we chose to warp the planning volume instead of the image slices is simply because the Landwarp landmark deformable registration works better with volumetric images. The three orthogonal image slices were then generated using the warped volume, and were registered to back to the original planning volume using the B-spline deformable algorithm that we developed. The displacement vectors of the five points were computed and compared with the ground truth. The process was repeated once for each of the 11 planning images, and all TREs were calculated and recorded as an accuracy assessment.

The numerical ranges for the ground truth initial rigid misalignment and warping were chosen based on our previous study of prostate motion during MRI-guided biopsy [109]. It was found that the majority (88%) of the intra-operative motion were rigid and the amount of tissue deformation was small (mean: 0.7 mm, max: 4.9 mm).
5.3. METHODS

Therefore, a range of ± 20 mm translation and ± 10° rotation along each of the three axes, and ± 5 mm control points displacement for image warping are large enough to cover most of the intra-operative prostate behaviour.

Experiment 2 - Clinical Images

For the clinical images, a different validation method was applied since the exact correspondence of the prostate anatomy (calcifications or tissue morphology) between different images cannot be easily identified. The fixed and moving images were overlaid in 3D Slicer before and after registration, and the prostate contour alignment were examined. After the contour alignment validation, the transformations produced by the algorithm were used as the ground truth. The above validation procedures used on simulated images were repeated on the actual clinical images to test the robustness of the registration.

Experiment 3 - Multi-slice-to-volume vs. Volume-to-volume

To determine whether the multi-slice-to-volume registration is sufficient in capturing prostate motion intra-operatively, we compared it with volume-to-volume registration. Since volumetric images contain much more information than the three orthogonal slices, its registration results can be used as a reference to evaluate the accuracy of the multi-slice-to-volume registration. The needle confirmation image volume (Figure 5.1) for each biopsy was registered with its corresponding planning volume using an initial rigid alignment of the whole image, followed by a B-spline deformable transform with only the prostate as region of interest. This is similar to what Xu et al. [109] proposed for the registration of pre- and post-needle insertion volumetric MRIs for transrectal
Table 5.1: Registration validation experiments summary

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Registration</th>
<th>Fixed Image(s)</th>
<th>Moving Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Rigid, MSV</td>
<td>3 orthogonal slices resampled from planning volume</td>
<td>Planning volume</td>
</tr>
<tr>
<td>1b</td>
<td>Deformable, MSV</td>
<td>3 orthogonal slices resampled from warped planning volume</td>
<td>Planning volume</td>
</tr>
<tr>
<td>2a</td>
<td>Rigid, MSV</td>
<td>3 orthogonal slices</td>
<td>Planning volume</td>
</tr>
<tr>
<td>2b</td>
<td>Rigid+ deformable, MSV</td>
<td>3 orthogonal slices</td>
<td>Warped planning volume</td>
</tr>
<tr>
<td>3a</td>
<td>Rigid+ deformable, MSV</td>
<td>3 orthogonal slices resampled from needle confirmation volume</td>
<td>Planning volume</td>
</tr>
<tr>
<td>3b</td>
<td>Rigid+ deformable, VV</td>
<td>needle confirmation volume</td>
<td>Planning volume</td>
</tr>
</tbody>
</table>

Abbreviations: Exp. = Experiment; MSV = Multi-Slice-to-Volume; VV = Volume-to-Volume.

prostate biopsy. The results were compared to the multi-slice-to-volume registration between the planning volume and simulated intra-operative orthogonal images slices generated from the needle confirmation volume. The 5 points on the prostate (Figure 5.3) were selected on the fixed (needle confirmation) images, and were transformed by the results obtained from both registrations separately. The distances between target reconstructions from volume-to-volume registration and multi-slice-to-volume registration were also calculated.

Table 5.1 summarizes all of the images and methods used for these three registration validation experiments.
5.4. RESULTS

Figure 5.4: Examples of clinical image prostate contour overlay in the transverse plane. Each of the three images are copies of the same fixed image overlaid with the contours from the moving image a) before registration, b) after rigid registration, c) after deformable registration.

5.4 Results

A total of 14 planning volume and orthogonal image slices pairs from 10 patients were obtained from the Brigham and Women's Hospital and were used in our study.

All resulting images after the multi-slice-to-volume registration were overlaid with their corresponding fixed images in 3D Slicer. Based on prostate contour evaluations, the misalignments were all under 2 mm (measured using the RAS physical space feature in 3D Slicer). An example of the image overlay before and after registration of the clinical image pairs is shown in Figure 5.4. The contours are all verified with radiologists involved in the project. Even taking into account of the intraobserver variability in the contouring [84], the registration is still considered to be fairly accurate.

The mean execution time for rigid and deformable registrations were 3.3 and 31 seconds, respectively, on an Intel Core i7-2600K processor running at 3.40GHz. This is summarized in Table 5.2. Furthermore, the N4ITK bias field correction only takes
Table 5.2: Summary of execution time statistics for multi-slice-to-volume registration with clinical images

<table>
<thead>
<tr>
<th></th>
<th>Rigid</th>
<th>Deformable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>3.3 sec</td>
<td>31 sec</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>2.5-4.2 sec</td>
<td>13.7-68.1 sec</td>
</tr>
<tr>
<td><strong>Standard deviation</strong></td>
<td>0.6 sec</td>
<td>14.8 sec</td>
</tr>
</tbody>
</table>

Table 5.3: Gradient descent optimizer parameters for the rigid registration step.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max step length</td>
<td>2</td>
</tr>
<tr>
<td>Max step length</td>
<td>0.01</td>
</tr>
<tr>
<td>Relaxation factor</td>
<td>0.9</td>
</tr>
<tr>
<td>Max number of iterations</td>
<td>250</td>
</tr>
</tbody>
</table>

less than 2 seconds to complete, and therefore does not have a major impact on the overall computation time.

The difference between rigid and deformable registrations was studied. The results were significantly different ($p = 7.0 \times 10^{-10}$), but rigid registration was able to recover 95% of the total prostate displacement on average.

Values of the optimizer parameters for both rigid and deformable steps are listed in Table 5.3 and Table 5.4, respectively. For rigid registration, a variation of the gradient descent optimizer was used. The maximum step length and relaxation factor define the convergence rate and robustness of the algorithm. The minimum step length and maximum number of iterations specify the stopping conditions. In the deformable step, L-BFGS-B was used as the optimizer. The bounds parameter sets the maximum amount of allowed deformation, while maximum number of corrections is used for updating the limited memory Hessian matrix. Convergence factor, projected gradient tolerance, and maximum number of iterations are the terminating conditions. Their values were chosen based on both speed and accuracy of the results.
5.4. RESULTS

Table 5.4: L-BFGS-B optimizer parameters for the deformable registration step.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convergence factor</td>
<td>$1 \times 10^{12}$</td>
</tr>
<tr>
<td>Projected gradient tolerance</td>
<td>$1 \times 10^{-7}$</td>
</tr>
<tr>
<td>Number of corrections</td>
<td>10</td>
</tr>
<tr>
<td>Max number of iterations</td>
<td>250</td>
</tr>
<tr>
<td>Upper and lower bound</td>
<td>$\pm 5$</td>
</tr>
</tbody>
</table>

Table 5.5: TRE statistics for Experiment 1a: multi-slice-to-volume rigid registration between the planning volume and simulated intra-operative orthogonal image slices. The simulated images were undistorted (no deformation was applied).

<table>
<thead>
<tr>
<th>Rigid Registration TRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Standard deviation</td>
</tr>
</tbody>
</table>

5.4.1 Registration Validation

Experiment 1 - Simulated Images

The accuracy of both rigid and deformable registrations were studied separately using simulated intra-operative orthogonal image slices. For rigid registration, a mean TRE of 0.1 mm was found. All TREs from 55 simulations are shown in Figure 5.5, and Table 5.5 provides a summary of the TRE statistics for the rigid step. For the deformable part of the algorithm, the mean TRE was 0.5 mm. This is summarized in Table 5.6. Figure 5.6 shows all TREs from the 11 experiments and their corresponding initial misalignments. The prostate contour alignment before and after deformable registration using the simulated images are shown in Figure 5.7.
5.4. RESULTS

Figure 5.5: TREs for Experiment 1a: the 55 multi-slice-to-volume rigid registrations using simulated images. The simulated images were undistorted (no deformation was applied). A random initial transform of $\pm 20$ mm translation and $\pm 10^\circ$ rotation along each axis were set to the registrations. The distance between the initial target and the ground truth target was defined as the initial misalignment.

Table 5.6: TRE statistics for Experiment 1b: multi-slice-to-volume deformable registration between the planning volume and simulated intra-operative orthogonal image slices

<table>
<thead>
<tr>
<th>Deformable Registration TRE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.5 mm</td>
</tr>
<tr>
<td>Range</td>
<td>0-1.6 mm</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.4 mm</td>
</tr>
</tbody>
</table>
5.4. RESULTS

Figure 5.6: TREs for Experiment 1b: the 11 multi-slice-to-volume deformable registrations using simulated images. The simulated images were warped ± 5 mm based on two sets of manually defined points using Landwrap landmark deformable registration in 3D Slicer.

Figure 5.7: Examples of prostate contour overlay on the simulated fixed transverse image slice a) before registration, b) after deformable registration.
Table 5.7: TRE statistics for Experiment 2a: multi-slice-to-volume rigid registration between the planning volume and clinical intra-operative orthogonal image slices

<table>
<thead>
<tr>
<th></th>
<th>Rigid Registration TRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.04 mm</td>
</tr>
<tr>
<td>Range</td>
<td>0-0.2 mm</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.1 mm</td>
</tr>
</tbody>
</table>

Table 5.8: TRE statistics for Experiment 2b: multi-slice-to-volume deformable registration between the planning volume and clinical intra-operative orthogonal image slices

<table>
<thead>
<tr>
<th></th>
<th>Rigid Registration Step TRE</th>
<th>Deformable Registration Step TRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.9 mm</td>
<td>1.1 mm</td>
</tr>
<tr>
<td>Range</td>
<td>1-6.9 mm</td>
<td>0.3-2.6 mm</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.7 mm</td>
<td>0.6 mm</td>
</tr>
</tbody>
</table>

Experiment 2 - Clinical Images

Using the original registration results from the actual clinical image pairs as the ground truth, we further tested the accuracy and robustness of the algorithm with only clinical images. In the rigid step, a random initial transform of $\pm 20$ mm translation and $\pm 10^\circ$ rotation along each of the three axes was set. A total of 70 registrations were performed on 14 image pairs, and the TREs were all below 0.2 mm. Table 5.7 and Figure 5.8 contains more detailed information regarding TRE statistics for the rigid step. In the deformable step, the planning volumes were warped $\pm 5$ mm and were then registered to the three orthogonal clinical image slices using the two-step algorithm. The final mean TRE was found to be 1.1 mm for 14 registrations. This is summarized in Table 5.8 and Figure 5.9. The rigid step recovered 93% of the ground truth value, while the deformable alignment recovered 98%.
Experiment 3 - Multi-slice-to-volume vs. Volume-to-volume

The results of multi-slice-to-volume registration between the needle confirmation images and the planning volumes were compared with volume-to-volume registration. The target reconstruction distances of the two algorithms are plotted in Figure 5.10 (mean: 1 mm, range: 0.1-2.7 mm, standard deviation: 0.7 mm).

5.5 Discussion

The radius of a clinically significant tumor is 5 mm [69], hence a registration error less than 5 mm is considered as sufficiently accurate for needle placement purposes. In addition, it is also less than the slice spacing (3.6 mm) of our data set from Brigham
5.5. DISCUSSION

Figure 5.9: TREs for Experiment 2b: the 14 multi-slice-to-volume deformable registrations using clinical images. The image volumes were warped ± 5 mm based on two sets of manually defined points using Landwrap landmark deformable registration in 3D Slicer.

It is important for the algorithm to be able to handle a large variety of MR images with different intensities and initial misalignments. We performed several validation methods to ensure the accuracy and robustness of our algorithm. Since the exact correspondence of the prostate anatomy cannot be easily identified in clinical MR images, typical validation methods such as using landmarks to evaluate the accuracy of our registration are not applicable in this case. Therefore, we generated simulated intra-operative orthogonal image slices from the pre-operative planning volume in order to obtain ground truth.
With regards to the actual clinical images, the image overlay after registration showed obvious improvements to the initial contour alignment before registration (Figure 5.4). The registration errors based on prostate contours were also clinically acceptable (less than 5 mm). Since the patients were sedated, intra-operative patient motion was limited. Therefore, the initial prostate misalignments before registration were small for the Brigham and Women’s Hospital data. However, this is not the case for transrectal biopsies. The registration results from both real and simulated images demonstrated that our algorithm was able to recover initial rigid misalignments (± 20 mm translation and ± 10° rotation) and correct for prostate deformation (± 5 mm warping of the images) with less than 1.1 mm accuracy on average, which is well under the 5 mm upper limit mentioned earlier. In an actual clinical setting, target displacement that is parallel to the needle is less of a concern since the biopsy needle core is about 20 mm long. Therefore, it is the orthogonal component of the target
5.5. DISCUSSION

The fact that our multi-slice-to-volume registration was able to produce results that were less than 3 mm different from that of the volume-to-volume registration further indicates the reliability of our algorithm.

Clinically, a processing time of approximately 1 minute to compute the current biopsy target position prior to needle insertion is reasonable. The mean execution time of 34.3 seconds fulfills this time requirement. The deformable step was much more computationally expensive than the rigid step. Since rigid registration can capture 95% of the target displacement, it may also be tolerable to omit the deformable step.

To summarize, we developed an image-based multi-slice-to-volume registration algorithm for MRI-guided prostate biopsy to detect cases with large intra-operative prostate motion prior to needle insertion. Contour alignments were used to validate the registration results of clinical images, and both simulated and clinical images were used for quantitative evaluation of the algorithm. All registration errors were well below the radius of a clinically significant tumour (5 mm), and can be considered as clinically acceptable. It was found that the majority of the prostate motion (95%) during biopsy was rigid. The overall execution time for biopsy target dislocation computation (34.3 seconds) was also short enough for clinical practice.

In conclusion, the multi-slice-to-volume registration can be used to alert the clinician if the biopsy target has moved significantly after the planning volume acquisition and before needle insertion. Decisions can be made to either compensate the insertion plan by the results of the slice-to-volume registration or to re-acquire another set of planning images. The latter method takes more time and we hope in most cases it
will not be necessary and the registration result can be used for motion compensation instead. Furthermore, a short image slice acquisition and registration time is needed when a quick feedback loop is essential, such as in real-time image guided needle steering. Currently, this method adds an extra step to the clinical protocol in order to increase the needle targeting accuracy. In the future, needle tracking can also be included to increase the speed of the procedure by reducing the need of the volumetric needle confirmation imaging step. We expect further testing with more image data and possible future integration of this methodology into clinical practice so that we can make a tangible difference in the lives of patients.
Chapter 6

Conclusion

This chapter summarizes the main contributions and findings of this thesis, and proposes directions for future research.

6.1 Summary

A survey of the recent literature on the state-of-art in clinical image-guided prostate needle placement procedures was presented in Chapter 2, and the prostate behaviour upon needle insertion was reviewed in Chapter 3. Undeniably, research findings have confirmed that there are a substantial amount of prostate motion and deformation intra-operatively. Chapter 4 showed the effect of this motion and deformation on the biopsy accuracy of the APT-MRI system. Finally, a motion compensation method was proposed and validated in Chapter 5 to improve the needle targeting accuracy for biopsy under MRI guidance.
6.1. SUMMARY

6.1.1 Prostate Motion and Deformation Upon Needle Insertion

Chapter 2 and 3 review the current image-guided needle placement procedures for prostate cancer diagnosis and treatment. The extent of intra-operative prostate motion and deformation, and motion reduction methods used in the operating room were included. The different kinds of procedures were organized based on their imaging modalities and needle puncture path. The following is a list of the topics covered in these chapters:

- Types of imaging modalities for needle guidance
- Needle puncture paths for prostate access
- Patient positioning for different types of procedures
- Patient-induced prostate motion
- Prostate deformation due to imaging probes
- Target dislocation during needle insertion and tissue acquisition
- Motion reduction using special devices or equipment
- Methods of intra-operative image registration

Overall, studies have shown that there is a substantial amount of prostate motion and deformation during image-guided needle placement procedures. Despite the efforts to improve the basic TRUS-guided protocols, its image quality is a limiting factor. MRI has been serving as an alternative to ultrasound for needle guidance. However, due to its high cost and low availability, it is still at its early stages of research.
6.1.2 Accuracy Analysis in MRI-guided Robotic Prostate Biopsy

Knowing the possible intra-operative prostate motion and deformation during the biopsy procedure, Chapter 4 aims to find out how much of the biopsy accuracy is affected by this. The major contributions of this chapter include:

- The development of a three-stage registration algorithm that aligns the pre- and post-needle insertion image volumes to capture prostate motion and deformation during MRI-guided biopsy
- Retrospective accuracy validation of the APT-MRI robotic biopsy system that was used at the NCI for over 6 years
- Quantitative analysis of the biopsy target dislocation during MRI-guided transrectal biopsy under the APT-MRI system

The results have shown that even though the robotic needle placement is clinically acceptable, there was still an average biopsy error of 4.3 mm due to intra-operative prostate motion and deformation. It was also found that the majority of the prostate motion during biopsy was rigid, and the prostate moved differently from its surrounding structures. Therefore, the incorporation of motion compensation techniques are recommended in order to improve the overall biopsy needle targeting accuracy.

6.1.3 Target Localization in MRI-guided Transperineal Prostate Biopsy using Multi-Slice-to-Volume Registration

Chapter 5 focused on developing a method to alert the clinicians if the biopsy target has moved significantly prior to needle insertion. The insertion plan can then be
adjusted accordingly in order to increase the needle targeting accuracy. The two major contributions of this chapter include:

- The development of a multi-slice-to-volume registration algorithm that aligns the pre-operative image volume with 3 intra-operative image slices for biopsy target localization

- Accuracy validation of the algorithm on both clinical and simulated MR images

All quantitative and qualitative validation results of the registration algorithm were clinically acceptable since the registration errors were well all below the radius of a clinically significant tumour. In addition, the average execution time of the registration was also short enough to be clinically compatible. The multi-slice-to-volume registration results were comparable with that of the volume-to-volume registration, and therefore further confirms the accuracy of the algorithm. It was also found that rigid registration can capture the majority of the target dislocation, which is consistent with previous findings.

6.2 Future Work

The actual clinical integration of the proposed multi-slice-to-volume registration for motion compensation would require further testing with more clinical MR images and the development of a user-friendly software interface. To significantly decrease the procedure time, needle tracking can also be implemented so that the need of the volumetric needle confirmation imaging step can be reduced. The ultimate goal is to track both the intended biopsy target and the needle tip in real-time. The algorithm can also be enhanced so that it can be applied to any needle placement procedures
instead of just biopsy. In the long term, the software can even be further extended beyond prostate cancer to other organ systems, especially for gynecology.
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