IMAGE-GUIDED ROBOTIC INTERVENTIONS
FOR CORE NEEDLE BIOPSY

by

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Abstract

Image-guided core needle biopsy (CNB) is a common procedure to diagnose cancer in patients with clinical symptoms and/or cancer suspicious regions (CSR) of imaging abnormality. While image-guided CNB can be performed manually, the quality control of the procedure is often subjective, outcomes are variable depending on the training and skills of the physicians, and significant challenges exist in navigating the biopsy needle accurately under image-guidance. Robotic assistance for needle guidance has the potential to increase needle targeting accuracy in CNB. This work presents two types of robotic systems for image-guided CNB.

The first system is a magnetic resonance imaging (MRI)-guided robotic system, which was developed to assist pediatricians in performing bone biopsy. A bone biopsy is frequently needed if a CSR is observed on MRI. Currently, the biopsy can only be performed in open surgery, under X-ray, or computed tomography (CT) guidance. These involve either general anesthesia or exposure to ionizing radiation, respectively, which are especially concerning in children. Most importantly, neither method can use direct MRI as feedback to guide the biopsy. Bone marrow lesions are difficult to visualize during surgery or with X-ray and CT imaging, increasing the possibility of missed sampling and inaccurate diagnosis. Instead, direct MRI-guided targeted robotic biopsy may be performed in the same session with the MRI diagnosis, and allow direct confirmation of needle sampling the CSR. This may also reduce trauma and eliminate radiation exposure in children. Comprehensive validation tests including bench, mockup tests, and human cadaveric studies are presented, showing the feasibility of the system.

The second system is a transrectal ultrasound (TRUS)-guided robotic system, which was developed to assist urologists in performing prostate biopsy. Current challenges and deficiencies of manual biopsy are: the difficulty navigating the needle under 2D ultrasound guidance; the deformations of the prostate by free-hand probe manipulation during biopsy; and the use of the same biopsy plan for all patients. Instead, the TRUS robot enables accurate needle targeting under 3D ultrasound guidance, with minimized prostate deformations, and personalized for each patient to maximize the likelihood of detecting cancer. Extensive pre-clinical validation tests and clinical trial results are presented.
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1 Introduction

Chapter 1 is organized as follows. Section 1.1 presents a literature review about the main topics involved in this dissertation, including core needle biopsy (CNB), pediatric bone biopsy, prostate biopsy, magnetic resonance imaging (MRI)-guided robotic interventions, and ultrasound-guided robotic interventions. Section 1.2 presents a list of the contributions that this dissertation makes to the area of Computer-Assisted Intervention. Section 1.3 describes the organization of the dissertation.

1.1 Literature Review

1.1.1 Core Needle Biopsy

A biopsy is a medical procedure that takes and examines a sample of fluids or tissues from a patient's body to determine its etiology. In most cases, a biopsy is done to diagnose a problem or to help determine the best therapy option. Particularly, as a solid diagnostic method for various types of cancer, a biopsy is recommended for patients with cancer suspicious regions (CSR) of imaging abnormality.

Biopsies are categorized into three distinct types such as fine needle aspiration (FNA), core needle biopsy (CNB), and surgical biopsy [1]. A surgical biopsy requires a hospital setting and is more invasive than a CNB or an FNA. On the other hand, a CNB has a benefit in reducing the risk of complications encountered with classic surgical biopsies such as scarring, infection, and damage to healthy tissue. Accordingly, a CNB is commonly the preferred biopsy option.

CNB is commonly performed in most parts of the body. It is commonly performed on bone, prostate, kidney, liver, and lymph nodes under the guidance of medical images such as ultrasound, X-ray, computed tomography (CT), and MRI [2].

Figure 1.1a shows the working mechanism of a CNB for bone marrow. In the first step, the biopsy needle is inserted into the cortical bone by rotating the whole needle. In the second step, the inner needle is removed once the needle passes through the cortical bone. In the third step, the outer sheath is spun and inserted into the bone marrow. Finally, a core of bone marrow is withdrawn together with the outer sheath.
Figure 1.1b shows the most common working mechanism of a CNB for soft tissue. In the first step, the biopsy needle is loaded with a spring. In the second step, the inner needle is fired first and inserted into the soft tissue. In the third step, the outer sheath is fired and contains a sample of the soft tissue into the specimen notch of the inner needle. In the final step, a core of soft tissue is withdrawn together with the biopsy needle.

1.1.2 Pediatric Bone Biopsy

Bone pain is commonly reported in children. The causes of bone pain could be benign etiologies such as a bone infection or malignant etiologies such as a bone tumor. Typical symptoms of pediatric patients include pain, tenderness, reluctance to bear weight or use the affected limb. Fevers can be observed in patients with both bone infections and bone cancers. Particularly in the early stage of the disease, conventional radiographs such as X-ray or CT could show normal results. On the other hand, MRI improves soft tissue visualization, marrow, and joint space resolution. Therefore, MRI is commonly used for diagnostic purposes. However, the infectious and neoplastic bone pathology have a similar appearance in MRI. It is occasionally not possible to distinguish the two etiologies, even though there is a significant difference between their clinical management and treatment requirements.

Infection with bacterial or fungal organisms could cause an inflammation of bone called osteomyelitis (Figure 1.2a). Osteomyelitis is a rare but serious condition. More than 50% of reported cases are seen in preschool-aged children and acute hematogenous from symptomatic or asymptomatic bacteremia is the main
Since the treatment for osteomyelitis includes long-term antibiotics or surgical debridement in advanced cases, a bone biopsy for accurate and timely diagnosis of bone infection is often needed for implementing the optimal therapy.

Malignant bone cancers are the fourth most common pediatric solid tumors, followed by central nervous system tumors, sarcomas, and retinoblastoma [4]. Osteosarcoma (Figure 1.2b) and Ewing sarcoma (Figure 1.2c) are the most common malignant bone tumors in children [5]. Accurate histologic diagnosis is a key for treatment planning of those malignant bone tumors. Complex treatment is usually required for bone tumors and those treatments can be performed with various combinations of chemotherapy, radiation therapy, surgical resection, and even amputation. Therefore, a bone biopsy for tissue diagnosis is often needed before implementing the appropriate treatment plan.

An X-ray scan and blood test could be chosen as initial steps to make the diagnosis of bone infection and bone tumor [6]. In the early stage of the disease, however, those tests commonly show false negative results. Therefore, an MRI scan is usually selected as the next step if a suspicious bone lesion is observed on X-ray images and there is clinical suspicion for infection or malignancy [6]. MRI is preferred due to its superior soft tissue contrast and excellent visualization of bone marrow and joint spaces [6]. Despite those superiorities of MRI, it is occasionally not possible to distinguish the infectious and neoplastic pathology in children because those etiologies have a similar appearance in MRI. Therefore, imaging alone may not be enough to make a definitive diagnosis. A bone biopsy is usually required in these cases [6].

Figure 1.2 MRI images showing (a) Osteomyelitis (T1), (b) Osteosarcoma (T2), (c) Ewing sarcoma (T2)

(Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 7651, 7527, 7842)
(Images are licensed under the Creative Commons Attribution-Non-commercial-Share Alike 3.0 Unported)
There are two approaches exist in the bone biopsy, one is an open surgical biopsy and the other is an image-guided percutaneous core needle biopsy. An open surgical biopsy is usually performed in the operating room by an orthopedic surgeon, while an image-guided percutaneous core needle biopsy is usually performed in the CT scanner by an interventional radiologist. In the current clinical workflow for a bone biopsy, the initial diagnostic MRI scan is performed and interpreted first [6]. If a bone biopsy is required based on the final report of the MRI scan, preparing for the separate biopsy procedure starts [6]. The preparing steps include reserving time in the operating room or CT scanner room, coordinating anesthesia, and scheduling the biopsy procedure. These steps may take a long time depending on resource availability and timely communication.

1.1.3 Prostate Biopsy

Prostate cancer (PCa) is one of the most common cancers in North America, Europe, and Australasia [7]. More than 1 million cases of PCa are diagnosed every year, and more than 30% of those cases end in death worldwide [7]. In 2019, 174,650 cases of PCa are estimated to be diagnosed and 31,620 of deaths from PCa are expected in the United States alone [8].

As preliminary screening tests of PCa, a digital rectal examination (DRE) and a prostate-specific antigen (PSA) blood test are generally performed [9], [10]. In DRE, the urologist inserts a lubricated, gloved finger

![Figure 1.3 (a) Prostate and Nearby Organs, (b) Digital Rectal Exam (DRE)](image)

(Image credit: National Cancer Institute)
(This image is in the public domain and can be freely reused. Attribution required.)
into the rectum and feels the prostate for lumps or abnormal areas through the rectal wall, as shown in Figure 1.3b [11]. In the PSA blood test, the level of PSA in the blood is measured. PSA is a substance made by the prostate. It may be found in higher than normal concentrations in the blood of men with PCa [11]. However, PSA levels may also be high in men with an infection or inflammation of the prostate or benign prostatic hyperplasia (BPH), which is an enlarged but noncancerous prostate [11]. In the case that one of these test results is abnormal, a prostate biopsy is recommended to confirm the diagnosis of PCa.

In prostate biopsy, a thin core biopsy needle (18 gauge) is inserted through the rectal wall (transrectal biopsy, shown in Figure 1.4a) or through the perineum (transperineal biopsy, shown in Figure 1.4b) and take tissue samples under the guidance of a transrectal ultrasound (TRUS). The obtained tissue samples are checked by a pathologist using a microscope. The pathologist checks the tissue sample to see if there are cancer cells and determines the Gleason score. The Gleason score varies between 2-10 and describes how likely it is that a tumor will spread. The tumor with a lower number has a lower chance of dissemination [11].

No differences between the transrectal and transperineal approaches have been reported in terms of the cancer detection rates (CDR) [12], [13]. Traditionally, transperineal approach was uncommon because it requires higher anesthesia and an operating room setting. However, it offers the advantage of lower infection rates [14]. New transperineal biopsy is emerging with less anesthesia and at the clinic [15]. However, the mainstream of prostate biopsy stays in transrectal biopsy [13].

Figure 1.4 Two types of prostate biopsy; (a) Transrectal approach and (b) Transperineal approach

(Image credit: Cancer Research UK)
(Images are licensed under the Creative Commons Attribution-Share Alike 4.0 International License.)
As it is not possible to differentiate cancerous tissue from benign prostate tissue on standard 2D ultrasound images, TRUS-guided prostate biopsies take samples of prostate tissue systematically over the prostate gland rather than aiming at the CSR. An extended 12-cores prostate biopsy, which samples prostate tissues from the systematically distributed 12 places, has been shown its validity [16].

In practice, however, the biopsy samples do not follow the systematic schema, clustering and/or missing regions [17]. Furthermore, CDR of PCa varies significantly depending on the physician [18]. The urologists need to freehand the probe together with the biopsy gun to aim at a specific position of the prostate gland based on the 2D images. It is a challenging task for the urologists. Accordingly, the freehand TRUS-guided transrectal prostate biopsy includes limitations such as under-sampling clinically significant PCa and over-sampling insignificant lesions [19]. As a solution to these problems, several systems that track the position and orientation of the ultrasound probe emerged. These systems are using electromechanical [20], [21], electromagnetic [22], [23], or optical [24] trackers.

Recently, systems with MRI-ultrasound fusion techniques were introduced [25], [26], which allows urologists to target the CSR that is identifiable in MR images [27]. Several publications reported that the targeted biopsy using the MRI-ultrasound fusion technique improves sampling efficiency, increases CDR of clinically significant cancers, and reduces CDR of clinically insignificant cancers [19], [28]. However, despite those advantages, most of the patients are undergoing the freehand TRUS-guided transrectal prostate biopsy. A major limitation is that it requires a special MRI scan and an experienced radiologist, which are not readily available in small-sized institutions and could result as financial burdens for the patients.

1.1.4 MRI-Guided Robotic Interventions

Development of MRI-compatible robots has been investigated by several research groups worldwide. Comprehensive review articles describing MRI-compatible robots include the articles by Tsekos et al. [29], Gassert et al. [30], Arnolli et al. [31], and Monfaredi et al. [32].

There could be many ways to categorize MRI-compatible robots in medical applications. One way is to categorize the robots based on the basic four classifications, such as clinical application, mounting method, actuation method, and MR classification. The MRI-compatible robots could be categorized into two subcategories for each classification.
Table 1.1: Categorization of MRI-compatible robots

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
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<tbody>
<tr>
<td>Clinical application</td>
<td>Needle-based procedure</td>
</tr>
<tr>
<td></td>
<td>Rehabilitation application</td>
</tr>
<tr>
<td>Mounting method</td>
<td>Patient-mounted</td>
</tr>
<tr>
<td></td>
<td>Bed-mounted</td>
</tr>
<tr>
<td>Actuation method</td>
<td>Pneumatic/hydraulic motor</td>
</tr>
<tr>
<td></td>
<td>Piezoelectric motor</td>
</tr>
<tr>
<td>MR classification</td>
<td>MR conditional</td>
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<tr>
<td></td>
<td>MR safe</td>
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</table>

Table 1.1 shows the categorization of MRI-compatible robots. Under the classification of clinical application, the robots are categorized into needle-based procedures and rehabilitation applications. Under the classification of mounting method, the robots are categorized into patient-mounted and bed-mounted. Under the classification of actuation method, the robots are categorized into pneumatic/hydraulic motor based and piezoelectric motor based. Under the MR classification of the American Society for Testing and Materials (ASTM F2503), the robots are categorized into MR conditional and MR safe. Under this aspect, some of the representative literature is summarized below.

1.1.4.1 Clinical Application

Under the classification of clinical application, the MRI-compatible robots could be categorized into two distinct applications, such as needle-based procedures and rehabilitation applications.

For needle-based procedures, Moreira et al. reported an MR-compatible robot named MIRIAM (Minimally Invasive Robotics In An MR environment) to steer and fire a biopsy needle during the prostate biopsy [33]. This robot has 9 degrees of freedom (DoF) and it consists of a 5-DoF parallel robot driven by piezoelectric motors to position the needle-guide and a 4-DoF needle driver to insert, rotate, and fire the biopsy gun. An MR Safe robot for endorectal prostate biopsy was also developed in our laboratory [34]. This robot was designed to orient the needle-guide during the endorectal prostate biopsy under MRI guidance. Promising results were reported for both in vitro and in animal studies. Recently, a different type of MR Safe robot was reported in our laboratory. The robot was designed to orient the biopsy needle-guide during the transperineal prostate biopsy under MRI guidance [35]. Promising results were reported in FDA and IRB-approved clinical trials.
For rehabilitation applications, Estévez et al. used an MRI compatible robotic arm in healthy subjects to define the brain network activated while performing active and passive elbow movements [36]. The arm was also used to test the reproducibility of the activation over time. Yap et al. [7] reported a wearable soft robotic glove for hand rehabilitation [37]. The authors presented the design, fabrication, and evaluation of the glove. A set of soft pneumatic actuators made of silicone elastomers was used to actuate the glove. The glove was used for brain activity study under MRI during hand rehabilitation.

1.1.4.2 Mounting Method

Under the classification of mounting method, the MRI-compatible robots could be categorized into two distinct categories, patient body mounted and MRI table mounted.

For patient body mounting method, Monfaredi et al. reported a 4-DoF patient body mounted MRI-compatible robot for shoulder arthrography [38]–[40]. The authors showed the robot could be stably mounted using straps. The results of gel mockup targeting studies showed an average needle placement error of 1.64 mm with a standard deviation of 0.90 mm. Walsh et al. developed a 4-DoF telerobotic system [41]. Hungr et al. developed a body-mounted robot to perform interventional CT/MRI procedures [42]. Wu et al. developed an MRI coil-mounted 2-DoF robotic positioner for cryoablation [43]. Hata et al. presented a patient body mounted robot with double ring remote-center-of-motion (RCM) mechanism for cryotherapy of renal cancer [44][45]. With the robot, a probe placement was possible in an average targeting error of 4.1 mm with a standard deviation of 3.1 mm using an organ motion mimicking mockup.

For MRI table mounting method, Melzer et al. developed the INNOMOTION MRI table mounted robot for percutaneous image-guided interventions [46]. The animal experiment showed a maximum error of 3 mm and 3 deg. Franco et al. reported an MRI table mounted robot for MRI-guided laser ablation of liver tumors [47]. The results of the mockup study indicated below 5 mm targeting error. Fischer et al. developed a table mounted MRI-compatible robot for transperineal prostate biopsy [48]. The authors developed custom MRI-compatible pneumatic cylinders, which were used for robot actuation. MRI-compatible brakes were also developed by the authors to lock the robot in position for stable needle insertion. The robot has 2-DoF which are actuated with modified versions of the scissor lift and planar bar mechanisms. All five 1-cm targets were successfully targeted in the mockup study. Fichtinger et al. reported a table mounted prostate biopsy robot to be used inside an MRI scanner [49]. The robot includes 3-DoF for a translation of the end-effector inside the...
rectum, a rotation of the end-effector around the axis of translation, and an insertion of the needle. The feasibility and accuracy of the device were validated in the canine study by Susil et al. [50]. Krieger et al. developed an MRI-guided remotely actuated manipulator for access to prostate tissue (APT) [51]. The manipulator includes a needle guide with a curved needle channel. A super-elastic needle made of Nitinol was used to prevent the plastic deformation of the needle at an exit angle of 45 [deg]. The targeting accuracy and the feasibility of the device were validated in the clinical trials with five patients. The in-plane displacement error was 1.8 [mm] on average for 20 needle insertions. Susil et al. reported the needle placement accuracy in the clinical trials with five patients using the APT system under the guidance of a standard 1.5T MRI scanner [52]. The accuracies of the needle placement were 1.9 [mm] and 1.8 [mm] for the marker placement and the biopsy procedure, respectively. Krieger et al. also developed an improved version of the manually actuated manipulator for access to prostate tissue (APT II) [53]. The manipulator has two knobs to rotate the needle guide in two different directions. The manipulator also includes four MR markers for initial registration and robot tracking. The mockup study showed the average in-plane error of 0.6 [mm]. The feasibility of the robot was also validated in the clinical trials with two patients. Two actuated versions of the manipulator were also reported by the same research team (APT III [54], APT IV [55]). Piezoceramic motors were used to actuate the robots. The APT III has two actuated DoF for orienting the needle, and a manual needle-insertion DoF while the APT IV includes three actuated DoF. Song et al. [56] and Xu et al. [57] reported methods and techniques to analyze the needle insertion accuracy using the APT system.

1.1.4.3 Actuation Method

Van den Bosch et al. [58] developed a robotic system with pneumatic and hydraulic actuators for prostate seed implantation with automated needle insertion. Su et al. [59] reported a 6-DoF robot with piezoelectric motors for prostate therapy under MRI guidance, consisting of a 3-DoF needle driver module (cannula translation and rotation and stylet translation) and a 3-DoF Cartesian motion stage. A pneumatically actuated step motor [60] and a fully automated, pneumatically actuated robot for transperineal prostate brachytherapy was also previously developed by our laboratory [61].

1.1.4.4 MR Classification

Standard F2503 has been developed by the American Society for Testing and Materials (ASTM) to classify devices for the MRI environment. Table 1.2 shows the ASTM F2503 standard for materials near the
Table 1.2: American Society for Testing and Materials (ASTM) classifications for materials near the MRI environment

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>MR Safe</td>
<td>An item that poses no known hazards in all MRI environments. Includes all non-conducting, non-metallic, non-magnetic items.</td>
</tr>
<tr>
<td>MR Conditional</td>
<td>An item that has been demonstrated to pose no known hazards in a specified MRI environment with specified conditions of use. MR Conditional items are labeled as to limitations that might exit in the MRI environment.</td>
</tr>
<tr>
<td>MR Unsafe</td>
<td>An item that is known to pose hazards in all MRI environments. MR Unsafe items include magnetic items such as pair of ferromagnetic scissors.</td>
</tr>
</tbody>
</table>

MRI environment [62]. In the United States, compliance with these standards is required for medical device regulatory clearance by the Food and Drug Administration (FDA). "MR Safe" is entitled to a device that poses no known hazards in all MRI environments. MR Safe devices include prostate biopsy robots from Schouten et al. [63] and our lab [34], [35] "MR Conditional" is entitled to a device that has been demonstrated to pose no known hazards in a specified MRI environment with specified conditions of use such as field strength. MR Conditional devices include the pneumatic stepper motor from Chen et al. [64] and the prototype robot for transcranial focused ultrasound surgery from Price et al. [65]. "MR Unsafe" is entitled to a device that has been demonstrated to pose hazards in all MRI environments.

1.1.5 Ultrasound-Guided Robotic Interventions

Development of ultrasound-guided robotic systems has been investigated by several research groups worldwide. Comprehensive review articles describing the ultrasound-guided robotic systems include the articles by Priester al. [66] and Kaye et al. [67].

In this review, the representative literature describing the ultrasound-guided robotic systems are first categorized according to its medical application. Subsequently, this review focuses on the systems developed for prostate biopsy, which is the main topic of this dissertation. These systems are categorized according to two different aspects, such as a method on prostate access and a method on ultrasound probe manipulation.
Under the aspect of the method on prostate access, the systems are subcategorized into transperineal and transrectal accesses. Under the aspect of the method on ultrasound probe manipulation, the systems are subcategorized into freehand and robotic manipulations.

### 1.1.5.1 Clinical Application

One of the fundamental clinical applications of ultrasound-guided robotic systems is diagnostic imaging. Degoulange et al. developed a robotic system with an industrial robot (Mitsubishi PA-10) to manipulate an ultrasound probe [68]. The robotic system was used to monitor arteries for cardiovascular disease prevention. To maintain a constant force between the skin and the ultrasound probe, an external force control scheme was applied. Abolmaesumi et al. developed a robotic system with a 6-DoF parallelogram linkage robot to manipulate an ultrasound probe [69]. The robotic system was used for carotid artery examination. The authors presented an ultrasound image servoing technique that automatically compensates unwanted motions of the ultrasound probe. Monfaredi et al. developed a 6-DoF parallel mechanism telerobotic system with force control capability [70]. The robotic system was developed to enable a remote ultrasound scanning through teleoperation and the feasibility of the system was verified with an in-vitro study.

In addition to the systems for diagnostic imaging, some of the ultrasound-guided robotic systems were developed for intraoperative guidance. Leven et al. presented a telerobotic surgical system with integrated robot-assisted laparoscopic ultrasound capability (daVinci Canvas) [71]. The authors integrated a rigid laparoscopic ultrasound probe with the daVinci robot, which enables video tracking of ultrasound probe motions, autonomous robot motions, and display of registered 2D and 3D ultrasound images. Clinical trials with 3 patients showed the feasibility of the system. Schneider et al. presented an updated version of the intraoperative ultrasonography tool used in the daVinci Canvas [72]. A “wrist” was added to the tool so that the surgeon can obtain the view desired for tasks such as placing a biopsy needle or ablation probe. Hung et al. modified a commercial endoscope manipulator (ViKY System, EndoControl Medical, Grenoble, France) to hold the TRUS probe [73]. The system was used for real-time monitoring of prostate and periprostatic anatomy during RALP. The feasibility of the system was validated with clinical trials with 10 patients. Adebar et al. introduced a robotic TRUS manipulator and a method for tracking daVinci surgical instruments during RALP [74]. Mohareri et al. presented a fully automatic registration technique for rapid registration of the daVinci surgical system and the robotic TRUS manipulator [75]. Our laboratory also reported a transrectal
ultrasound probe manipulator to visualize the blood vessels in the neurovascular bundle using Doppler ultrasound imaging during robot-assisted laparoscopic radical prostatectomy (RALP) [76].

A needle-based interventional procedure has been focused as a main clinical application of the ultrasound-guided robotic system. Yu et al. developed a 16-DoF robotic system for robot-assisted brachytherapy [77]. The robotic system consists of a positioning module and a surgery module. The positioning module has 9-DoF including a 3-DoF cart and a 6-DoF platform. The surgery module has 7-DoF including a 2-DoF ultrasound prove driver, a 3-DoF gantry, and a 2-DoF needle driver. The ultrasound probe driver can translate and rotate the probe to acquire 3D images. The gantry has two XY translational motions and one rotational motion (pitch) to orient the needle driver. The needle driver has one translational motion and one rotational motion to insert and rotate the needle. The mockup study showed an RMS error of 0.69 [mm]. Fichtinger et al. reported a TRUS-guided prostate brachytherapy system. [78]. The system includes a TRUS probe manipulator (2-DoF) and a needle insertion robot (3-DoF). The needle insertion robot is spatially co-registered to the probe manipulator and mounted to the 7-DoF passive arm, which is attached to the 3-DoF Cartesian stage. The mockup test showed the average errors of 2 [mm] and 2.5 [mm] in transverse and sagittal needle placements, respectively. Fichtinger et al. also presented a different type of the robotic system for robotically assisted prostate brachytherapy [79]. The system includes a TRUS probe manipulator used to rotate and translate the probe, and a small parallel robot affixed to the mounting posts of the template. The parallel robot consists of two XY stages to adjust the position and orientation of the needle. The needle tip placement error was 1.04 [mm] in mockup tests. Bassan et al. developed a 5-DoF robot for percutaneous needle insertion [80]. The robot has a 2-DoF double-parallelogram-based RCM driver and a 3-DoF needle driver. The RCM driver orients the needle and the needle driver is capable of translating the needle, rotating the needle, and inserting the seed. An averaged error of 1.45 [mm] was reported in the mockup study. Nelson et al. used a commercial robot arm (F3 robot, CRS Robotics Corp., Burlington, Ontario, Canada) to develop a robotic system for performing breast biopsy [81]. The authors modified the robotic arm to incorporate a force-torque sensor and a breast biopsy device. The mockup study demonstrated submillimeter accuracy.

1.1.5.2 Transperineal vs. Transrectal

Ultrasound-guided robotic system for transperineal prostate biopsy has been investigated by several research teams. Ho et al. reported a robotic system for transperineal prostate biopsy [82]. The system consists
of a robotic positioning system, a gun-holder, and an ultrasound probe holder. The robotic positioning system adjusts the orientation and insertion depth of the biopsy needle. The robotic positioning system includes two pivot points where the needle passes through. The gun-holder adjusts the insertion depth of the needle. The ultrasound probe holder holds a commercial biplane ultrasound probe. The 3D image of the prostate is generated by translating the ultrasound probe while the system collects the transverse ultrasound images. The ultrasound probe is enclosed with a rectal sheath supporting the rectal wall to keep the prostate constantly deformed. The mockup study demonstrated submillimeter accuracy. Long et al. developed a 7-DoF robotic system for multiple purposes on prostate therapy such as brachytherapy, focal therapy, and transperineal prostate biopsy [83]. The system includes an intraoperative prostate tracking system and a mechanical needle release system. The targeting test in mockups showed a median accuracy of 2.73 \( \text{mm} \).

In addition to the transperineal approach, the transrectal approach has been also focused by several research groups worldwide. Schneider et al. designed a robotic system for transrectal prostate biopsy [84]. The systems include a partial sheath made of biocompatible material (Nylon 66) and mounted on TRUS probe. A needle is inserted through one of two parametric guides on the sheath, which is driven by the motor. A special needle made of nitinol was used because of its elastic properties. The mockup study showed an averaged error of about 2.5 \( \text{mm} \). Bax et al. reported a 3D navigation system for transrectal prostate biopsy [20]. The system consists of a 3D ultrasound imaging system and a passive mechanical arm with RCM structure. The passive mechanical arm is capable of guiding, tracking, and stabilizing the position of a commercial end-firing TRUS probe. It also minimizes prostate displacement and deformation during the biopsy procedure. The robot was able to reach the targets in a mockup with a mean error of 2.1 \( \text{mm} \).

1.1.5.3 Freehand vs. Robot-assisted

Although the transperineal approach offers the advantage of lower infection rates, it is uncommon because it requires higher anesthesia and an operating room setting. Accordingly, most of the commercialized systems are designed for the transrectal approach and have been used for patients with suspected abnormalities. These systems could be categorized into two different types according to the manipulation method, such as freehand probe manipulation [26], [85] and robot-assisted probe manipulation [25], [86].

The UroStation (Koelis, La Tronche, France) is a commercial software platform system developed to assist TRUS-guided freehand prostate biopsy procedure with 3D imaging and intraoperative MRI-ultrasound
fusion capabilities [85]. The system connects to a commercial ultrasound device equipped with a 3D ultrasound probe. The system allows live planning, guiding and recording of prostate biopsy maps [87]. The system is also capable of tracking of the prostate to compensate patient- and probe-induced movements based on the image registration technique [87], [88]. The UroNav (InVivo, Gainesville, FL) is another type of commercial software platform system developed for TRUS-guide freehand prostate biopsy [26]. The system includes an electromagnetic tracking device to track a commercial 2D TRUS probe, enabling 3D imaging of the prostate. The system has live planning, guiding and recording of prostate biopsy maps, and MRI-ultrasound fusion capabilities [89].

The TargetScan (Envisioneering Medical Technologies, St. Louis, MO) is a robot-assisted, TRUS-guided prostate biopsy system [86]. The system is composed of a biplane TRUS probe, a needle-guide, and a 2-DoF robotic probe manipulator. The needle-guide is attached to the probe, which is mounted on the robot. The robot translates the needle-guide and rotates the probe to place and track the needle. A special bendable nitinol biopsy needle is used so that the needle is inserted into the needle-guide parallel to the probe and exited at a 45 [deg] angle [90]. The Artemis (Eigen Inc., Grass Valley, CA) is a passive mechanical arm-assisted, TRUS-guided prostate biopsy system [25], [91]. The passive mechanical arm has an RCM structure and it enables guiding, tracking, and stabilizing the position of a commercial end-firing TRUS probe. A semi-automatic segmentation algorithm is used to generate the prostate model, which is used in planning and executing the biopsy [92], [93]. The biopsy locations are also recorded on this prostate model.

The UroStation and the UroNav are developed to minimally modify the conventional clinical workflow of freehand prostate biopsy. While these systems have the additional benefits of 3D imaging and MRI-ultrasound fusion capabilities, the drawback of the freehand probe manipulation in prostate shifting and deformation remains unchanged. Although the UroStation includes an image registration technique that can possibly track and compensate prostate shifting and deformation, the registration is not able to be done in real-time. While the Artemis system with passive mechanical arms allows passive guidance for the needle targeting and stabilization of the probe manipulation, a motorized robotic arm can additionally enable automated needle targeting and may provide better manipulation of the ultrasound probe in minimizing the prostate shifting and deformation during the biopsy procedure. The patient-induced prostate shifting and deformation still remain a mountain to climb though.
1.2 Dissertation Contributions

Most of the work discussed in this dissertation has been accomplished in close collaboration with engineering and clinical researchers from Johns Hopkins University and Children’s National Medical Center (Washington D. C.). The work done by the collaborators is not discussed in detail in this dissertation. The main contents of this dissertation are based on my personal contributions and they are explained in detail at the beginning of each following section.

In this section, the scientific contributions and significance of the work involved in this dissertation are summarized. The main scientific contributions of this dissertation are the development of the image-guided robotic system for interventional CNB. This dissertation presents several novel robotic systems, uniquely designed algorithms, and important experimental methods and results that may have a significant effect on clinical treatment.

1.2.1 MRI-Guided Robotic Interventions for Core Needle Biopsy

1.2.1.1 Scientific Contributions
- MR Safe RCM Robot, a novel MRI-guided robot for needle guidance, which is designed to be compact, stiff, accurate, safe to operate in the MRI, and not to deteriorate the image quality.
- Custom-written software for robot control and image guidance, which enables expedited image-robot registration, visual robotic targeting simulation, and safe robot control.
- In-vitro experiments evaluating the mechanical performance of the MR Safe RCM Robot.
- A preclinical study demonstrating the effectiveness of the MR Safe RCM Robot in pediatric bone biopsy.
- Cadaver study demonstrating the feasibility of the MR Safe RCM Robot in pediatric bone biopsy.
- A preclinical study demonstrating the effectiveness of the MR Safe RCM Robot in deep brain access.

1.2.1.2 Significance

An MRI-compatible robotic system was developed for MRI-guided needle insertion. The robot was entirely made of nonconductive, nonmetallic, and nonmagnetic materials. Moreover, to work within the MR scanner, the robot was designed and developed to be compact, stiff, accurate, safe to operate in the MRI, and
not to deteriorate the image quality. In addition to the robot, the custom-written software enables expedited image-robot registration, visualized robotic targeting simulation, and safe robot control.

The MR Safe robotic system can be utilized to be a part of an improved clinical workflow in which the pediatric bone biopsy can be performed earlier, ideally at the same time of the diagnostic MRI scan being completed. Since the robot enables the bone biopsy to be performed in the MRI scanner, the time needed to schedule a separate biopsy procedure in the operating room or CT scanner room is eliminated. Performing the biopsy with MRI guidance would also allow more accurate sampling, especially for bone marrow lesions that are best seen with MRI. These lesions are invisible to the naked eye during surgical biopsy and much less conspicuous on CT scans, increasing the possibility of false diagnoses from inaccurate sampling. Furthermore, the use of the MR Safe robot to perform MRI-guided bone biopsy would eliminate the radiation exposure from CT guidance for both the patient and the physician.

The MR Safe robotic system can be also used for stereotactic brain biopsy with an intraoperative MRI scanner. The system would allow neurosurgeons to formulate surgical plans based on most recent images, utilize continuous imaging for immediate feedback, and maintain the operative rhythm by eliminating the common in-out moves of the patient bed into the scanner, operating within the scanner under direct imaging. Furthermore, the robotic system could be potentially used not only for brain biopsy, but also for numerous neurosurgical procedures that require deep brain access such as deep brain stimulation (DBS), ventriculoperitoneal shunting, and laser ablation of the hippocampus.

1.2.1.3 Relevant publications


1.2.2 TRUS-Guided Robotic Interventions for Core Needle Biopsy

1.2.2.1 Scientific Contributions

- TRUS Robot, a novel ultrasound-guided robot for prostate biopsy, which enables minimization of the prostate deformation and accurate, hands-free, skill-independent prostate biopsy.
- Cohesive TRUS Probe-Robot, a novel ultrasound-guided robot for prostate biopsy, which is designed to minimize the prostate deformation and be accurate, compact and light.
- Custom-written software for 3D TRUS imaging, biopsy planning, robot control, and navigation.
- Novel algorithms to minimize the prostate deformation during the biopsy.
- In-vitro experiments evaluating the mechanical performance of the robots.
- A preclinical study demonstrating the effectiveness of the TRUS-guided robotic prostate biopsy.
- FDA/IRB-approved clinical trials demonstrating the feasibility of the TRUS-guided robotic prostate biopsy system.

1.2.2.2 Significance

A concept of the robotic system for TRUS-guided transrectal prostate biopsy was proposed. The robotic system takes transrectal prostate biopsy one step further, with an actuated TRUS probe manipulation robot and a custom-written software for robot control and image guidance. Like no other, the system enables minimization of the prostate deformation and accurate, hands-free, skill-independent prostate biopsy.

The TRUS robot was developed to assist urologists in performing prostate biopsy under TRUS guidance. The TRUS robot moves an ultrasound probe with the same 4 DoF that is used manually in transrectal procedures, closely replicating its movement by hand. In addition to the TRUS robot, novel techniques for minimizing the prostate deformation during the biopsy were developed. By applying the techniques uniquely designed for the TRUS robot, it is possible to minimize the movement of the ultrasound probe during the biopsy, reducing the prostate deformation and increasing the targeting accuracy.
The cohesive TRUS probe-robot was developed to assist urologists in performing prostate biopsy under TRUS guidance. While the robot is able to carry out the same transrectal prostate biopsy as the TRUS robot, the robot has only 2-DoF, 1-DoF for rotating the ultrasound probe and 1-DoF for rotating the needle-guide. The lower DoF enables not only accurate needle targeting but also compact and light system. As prostate biopsy is commonly performed in a small clinic room by a urologist, the size and weight of the robotic system is an important factor to be considered. The robotic prostate biopsy system including the software and the robot would be potentially integrated into the ultrasound machine, making the system even more compact and simple.

1.2.2.3 Relevant publications

- M. Han, S. Lim, C. Jun, D. Petrisor, and D. Stoianovici, “TRUS Robot Guided Prostate Biopsy,” in *Proc. 32nd Annual Meeting of Engineering and Urology Society (EUS2017)*, 2017. (My personal contribution: 50%)

1.2.3 Personalized Systematic Prostate Biopsy

1.2.3.1 Scientific Contributions

- Personalized robotic prostate biopsy, a novel concept for prostate biopsy, which enables a patient specific optimal biopsy plan that maximize the detection probability of PCa.
- A novel prostate segmentation method, which is efficient, robust, and functional in clinical practice.
- A novel algorithm to maximize the detection probability of PCa by enabling a uniform distribution of the systematic biopsy plan over the prostate gland.
- FDA/IRB-approved clinical trials demonstrating the feasibility of the personalized robotic prostate biopsy system.
- A novel MRI-ultrasound fusion technique based on the prostate associated coordinate system.
1.2.3.2 Significance

A novel methodology for personalized robotic prostate biopsy was developed. The personalized robotic prostate biopsy has the potential to increase the CDR of clinically significant PCa with 12-cores biopsy. Novel methods and algorithms for geometric optimization of the 12-cores biopsy plan were developed and integrated with the robotic prostate biopsy system.

The orthogonal-planes based segmentation enables expedited, robust, and functional prostate segmentation for clinical practice. With this method, the prostate is able to be represented using only 26 nodes. The averaged prostate model generated based on the node points expedites the segmentation even further. Moreover, the novel algorithms developed for the geometric optimization of the 12-cores biopsy plan could potentially increase the detection probability of clinically significant PCa and decrease the infection risk. The algorithms are used to evenly distribute the biopsy plan over the prostate, avoid the urethra, and cover the peripheral zone where the majority of prostate tumors are found (68% [94]). FDA/IRB-approved clinical trials showed that optimizing the 12-cores biopsy plan for each patient is feasible.

The geometric optimization of the 12-cores biopsy plan maximizes the sampling probability of significant PCa. Moreover, the robotic biopsy approach enables the optimized plan to be executed precisely, with hands-free TRUS guidance that makes the procedure less dependent on the urologist’s skills. Together, these have the potential to increase the detection rate of clinically significant PCa. To the best of our knowledge, this is the first report of personalized systematic prostate biopsy.

1.2.3.3 Relevant publications

- S. Lim, D. Chang, C. Jun, P. Li, D. Petrisor, D. Stoianovici, M. Han, “First Systematic Personalized Prostate Biopsy,” in Proc. 33rd Annual Meeting of Engineering and Urology Society (EUS2018), 2018. (My personal contribution: 70%)
1.3 Dissertation Organization

This dissertation presents two types of image-guided robotic intervention systems for CNB.

In Chapter 2, the MRI-Guided Robotic Interventions for CNB are reported. In this chapter, a robot system is presented, and two types of medical applications are introduced. Section 2.1 presents the structure and kinematics of the MR Safe RCM robot, which was developed for needle guidance under MRI. This section also reports various tests to evaluate the mechanical performance of the robot. Section 2.2 presents the custom-written software for the MRI-guided robotic needle guidance. Section 2.3 presents the first medical application of the robot for pediatric bone biopsy. The validation tests of the robot for pediatric bone biopsy are reported in this section. Section 2.4 presents the second medical application of the robot for stereotactic brain biopsy. The validation tests of the robot in deep brain access are reported in this section.

In Chapter 3, the TRUS-Guided Robotic Interventions for CNB are reported. In this Chapter, a medical application is introduced, and two types of robots are presented. Section 3.1 introduces the basic concept of the TRUS-guided robotic prostate biopsy, including background, motivation, and system overview. Section 3.2 presents the custom-written software for the TRUS-guided robotic prostate biopsy. Section 3.3 presents the first robot, the TRUS Robot, which is developed for the TRUS-guided robotic prostate biopsy. The comprehensive validation tests of the system including bench tests, in-vitro test, and clinical trials are reported in this section. Section 3.4 presents the second robot, the cohesive TRUS Probe-Robot, which is also developed for the TRUS-guided robotic prostate biopsy. The extensive validation tests of the system including bench and in-vitro tests are reported in this section.

In Chapter 4, the concept, implementation, and validation of the personalized robotic prostate biopsy are reported. Section 4.1 presents the background and motivation of the personalized robotic prostate biopsy. Section 4.2 presents a new approach for prostate segmentation, the orthogonal-planes based prostate segmentation. Section 4.3 presents the optimization algorithms uniquely designed for the personalized robotic prostate biopsy. Section 4.4 reports the results of its clinical trials. Section 4.5 presents an MRI-ultrasound fusion technique and its feasibility test.

In Chapter 5, the main work of this dissertation is summarized, and possible future extensions are discussed.
2 MRI-Guided Robotic Interventions for CNB

Chapter 2 is organized as follows. Section 2.1 presents a description of the MR Safe RCM Robot, followed by its validation experiments. Section 2.2 presents a description of the custom-written software for MRI-guide robotic needle guide. Section 2.3 presents a description of the system in a pediatric application, followed by its validation experiments. Section 2.4 presents a description of the system in a neurosurgical application, followed by its validation experiments. Section 2.5 and Section 2.6 present a summary and conclusion of Chapter 2, respectively. At last, Section 2.7 presents a list of the scientific contributions involved in this chapter.

2.1 MR Safe RCM Robot for Needle Intervention

The main goal of the work involved in this section was to develop and evaluate a compact and accurate MR safe robot to aid medical specialists in performing needle insertion under MRI guidance. The development of the robot has been reported in a journal article [95].

2.1.1 Personal Contributions

The design of the robot was done by Dr. Dan Stoianovici and the manufacturing of the robot was done by Dr. Doru Petrisor. The image quality tests including signal to noise ratio (SNR) and image change factor (ICF) analyses of the robot were done by Changhan Jun. Those works are not discussed in detail here.

My personal contribution includes:

- System integration.
- Formulation and analysis of the robot kinematics.
- Design, implementing, and debug of the robot control software.
- Design, execution, and analysis of all the experiments discussed here.

2.1.2 Robot Structure

An MR Safe (ASTM F2503) robot has been developed with 3 DoF [95]. The robot is mounted on the MRI table using a custom mounting platform, and its location is manually positioned to move the tip of the
needle-guide to the region of interest with 4 degrees of adjustment (DoA). The robot orients a needle-guide about two orthogonal axes intersecting at a point located below the needle-guide, a remote center of motion (RCM) point [96], [97]. The two axes are actuated with independent PneuStep motors [60] coaxially located on the robot base [34], as shown in Figure 2.1. The range of the pitch rotation is -50 to +30 [deg] implemented with a custom ACME Ø10 x 2 [mm] pitch screw. The step resolution varies between 0.029-0.044 [deg/step], depending on the position of the RCM mechanism. The roll rotation is unlimited by the joint but effectively constrained by the interference with the clinical site (±40 [deg]). Its step resolution is 0.082 [deg/step].

The needle is inserted manually through the needle-guide. The depth of needle insertion is set by the third PneuStep motor remotely located on the top of the interface box, as shown in Figure 2.1. Before the needle insertion, this depth driver pre-adjusts the location of a depth stopper that fits around the needle [34]. Two sterilizable parts are attached to the top of the depth driver, as shown in Figure 2.2a, b, c. The two parts can be replaced based on the diameter and length of the needle for a particular medical application, as shown in Figure 2.2a, b.

The robot is electricity free, uses pneumatic actuation, optical sensors for position sensing, and is entirely made of nonconductive, nonmetallic, and nonmagnetic materials, such as polycarbonate, polysulfone, ultem, garolite, etc. Consequently, the robot is MR Safe according to ASTM standards, such as F2052, F2213,

![Figure 2.1 MR safe remote center of motion (RCM) robot and Interface box](image)
and F2182 based on the scientific rationale [95]. Certified biocompatible material (ISO-10993) has been used to build the needle-guide, which comes into direct contact with the patient. The inner diameter of the needle-guide can be customized to accommodate various sizes of needles for multiple medical applications, as shown in Figure 2.2d. The needle-guide can be easily detached by pressing a button and is the only component to be sterilized since the entire robot can be covered with a sterile bag. Four high-contrast MRI markers have been made of glass tubes filled with MR-Spots contrast (Beekley, Bristol, CT). The lengths of the markers are 75, 75, 45, and 28 [mm]. The MRI markers are rigidly attached to the top link of the robot for image-robot registration (Figure 2.1).

Figure 2.2 Depth guide change for (a) pediatric and (b) neurosurgical applications, (c) Depth guides and needle guides, and (d) Needle guides showing different inner diameters
2.1.3 System Layout

Figure 2.3 shows a system diagram showing the placement of system components. The robotic system is composed of three main components: the robot, the interface box, and the robot controller. Those components have separate labels based on the ASTM F2503 standard. The robot is mounted on the MRI table and located inside the MRI scanner. The robot is made of electrically nonconductive, nonmetallic, and nonmagnetic materials. Therefore, the robot is classified as an MR Safe device according to ASTM standards F2052, F2213, and F2182 [95]. The interface box is located in the scanner room (ACR Zone IV), but outside the 0.5 mTesla (5-Gauss) line. The interface box is nonmagnetic but uses electricity. Therefore, the interface box is classified as an MR Conditional device. The robot controller (Figure 2.28a) is located outside the scanner room (ACR Zone IV) in the control room (ACR Zone III). The robot controller is magnetic and uses electricity. Therefore, the robot controller is classified as an MR Unsafe device.

Once an MRI scan is finished, a set of MRI images are transferred to the navigation software through an Ethernet cable in DICOM format. The navigation software is then connected to the robot controller with an Ethernet cable and sends and receives the target position and the robot position, respectively. The robot controller is connected to the interface box with a shielded cable passing through the patch panel and sends control signals to the robot. The interface box and the robot are connected via a bundle of hoses that compressed air and optical fibers are passing through, as shown in Figure 2.3.

![Figure 2.3 System diagram showing the placement of MR Safe, Conditional, and Unsafe components](image-url)
2.1.4 Forward Kinematics

Forward kinematics problem is to calculate the position of the biopsy needle tip $\mathbf{\hat{p}}$ for given step counts of the three PneuStep motors $[\text{step}_1, \text{step}_2, \text{step}_3]$. Figure 2.4 shows a schematic diagram of the robot kinematics. The forward kinematics of the robot is calculated in the following manner.

First, we calculate the direction of the needle-guide for a given robot joint angles ($\theta_1$ and $\theta_2$). The PneuStep motor 2 rotates the needle-guide about the Z-axis in the amount of $\theta_2$. As the direction of needle-guide has an offset angle of 20 [deg] on the ZY plane in the initial state, the direction of the needle-guide with the offset angle of 20 [deg], $\mathbf{\hat{v}}_2$, is calculated as:

$$
\mathbf{\hat{v}}_2 = \begin{pmatrix}
\cos \theta_2 & -\sin \theta_2 & 0 \\
\sin \theta_2 & \cos \theta_2 & 0 \\
0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
1 & 0 & 0 \\
0 & \cos 20 & -\sin 20 \\
0 & \sin 20 & \cos 20
\end{pmatrix}
\begin{pmatrix}
0 \\
-1 \\
0
\end{pmatrix}
= \begin{pmatrix}
\cos 20 \sin \theta_2 \\
-\cos 20 \cos \theta_2 \\
-\sin 20
\end{pmatrix}
$$

(2.1)

Also, the direction of the needle-guide without the offset angle of 20 [deg], $\mathbf{\hat{v}}_1$, is calculated as:

$$
\mathbf{\hat{v}}_1 = \begin{pmatrix}
\cos \theta_2 & -\sin \theta_2 & 0 \\
\sin \theta_2 & \cos \theta_2 & 0 \\
0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
0 \\
-1 \\
0
\end{pmatrix}
= \begin{pmatrix}
\sin \theta_2 \\
-\cos \theta_2
\end{pmatrix}
$$

(2.2)

Figure 2.4 Schematic diagram for robot kinematics calculation
Therefore, we have a relationship between \( \mathbf{v}_1 \) and \( \mathbf{v}_2 \) such that

\[
\mathbf{v}_2 = \mathbf{v}_1 \cos 20 - \mathbf{e}_3 \sin 20
\]
\[
\mathbf{v}_1 = \frac{\mathbf{v}_2 + \mathbf{e}_3 \sin 20}{\cos 20}
\] (2.3)

where \( \mathbf{e}_3 = (0 \ 0 \ 1)^T \)

Meanwhile, the PneuStep motor1 translates the point \( p \) on the link1 along the Z-axis, changing the direction of the needle-guide \( \mathbf{v}_2 \) into \( \mathbf{v}_3 \).

Therefore, the final direction of the needle-guide \( \mathbf{v}_3 \) is calculated as:

\[
\mathbf{v}_3 = \mathbf{v}_1 \cos (\theta_1 + 20) - \mathbf{e}_3 \sin (\theta_1 + 20)
\]
\[
= (\mathbf{v}_2 + \mathbf{e}_3 \sin 20) \frac{\cos (\theta_1 + 20)}{\cos 20} - \mathbf{e}_3 \sin (\theta_1 + 20)
\]
\[
= \begin{pmatrix}
    \cos(\theta_1 + 20) \sin \theta_2 \\
    -\cos(\theta_1 + 20) \cos \theta_2 \\
    -\sin(\theta_1 + 20)
\end{pmatrix}
\] (2.4)

Next, we calculate the robot joint angles (\( \theta_1 \) and \( \theta_2 \)) for a given motor steps (\( \text{step}_1 \) and \( \text{step}_2 \)). \( \theta_2 \ [\text{deg}] \) is simply calculated as:

\[
\theta_2 = -MH \text{step}_2
\] (2.5)

where \( M = 4.00 \ [\text{deg/step}] \) is the transmission ratio of the PneuStep motor and \( H = -1/49 \) is the transmission ratio of the harmonic drive.

Let the angles of the link2 from the vertical and horizontal lines \( \beta \) and \( \alpha \), respectively, as shown in Figure 2.5. Then, we have \( \beta = 90 - \alpha \). As \( \theta_1 \) is limited in the range of \(-50 \ [\text{deg}] \leq \theta_1 \leq 30 \ [\text{deg}] \) by the robot hardware design, \( \beta \) is also limited in the range of \(-30 \ [\text{deg}] \leq \beta \leq 50 \ [\text{deg}] \).

By the cosine rule,
Finally, \( \theta_1 [\text{deg}] \) is calculated as:

\[
\theta_1 = \beta - 20 = 70 - \alpha = 70 - \cos^{-1}\left(\frac{L_2^2 + (z_0 + dz)^2 - L_1^2}{2L_2(z_0 + dz)}\right)
\]  
\[(2.8)\]

where \( L_1 = 114.219 [\text{mm}] \) and \( L_2 = 41.572 [\text{mm}] \) are constant lengths of the link1 and the link2, respectively. \( dz \) is the translation distance of the point \( \vec{q} \) by the motor1 and motor2 and \( z_0 = 121.549 [\text{mm}] \) is the initial distance between (when \( \theta_1 = 0 \)) the point \( \vec{q} \) and the fixed point of the link2, as shown in Figure 2.5.

Since a screw-nut mechanism is applied to translate the point \( \vec{q} \) on the link1, the movement of the motor2 (\( \theta_2 \)) changes the joint value \( \theta_1 \). Therefore, to keep the joint value \( \theta_1 \) constant during the movement of the motor2 (\( \theta_2 \)), the motor1 need to move in the opposite direction to compensate for the motion caused by the motor2. Therefore, the translation distance of the point \( \vec{q} \) on the link1 is calculated as:
\[ dz = P \left( \frac{M}{360} step_1 - \frac{HM}{360} step_2 \right) \]  

(2.9)

where \( P = 2.00 [\text{mm/turn}] \) is the pitch of the screw transmission.

The final position of the inserted needle tip \( \vec{p} \) is then given by,

\[ \vec{p} = \tau v_3 \]  

(2.10)

where \((L_2 + D + \tau)\) is a length of the needle adjusted by needle stopper travels distance \( \tau \) such that

\[ \tau = -\frac{NM step_3}{360} \]  

(2.11)

where \( N = 4.50 [\text{mm/turn}] \) is the pitch of the screw on which the stopper nut translates and \( D = 5 [\text{mm}] \) is a constant design parameter.

### 2.1.5 Inverse Kinematics

Inverse kinematics problem is to calculate the required step counts of the three PneuStep motors \([step_1, step_2, step_3]\) for a given target point \( \vec{p} = (p_x \quad p_y \quad p_z)^T \). The inverse kinematics is calculated in the similar manner as below.

First, by rotating motor2, the YZ plane is rotated into the Y'Z plane by \( \theta_2 \) such that the target is lying on the rotated plane. Thus, the counts of motor2 steps is calculated as:

\[ step_2 = -\frac{\theta_2}{MH} = -\frac{1}{MH} \tan^{-1} \left( \frac{p_x}{p_y} \right) \]  

(2.12)

Once the target is on the Y'Z plane, by rotating motor1, the direction of the needle-guide is adjusted to be aligned with the line between the RCM and \( \vec{p} \) points. Thus, \( \theta_1 \) is determined from the equation below.
$v_3 = \begin{pmatrix} \cos(\theta_1 + 20)\sin\theta_2 \\ -\cos(\theta_1 + 20)\cos\theta_2 \\ -\sin(\theta_1 + 20) \end{pmatrix} = \frac{\vec{p}}{|\vec{p}|}$ (2.13)

Next, for a given $\theta_1$ [deg], $dz$ is calculated. Let the angle between the link 1 and the horizontal line as $\gamma$, as shown in Figure 2.6. Then, $\gamma$ [deg] is calculated for a given $\theta_1$ as:

$L_1 \sin \gamma = L_2 \cos \beta$

$\gamma = \sin^{-1}\left(\frac{L_2 \cos \beta}{L_1}\right) = \sin^{-1}\left(\frac{L_2 \cos(\theta_1 + 20)}{L_1}\right)$ (2.14)

Then, the distance between $z_0 + dz$ is calculated as:

$z_0 + dz = L_1 \cos \gamma + L_2 \sin \beta = L_1 \cos\left(\sin^{-1}\left(\frac{L_2 \cos(\theta_1 + 20)}{L_1}\right)\right) + L_2 \sin(\theta_1 + 20)$

$= \pm L_1 \sqrt{1 - \frac{L_2^2 \cos^2(\theta_1 + 20)}{L_1^2}} + L_2 \sin(\theta_1 + 20)$ (2.15)

Since $\theta_1$ is limited by the robot hardware design ($-50$ [deg] $\leq \theta_1 \leq 30$ [deg]), the translation distance of the point $\vec{q}, dz$, is uniquely determined for a given $\theta_1$ as:
\[ dz = L_1 \sqrt{1 - \frac{L_2^2 \cos^2(\theta_1 + 20)}{L_1^2}} + L_2 \sin(\theta_1 + 20) - z_0 \] (2.16)

Then, the number of motor1 steps is calculated for a given \( dz \) as

\[ \text{step}_1 = \frac{dz}{M}360 + H \text{step}_2 \] (2.17)

Finally, the counts of motor3 steps required to place the needle tip at the target is calculated as:

\[ \text{step}_3 = -360 \frac{\tau}{NM} = -360 \frac{[\bar{p}]}{NM} \] (2.18)

### 2.1.6 Step Resolution

The step resolution of the first axis (\( \theta_1 \)) varies depending on its position, while the step resolutions of the second (\( \theta_2 \)) and third (\( \tau \)) axes are constant. The step resolutions of the three axes are calculated as below.

The step resolution of the first axis \( \Delta \theta_1 \) can be calculated from the equation (2.8), (2.9). By applying the constant numbers, such as \( L_1 = 114.219 \, [mm] \), \( L_1 = 114.219 \, [mm] \), and \( dz_0 = 121.549 \, [mm] \), \( \theta_1 \) and \( \Delta \theta_1 \) are calculated as shown in Figure 2.7. As \( \theta_1 \) is limited in the range of \( -50 \, [deg] \leq \theta_0 \leq 30 \, [deg] \), \( \text{step}_1 \) is also limited in the range of \( -1527 \, [steps] \leq \text{step}_0 \leq 960 \, [steps] \). The step resolution of the first axis varies between 0.0288 [deg/step] and 0.0437 [deg/step] depend on its position, as shown in Figure 2.7b.

The step resolution of the second axis \( \Delta \theta_2 \) is calculated as \( \Delta \theta_2 = MH \equiv -0.08163 \, [deg/step] \), where \( M \) is the transmission ratio of the PnuStep motor (\( M=4.00 \, [deg/step] \)) and \( H \) is the transmission ratio of the harmonic drive (\( H = -1/49 \)).

The step resolution of the third axis \( \Delta \theta_3 \) is calculated as \( \Delta \theta_3 = \frac{MN}{360} = 0.05 \, [mm/step] \), where \( N \) is the pitch of the screw transmission (\( N = 4.50 \, [mm/turn] \)).
2.1.7 Joint Accuracy Test

2.1.7.1 Methods

A bench test was performed to verify the joint accuracies of the robot. The accuracies were measured using two different devices, a protractor and caliper, and an optical tracker (Polaris, NDI, Canada).

In the measurement, each joint of the robot moved one at a time with an increment of 5 $[deg]$ for the joint1($\theta_1$) and the joint2($\theta_2$), and 5 $[mm]$ for the joint3($\tau$). The movement ranges were $-45 [deg] \leq \theta_1 \leq 30 [deg]$, $-90 [deg] \leq \theta_2 \leq 90 [deg]$, and $0 [mm] \leq \tau \leq 45 [mm]$, respectively.

In the first measurement, a protractor (No. C183, Starrett) and caliper (Mitutoyo, Japan) were used to measure the rotational errors and translational errors of the robot, as shown in Figure 2.8. The minimum accuracy of the protractor and the caliper were 0.25 $[deg]$ and 0.01 $[mm]$, respectively. The measurements were repeated for three times.

In the second measurement, an optical localizer (Polaris, NDI, Canada) was used to measure the 3D position of a reflective marker on a light and rigid rod attached to the robot, as shown in Figure 2.9a. The manufacturer-stated RMS error of the localizer is 0.35 $[mm]$. The distance between the reflective marker and the RCM point was about 214 $[mm]$ and the optical localizer was approximately located 1100 $[mm]$ away from the marker. The accuracy of the localizer can be improved in this environment up to 0.078 $[mm]$ [98].
The 3D positions of the marker were measured for 500 frames and averaged at each position. Using the obtained three sets of the mean points, the rotational errors of the joint1(θ₁) and the joint2(θ₂), and the translational error of the joint3(τ) were estimated.

A rotational center was estimated to calculate the rotational errors. To estimate a rotational center, first, a plane was fitted to the point set using a least-square technique and a normal vector of the plane was found. Second, the point set was projected onto the plane. Third, a circle was fitted to the projected point set using a least-square technique and a center point was found. The rotational center was defined as the center point.

---

**Figure 2.8** Joint accuracy measurement of (a) Axis1 (θ₁), (b) Axis2 (θ₂), and (c) Axis3 (τ)

**Figure 2.9** Joint accuracy measurement of (a) Axis1 (θ₁), Axis2 (θ₂), and (b) Axis3 (τ)
of the circle. Then, the rotational errors of the joint1(\(\theta_1\)) and the joint2(\(\theta_2\)) were measured by calculating the angles between the lines that connect the projected points and the center point of the estimated circle, as shown in Figure 2.10.

A translational axis was estimated to calculate the translational errors. To estimate a translational axis, first, a principal component analysis (PCA) was applied to the point set. Second, a mean point of the point set was calculated. The translational axis was defined with the mean point and the first principal axis of the point set. The translational errors of the joint3(\(\tau\)) were measured by calculating the distances between the points projected onto the first principal axis of the point set, as shown in Figure 2.11.

2.1.7.2 Results

Results of the measurement using the protractor and caliper are shown in Table 2.1. The accuracy of the joint1(\(\theta_1\)) was 0.11 [\(mm\)], which is less than the minimum accuracy of the measurement (0.25 [\(deg\)]). The accuracy of the joints2(\(\theta_2\)) was 0.0, which is less than the minimum accuracy of the measurement (0.25 [\(deg\)]). The accuracy of the joint3(\(\tau\)) was 0.01 [\(mm\)], which is equal to the minimum accuracy of the measurement (0.01 [\(mm\)]).

Table 2.2 shows the measurement results using the optical localizer. The plots of the rotational errors and translational errors were presented in Figure 2.10 and Figure 2.11.

Table 2.1: Measurement results with protractor and caliper

<table>
<thead>
<tr>
<th></th>
<th>Joint1 ((\theta_1))</th>
<th>Joint2 ((\theta_2))</th>
<th>Joint3 ((\tau))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy [(deg)]</td>
<td>0.09 0.11 0.13</td>
<td>0.0 0.0 0.0</td>
<td>0.03 0.01 0.01</td>
</tr>
<tr>
<td>Precision [(deg)]</td>
<td>0.11</td>
<td>0.0</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Test1</td>
<td>Test2</td>
<td>Test3</td>
</tr>
<tr>
<td>0.13</td>
<td>0.13</td>
<td>0.16</td>
<td>0.0</td>
</tr>
<tr>
<td>0.14</td>
<td>0.0</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.2: Measurement results with optical localizer

<table>
<thead>
<tr>
<th></th>
<th>Joint1 ($\theta_1$)</th>
<th>Joint2 ($\theta_2$)</th>
<th>Joint3 ($\tau$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy [deg]</td>
<td>0.0239</td>
<td>0.0605</td>
<td>0.0374</td>
</tr>
<tr>
<td>Precision [deg]</td>
<td>0.0220</td>
<td>0.0729</td>
<td>0.0465</td>
</tr>
</tbody>
</table>

Figure 2.10 Joint accuracy test results of (a) Joint1 ($\theta_1$) and (b) Joint2 ($\theta_2$)

Figure 2.11 Joint accuracy test results of Joint3 ($\tau$)
2.1.8 Robot Space Set Point Test

2.1.8.1 Methods

An additional bench test was performed to verify the virtual needle-tip positing accuracy. All the experimental setups were equivalent to the previous tests. The experimental setup for the test is presented in Figure 2.1.

In the measurement, the joint1 ($\theta_1$) was moved from -45 [deg] to 25 [deg] with an increment of 5 [deg]. For each position, the joint2 ($\theta_2$) moved from 180 [deg] to 360 [deg] with an increment of 12 [deg]. The 3D positions of the marker were measured for 500 frames at each position and 240 points $\vec{p}_{i,j}, i = 1,2, ..., N_i, j = 1,2, ..., N_j$ ($N_i = 16, N_j = 15$) averaged at each position were obtained.

The point set was analyzed as follows:

1. Fit a sphere to the data set $\vec{p}_{i,j}$ using a least square approach with Gauss-Newton algorithm in order to estimate the distance from the RCM point to the optical marker $D$.

2. Generate a data set $\vec{q}_{i,j}, i = 1,2, ..., N_i, j = 1,2, ..., N_j$ by solving the forward kinematics problems of the robot using the distance estimated in the previous step.

3. Perform a rigid point cloud registration to estimate the transformation $F$ between the optical tracker coordinate system and the robot coordinate system [99].

$$\vec{p}_{i,j} = F \cdot \vec{q}_{i,j}$$  \hspace{1cm} (2.19)

Figure 2.12 Experimental setup showing (a) rotational axis and (b) optical marker
4. Transform the points \( \overline{q}_{i,j} \) to the points \( \overline{q}'_{i,j} \), which are defined in the optical localizer coordinate system.

\[
\overline{q}'_{i,j} = F \cdot \overline{q}_{i,j}
\]  

(2.20)

5. Evaluate the error \( e \) [mm] as an average distance between the two data sets.

\[
e = \frac{\sum_{i,j} \| \overline{p}_{i,j} - \overline{q}'_{i,j} \|}{N_i N_j}
\]  

(2.21)

6. Calculate the angular accuracy \( \delta \) [deg].

\[
\delta = \frac{180 e}{D \pi}
\]  

(2.22)

7. Calculate the estimated targeting accuracy \( e_{10} \) expected due to the robot at a target depth of 10 [mm].

\[
e_{10} = \frac{10 e}{D}
\]  

(2.23)

2.1.8.2 Results

Figure 2.13 shows a plot of the two point sets. The average error between the actual and set point datasets was 0.645 [mm] with a standard deviation of 0.279 [mm]. The angular accuracy \( \delta \) of the robot was 0.177 [deg] with a precision of 0.077 [deg]. The estimated targeting error \( e_{10} \) that may be expected due to the robot was 0.031 [mm] with a standard deviation of 0.013 [mm] per cm of target depth.
2.1.9 Repeatability Test

2.1.9.1 Methods

The same optical localizer setup was used, as shown in Figure 2.12. The robot was sent to 9 end positions at $\theta_1 = \{-15, 0, 15 \text{ [deg]}\}$ and $\theta_2 = \{-15, 0, 15 \text{ [deg]}\}$. Each position was approached on each axis from $\pm 5 \text{ [deg]}$ of the start position, as shown in Figure 2.14. The experiment was repeated 5 times for a total of $9 \times 4 \times 5 = 180$ tests. The position of the optical marker was measured for 500 frames and averaged at the 9 end positions. The angular errors were calculated as in the previous test. The repeatability was calculated as the standard deviation of the angular errors.

2.1.9.2 Results

Table 2.3 shows the results of the repeatability test. The repeatability measured 0.136 [deg]. The manipulator has no perceivable play or backlash in any direction and appears stiff.
Table 2.3: Results of repeatability test (Robot coordinate)

<table>
<thead>
<tr>
<th>Robot position (Rx [deg], Rz [deg])</th>
<th>StdDev. in X direction [mm]</th>
<th>StdDev. in Y direction [mm]</th>
<th>StdDev. in Z direction [mm]</th>
<th>StdDev. of Norms [mm]</th>
<th>Angular Deviation [deg]</th>
<th>Deviation with a target depth of 50 [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-15.0, -15.0)</td>
<td>0.067</td>
<td>0.053</td>
<td>0.495</td>
<td>0.490</td>
<td>0.135</td>
<td>0.117</td>
</tr>
<tr>
<td>(-15.0, 0.0)</td>
<td>0.183</td>
<td>0.080</td>
<td>0.460</td>
<td>0.489</td>
<td>0.134</td>
<td>0.117</td>
</tr>
<tr>
<td>(-15.0, 15.0)</td>
<td>0.099</td>
<td>0.090</td>
<td>0.479</td>
<td>0.485</td>
<td>0.133</td>
<td>0.116</td>
</tr>
<tr>
<td>(0.0, -15.0)</td>
<td>0.100</td>
<td>0.174</td>
<td>0.452</td>
<td>0.482</td>
<td>0.132</td>
<td>0.116</td>
</tr>
<tr>
<td>(0.0, 0.0)</td>
<td>0.184</td>
<td>0.195</td>
<td>0.454</td>
<td>0.513</td>
<td>0.141</td>
<td>0.123</td>
</tr>
<tr>
<td>(0.0, 15.0)</td>
<td>0.113</td>
<td>0.192</td>
<td>0.444</td>
<td>0.484</td>
<td>0.133</td>
<td>0.116</td>
</tr>
<tr>
<td>(15.0, -15.0)</td>
<td>0.121</td>
<td>0.287</td>
<td>0.397</td>
<td>0.492</td>
<td>0.135</td>
<td>0.118</td>
</tr>
<tr>
<td>(15.0, 0.0)</td>
<td>0.168</td>
<td>0.313</td>
<td>0.403</td>
<td>0.524</td>
<td>0.144</td>
<td>0.126</td>
</tr>
<tr>
<td>(15.0, 15.0)</td>
<td>0.120</td>
<td>0.303</td>
<td>0.403</td>
<td>0.505</td>
<td>0.139</td>
<td>0.121</td>
</tr>
<tr>
<td>Average</td>
<td>0.128</td>
<td>0.187</td>
<td>0.443</td>
<td>0.496</td>
<td>0.136</td>
<td>0.119</td>
</tr>
</tbody>
</table>

Figure 2.14 End positions (red) and start positions (blue) for repeatability test
2.1.10 Stiffness Test

2.1.10.1 Methods

A spring with the weight of 22 \( [g] \) and the initial length of 80.0 \( [mm] \) was used to measure the stiffness of the robot. First, the spring was calibrated to estimate the spring constant \( K \) as:

1. Fix a spring to the milling machine and compress the spring. Then, measure its force for each compression length using an electronic scale.

2. Estimate the spring constant \( K \) such that \( F = Kx \) where \( F \) is a force and \( x \) is a compression length.

Next, the stiffness of the robot was measured using the calibrated spring as:

1. Fix the robot to the milling machine as shown in Figure 2.15.

2. Fix the spring calibrated in advance to the needle insertion position of the robot and the milling machine.

3. Compress the spring and measure the travel distance of the milling machine \( C \) and the deflection of the robot \( D \).

4. The resolution of the vertical encoder (Mitutoyo, Japan) for the travel distance of the milling machine was 0.01 \( [mm] \).

5. The resolution of the digimatic indicator (ID-C125EB, Mitutoyo, Japan) for the deflection of the robot was 0.001 \( [mm] \).

6. The compression length of the spring \( L \) is given by \( L = C - D \) and the force \( F \) is calculated as \( F = KL \).

Figure 2.15 (a) Experimental setup for stiffness test and (b) its enlarged view
2.1.10.2 Results

The spring constant $K$ was estimated as $4.123 \ [N/mm]$, as shown in Figure 2.16. Figure 2.17 shows the deflection of the robot due to the force at the needle-guide. About $1 \ [mm]$ of deflection was observed with 3.5 $[kg]$ of weight at the needle-guide. The robot constant $K$ was estimated as $33.376 \ [N/mm]$.

![Figure 2.16 Results of spring calibration](image1)

![Figure 2.17 Results of robot stiffness test](image2)
2.1.11 MR Safe Test

2.1.11.1 Methods

The safety of the robot in the MR environment was validated based on the ASTM F2503-13 standard [62]. The scientific rationale about the MR safe materials, which were used to build the robot, was initially considered. The robot was then tested for the magnetically induced displacement force and torque according to ASTM F2052 and ASTM F2213, respectively. In the displacement force measurement, the robot was suspended at the entrance of the MR scanner (Siemens MAGNETOM Aera, 1.5T), and the deflection and oscillating motion were observed, as shown in Figure 2.18a. In the torque measurement, the robot was suspended from the wooden support that was mounted to the patient table. The robot together with the patient table was sent into the MRI scanner while observing the deflection and oscillating motion, as shown in Figure 2.18b. The RF field-induced heating and gradient field-induced heating and vibration were also observed based on the standards such as ASTM F2182, ISO TS 10974 and ISO TS 10974. In addition, the magnetically induced forces were observed during carrying the interface box into the MR scanner room (ACR Zone IV). The interface box was stayed outside the 5-Gauss line and labeled as MR Conditional device [62].

2.1.11.2 Results

According to ASTM F2503-13 standard, “An item composed entirely of electrically nonconductive, nonmetallic and nonmagnetic materials may be determined to be MR Safe by providing a scientifically based rationale rather than test data” [62]. Thus, the robot is MR Safe. Nevertheless, several validation tests were performed. There was no noticeable deflection or oscillating motion. Induced heat or vibrations were not observed. Induced force on the Interface controller was not observed outside the 5-Gauss line.

Figure 2.18 Measurement of magnetically induced (a) displacement force and (b) torque
2.1.12 Image-Guided Targeting Test

2.1.12.1 Methods

A targeting test was performed with a custom-made grid mockup under the MRI guidance. Figure 2.19a shows an experimental setup for the targeting test. The grid mockup was 3D printed in the shape of a box with double 9-by-9 square grid layers at the bottom and the top. The mockup was then filled with a solution of 0.5 [%] Magnevist (Bayer Health Care LLC.) and 95.5 [%] water. Four MR markers made of glass and filled with MR-Spots contrast (Beekley, Bristol, CT) were attached to the top surface of the mockup. These linear markers were used for image-model registration to evaluate an image distortion and set predefined target points. The mockup was mounted on a wooden support (Figure 2.19a) and the support was fixed to the MRI table with hooks as shown in Figure 2.19b. The grid mockup was then positioned at the isocenter of the MRI scanner (Siemens MAGNETOM Aera, 1.5T). The robot was then fixed to the MRI table and its initial position was adjusted so that the RCM point of the robot locates at the center of the top grid, as shown in Figure 2.19a.

In the experiment, a series of T1-weighted MR images of the grid mockup and the robot was obtained. A volume image is then reconstructed based on the series of the MR images. The MR markers on the robot were segmented from the volume image using a general region growing technique and used for the image-
robot registration. The image-robot registration was performed with a custom-written software, which will be described in Section 2.2 in detail. Using a result of the image-robot registration, the volume image was registered to the robot space. The detailed explanation of the image-robot registration is presented in Section 2.2.

The MR markers on the mockup were then segmented using the same technique used for the robot markers. PCA was applied to the segmented marker models and their principal axes were estimated. Based on the estimated principal axes, the marker coordinate system was defined. Once the marker coordinate system was defined in the image space, the computer-aided design (CAD) model of the mockup was registered to the image space by matching the marker coordinate systems defined in the model and image spaces. Subsequently, the mockup CAD model was registered to the robot space by applying the image-robot registration transformation.

First, image distortions of the MR images were verified by checking the alignment of the grid lines. The volume image was resliced by a plane that is parallel to the top surface of the mockup CAD model and located at the bottom grid. Then, an ideal grid line of the CAD model was superimposed to the resliced image plane, as shown in Figure 2.22. The alignment between the grid MR image and the overlaid grid line were visually compared to evaluate image distortions and geometric artifacts of the MR images. In addition to the grid line alignment, the intersection angles between the MR markers were evaluated. Each MR marker needs to be perpendicular to the neighboring MR markers.

![Figure 2.20 MRI scan for image-robot registration](image-url)
Next, an image-guided targeting accuracy of the robot was evaluated. Nine target points predefined at the centers of the bottom grid were registered to the robot space by applying the two transformations obtained from the image-mockup and image-robot registrations, as shown in Figure 2.21. Based on these 9 target points, the inverse kinematics problems of the robot were solved, and the robot adjusted the orientation of the needle-guide and preset the depth of insertion. Since the clinical MRI bone biopsy needle (Invivo 15100) made of titanium and it makes artifacts on MR images, a needle with the same diameter was made of acryl instead, and the plastic needle was manually inserted through the needle-guide up to the indicated depth. Using this plastic needle, the location of the needle tip can be more exactly measured without the artifacts. The entire experiment was repeated for two times, a total of 18 targets. After each insertion of the needle for each target, an MRI scan was obtained for a verification purpose, as shown in Figure 2.20.

Since the grid mockup was filled with the solution, inside of the mockup was imaged gray and the plastic needle was imaged black (void of the signal), as shown in Figure 2.23a. Accordingly, the needle region was easily segmented by applying an iso-surface extraction algorithm, as shown in Figure 2.23b. The direction of the needle was determined as a first principal axis of the segmented surface. The depth of the needle was estimated by registering the needle CAD model to the segmented needle surface along its direction so that the sum of the distances between the vertices of the segmented surface and the corresponding projected points on the needle CAD model is minimized, as shown in Figure 2.24. The 2D targeting error was measured as the closest distance between the target point and the axis of the needle. The 3D targeting error was measured as the distance between the tip of the needle CAD model and the target point.
2.1.12.2 Results

Figure 2.22 shows a grid line overlaid on the resliced image of the bottom grid. A slight misalignment of the grid towards the perimeter on the order of 0.4 [mm] is shown in Figure 2.22b. The intersection angles between the four mockup markers are listed in Table 2.4.

At the time of the experiment, one target point was excluded among the nine target points because the needle path interfered with the top grid. The segmented surfaces of the inserted needles are shown in Figure 2.24a, c. The needle CAD models registered to the segmented surfaces are shown in Figure 2.24b, d. The accuracy and precision results of the 16 experiments are listed in Table 2.5, together with the estimated accuracy at a target depth $A_d$, and an example at 7 [cm], $A_{70}$.

Table 2.4: Mockup registration results

<table>
<thead>
<tr>
<th>Markers</th>
<th>Angle [deg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marker 1 &amp; Marker 2</td>
<td>89.901</td>
</tr>
<tr>
<td>Marker 1 &amp; Marker 3</td>
<td>89.827</td>
</tr>
<tr>
<td>Marker 2 &amp; Marker 4</td>
<td>89.747</td>
</tr>
<tr>
<td>Marker 3 &amp; Marker 4</td>
<td>89.723</td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.201</td>
</tr>
<tr>
<td>Precision</td>
<td>0.081</td>
</tr>
</tbody>
</table>

Figure 2.22 Image distortion check: (a) segmented markers and (b) grid lines overlaid on resliced image
Figure 2.23 Needle segmentation: (a) reconstructed MR image and (b) segmented needle (green)

Figure 2.24 Targeting results: (a, c) segmented needles and (b, d) registered needle models for each test
Establishing appropriate evaluation and testing methods has been challenging. In particular, in the image-guided targeting test, the MRI-compatible bone biopsy needle made with titanium (Invivo 15100) was not able to be used for the evaluation purpose because it makes artifacts on MR images. The tip position of the needle was not identifiable on the MR images. As such, an acrylic needle with the same diameter was prepared. However, the acrylic needle was invisible on MR images. Thus, a special mockup, which has a target grid at the bottom and can be filled with a solution of contrast agent inside, was designed and 3D printed. The region of the acrylic needle, which was inserted into the solution of the MRI contrast agent, was able to be easily segmented out using a marching cubes approach [100].

The targeting mockup was improved further after the validation tests and a standardized targeting mockup for MRI-compatible robots was developed and posted on the website for public access. Resources of the mockup are available at http://urobotics.urology.jhu.edu/share/qarai.

### Table 2.5: Targeting accuracy results

<table>
<thead>
<tr>
<th>Target Number</th>
<th>Target Depth [mm]</th>
<th>2D Error [mm]</th>
<th>3D Error [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Test1</td>
<td>Test2</td>
</tr>
<tr>
<td>1</td>
<td>38.13</td>
<td>1.62</td>
<td>1.58</td>
</tr>
<tr>
<td>2</td>
<td>36.98</td>
<td>1.27</td>
<td>1.52</td>
</tr>
<tr>
<td>3</td>
<td>39.03</td>
<td>1.26</td>
<td>0.88</td>
</tr>
<tr>
<td>4</td>
<td>37.20</td>
<td>1.65</td>
<td>1.58</td>
</tr>
<tr>
<td>5</td>
<td>36.03</td>
<td>0.72</td>
<td>1.10</td>
</tr>
<tr>
<td>6</td>
<td>38.13</td>
<td>0.45</td>
<td>0.80</td>
</tr>
<tr>
<td>7</td>
<td>39.45</td>
<td>1.82</td>
<td>1.54</td>
</tr>
<tr>
<td>8</td>
<td>38.34</td>
<td>0.53</td>
<td>0.75</td>
</tr>
</tbody>
</table>

| Accuracy (Average) | 37.91 | 1.17 | 1.22 | 1.85 | 1.57 |
| Precision (Std. Dev.) | 1.12 | 0.53 | 0.60 | 0.38 | 0.39 |

Accuracy $A_{(d)}$ = $1.07 + 0.0031d$

Accuracy $A_{(70)}$ = 1.29

2.1.13 Discussion and Conclusion

Establishing appropriate evaluation and testing methods has been challenging. In particular, in the image-guided targeting test, the MRI-compatible bone biopsy needle made with titanium (Invivo 15100) was not able to be used for the evaluation purpose because it makes artifacts on MR images. The tip position of the needle was not identifiable on the MR images. As such, an acrylic needle with the same diameter was prepared. However, the acrylic needle was invisible on MR images. Thus, a special mockup, which has a target grid at the bottom and can be filled with a solution of contrast agent inside, was designed and 3D printed. The region of the acrylic needle, which was inserted into the solution of the MRI contrast agent, was able to be easily segmented out using a marching cubes approach [100].

The targeting mockup was improved further after the validation tests and a standardized targeting mockup for MRI-compatible robots was developed and posted on the website for public access. Resources of the mockup are available at http://urobotics.urology.jhu.edu/share/qarai.
2.2 Software for MRI-Guided Robotic Intervention

The main goal of the work involved in this section was to develop two software programs for image guidance and robot control. The development of the software has been partially reported in journal articles [95], [101]–[103].

2.2.1 Personal Contributions

I was exclusively responsible for developing software programs. My personal contribution to this work includes all the process of software development, such as design, implementation, and debug of the software programs.

2.2.2 Image Guidance Software

A custom-written software was developed in C/C++ with open source libraries such as VTK [104], ITK [105], GDCM [106], and Eigen [107]. The software GUI is composed of a control menu (Figure 2.25a), a 3D virtual space (Figure 2.25b), and 2D resliced plane views (Figure 2.25c).

The main functions of the software include image-robot registration, volume rendering, volume reslicing, iso-surface extraction, segmentation based on region growing technique, principal axis estimation, targeting simulation, etc. The software internally solves the forward and inverse kinematics of the MR safe
robot. It also visualizes the virtual robot model and its workspace in the 3D virtual space (Figure 2.25b) based on the kinematics calculation.

The software is connected to the robot controller (Figure 2.28) through an Ethernet cable. Once a target point is selected in the 3D virtual space within the robot workspace (Figure 2.25b), the software sends the step numbers, which is obtained by solving an inverse kinematics problem for the target point, to the robot controller in order to move the robot to the target position. Moreover, through the connection, the software checks the current joint values of the robot and keeps the virtual robot model updated by periods. The software is able to be installed on a desktop or a laptop, which is classified as an MR Unsafe device and needs to stay outside the MRI scanner room (ACR Zone III).

2.2.3 Image-Robot Registration and Targeting

Image-robot registration is an important procedure for image-guided medical robots. A transformation matrix calculated from the image-robot registration allows transforming target points defined in the image space to the robot space. Based on the target point in the robot space, the robot can move its end-effector to the target position. Among the four MR markers attached on the robot, three MR markers arranged in a Z-shape (Figure 2.25) are used to calculate the actual registration. The fourth marker is optionally used to determine the direction of the Z-shape markers. The image-robot registration is performed by the image guidance software for the MR safe robot as follows.

In the first step, the three linear markers are segmented. To segment the linear markers, a volume image is first reconstructed from the series of MR images that includes the MRI markers of the robot. A seed point is then selected at the region of the marker on the resliced 2D image of the volume. A region growing and marching cube [100] algorithms are applied to segment and generate the surface data of the markers. The segmented marker surface data is presented in Figure 2.26.

In the second step, the center axis of each marker is estimated by applying a PCA and computing a centroid of the vertices of the surface data. The center line is defined as a line, which is oriented along the first principal axis and passes through the centroid, as shown in Figure 2.26. The three lines are defined as \( l_i(\vec{p}_i, \vec{n}_i), i = 1, 2, 3 \), where \( \vec{p}_i \) is a point on the line and \( \vec{n}_i \) is a direction vector.
In the third step, the marker coordinate system is defined in the image space using the three lines. The marker coordinate system $\Sigma_M$ is delineated at the center of the $Z$ markers, on the plane defined by the two parallel markers (left and right markers in Figure 2.26). The plane $P(\vec{p}_0, \vec{n}_0)$ is defined by the two lines $l_1(\vec{p}_1, \vec{n}_1)$ and $l_2(\vec{p}_2, \vec{n}_2)$ as

$$\vec{p}_0 = \frac{1}{2} (\vec{p}_1 + \vec{p}_2)$$
$$\vec{n}_0 = \frac{1}{\|\vec{p}_1 - \vec{p}_2\|} (\vec{p}_1 - \vec{p}_2) \times \frac{1}{\|\vec{n}_1 + \vec{n}_2\|} (\vec{n}_1 + \vec{n}_2)$$

where $\vec{p}_0$ is a point on the plane and $\vec{n}_0$ is a normal vector of the plane.

Subsequently, the three lines are projected onto the plane as

$$\vec{p}'_i = \vec{p}_i - (\vec{n}_0 \cdot (\vec{p}_i - \vec{p}_0))\vec{n}_0, i = 1,2,3$$
$$\vec{n}'_i = \vec{n}_i - (\vec{n}_0 \cdot \vec{n}_i)\vec{n}_0, i = 1,2,3$$

The projected lines $l'_1(\vec{p}'_1, \vec{n}'_1), i = 1,2,3$ are intersecting at the two points $\vec{s}_1$ and $\vec{s}_2$ such that

$$\vec{s}_1 = \vec{p}_1 + a\vec{n}_1 = \vec{p}_3 + b\vec{n}_3, a, b \in \mathbb{R}$$
$$\vec{s}_2 = \vec{p}_2 + c\vec{n}_2 = \vec{p}_3 + d\vec{n}_3, c, d \in \mathbb{R}$$

Figure 2.26 Robot marker coordinate system
The marker coordinate system $\Sigma_M$ is placed at the center point of $\vec{s}_1$ and $\vec{s}_1$, with the $y$-direction normal to the plane $P(\vec{p}_0, \vec{n}_0)$, and $z$-direction aligned with the parallel markers, as shown in Figure 2.26. Therefore, the transformation from the image space $\Sigma_I$ to the marker space $\Sigma_M$ is given by

$$T_{IM} = \begin{bmatrix} \vec{x} & \vec{y} & \vec{z} & \vec{t} \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

where

$$\vec{y} = \vec{n}_0$$

$$\vec{z} = \frac{1}{\|\vec{n}_1' + \vec{n}_2'\|}(\vec{n}_1' + \vec{n}_2')$$

$$\vec{x} = \vec{y} \times \vec{z}$$

$$\vec{t} = \frac{1}{2}(\vec{s}_1 + \vec{s}_2)$$

In the fourth step, the transformation of the image-robot registration is calculated. The robot coordinate system $\Sigma_R$ is defined at the RCM point of the robot as shown in Figure 2.4. The location of the marker $\Sigma_M$ in the robot space $\Sigma_R$ when the marker were imaged is known from the robot kinematics calculation, and it defines $T_{RM}$ the corresponding transformation from the robot space $\Sigma_R$ to the marker space $\Sigma_M$. Finally, the transformation of the image-robot registration is given by

![Figure 2.27 Schematic diagram of image-robot registration](image-url)
\[ T_{RI} = T_{RM}^{-1} T_{IM} \]  

(2.28)

Figure 2.27 shows a schematic diagram of the image-robot registration. The transformation \( T_{RI} \) allows transforming a target point \( \vec{p} \) defined in the image space to the point \( \vec{p}'' \) defined in the robot space as

\[ \vec{p}'' = T_{RI} \vec{p} \]  

(2.29)

Finally, the desired step numbers and joint values are calculated by solving the inverse kinematics problem of the robot as described in Subsection 2.1.5.

### 2.2.4 Robot Control Software

A custom-written motion control software was developed in C/C++. The software used the motion control library that the motion control board (MC8000, Precision Micro Dynamics Inc., BC, Canada) company provides. Figure 2.28 shows the robot controller with the motion control software installed.

The software is capable of homing and moving the robot. The forward and inverse kinematics of the robot are internally calculated in the software. Accordingly, the software can move the robot with step numbers, joint values, and a target position defined in the robot space. In general, the motion control software

![Figure 2.28 (a) Robot controller and (b) robot control software](image)
receives the target position from the image guidance software through the Ethernet connection. Then, it calculates the joint values and the step numbers by solving the inverse kinematics problem of the robot. The software also sends the joint values to the image guidance software so that the image guidance software keep the virtual robot model updated.

The motion control software has a special structure to secure safety while it is running. The software includes a separated thread named 'Watch Dog thread' to monitor the robot status in real-time. The watchdog thread monitors all the digital inputs from the motion controller, such as cable connection status, power status, emergency switch status, and error status. In addition to the digital inputs, the watchdog thread also monitors the status of the software itself. If any malfunction is observed, the watchdog thread stops to send a pulse signal to the safety circuit, and the safety circuit cuts the robot power immediately. The safety circuit is designed to send power to the robot only when it is receiving the pulse signal with enough frequency.

2.3 Pediatric Application

The main goal of the work involved in this section was to validate the MR safe RCM robot in performing needle insertion for pediatric bone biopsy under MRI guidance. The work of this section has been reported in journal articles [102], [103].

2.3.1 Personal Contributions

Most of the clinical work and protocol design was done by Dr. Kevin Cleary and Dr. Karun Sharma. The design and manufacturing of the needle-guide and the mounts for robot and cadaver leg were done by Dr. Dan Stoianovici and Dr. Doru Petrisor. The fabrication of the leg mockup was done by Dr. Reza Monfaredi. Those works are not discussed in detail here.

My personal contribution includes:

- Modification of the robot control and imaging software for pediatric application.
- Running all the experiments discussed here.
- Analysis of all the experimental data discussed here.
2.3.2 Background and Motivation

The work in developing an MRI-compatible robotic system for long bone biopsy in pediatrics is described in this section. The MR Safe robot is used to enable a novel clinical workflow for image-guided pediatric bone biopsy. The main advantages of the novel clinical workflow include minimizing trauma and eliminating radiation exposure in children with bone cancers and bone infections.

Bone infection and bone neoplasm are common etiologies that can cause bone pain and tenderness on the inner side of the leg in pediatric patients. However, the clinical treatment approach of infectious bone lesions is very distinct from the clinical treatment approach of neoplastic bone lesions. Thus, it is very important to precisely and quickly diagnose suspicious bone lesions and provide appropriate clinical management to the children with the symptoms. According to the recent review article in pediatric osteomyelitis, “a delay in the diagnosis of pediatric acute and subacute hematogenous osteomyelitis can lead to potentially devastating morbidity [108].”

Osteomyelitis, or infection of the bone, is commonly treated with antibiotics alone or in combination with surgical debridement in severe cases, while bone tumors are treated with chemotherapy, radiation, and/or surgical resection, depending on their specific histology. Bone infection and bone neoplasms are common in the pediatric population. More than 50% of cases of osteomyelitis occur in preschool-age children and the most common location of infection is the long bones, especially the femur and tibia, while any bone may be affected [109], [110]. Bone tumors including Osteosarcoma and Ewing sarcoma are the fourth most common solid tumors in pediatric patients [4], [5].

If a suspicious abnormality is observed in the bone marrow region on MR images, and the diagnosis is not able to be made with other information such as clinical history, examination, laboratory tests, and imaging findings, a biopsy is frequently required for definitive diagnosis, which could provide a proper suggestion for treatment. Two different approaches exist for the bone biopsy [111]. One is the surgical biopsy that is performed in the operating room by the orthopedic surgery team. The other is the image-guided needle biopsy that is performed in the radiology suite by the interventional radiologist under the guidance of X-ray and/or CT. A general anesthesia and invasive procedures are required in surgical biopsy and exposure to ionizing radiation occurs in image-guided needle biopsy.
The MR Safe robot presented the previous section is used to be a part of the novel clinical workflow in which the bone biopsy can be performed earlier, ideally within a few hours of the diagnostic MRI scan being completed, and perhaps even at the same time in some cases. Since the robot enables the bone biopsy to be performed in the MRI scanner, the time required to schedule a separate biopsy procedure is eliminated. Performing the bone biopsy under MRI guidance would also allow more precise sampling because MRI shows superior contrast resolution in bone marrow lesions. These lesions are invisible to the naked eye during surgical biopsy and much less visible on CT scans, causing inaccurate sampling. Eventually, it would increase the possibility of false diagnoses. Moreover, the MRI-guided bone biopsy using the MR Safe robot would eliminate the radiation exposure from CT guidance for both the patient and the physician.

To the best of our knowledge, an MRI-compatible robot designed for bone biopsy has not been reported yet. While several MRI-compatible robots have been reported for interventions in the brain [112], liver [44], breast [113], and prostate [34], [35], these robots were designed for needle targeting in soft tissue. Since inserting a needle into the soft tissue requires lower insertion forces than drilling into bone, the robots for bone biopsy require a sturdier support, which is a challenging engineering task considering that the structure of the robot is primarily made of plastic materials. To be compatible with MR environment, furthermore be classified as MR Safe, and do not deteriorate image quality, the robots are preferred to be made with nonmetallic materials, which makes further constraints on the robot design.

2.3.3 Preclinical Study with Long Bone Mockup

2.3.3.1 Materials and Methods

The novel clinical workflow consists of five steps as follows:

Step 1. **Positioning of patient and robot:** The patient is positioned on the MRI table in the usual manner. The robot is then mounted onto the table between the patient’s legs so that the needle-guide is located at the skin entry point. MR imaging coils are placed around the leg and the robot. The robot is already turned on and homed.

Step 2. **MR imaging and trajectory planning:** Standard MR diagnostic imaging sequences for bone infections or tumors are obtained, including multi-planar T1/T2 weighted and contrast-enhanced sequences. The interventional radiologist reviews the images and selects bone target point as well as the skin
entry point which defines the trajectory for the needle along a safe path that avoids critical structures such as blood vessels and nerves.

Step 3. **Robot registration and alignment**: The robot has built-in markers for registering the image coordinate system to the robot coordinate system. Once the image is registered, it is commanded to align the end-effector along the safe trajectory defined in Step 2.

Step 4. **Confirmation of trajectory**: An MRI-visible fiducial of the same size as the bone biopsy needle is placed through the needle-guide and the tip is positioned on the “skin.” A confirming set of MR images are taken to verify that the trajectory of the fiducial matches the desired trajectory. This step may be eliminated when the reliability of robotic needle guidance is documented in clinical experiments. This has the potential to reduce the procedure time.

Step 5. **Insert bone biopsy needle and take a sample**: The interventional radiologist manually drives the biopsy needle to the target. The depth indicator on the needle is set based on the planned trajectory. Confirming images may be acquired with the needle in place. The bone samples are obtained as usual.

![Figure 2.29 Experimental setup](image)

Figure 2.29 Experimental setup; (a) 4 targets used in experiments, (b) robot mounted on table with long bone mockup, (c) MRI coils on both sides of mockup, and (d) robot in scanner isocenter.
A preclinical experiment to validate the robotic system with the novel clinical workflow was performed. An MR scanner (1.5T, Aera, Siemens, Munich, Germany) at Children’s National Medical Center (Washington, D.C.) was used to evaluate the targeting accuracy of the system in a leg mockup. Small holes were drilled in a femur mockup model (Sawbones, Pacific Research Laboratories, Vashon Island, WA). The femur model was then placed inside a long cylindrical tube, and the tube was filled with a gelatin mixture, as shown in Figure 2.29b. The top of the mockup was opened to allow access for targeting experiments. Four holes were selected and used for this study, as shown in Figure 2.29a. Each hole was targeted twice.

Figure 2.29b–d show the experimental setup. Figure 2.29b shows the robot mounted to the table with a long thin fiducial in the needle-guide. This fiducial was used to confirm the desired trajectory of the biopsy needle. The figure also shows the planned positioning of the robot where it could go between the legs of the patient. Figure 2.29c shows the robot mounted to the table with the long bone mockup between the imaging coils. A custom-built table mount (blue frame in figure) was anchored to the mounting slots in the MRI table and the robot was attached to this mount. Figure 2.29d shows the robot at isocenter with the same configuration as Figure 2.29c. Since the robot is made entirely of nonmetallic materials and has no electrical parts, it does not deteriorate the image quality when scanning. As such, the robot could be manipulating an instrument at the scanner isocenter while scanning in real time.

In the experiment, the proposed clinical workflow was slightly modified. For each of the four targets (Figure 2.29a),

1. The robot was manually positioned near the target of interest. This was accomplished by loosening the plastic retaining screws on the passive base and moving the robot by hand until the remote center of motion point of the robot (located slightly below the needle-guide) was near the desired entry site of the mockup.

2. The MRI table was moved into the scanner with the center of our region of interest at the scanner isocenter. A series of MRI scans were done using 3D T1 Vibe sequence. The following T1 vibe parameters were used for the pneumatic bone biopsy: repetition time = 8.85 [ms], echo time = 1.35 [ms], field of view = 380 [mm], matrix = 320 × 320, slice thickness = 1.2 [mm], gap = 1.24 [mm], flip angle = 14.5 [deg], and integrated parallel imaging techniques = 3.
3. DICOM images were read into the image guidance and robot control workstation. These were used for image-robot registration and target selection, as shown in Figure 2.30.

4. The image guidance software confirms the target point to be within the robot workspace. The robot is then commanded to align the end-effector to point at the target point. The needle insertion depth is also computed.

5. An acrylic needle of the same diameter and length as the biopsy needle (4.87 [mm], length 135 [mm]) with a pencil point was inserted through the needle-guide toward the target. The depth of insertion was controlled by an O-ring on the acrylic needle whose position was set by the third stage of the robot system. The plastic needle was used as the metal needle resulted in too much artifact to accurately segment and precisely evaluate its point location for this accuracy study.

6. A confirming MRI scan was then done to evaluate the actual tip position.

7. The time required for the targeting was measured.

Four targets were selected and used for this feasibility study, as shown in Figure 2.29a. Two targeting attempts were made for each target on two different days. The targeting attempts were done by one of the engineers working on the project. All the targeting attempts were made at slightly oblique angles as shown in Table 2.7, illustrating the ability of the robot to help with oblique trajectories, which can be challenging. An error analysis was then performed to compute two error values: the perpendicular distance from the needle
path to the target (2D error) and the distance from the needle tip to the target (3D error). The error analysis was done using the confirming MRI images as follows:

1. The center of the target hole was first determined. The target was semi-automatically segmented using a marching cubes algorithm [100]. Next, to find the center of the target, a hemisphere was registered to the segmented target surface using an iterative closest point algorithm [114].

2. The axis of the needle was next determined. The needle was semi-automatically segmented using a marching cubes algorithm [100]. The center axis of the segmented needle was then estimated as the first principal axis of the PCA results [115]. To estimate the tip position of the needle, the 3D CAD model of the needle was registered to the segmented needle by aligning the two center axes, as shown in Figure 2.31 and Figure 2.32. The position along the axes was manually adjusted by sight until the two models were superimposed, as shown in Figure 2.31 and Figure 2.32.

3. The 2D error was calculated as the shortest distance between the target point and the estimated needle axis.

4. The 3D error was calculated as the distance between the target point and the tip point of the needle CAD model.

2.3.3.2 Results

The time required for each of the eight targeting attempts are shown in Table 2.6. The precise times were extracted from time stamps in the DICOM files and the other times were estimated. All times are shown in minutes.

Figure 2.31 and Figure 2.32 show the alignment of the segmentation and 3D CAD models of the plastic needle. The segmented model is in red and the 3D CAD model is in cyan. The green dot is the needle tip point and the red dot is the target. The results for the eight trials are shown in Table 2.7. The target depth is shown, followed by the two needle insertion angles, along with the 2D and 3D errors. In the needle insertion angles, negative values indicate a medial or superior direction, whereas positive values indicate a lateral or inferior direction. The maximum 2D error was 1.72 [mm] and the maximum 3D error was 1.89 [mm]. The average 2D error was 1.25 [mm] and the average 3D error was 1.39 [mm]. The standard deviation was 0.39 [mm] for 2D and 0.40 [mm] for 3D.
Table 2.6: Time required for each targeting attempt*

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Targets</th>
<th>1</th>
<th>2</th>
<th>Average</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td>Robot and mockup mounting on MR table (approx.)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Robot cable connection and homing (approx.)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Robot positioning with RCM at skin entry point (approx.)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MR coil placement (approx.)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
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<tr>
<td>MRI scan for registration</td>
<td>3.78</td>
<td>3.78</td>
<td>2.27</td>
<td>2.27</td>
<td>3.80</td>
</tr>
<tr>
<td>Image-robot registration</td>
<td>3.05</td>
<td>3.25</td>
<td>3.50</td>
<td>3.38</td>
<td>3.77</td>
</tr>
<tr>
<td>Robotic orientation of needle guide on target and setting the depth of needle insertion</td>
<td>0.72</td>
<td>1.13</td>
<td>0.65</td>
<td>0.80</td>
<td>0.65</td>
</tr>
<tr>
<td>Manual needle insertion (approx.)</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
<td>2.50</td>
</tr>
<tr>
<td>MRI scan for targeting error measurement</td>
<td>2.85</td>
<td>2.77</td>
<td>2.28</td>
<td>2.30</td>
<td>3.78</td>
</tr>
<tr>
<td>Total time</td>
<td>31.90</td>
<td>32.43</td>
<td>30.20</td>
<td>30.25</td>
<td>33.50</td>
</tr>
</tbody>
</table>

*All numbers in minutes, first four rows are estimates, last five rows are from DICOM time stamps.
Table 2.7: Results from eight targeting trials

<table>
<thead>
<tr>
<th>Target</th>
<th>Trial</th>
<th>Target Depth [mm]</th>
<th>Needle Insertion Angle [deg]</th>
<th>2D Error [mm]</th>
<th>3D Error [mm]</th>
<th>2D Error [mm]</th>
<th>3D Error [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medial-Lateral</td>
<td>Superior-Inferior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>27.34</td>
<td>18.86</td>
<td>-11.22</td>
<td>1.17</td>
<td>1.25</td>
<td></td>
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<tr>
<td></td>
<td>2</td>
<td>21.69</td>
<td>28.60</td>
<td>2.74</td>
<td>0.67</td>
<td>0.69</td>
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<tr>
<td>B</td>
<td>1</td>
<td>30.14</td>
<td>-6.52</td>
<td>16.97</td>
<td>1.50</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>26.23</td>
<td>-7.06</td>
<td>-6.55</td>
<td>1.31</td>
<td>1.51</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>26.74</td>
<td>18.92</td>
<td>-10.43</td>
<td>1.35</td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>22.20</td>
<td>-10.10</td>
<td>7.72</td>
<td>0.69</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>28.02</td>
<td>6.72</td>
<td>2.88</td>
<td>1.58</td>
<td>1.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>26.29</td>
<td>-4.40</td>
<td>9.81</td>
<td>1.72</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
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<td>MAX</td>
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<td></td>
<td></td>
<td>1.72</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVERAGE</td>
<td></td>
<td></td>
<td></td>
<td>1.25</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>STDDEV</td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2.31 Targeting results: (a) A1, (b) B1, (c) C1, (d) D1
2.3.3.3 Discussion and Conclusion

One of the challenging problems encountered in the validation test was to visualize the RCM point of the robot (needle entry point). Since the robot was made with nonmetallic, nonmagnetic, and nonconductive materials, it was invisible to the MR images. However, if the robot including the needle-guide is not visible on the MR images, the initial positioning of the needle entry point is not possible. The needle entry point needs to be determined so that the desired target point is included inside of the robot workspace and the path to the target point is clinically feasible. For this, an MRI-visible fiducial marker was made with a glass tube and filled with MRI contrast (Beekley, Bristol, CT). The fiducial marker has the same diameter as the bone biopsy needle and is placed through the needle-guide. The desired trajectory of the biopsy needle can be confirmed by verifying the relative position of the fiducial marker with respect to the target point.

Figure 2.32 Targeting results: (a) A2, (b) B2, (c) C2, (d) D2
In this section, a feasibility study of the MR Safe robot system in placing a bone biopsy needle under MRI guidance was presented. A novel workflow was introduced and targeting accuracy of the robotic system was analyzed using the workflow. The results showed that the robotic system can be used to accurately place a needle-guide for bone biopsy in a long bone mockup under MRI guidance. All the targeting trials were successfully completed, and no system failures were reported during the trials.

Time-wise, the average time for each targeting attempt was 32.37 minutes, with a standard deviation of 1.46 minutes. These results lead us to believe that with some practice we could complete a clinical case in 60–90 minutes, allowing for variability in the time required for patient positioning. This amount of time would be within the range allocated for MRI procedures at the Children’s National Medical Center, thus indicating that the proposed bone biopsy procedure would not interrupt normal clinical workflow.

Next step of the study would be a feasibility validation in an in-vivo environment that provides realistic anatomy and mechanical properties of bone and soft tissues.

### 2.3.4 Cadaveric Study

The mockup study convinced us that the MR Safe robot was accurate and ready to move to the cadaver study described here. The cadaver provides human anatomy and realistic mechanical properties of bone and soft tissues. Therefore, it is an important step before moving to clinical trials in future work.

#### 2.3.4.1 Materials and Methods

The cadaver study was performed in a 1.5T Siemens Aera scanner at Children’s National Medical Center (Washington D. C.). The goal of this study was to demonstrate the ability of the robot to provide needle biopsy accuracy in vivo following the promising results from a previous mockup study [102]. We designed the study to target 10 locations in the long bones of the leg, specifically the femur and tibia (five targets in each). The robot was mounted on the MRI table and connected to the air supply in the room for compressed air to power the pneumatic motors. The optical connections to the encoders were run along the table to the robot controller mounted on the floor near the patch panel in the room. From the patch panel, cables were run to the control room to connect to the robot control computer.
Approval for the study was obtained from the hospital infection control team, and the room was thoroughly cleaned after the study. The cadaver was procured from Science Care (Phoenix, Arizona, USA), a commercial anatomy provider. According to the report provided with the specimen by the company, the donor was a Caucasian 56-year-old male of height 72 inches, weight 160 lb, and a BMI of 21.70. The cause of death was a severe chronic obstructive pulmonary disease (COPD). The cadaver was screened for infectious diseases by the company before shipment to our research group. Research protocols for biohazards were strictly followed including the wearing of personal protective equipment (PPE). The experimental setup is shown in Figure 2.33, including the robot wrapped in a sterile bag, the leg covered in blue absorbable material, and the wooden support made by the research team. Both the wooden support and robot are mounted on wooden cross members which are secured to the table using custom designed plastic bolts and hooks.

The experimental workflow proceeded as follows:
1. Mount the robot and the cadaver leg on the MRI table as shown in Figure 2.33.
2. Place the interface box at the back of the room and connect the cables to the robot. A homing sequence is then run so the robot starts at the known home position.
3. Obtain MR images of the region of interest. We used proton density (PD) weighted images with turbo spin echo (TSE) imaging technique for all MRI scanning.

Figure 2.33 Experimental setup for cadaveric study
4. The radiologist views the MR images and selects the skin entry and target point.
5. Manually position the robot guide near the region of interest by loosening the position knobs on the support arm, moving the guide to the desired location, and tightening the knobs.
6. Obtain MR images for registration purposes. The field of view must also include the registration markers on the robot.
7. Register the MR images to the robot coordinate system using the markers on the robot. The registration technique is described below.
8. The robot is commanded to orient the biopsy guide to the target point.
9. The radiologist then inserts the drill through the needle-guide after adjusting the position of the depth stopper using the depth driver.
10. Perform an additional MRI scan for verification.
11. Repeat Step 4 to Step 10 for each of the 10 targets.

Figure 2.34 shows a schematic diagram of the robot–image registration. First, the markers are segmented from the MR images using a region growing algorithm, and the marker coordinate system $\Sigma_M$ is defined in the image coordinate system $\Sigma_I$ [101]. The transformation from $\Sigma_I$ to $\Sigma_M$ ($T_{MI}^r$) is calculated in this

Figure 2.34: Schematic diagram of image-robot registration
procedure. Next, the transformation from the robot coordinate system $\Sigma^R$ to $\Sigma^M (T^R_M)$ is calculated from the robot design parameters and the robot position when the markers were imaged. Finally, the transformation from $\Sigma^R$ to $\Sigma^I (T^R_I)$ is calculated as

$$T^R_I = T^R_M (T^I_M)^{-1}$$  \hspace{1cm} (2.30)

For a selected image target $\vec{p}$, the target point $\vec{p}'$ in the robot coordinate system $\Sigma^R$ is calculated as

$$\vec{p}' = T^R_I \vec{p}$$  \hspace{1cm} (2.31)

Ten locations were selected for this targeting study: five in the femur and five in the tibia. In our initial attempt, we tried to obtain the biopsy core using a manual bone biopsy drill from Invivo Corporation (Gainsville, Florida, USA). The robot is extremely stiff (33 [N/mm] [95]) and provided good support, but the bone cortex was thick and too tough to penetrate any significant distance using this technique. On close inspection of the manual drill, we noticed that the titanium inner needle was slightly bent. Therefore, we used a portable commercial battery-powered drill for this study as shown in Figure 2.35 (Arrow OnControl

![Figure 2.35: MRI-guided robotic bone biopsy (samples obtained show at upper right).](image)
Powered Bone Access System from Teleflex, Morrisville, North Carolina, USA). However, this drill is not certified for the MRI environment. As such, the drill was tested outside the 5-gauss line of the scanner where no perceptible pull from the magnet was detected. Then we tied a tether cord to the wall of the room which was used when the drill came inside the 5-gauss line as a safety measure. This methodology was approved by the institutional MRI safety officer.

After all the locations were biopsied under MRI guidance, we performed a CT scan of the cadaver leg to confirm and visualize the biopsy tracks/holes, as shown in Figure 2.37b and Figure 2.39b. The biopsy holes in the bone cortex and marrow space could be more clearly seen with high-resolution CT imaging. The CT scan was performed using a GE Discovery 60 PET/CT using standard protocols, and the images were reconstructed with 0.6 [mm] axial spacing.

The accuracy of each biopsy site was then analyzed as follows.

1. Reconstruct 3D models of the femur and tibia from the CT images.
2. Extract the holes on cortical bone and fit a cylinder model to estimate the center axes.
3. Reconstruct 3D models of the femur and tibia from the MR images.
4. Register the two bone surface models, which were constructed from CT and MR images, using iterative closest point (ICP) algorithm, as shown in Figure 2.36a and Figure 2.38a.
5. Evaluate the targeting error as the closest distance from the target point to the center axis estimated in the previous step, as shown in Figure 2.36b, Figure 2.38b.

The targeting error is measured by computing the distance between the target in MRI and the projected line based on the CT data. This means that registration errors between MRI and CT can significantly affect the error measurement. However, the bone is a good anatomical marker since it has numerous unique features and is clearly visible in both the MRI and CT images. Therefore, we used the bone as an anatomical marker rather than implanting reference markers to the bone since implanting markers could cause image artifacts.

It is not possible to estimate the MRI-CT registration error directly since we do not have a perfect reference. However, we calculated the averaged distances between two surface models after the registration.
The distances from the vertices of the surface model from MRI to the corresponding closest points on the surface model from CT were calculated and averaged after the MRI-CT registration.

Time required for each procedure was measured in minutes. Procedure times were calculated using the clock on the control computer and time stamps in the DICOM image files. The procedures are categorized as follows:

- Mounting robot and leg on the MRI table: This step was also done once each day and took 10 minutes.
- Cable connection and robot homing: The procedures were done on two separate days, with the five femur targets were done the first day and the five tibia targets were done the second day. The time for this step, which was done once each day, was 6 minutes.
- MRI scan to select entry point: Here we acquired planning images of the region of interest in the femur and tibia. These scans were then used for each target point. This step took 3 minutes.
- Selecting entry and target points: The radiologist checked the MR images and selected the skin entry and target point. This step took 5 minutes.
- Robot initial positioning: Once the target point was identified, the robot was manually moved to position the tip of the needle-guide close to the desired skin entry point.
- MRI scan for registration: An MRI of the local region around the robot was then taken for registration purposes. In the femur targets, we only had to register once, but in the tibia targets, we had to register twice since we had to move the leg support once.
- Image–robot registration: This step was also done once for the femur and tibia and is done by the control software. The fiducials on the MR images are used to register the scanner coordinate system to the robot coordinate system. This time represents the time needed to find the fiducials on the MR images and for the software to register the two coordinate systems.
- Robotic targeting: In this step, the robot is commanded to align the needle-guide toward the target point. This is done quickly as can be seen from the times in the table.
- Needle insertion: In this step, the radiologist uses the guide on the robot and the portable drill to drill in the bone to the desired depth. The needle insertion time was the biggest contributor to the standard deviation and there was a learning curve as the first attempts took longer. While the depth of the sample
is a factor, the most important factor is cortical bone thickness, which is greater in the femur than in the tibia.

- Confirming MRI scan: Once the desired depth is reached, the drill is removed, and the needle is placed in the hole. A confirming MRI scan (Proton Density, PD weighted) is then taken as shown in Figure 2.37a and Figure 2.39a.
- Time for the first biopsy: This is computed by summing all the times in the cells above this line.
- Time for each additional biopsy: Once the first biopsy is done, additional biopsies would require selecting the skin entry and target point, manually moving the robot to the skin entry point, then registering the robot with the MR images, and so on, but would not require the setup steps. Therefore, this time is much shorter.

### 2.3.4.2 Results

Table 2.8 shows time required for each procedure in minutes. The overall average time for the first biopsy was 41.32 minutes with a standard deviation of 3.53 minutes. Each additional target was biopsied within an average of 22.32 minutes and a standard deviation of 3.53 minutes.

Figure 2.36a and Figure 2.38a show MRI-CT registration results. The averaged distances between two surface models after was $0.45\pm0.03 \ [mm]$. From these values, we can conclude that the MRI-CT registration results are reliable. The averaged distances are shown along with the results in Table 2.9.

The results for the 10 trials are shown in Table 2.9. All 10 targets were successfully located with an average error of $1.43 \ [mm]$ and a maximum error of $2.38 \ [mm]$ at an average depth of $38.49 \ [mm]$. The average error is given as the accuracy, and the standard deviation is given as the precision in this table. The first five targets were in the femur (T1–T5), and the second five targets were in the tibia (T6–T10). Two example images from targets T1 and T6 in the femur and tibia is shown in Figure 2.37 and Figure 2.39, respectively.
<table>
<thead>
<tr>
<th>Step from workflow described earlier</th>
<th>Target number</th>
<th>Femur</th>
<th>Tibia</th>
<th>Average Time [min]</th>
<th>Standard Deviation [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mounting robot and leg on the MRI table</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2 Cable connection and robot homing</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3 MRI scan to select entry point</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4 Selecting entry and target points</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5 Robot initial positioning</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6 MRI scan for registration</td>
<td>2.53</td>
<td>2.53</td>
<td>2.53</td>
<td>2.53</td>
<td>1.82</td>
</tr>
<tr>
<td>7 Image-robot registration</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8 Robotic targeting</td>
<td>0.82</td>
<td>0.75</td>
<td>0.28</td>
<td>0.20</td>
<td>0.52</td>
</tr>
<tr>
<td>9 Needle insertion</td>
<td>12</td>
<td>10</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>10 Confirming MRI scan</td>
<td>2.53</td>
<td>2.53</td>
<td>2.53</td>
<td>2.53</td>
<td>1.82</td>
</tr>
<tr>
<td>Time for the first biopsy (total)</td>
<td>47.88</td>
<td>45.81</td>
<td>40.34</td>
<td>45.26</td>
<td>40.58</td>
</tr>
</tbody>
</table>
Figure 2.36 (a) Targets T1–T5 on femur and (b) targeting error evaluation (detail of (a))

Figure 2.37 Target T1 in the femur (MRI on the left and CT on the right)
Figure 2.38 (a) Targets T1–T5 on tibia and (b) targeting error evaluation (detail of (a))

Figure 2.39 Target T6 in the tibia (MRI on the left and CT on the right)
2.3.4.3 Discussion and Conclusion

One of the challenging aspects of this study was the use of the manual bone biopsy needle. The existing manual biopsy needle was suboptimal in current practice as the bone cores are often fragmented and its titanium composition leads to needle bending and long procedure times. As such, the battery-powered drill was used to insert a needle into the bone to obtain the biopsy cores. Based on the experience in this study, it was concluded that a powered drill is necessary to enable MR-guided bone biopsy in clinical practice, while the cadaver bones were most likely more dehydrated and harder than the typical bones encountered in the pediatric population. In fact, there has been a recent shift from the use of manual to power drills for CT-guided bone biopsy as well. According to an article in 2015 [116], the use of a battery-powered bone drill improves diagnostic yield overuse of a manual system. Future works include the development of an MRI-compatible drill, which is pneumatically actuated, thus safe in the MRI environment. The availability of an MRI-compatible drill will greatly facilitate the bone biopsy application described here.

<table>
<thead>
<tr>
<th>Target Number</th>
<th>Averaged Distance between Two Surface Models [mm]</th>
<th>Target Depth [mm]</th>
<th>Targeting Error [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0.50</td>
<td>47.56</td>
<td>1.30</td>
</tr>
<tr>
<td>T2</td>
<td>0.46</td>
<td>50.72</td>
<td>1.07</td>
</tr>
<tr>
<td>T3</td>
<td>0.46</td>
<td>35.11</td>
<td>2.02</td>
</tr>
<tr>
<td>T4</td>
<td>0.45</td>
<td>49.34</td>
<td>0.51</td>
</tr>
<tr>
<td>T5</td>
<td>0.48</td>
<td>48.13</td>
<td>1.53</td>
</tr>
<tr>
<td>T6</td>
<td>0.44</td>
<td>31.36</td>
<td>1.69</td>
</tr>
<tr>
<td>T7</td>
<td>0.41</td>
<td>35.94</td>
<td>1.11</td>
</tr>
<tr>
<td>T8</td>
<td>0.41</td>
<td>35.37</td>
<td>2.38</td>
</tr>
<tr>
<td>T9</td>
<td>0.43</td>
<td>30.27</td>
<td>1.69</td>
</tr>
<tr>
<td>T10</td>
<td>0.42</td>
<td>21.11</td>
<td>1.00</td>
</tr>
<tr>
<td>Max</td>
<td>0.50</td>
<td>50.72</td>
<td>2.38</td>
</tr>
<tr>
<td>Average</td>
<td>0.45</td>
<td>38.49</td>
<td>1.43</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>0.03</td>
<td>9.44</td>
<td>0.52</td>
</tr>
</tbody>
</table>
This section presented experimental results from a cadaver study of targeted bone biopsy performed under MRI guidance using a novel MR Safe robotic system. Bone marrow samples were successfully obtained from five targets in the femur and five targets in the tibia for a total of 10 targets with an average accuracy of 1.43 [mm]. The results show that our robotic system can be used to accurately target bone lesions under MRI guidance. All the targeting trials were completed without any problems, and no system failures were observed with the robot.

There were some limitations to the work. A pediatric cadaver leg was not used as one was not available. The anatomy and structure of the adult cadaver leg used were not different, but children do have growth plates, which were not present in this cadaver.

In future work, we plan to develop an MRI-compatible drill, improve the custom mounting scheme and fixation of the leg, and then move to clinical trials.

### 2.3.5 Discussion

To the best of our knowledge, an MR compatible robot designed for bone biopsy has not yet been reported. Several MRI-compatible robots have been introduced for interventions in soft tissues such as brain, liver, breast, and prostate. Li et al. reported a robot for MRI-guided stereotactic neurosurgery with an accuracy of 1.38 [mm] in an in-vitro study [112]. Song et al. presented a robot for MRI-guided liver intervention with an accuracy of 6 [mm] in an in-vitro study [44]. Abdelaziz et al. presented a robot for MRI-guided breast biopsy with an accuracy of 4.7-7.3 [mm] in an in-vitro study [113]. Our previous work reported an MR Safe robot for transrectal prostate biopsy with accuracies of 2.09 and 2.58 [mm] in in-vitro and in-vivo studies, respectively [34]. Our laboratory also reported another MR Safe robot for transperineal prostate biopsy with an accuracy of 2.55 [mm] in clinical trials [35].

While our accuracy results for bone biopsy are better than most of these results, the studies are not directly comparable. In routine clinical practice, the lower end of the size range of suspicious bone lesions requiring needle biopsy is 1-2 [cm]. Based on this clinical experience and the size of currently available bone biopsy needles (11-15 gauge), we believe that the accuracy determined in the cadaver study will be enough for clinical requirements.
Most of the MRI-compatible robots for needle intervention were designed to be used in soft tissue [34], [35], [44], [112], [113]. On the other hand, puncturing or drilling into the cortical bone usually requires a stronger support for guiding the needle/drill. The interventional radiologists need to apply stronger force to the biopsy needle. Meanwhile, to minimize image artifacts, MRI-compatible robots are preferred to be built with nonmetallic materials, which is less stiff than metals. The MR Safe RCM robot has a unique structure made with nonmetallic materials and it enables a steady needle support with enough stiffness (33.38 [N/mm]) for bone biopsy while obtaining full MRI-compatibility (nonmetallic, nonmagnetic, nonconductive) and high targeting accuracy.

2.3.6 Conclusion

The MR Safe robot system has several potential advantages in pediatric bone biopsy: 1) It can serve as a steady and accurate needle-guide for the interventional radiologist. 2) The position and orientation of the needle can be verified before inserting into the leg if desired. 3) The robot can work at the scanner isocenter as well as provide improved ergonomics for the operator. 4) The robot should allow for decreased tissue trauma resulting from a single accurate needle pass as compared to multiple passes needed to adjust the trajectory by free hand. 5) The single pass should also allow for decreased total procedure anesthesia time. Moreover, in the future, if the diagnostic imaging and biopsy could be completed in the same setting as outlined here, it would eliminate the need for second anesthesia.

The feasibility of the MR Safe robot system in bone biopsy was verified in this section. The robotic system could also be used for other clinical applications such as a needle probe placement in the thermal ablation of bone and soft tissue tumors and a percutaneous screw and pin placement in the treatment of traumatic bone fractures. Currently, these image-guided percutaneous interventions are performed under CT guidance [117]–[120]. If these interventions could be directly performed under the MRI guidance using the MR Safe robot, the radiation exposure problem would be potentially eliminated.
2.4 Neurosurgical Application

The main goal of the work involved in this section was to validate the MR safe RCM robot in performing needle insertion for stereotactic brain biopsy under MRI guidance. The work of this section has been reported in a journal article [101].

2.4.1 Personal Contributions

Most of the clinical work and protocol design was done by Dr. Jean-Paul Wolinsky and Dr. Dan Stoianovici. The manufacturing of the robot mount and needle-guide was done by Dr. Doru Petrisor. The design and fabrication of the skull mockup were done by Changhan Jun. Those works are not discussed in detail here.

My personal contribution includes:
- Modification of the robot control and imaging software for the neurosurgical application.
- Running all the experiments discussed here.
- Analysis of all the experimental data discussed here.

2.4.2 Background and Motivation

The work in developing an MRI-compatible robotic system for brain biopsy is described in this section. The MR Safe RCM robot was used for an intraoperative MRI-guided stereotactic brain biopsy for intracranial lesions. The main advantages of the system include enabling immediate image feedback and improving the accuracy of tissue sampling.

A brain tumor can be categorized into two different types such as primary brain tumor and metastatic brain tumor according to its place of origin. A primary brain tumor is a mass of abnormal cells that start in the brain, while a metastatic brain tumor is a mass of abnormal cells that started in another part of the body and has spread to the brain. Each year in the United States, almost 30,000 individuals are involved in primary brain tumors and almost 200,000 individuals are involved in metastatic tumors [121]. The most common primary tumors include glioma and meningioma [121]. If an abnormality is observed in 3D imaging
modalities such as CT and MRI, and it does not require a prompt and complete removal, a brain biopsy is commonly performed to diagnose a brain lesion.

A stereotactic brain biopsy is commonly performed to allows a neurosurgeon to diagnose the brain lesion. The stereotactic brain biopsy is done in the operating room under general anesthesia and the neurosurgeon takes a small tissue sample from the brain using a thin needle. The needle for brain biopsy consists of 2 hollow tubes. Both tubes have a side-hole to their distal end. The outer tube is used as a cannula that is inserted into the brain while the inner tube can be slid in and out of the outer tube. The needle is inserted into the brain with the status that the two distal side-holes are not aligned (specimen notch closed). Once the needle is inserted into the tumor, the inner tube is rotated so that the two distal side-holes are aligned (specimen notch opened), exposing brain tissue into the interior of the inner tube. Then, the inner tube is further rotated so that the two distal holes are not aligned (specimen notch closed) and the tissue sample, which is contained inside of the inner needle, is withdrawn together with the biopsy needle (Figure 2.40b).

Traditionally, a stereotactic brain biopsy has been performed in the operating room based on preoperative images that visualize the brain lesion and reference landmarks. Once a target point is selected at the lesion on the image, the biopsy needle is navigated based on the relative position of the target point with respect to the position of the reference landmarks. Formerly, this was done by the frame-based approach.

![Figure 2.40 (a) Brain tumor and (b) working mechanism of brain biopsy needle](https://www.radiopaedia.org/articles/surgical-brain-biopsy)

(a) Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 5687)
(Images are licensed under the [Creative Commons Attribution-Non-commercial-Share Alike 3.0 Unported](https://creativecommons.org/licenses/by-nc-sa/3.0/))
that places a metal frame (stereotactic head frame) on the patient’s head. Since the metal frame is bulky and invasive to the patient, this has been rapidly supplanted by the frameless approach that uses small scalp fiducial markers, providing reference landmarks. However, as these approaches are still performed based on the preoperative images, the current position of the biopsy needle cannot be directly visualized during the biopsy. Moreover, the shift and deformation of the brain matter during the biopsy procedure have remained in its critical issues that may cause undetected errors.

The use of intraoperative imaging allows surgeons to confirm the current position of the biopsy needle at critical points of the operation. Several robotic systems have been developed to assist the surgeon under CT guidance [122], [123]. However, CT-guided procedures expose the patient and surgeon to ionizing radiation. Furthermore, the image quality of soft tissue in CT images is substantially inferior compared to the image quality in MRI.

Receiving a direct MR image feedback during the stereotactic brain biopsy could be an ultimate situation for the accurate and definitive diagnosis of the brain tumor. However, as the space inside of the MRI scanner is limited, it is challenging to perform a brain biopsy within the MRI scanner. In the general intraoperative MRI-guided stereotactic brain biopsy, the MRI table with the patient needs to be moved in and out of the scanner. It may distract surgeons and increase the operation time. On the other hand, the direct method that enables surgeons to perform a biopsy directly within the scanner has benefits in eliminating those limitations. However, to work with the surgeon within the scanner, a special device is required, and the device should be compact, accurate, safe to operate in the MRI, and not deteriorate the image quality. Moreover, the motion of needle is restricted at the entry point (burr hole) made in the skull for minimally invasive procedures, requiring a robot with RCM mechanism, which makes further constraints on the robot design.

Several research teams developed MRI-compatible robots for neurosurgery [112], [124]–[127]. Su et al [127] and Comber et al. [125] reported MRI-compatible active cannula robots for neurosurgical intervention. The robots are actuated by piezoelectric motors and nonmagnetic pneumatic piston-cylinders, respectively. While the active cannula has an advantage over the straight needle in accessing the desired image target through a curved trajectory, the robots include limitations such as small workspace, absence of RCM mechanism, and relatively large size. Li et al. developed a robot for MRI-guided stereotactic neurosurgery [112]. The robot is designed to have the same DoF as a traditional manual stereotactic frame (6-DoF, 3
translations and 3 rotations). The robot is actuated with piezoelectric motors, which can potentially deteriorate the image quality and losing SNR. Sutherland et al. developed an MRI-guided robotic system, named neuroArm [126]. The robotic system includes a workstation, a system control cabinet, and two remote slave-arms. The arms are MRI-compatible, and each arm has 7-DoF. The arms are mounted on a moveable base and controlled by the remote workstation. The right arm can be independently used for stereotaxy. While the robotic system can be used in multiple neurosurgical applications, the robot does not include an RCM mechanism, includes metallic components, and can only operate outside of the scanner but not at the isocenter.

Intraoperative MRI-guided robotic system with RCM mechanism for stereotactic brain biopsy would allow neurosurgeons to formulate surgical plans based on most recent images, utilize continuous imaging for immediate feedback, and maintain the operative rhythm by eliminating the common in-out moves of the patient bed into the scanner, operating within the scanner under direct imaging. Furthermore, the robotic system could be potentially used not only for brain biopsy, but also for numerous neurosurgical procedures that require deep brain access such as deep brain stimulation, ventriculoperitoneal shunting, and laser ablation of the hippocampus.

2.4.3 Preclinical Study with Skull Mockup

2.4.3.1 Materials and Methods

The MR Safe RCM robot presented in Section 2.1 was used. For the neurosurgical application in the intraoperative MRI scanner (iMRIS, Minnetonka, MN), a special needle-guide and needle depth offset component were made for 18G needles, as shown in Figure 2.2. In the pediatric bone biopsy application [95], the robot was attached to the MR table. For the brain application, a new support arm was built to mount the robot directly on the Mayfield head holder (3-point skull fixation device) of the iMRIS scanner. The new support arm comprises 3-DoA and attaches to the head holder with a Hirth coupling, as shown in Figure 2.41a. When unlocked, the arm allows the RCM point to be manually located as needed. The location is then locked with 3 knobs. The support arm is made of polycarbonate, ultem, polysulfone, and garolite materials.

The robot includes a set of registration markers placed on the RCM structure. A set of MRI coils is placed on the lateral sides of the skull and robot, as shown in Figure 2.41b. Images of the markers and brain are acquired simultaneously and transferred over the network in DICOM format to the image guidance
software. In addition to the original image guidance software, an additional component was developed to improve needle localization in the images with a needle marker described later.

After initial scanning of the anatomy, target points are selected in the image. The relationship between the image coordinate and the robot coordinate is determined by the image-robot registration, as shown in Section 2.2.3 and Figure 2.42a. Image coordinates can then be transformed into robot space, further converted to the joint space of the robot through the inverse kinematics and passed to the motion controller to drive the robot. The robot orients the needle-guide towards the target point. Similarly, the needle depth driver sets the depth of needle insertion that corresponds to the selected target, by positioning an O-ring marker on the needle shaft at the corresponding depth. The surgeon then takes the needle from the driver and inserts it through the guide up to the marked depth, which should correspond to the needle point being centered on the selected target.

A series of tests were performed to test the accuracy of needle targeting. A mockup was designed to simulate the neurosurgical environment of procedures that require deep needle access such as biopsies, DBS, and laser ablation of seizure foci. To these regions, the depth of needle insertion from a frontal entry was estimated at approximately 100 [mm].

A skull model (Functional Physiological Skeleton Model) was prepared. CAD software (Creo, PTC Inc.) was used to design a grid of 12 targets within the skull. This is a grid of rectangular bars that form several 10x10 [mm] spaces. The grid was 3D printed (PLA, Makerbot Inc) and assembled in the designated position of the skull model. An appropriately located frontal entry point was selected and drilled in the skull.
The mockup was then filled with gelatin to simulate brain matters. The gelatin was made of a 300 bloom gelatin powder (FX Warehouse Inc., Florida) in solution with sorbitol, glycerin, and water (3:3:2:25 parts by mass, respectively).

The centers of the gaps in the grid were considered as targets. Unlike using rigid targets, the hollow targets allowed the needle to be inserted all the way to the center, to better simulate the real scenario and facilitate accuracy measurements.

A ceramic 1.61 [mm] diameter (slightly larger than 18 Gauge) needle with a symmetric point was built for the experiments, to eliminate possible artifact from the image and facilitate imaging the needle for targeting accuracy measurements. A hollow ball made of plastic (ID:4.0 [mm]) was filled with Beekley MR contrast and precisely assembled at the top of the needle (Figure 2.41a). The needle length to the ball center is 200 [mm]. This was subsequently used to measure the depth of needle insertion from the images.

The experiment was performed as follows:

1. The skull mockup was mounted on the head holder of the iMRIS table, and the robot was mounted and positioned so that the RCM point was at the skull entry hole, as shown in Figure 2.41a.

2. An initial position of the robot was set, and MR imaging coils were placed near the skull and robot, as shown in Figure 2.41b.

![Figure 2.42](image-url)  
Figure 2.42 (a) Schematic diagram of image-robot registration, (b) Virtual environment shown by software and 12 target points at centers of grid gaps
3. MR images of the mockup and robot were acquired (T1/3D/1.5 Tesla, Number of images: 144, Field of view: 230.0×230.0×214.5 [mm], Image spacing: 0.898×0.898×1.50 [mm]) and transferred to the image guidance software.

4. The image was registered to the robot space, as shown in Figure 2.42a.

5. Twelve target points of the grid were chosen for targeting based on the 3D reconstructed grid image, as shown in Figure 2.42b.

6. Sequentially, the robot oriented the needle-guide and set the depth of needle insertion for each target.

7. The needle was inserted through the guide up to the marked depth. The insertion was performed manually by reaching within the scanner, without moving the gantry. The needle was spun by its shaft while inserting, to minimize the friction and reduce possible lateral deflections [128]).

8. An image scan was performed after each insertion with the needle in the final position to verify targeting. The position of the needle was not in any way adjusted.

9. Steps 6 to 8 were repeated for each of the 12 targets.

The acquired images were processed after the procedure, as follows:

1. Reconstruct the series of MR images and build a volume image for each target.

2. Segment the needle and the needle marker from the reconstructed volume image. Then, compute the axis of the needle by applying PCA and computing a centroid, in a similar manner to the marker registration.

3. Segment the ball marker at the needle top and find its centroid.

Figure 2.43 Schematic diagram for needle targeting error measurement
4. Register a 3D CAD model of the needle to the segmented needle by aligning the axes setting the depth based on the ball end marker.

5. Compute the target depth $D$ as a distance between the RCM point of the robot and the target point in the direction of the CAD model needle, as shown in Figure 2.43.

6. Compute 2D targeting errors $d_1$ as the shortest distance between the target point and the CAD model needle axis, as shown in Figure 2.43.

7. Compute 3D targeting errors $d_2$ as the shortest distance between the target point and the CAD model needle point, as shown in Figure 2.43.

8. Calculate targeting accuracy and precision as the average and standard deviation of the errors over all targets.

### 2.4.3.2 Results

Table 2.10 shows the partial and total times for the experiment. The experiment took 1.5 hours, and no problems with robot functionality or image interference were observed.

<table>
<thead>
<tr>
<th>Test Step</th>
<th>Time [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robot and mockup mounting</td>
<td>5</td>
</tr>
<tr>
<td>Robot cable connection and homing</td>
<td>6</td>
</tr>
<tr>
<td>Robot positioning with RCM at the entry point</td>
<td>5</td>
</tr>
<tr>
<td>MR coil installation</td>
<td>3</td>
</tr>
<tr>
<td>MRI scan for registration</td>
<td>3</td>
</tr>
<tr>
<td>Image-robot registration</td>
<td>3</td>
</tr>
<tr>
<td>Total time for preparation</td>
<td>25</td>
</tr>
<tr>
<td>For each target</td>
<td></td>
</tr>
<tr>
<td>Target selection</td>
<td>1</td>
</tr>
<tr>
<td>Robot orientation of needle-guide and setting the depth of needle</td>
<td>0.5</td>
</tr>
<tr>
<td>Manual needle insertion</td>
<td>1.5</td>
</tr>
<tr>
<td>MRI scan for targeting error measurement</td>
<td>3</td>
</tr>
<tr>
<td>Total time for 12 targets</td>
<td>72</td>
</tr>
<tr>
<td>Total</td>
<td>97</td>
</tr>
</tbody>
</table>
Table 2.11: Direct MRI-guided targeting error

<table>
<thead>
<tr>
<th>Target Number</th>
<th>Depth [mm]</th>
<th>2D Error [mm]</th>
<th>3D Error [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95.33</td>
<td>0.68</td>
<td>1.78*</td>
</tr>
<tr>
<td>2</td>
<td>93.02</td>
<td>1.09</td>
<td>2.12</td>
</tr>
<tr>
<td>3</td>
<td>93.71</td>
<td>1.66</td>
<td>1.97</td>
</tr>
<tr>
<td>4</td>
<td>91.34</td>
<td>2.12</td>
<td>2.68*</td>
</tr>
<tr>
<td>5</td>
<td>90.43</td>
<td>2.72</td>
<td>2.86*</td>
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<tr>
<td>6</td>
<td>92.13</td>
<td>1.55</td>
<td>1.90</td>
</tr>
<tr>
<td>7</td>
<td>98.93</td>
<td>0.63</td>
<td>0.98</td>
</tr>
<tr>
<td>8</td>
<td>97.31</td>
<td>0.57</td>
<td>0.58</td>
</tr>
<tr>
<td>9</td>
<td>98.41</td>
<td>0.44</td>
<td>0.45</td>
</tr>
<tr>
<td>10</td>
<td>96.14</td>
<td>0.87</td>
<td>1.05</td>
</tr>
<tr>
<td>11</td>
<td>101.76</td>
<td>0.37</td>
<td>0.37</td>
</tr>
<tr>
<td>12</td>
<td>95.31</td>
<td>1.77</td>
<td>1.84</td>
</tr>
<tr>
<td>Max</td>
<td>101.76</td>
<td>2.72</td>
<td>2.86</td>
</tr>
<tr>
<td>Accuracy</td>
<td>95.32</td>
<td>1.21</td>
<td>1.55</td>
</tr>
<tr>
<td>Precision</td>
<td>3.39</td>
<td>0.75</td>
<td>0.81</td>
</tr>
<tr>
<td>Accuracy (A_{(d)})</td>
<td>0.91+0.0031d</td>
<td>1.25+0.0031d</td>
<td></td>
</tr>
<tr>
<td>Accuracy (A_{(76)})</td>
<td>1.15</td>
<td>1.49</td>
<td></td>
</tr>
</tbody>
</table>

*Markers were invisible. Needle tip points were picked from resliced images to calculate the 3-D accuracies.
Figure 2.44 shows the 12 target points on the grid, and a targeting example for target number 6, with the segmented needle, its axis, a segmented ball marker of the needle, and the registered CAD model of the needle.

The results of all targeting experiments and the overall accuracy and precision result are listed in Table 2.11. Based on the results at the average target depth of 95 [mm] and the estimated accuracy $A(d)$ of needle targeting at a depth $d$, and an example at 76 [mm], $A(76)$ is also shown in the table.

### 2.4.3.3 **Discussion and Conclusion**

One of the challenging problems encountered in the validation test described in this section was to build a needle, which is valid not only for the orientation evaluation but also for the tip position evaluation. Since the diameter of the acrylic needle used in Section 2.1.12 and 2.3.3 was relatively large (4.87 [mm]), the angled tip surface was able to be segmented from the MR images. On the other hand, the ceramic needle used in this validation test has a small diameter (1.61 [mm]), thus the tip position of the needle was not able to be identifiable on the MR images. As such, a ball marker filled with MRI contrast (Beekley, Bristol, CT) was attached at the top of the needle. By segmenting the ball marker from the MR images, the insertion depth of the needle was able to be precisely estimated and it helped to estimate the accurate tip position of the needle inserted into the skull mockup.

The experiment showed that manually inserting the needle through the needle-guide within the iMRIS scanner is feasible. Access to the needle within the scanner was not difficult, and it was possible to manipulate the needle gently, without disturbing the needle and the accuracy of targeting. Although the needle insertion could be automatically performed by an additional actuator in the future, the automatic needle insertion was opted to keep the surgeon in direct control of the needle.

The experiment also showed that accurately guiding the needle under direct MRI guidance is feasible. Needle guidance and insertion were all performed within the scanner. The procedures usually involve frequent in-out of the scanner moves between needle manipulation and subsequent imaging. With the MR Safe robot and an MRI scanner with the relatively short bore, such as iMRIS, it is now feasible to perform the procedures under direct MRI guidance. The MR Safe robot navigates the needle-guide and the surgeon inserts the needle through the needle-guide while observing real-time MR images. Immediate MR image
feedback during the stereotactic brain biopsy could be the best situation for the accurate and definitive diagnosis of the brain tumor.

Time wise, as shown in Table 2.11, several robot preparatory steps can be performed concurrently with patient preparation, so these should not substantially contribute to the operative time. Then, actual targeting steps were fast, possibly helping to reduce overall operative time.

The overall targeting errors that we have measured at the needle tip consist of multiple errors, such that imaging, registration, manipulator, and needle insertion errors. In the experiment, the needle tip was able to be placed within $1.55\pm0.81 \text{ mm}$ from the target point selected in the image. In the aspect of demanding targeting accuracy, DBS is one of the most difficult and challenging brain interventions. The subthalamic nucleus is the smallest clinically relevant target for implantation of a DBS electrode and its volume varies from 20-105 $\text{mm}^3$ [129]–[131]. The corresponding radius range of spherical targets of these volumes is 1.68-2.92 $\text{mm}$. The reported accuracy of 1.55 $\text{mm}$ is enough to aim even the smallest 1.68 $\text{mm}$ radius target. Moreover, the shape to be targeted is not typically spherical. Therefore, the reported accuracy of the system should be sufficiently applicable to most brain interventions including DBS, stereotactic brain biopsy, ventriculoperitoneal shunting, and laser ablation of the hippocampus.

The needle targeting depth of ~95 $\text{mm}$ in the experiments is also covering for the clinical requirements. DBS of the subthalamic nucleus requires one of the deepest target locations in brain interventions. In a study [132], the distance from the entry point to the target measured in 10 patients undergoing DBS was found to be $76\pm8 \text{ mm}$. The targeting accuracy of the system could be estimated to be $1.49 \text{ mm}$ at a depth of 76 $\text{mm}$ from the equation in Table 2.11, which is lower than the smallest clinically relevant target of 1.68 $\text{mm}$. Targeting at shallower depths will provide even better accuracy.

### 2.4.4 Discussion

To fulfill the main requirements of the MRI-compatible robots for stereotactic brain biopsy, the robot should be compact, accurate, safe to operate in the MRI, and not deteriorate the image quality. The robot is also desired to have an RCM mechanism to be placed at the entry point (burr hole) on the skull for minimally invasive procedures. Several MRI-compatible robots were previously developed for neurosurgery [112], [124]–[127]. Some of the robots are too bulky to work within the MRI scanner [125], made with metallic
materials [125], [126], using piezoelectric motors [59], [124], [127], and do not include an RCM mechanism [125]–[127].

The MR Safe RCM robot was designed to be compact so that it works within the MRI scanner. The unique structure of the robot, which is made with nonmetallic materials, enables accurate and safe needle targeting in the MRI environment. Moreover, the pneumatic actuation allows the robot not to deteriorate the image quality. Pneumatic actuators have an advantage over their piezoelectric counterparts in eliminating the need for magnetic and electric components from the scanner room. The robot also has a unique and rigid parallelogram-based RCM mechanism that enables minimally invasive procedures.

### 2.4.5 Conclusion

The feasibility of the intraoperative MRI-guided robotic system for stereotactic brain biopsy was successfully confirmed in a skull mockup study. The high accuracy and precision of needle placement using the MR Safe robot under the intraoperative MRI guidance allow the conventional procedures to be directly performed together with the intraoperative MR imaging. The procedures include not only stereotactic brain biopsy but also procedures that require deep brain access such as deep brain stimulation, ventriculoperitoneal shunting, and laser ablation of the epileptogenic foci and neoplasms.

While the traditional methods for deep brain access such as a frame-based approach and frameless neuro-navigation approach completely rely on preoperative images, the intraoperative MRI-guided robotic system enables intraoperative, immediate image feedback during the needle insertion into the intracranial region of the brain. Using this approach, the risk of missing the targeted region arises from a shift and/or deformation of the intracranial region could be potentially avoided.

### 2.5 Chapter Summary

This chapter presented the work in developing the MRI-guided robotic system for CNB. First, the MR Safe RCM Robot was introduced. The robot is MR Safe according to the ASTM 2503-13 standard [62]. The robot also incorporates a parallelogram-based RCM mechanism, which provides an important safety feature to the system. Second, the two software programs for the image guidance and the robot control were
developed in C/C++. The image guidance software is capable of performing a marker segmentation and image-robot registration. The software also internally calculates the robot kinematics and enables a targeting simulation. The robot control software was developed to control the robot. The software includes a special structure to secure the safety of the system.

The first clinical application of the MRI-guided robotic system was for pediatric bone biopsy. A novel workflow that minimizing trauma and eliminating radiation exposure in children with bone cancer and infection was proposed. The robotic system with the new workflow was validated in the leg mockup study. The feasibility of the robotic system in pediatric bone biopsy was further evaluated in the cadaver study.

The second clinical application of the MRI-guided robotic system was for stereotactic brain biopsy. Intraoperative MRI-guided robotic needle insertion test with the skull mockup showed the feasibility of the robotic system not only in stereotactic brain biopsy but also in various neurosurgical procedures that require deep brain access.

2.6 Conclusion

An MRI-compatible robot with RCM mechanism was developed and validated for MRI-guided CNB. The robot was entirely made of nonconductive, nonmetallic, and nonmagnetic materials. Moreover, to work within the MR scanner, the robot was designed and developed to be compact, stiff, accurate, safe to operate in the MRI, and not to deteriorate the image quality. In addition to the robot, the custom-written software enables an expedited image-robot registration, visualized robotic targeting simulation, and safe robot control.

The MR Safe robotic system can be utilized to be a part of an improved clinical workflow in which the pediatric bone biopsy can be performed earlier, ideally within a few hours of the diagnostic MRI scan being completed, and perhaps even at the same time in some cases. Since the robot enables the bone biopsy to be performed in the MRI scanner, the time needed to schedule a separate biopsy procedure in the operating room or CT scanner is eliminated. Performing the biopsy with MRI guidance would also allow more precise sampling, especially for bone marrow lesions that are best seen with MRI. These lesions are invisible to the naked eye during surgical biopsy and much less conspicuous on CT scans, increasing the possibility of false diagnoses from inaccurate sampling. Furthermore, the use of the MR Safe robot to perform MRI-guided bone biopsy would eliminate the radiation exposure from CT guidance for both the patient and the physician.
The MR Safe robotic system can be also used for stereotactic brain biopsy with an intraoperative MRI scanner. The system would allow neurosurgeons to formulate surgical plans based on most recent images, utilize continuous imaging for immediate feedback, and maintain the operative rhythm by eliminating the common in-out moves of the patient bed into the scanner, operating within the scanner under direct imaging. Furthermore, the robotic system could be potentially used not only for brain biopsy, but also for numerous neurosurgical procedures that require deep brain access such as DBS, ventriculoperitoneal shunting, and laser ablation of the hippocampus.

2.7 Contributions

The scientific contribution of this chapter includes:

- MR Safe RCM Robot, a novel MRI-guided robot for needle guidance, which is designed to be compact, stiff, accurate, safe to operate in the MRI, and not to deteriorate the image quality.
- Custom-written software for robot control and image guidance, which enables expedited image-robot registration, visualized robotic targeting simulation, and safe robot control.
- In-vitro experiments evaluating the mechanical performance of the MR Safe RCM Robot.
- A preclinical study demonstrating the effectiveness of the MR Safe RCM Robot in a bone biopsy.
- Cadaver study demonstrating the feasibility of the MR Safe RCM Robot in a bone biopsy.
- A preclinical study demonstrating the effectiveness of the MR Safe RCM Robot in deep brain access.

The design of the robot was done by Dr. Dan Stoianovici and the manufacturing of the robot was done by Dr. Doru Petrisor. The clinical work and protocol design for the pediatric application was done by Dr. Kevin Cleary and Dr. Karun Sharma. The clinical work and protocol design for neurosurgical application was done by Dr. Jean-Paul Wolinsky. The fabrications of the leg and skull mockups were done by Dr. Reza Monfaredi and Dr. Changhan Jun, respectively.

My personal contribution to the work described in this chapter includes:

- System integration.
- Formulation and analysis of the robot kinematics.
- Design, implementation, and debug of the robot control and navigation software.
- Design, execution, and analysis of all the experiments discussed in this chapter.
3 TRUS-Guided Robotic Interventions for CNB

Chapter 3 is organized as follows. Section 3.1 presents a description of the background and overview of the TRUS-guided robotic prostate biopsy system. Section 3.2 presents a description of the custom-written image guidance software for the system. Section 3.3 presents a description of the TRUS Robot, followed by its validation experiments. Section 3.4 presents a description of the Cohesive TRUS Probe-Robot, followed by its validation experiments. Section 3.5 and Section 3.6 present a summary and a conclusion of Chapter 3, respectively. At last, Section 3.7 presents a list of the scientific contributions involved in this chapter.

3.1 TRUS-Guided Robotic Prostate Biopsy

The main goal of the work involved in this section was to develop a concept of robotic TRUS-guided transrectal prostate biopsy system to robotically assist urologists in performing prostate biopsy. The development of the system has been reported in a journal article [133]. In this section, the background and motivation of the TRUS-guided robotic prostate biopsy system are presented. The overview of the system is also presented at the end of this section. The contributions of each collaborator for this work will be described in the following sections.

3.1.1 Background and Motivation

PCa is the most common non-cutaneous malignancy and the second leading cause of cancer-related death among US men [8]. Nearly 1 of every 6 men will be diagnosed with the disease at some time in their lives [134]. The best current estimate of PCa aggressiveness is the Gleason score obtained from core needle biopsy [135]. The most common biopsy method is freehand TRUS-guided. Since ultrasound only rarely identifies PCa visually, a systematic biopsy intends to sample the prostate evenly. But freehand biopsy is highly inconsistent, subjective, and results in uneven sampling [17], [136], [137], leaving large regions of the prostate unsampled, which can lead to under-sampling of clinically significant PCa, and implicitly under-staging of PCa diagnosis. In response, the current trend is directed towards a targeted biopsy approach guided by multiparametric Magnetic Resonance Imaging (mpMRI) [138]. Targeted biopsy has advantages over
systematic biopsy because it allows the biopsy needle to be guided to sampling areas based on imaging that shows CSR. Targeted biopsy methods include direct in-bore MRI targeting [35], [139] and methods that register (fuse) pre-acquired MRI to interventional ultrasound [89], [140]–[142]: cognitive fusion [143] and device/software aided fusion [89], [140]–[142]. Current fusion biopsy devices include [144]: Artemis (Eigen) [25], PercuNav (Philips) [145], UroNav (Invivo) [26], UroStation (Koelis) [85], and BK Ultrasound [146] systems.

With the fusion, few cores directed towards the CSR are taken in addition to the 12-cores of systematic biopsy. Targeted biopsy cores yield a higher CDR of clinically significant PCa than systematic biopsy cores [138], [147]. But targeted biopsy cores miss a large number of clinically significant PCa detected by systematic biopsy [89], [140]–[142] because mpMRI itself has 5%–15% false-negative clinically significant CDR [135]. A recent multicenter randomized trial [148] allowed men with normal mpMRI (PI-RADS≤2 [149]) to avoid biopsy and reported that targeted biopsy alone may be preferable to the routine freehand systematic biopsy. But the study does not tell how many men in whom biopsy was not performed might harbor clinically significant PCa [150]. Targeted biopsy alone is risky and systematic biopsy plays an important role in prostate diagnosis [151]: 1) Fusion can only be offered to patients with mpMRI findings, yet 21% of biopsy patients have none (range 15%-30%, 3544 patients [89], [140], [141], [152]). Systematic biopsy on patients with no mpMRI findings found 42% of men to harbor PCa, of which 1/3 were clinically significant PCa [140]; 2) On equivocal mpMRI lesions (PI-RADS=3), targeted biopsy alone misses 56% of Gleason 7–10 cancers [152]; 3) The MRI for targeted biopsy adds $700-$1,500/case, and reliable mpMRI interpretation is limited [153]. The large majority of over 1 million prostate biopsies performed annually in the US [93] are systematic biopsy. Therefore, systematic biopsy plays an important role independently and together with targeted biopsy [151].

Commonly, systematic and targeted biopsies are freehand procedures performed under transrectal ultrasound guidance with the end-fire TRUS probe manually operated by a urologist [17], [137] and a needle passed alongside the probe [135], [138]. To acquire ultrasound images, the TRUS probe must maintain contact with the rectal wall for the sonic waves to propagate, in turn, pushes against the prostate. The end-fire TRUS probe is known to deform the prostate gland, and the amount of pressure is typically variable throughout the procedure. Images at different regions of the prostate use different compression. If the
deformed 2D images are rendered in 3D, the actual shape and volume of the gland are skewed. Further, if a biopsy plan (systematic or targeted biopsy) is made on the skewed images, the plan is geometrically inaccurate. Moreover, when the needle is inserted for biopsy, the probe deforms the prostate differently contributing to additional targeting errors. The errors can be significant, for example, 2.35 to 10.1 [mm] (mean of 6.11 [mm]) [154]. Ideally, targeting errors for PCa biopsy should be <5 [mm] [35] (clinically significant PCa lesion ≥0.5 [cm³] in volume [155]).

Biopsy planning and needle targeting errors are problematic for both systematic and targeted biopsies. At fusion targeted biopsy, pre-acquired mpMRI is registered to the interventional TRUS images [22]. The registration is typically performed by aligning the shapes of the gland in ultrasound and MRI. This alignment is challenging due to shape differences caused by the dissimilar timing, patient positioning, imaging modalities, etc. [22], [89], [137]. Prostate deformations by the TRUS probe further magnify the registration problem. Several elastic registration algorithms have been developed to reduce errors [88] and improved the initial registration. However, handling prostate deformations at the time of each needle insertion for biopsy remains problematic [89].

Reducing prostate deformations at biopsy has been achieved on the transperineal needle path, for example with the TargetScan [86] device and Mona Lisa [156] robot. However, no current transrectal biopsy device can reliably minimize prostate deformations. Most devices freehand the probe [26], [85], [145], [157]–[159] and inherently deform the prostate unevenly. The only device that offers probe handling assistance is the Artemis device [25], which uses a mechanical encoded passive TRUS support arm. This arm helps to reduce deformations, but its manual operation leads to variability among urologists.

In this chapter, two robotic systems developed for TRUS-guided robotic prostate biopsy are presented. The robotic systems take transrectal prostate biopsy one step further, with an actuated TRUS probe manipulation robot and a custom-written software for robot control and image guidance. Like no other, the systems enable minimization of the prostate deformation and accurate biopsy targeting. The systems also enable the performance of hands-free, skill-independent prostate biopsy.
3.1.2 System Overview

Figure 3.1 shows a schematic of the TRUS-guided robotic prostate biopsy system. A workstation, a commercial ultrasound device, and a patient bed are placed from left to right side of the urologist. A robot that holds a TRUS probe is mounted to the left side of the patient bed and connected to the workstation. The patient lies on the bed in the left lateral decubitus position. The TRUS probe is connected to the ultrasound device. The ultrasound device and the robot are connected to the workstation. A custom-written software program for robot control and image guidance is installed to the workstation, which receives ultrasound image signals from the ultrasound device and sends control signals to the robot. The detailed explanations of each system component will be described in the following sections.

3.2 Software for TRUS-Guided Robotic Prostate Biopsy

The main goal of the work involved in this section was to develop a software program for 3D TRUS imaging, biopsy planning, robot control, and navigation. The development of the software has been partially reported in a journal article [133].

3.2.1 Personal Contributions

I was exclusively responsible for developing the software. My personal contribution to this work includes all the process of software development, such as design, implementation, and debug of the software.
3.2.2 Software Overview

A custom-written software was developed in C/C++ using commercial libraries including MFC [160], MCI [161], and MIL [162], and open-source libraries including Eigen [107], OpenCV [163], OpenMP [164], GDCM [106], VTK [104], and ITK [105]. Figure 3.2 shows the graphical user interface (GUI) with three main parts: control menu (Figure 3.2a), robot control (Figure 3.2b), and virtual reality environment for biopsy planning and navigation (Figure 3.2c). In the aspect of functionality, the software consists of three main components such as 3D TRUS imaging, biopsy target planning, and robot control and navigation.

The 3D TRUS imaging component is used to perform a 3D scan of the prostate and reconstruct a volume image. The biopsy target planning component is used to generate a set of 12 systematic biopsy target points for the extended 12-cores prostate biopsy. It is also used to compute optimal approaches that minimize the deformation and displacement of the prostate, which will be explained later in detail. The robot control and navigation component is used to monitor and control the robot and show important navigational information to the urologist. The detailed explanations about how these components work will be fully described in the following sections.

Figure 3.2: Software GUI; (a) Control menu, (b) robot control, and (c) virtual reality environment
3.2.3 3-D TRUS Imaging

In 3D TRUS imaging, a volume image of the prostate is generated with an assumption such that the ultrasound acoustic beam has a certain width of $D$ due to the size of sensors. Figure 3.3 shows a schematic of the volume reconstruction. For a given set of the ultrasound images $u_n$, $n = 1, 2, \cdots, N_u$ and its configurations $U_n$, $n = 1, 2, \cdots, N_u$, a volume image of the prostate is computed as:

Step 1: The ultrasound images $u_n$ are cropped so that the whole prostate boundaries are included inside of the region of interest.

Step 2: Set a bounding box so that all the cropped images are included, as shown in Figure 3.3.

Step 3: Allocate a volume (3D array) data $V$ based on the size of the bounding box $(I, J, K)$ and the pixel size of the ultrasound image, $P$ [mm/pixel]. The volume data $V$ consists of voxels $v_{ijk}$, $i = 1, \cdots, N_i$, $j = 1, \cdots, N_j$, $k = 1, \cdots, N_k$, where $N_i = [I/P]$, $N_j = [J/P]$, $N_k = [K/P]$.

Step 4: For a voxel $v_{ijk}$, compute distances $d_n \in \mathbb{R}$, $n = 1, 2, \cdots, N_u$ between the center point of the voxel, $c_{ijk}$, and the ultrasound images $u_n$ with the corresponding configurations $U_n$ such that

$$d_n = Dist(c_{ijk}, U_n), n = 1, 2, \cdots, N_u \quad (3.1)$$

Step 5: Sort the ultrasound images $u_n$ in ascending order of the distance $d_n$ and keep a certain number of the ultrasound images such that

![Figure 3.3: Schematic diagram of 3D TRUS imaging](image-url)
\[ u_{m(n)}, m = 1, 2, \ldots, N_c \]  

where \( d_{N_c(n)} = \text{Dist}(c_{ijk}, U_{N_c(n)}) < D/2 \) and \( N_c \leq 5 \).

Step 6: Fill the voxel \( v_{ijk} \) with an average intensity of the closest pixels \( q_{m(n)} \) on the ultrasound images \( u_{m(n)}, m = 1, 2, \ldots, N_c \) such that

\[ v_{ijk} = \frac{1}{N_c} \sum_{m=1}^{N_c} \text{Intensity}(u_{m(n)}, q_{m(n)}) \]  

Step 7: Repeat from Step 4 to Step 6 for all voxels of the volume data \( V \).

### 3.2.4 Biopsy Planning

For systematic biopsy planning, the software helps the urologist formulate the plan, graphically, based on the acquired 3D ultrasound. The most common systematic biopsy plan is the extended sextant plan of 12-cores. The plan uses a Prostate Coordinate System (PCS) that we derived based on anatomic landmarks of the prostate [165]. The origin of the PCS is defined at the midpoint between the apex (A) and base (B) of the prostate. The direction of the PCS follows the anatomic Left-Posterior-Superior (LPS) system (same as in the Digital Imaging and Communications in Medicine (DICOM) standard). The S axis is aligned along the AB direction, and P is aligned within the sagittal plane.

Figure 3.4a shows an example with the apex (A) and base (B) in a central sagittal view of the gland. In the software, the A&B points are selected manually, and several steps allow their location to be quickly and successively refined: 1) Select A&B points in the original rotary slices (para-coronal); 2) Refine their locations in the current LP (axial) re-slices of the volume image and orient the P direction; 3) Refine the A and B in the current SL (coronal) re-slices; 4) Refine the A and B in the current PS (sagittal) re-slices. In the above, the PCS location is updated after each step.
The PCS facilitates the definition of the biopsy plan. A systematic biopsy template is centered over the PCS and scaled with the AB distance. As such, defining the PCS allows defining the plan without the need for prostate segmentation. For the extended sextant plan, the 12 cores are initially placed by the software on the central coronal (SL plane) image of the gland and scaled according to the AB distance. The software then allows the physician to adjust the location of the cores as needed (Figure 3.4b). Since prostate biopsies are normally performed more posteriorly, towards the peripheral zone where the majority of prostate tumors are found (68% [94]), the program switches the view to central sagittal (PS), and displays a curve that can be pulled posteriorly below the urethra (Figure 3.4c). The 12-cores are then projected in the P direction to the level of this curve to give the final 3D biopsy plan (Figure 3.4d).

Figure 3.4: (a) Apex (A) and base (B) landmarks, Prostate Coordinate System (PCS), (b) 12-core plan shown in LS (coronal) plane, (c) project plan posteriorly, (d) sextant plan shown in 3D over a coronal slice.
3.2.5 Robot Control and Biopsy Navigation

For a robot control, a software component is developed, as shown in Figure 3.2b. The robot is monitored by displaying detailed information in real time, as shown in Figure 3.2b. The information includes the states of the robot, the encoder values, the states of the cable connections, the joystick input values, etc. In addition to the robot monitoring, the component is used to control the robot. The control options include to send the robot to the desired position or the zero position, to stop moving, to perform a homing, etc. All the processes in the robot control component are monitored by the watchdog at 5Hz. The watchdog, which was built on the hardware and the software, stops the robot immediately if any abnormal process is detected [38].

For biopsy navigation, an additional software component is developed. The left side of the navigation screen (Figure 3.5a) shows an example of the navigation screen that shows a 3D virtual environment showing the robot, probe, and real-time ultrasound image. The position of all components is updated in real-time. Furthermore, the navigation screen shows the biopsy plan and the current target number and name. The names of the cores follow the clinical system (Left-Right, Apex-Mid-Base, and Medial-Lateral), and are derived automatically based on the positions of the cores relative to the PCS. The right side of the navigation screen (Figure 3.5b) shows real-time ultrasound images with an overlaid needle insertion guide. Most biopsy needles have a forward-fire sampling mechanism. The green guide marks how deep to insert the needle before firing.

Figure 3.5: Biopsy navigation screen; (a) virtual reality environment and (b) 2D navigation screen
the biopsy so that when fired, the core is centered at the biopsy target. The depth line is located along the needle trajectory and offset from the target. The offset depends on the needle type and it is measured between the point of the loaded biopsy needle and the center of the magazine sample of the fired needle.

3.2.6 Discussion and Conclusion

In defining the PCS, the urethra is commonly visible in the apex region but not in the base region. Accordingly, while the A point is selected at the center point of the urethra in the apex, the B point is selected at the farthest point from the A on the boundary of the prostate in the base region. A method to define a systematic biopsy plan based on the PCS is a novel approach.

The software was developed by strictly following the rules of the objective-oriented programming. Thus, each component of the software components can be easily detachable and reusable. The software was developed to work with two different robots for TRUS-guided prostate biopsy, which will be presented in detail in the following sections.

3.3 TRUS Robot for Prostate Biopsy

The main goal of the work involved in this section was to develop and evaluate a robotic system, the TRUS robot, to assist urologists in performing prostate biopsy under TRUS guidance. The development of the robotic system has been reported in a journal article [133].

3.3.1 Personal Contributions

The design of the robot was done by Dr. Dan Stoianovici and the fabrication of the robot was done by Dr. Doru Petrisor. Those works are not discussed in detail here.

My personal contribution includes:

- System integration.
- Formulation and analysis of the robot kinematics.
- Design and implementation of the optimization algorithms described here.
- Design, implementation, and debug of the robot control and imaging software.
- Design, execution, and analysis of all the experiments discussed here.
3.3.2 System Overview

Figure 3.6 shows the components of the robotic TRUS-guided prostate biopsy system. The system is comprised of three main components such as a custom-built endocavity ultrasound probe manipulator (TRUS Robot, 4-DoF) with an end-fire ultrasound probe (EUP-V53W, Hitachi Medical Corporation, Japan) mounted, a commercial ultrasound scanner (HI VISION Preirus, Hitachi Medical Corporation, Japan), and a custom-built workstation (Intel(R) Core(TM) i7 3.07-GHz CPU with NVIDIA GeForce GTX 970 GPU, Matrox Orion HD video capture board, PMDi MC8000 motion control board, 12V/4.25Ah UPS, and 8GB RAM) with the custom-written image guidance software installed.

3.3.3 Robot Structure

The TRUS robot is a TRUS probe manipulator [166] that moves the probe with the same 4 DoF that is used manually in transrectal procedures, closely replicating its movement by hand. As shown in Figure 3.7, the TRUS probe can pivot in two directions ($\xi_1$ and $\xi_2$) about a fulcrum point (RCM) that is to be located at the anus, can be inserted or retracted (along the axis $\xi_3$), and spun about its axis ($\xi_3$). The rotations about the fulcrum point are performed with a RCM mechanism. The RCM is the most common mechanism used in medical robots [95], [167]. Our RCM is relatively small and uses belts to implement the virtual parallelogram [96], [166]. The RCM module was also used for a steady-hand robot in microsurgical augmentation [168].
A preliminary version of the TRUS robot was reported [166] and used clinically for prostatectomy operations with ultrasound navigation assistance [76]. For a biopsy, the robot was updated with a backlash-free cable transmission for the $\xi_3$ rotary axis and (previous used gears), and larger translational range along the $\xi_3$ axis. The robot was designed and analyzed in Creo (Parametric Technology Corporation, Needham, MA) and manufactured at our laboratory. Figure 3.7 shows the latest version of the robot.

The robot consists of two main modules, an RCM module (2-DoF) and an RT driver (2-DoF). The RCM module includes two revolute joints that rotate the ultrasound probe about the axis $\xi_1(\theta_1)$ and axis $\xi_2(\theta_2)$, respectively. The RT driver includes a revolute joint that rotate the ultrasound probe about the axis $\xi_3(\theta_3)$ and a prismatic joint that translate the probe along the axis $\xi_3(\tau)$. The rotation axes $\xi_1$, $\xi_2$, and $\xi_3$ are intersecting at the RCM point. The axis $\xi_1$ and axis $\xi_3$ has a constant angle of 60°. The hardware limits of the joints are: $\theta_1$ about $\xi_1(\pm86$ [deg]), $\theta_2$ about $\xi_2(-17$ to $46$ [deg]), $\theta_3$ about $\xi_3(\pm98$ [deg]), $\tau$ along $\xi_3(\pm49$ [mm]).

With 3D printed probe adapters, which is a part of the RT driver, the robot can support various types of ultrasound probes. As shown in Figure 3.7, the probe is mounted so that the axis $\xi_3$ is centered over the semi-spherical shaped point of the probe. The robot is attached to a passive support arm (7-DoA), which can be mounted to the patient bed. The robot is controlled by the joystick device or the robot control component of the custom-written software.

Figure 3.7: TRUS Robot consisting of RCM module and RT driver
3.3.4 Ultrasound Probe Calibration

3D ultrasound imaging is acquired from a 2D probe with a robotic scan. A one-time calibration process is required, to determine the transformation and scaling $T^R_U$ (4x4 matrix) from the robot coordinate system $\Sigma_R$ to the image frame $\Sigma_U$, as shown in Figure 3.8b. The calibration method was previously reported [169]. A calibration rig was made of a thin planar plastic sheet submersed in a water tank, as shown in Figure 3.8a. In ultrasound image, this appears as a line, and was automatically detected using a RANSAC algorithm [170] at different poses of the probe set by the robot. The calibration matrix was then estimated by solving least-square problems [169]. The process was repeated at five depth settings of the ultrasound machine (50, 65, 85, 110, and 125 [mm]), to have the proper calibration if the machine depth is changed.

3.3.5 3D TRUS Imaging with Minimal Prostate Deformations

3D ultrasound is acquired with a robotic rotary scan about $\xi_3$ axis. During the scan, images are acquired from the ultrasound machine over the video capture board. At the time of each image acquisition, the computer also records the current robot joint coordinates and calculates the position of the respective image frame in robot coordinates ($\Sigma_R$) through the calibration and forward kinematics. Overall, the raw data is a series of image-position pairs. A 3D volume image is then constructed from the raw data using a variation of Trobaugh’s method [171]. Rather than filling voxels with the mean of two pixels that are closest to the voxel regardless of distance (needed to fill all voxels in the case of a manual scan), only the pixels within a given

Figure 3.8: Ultrasound probe calibration; calibration (a) setup and (b) schematic
distance (enabled by the uniform robotic scan) are used. The distance was set to half of the acoustic beam width ($D$), which is determined at calibration. The speed of the rotary scan, $V_{\text{scan}}$, is calculated to fill the voxels that are farthest from $\xi_3$, at radius $R$, as:

$$V_{\text{scan}} = \frac{D f}{R} \, \text{[rad/s]}$$

where $f$ [fps] is the ultrasound frame rate (read on the machine display). Due to the rotary scan, pixels that are closer to the axis are denser, so the number of pixels that were averaged in each voxel was limited (i.e. 5). Practically, the speed of the scan is limited by the frame rate of the ultrasound machine (i.e. 15fps).

Experimentally, it is found that the ultrasound array was not perfectly aligned with the shaft of the ultrasound probe and respectively with $\xi_3$. The rotary scan left blank voxels near the axis, as shown in Figure 3.18a, c. To fill these voxels, a small $\xi_2$ ($3^\circ$) motion normal to the image plane was performed before the pure rotary scan.

At the time of the scan, the end-fire probe is initially set to be near the central sagittal image of the gland and the current joint values of $\theta_1$ and $\theta_2$ are saved as a scan position ($\theta_1^s$ and $\theta_2^s$). The probe is then retracted (translation $\tau$ along $\xi_3$, typically under joystick control) until the quality of the image starts to deteriorate by losing contact, and is then slightly advanced to recover image quality. This insertion level sets the minimal pressure needed for imaging. The rotary scan is performed without changing the insertion depth. As such, the probe pressure over the gland is maintained to the minimum level throughout the scan since the axis of rotation coincides with the axis of the semi-spherical probe end and gel lubrication is used to reduce friction. The method enables 3D imaging with quasi-uniform, minimal prostate deformations. The method below will show that the minimal deformation can also be preserved at biopsy.

### 3.3.6 Needle Targeting with Minimal Prostate Deformations

For the accuracy of needle targeting according to and based on the acquired 3D image, it is essential that the gland maintains the same shape at biopsy. Therefore, the same level of prostate compression should be used as much as possible. The following two steps are used to minimize prostate deformation.
3.3.6.1 Optimizing the Probe Approach to Each Biopsy Site

The probe insertion level used at scanning is preserved ($\tau$ is locked). Still, infinitely many solutions for the joint angles $\theta_1, \theta_2,$ and $\theta_3$ exist to approach the same target point. This is fortunate, because it leaves room to optimize the approach angles in order to minimize prostate deformations. As shown above, the rotation about the probe axis ($\xi_3$) preserves prostate deformations due to the semi-spherical probe point. As such, needle targeting should be performed as much as possible with $\xi_3$, and motions in the RCM axes $\xi_1$ and $\xi_2$, which are lateral to the probe, should be reduced.

If a biopsy target point is selected in the 3D ultrasound image, the robot should automatically orient the probe so that the needle-guide points towards the target. The volume image is in robot coordinates, therefore, the target point is already in robot coordinates. Robot’s inverse kinematics is required to determine the corresponding joint coordinates. Robot’s inverse kinematics were presented in publications [50, 56]. Here, we show the specific inverse kinematics that includes the needle and solves the joint angles $\theta_1, \theta_2$ for a given target point $\vec{p} \in \mathbb{R}^3$, insertion level $\tau$, and joint angle $\theta_3$.

As shown in Figure 3.9, the needle-guide passes through a point $\vec{o} = (o_x, o_y, 0)^T$ (known from design and calibration [169] and is parallel to $\xi_3$. For the target point $\vec{p}$ and chosen $\theta_3$, joint angles $\theta_1$ and $\theta_2$ have unique solutions, calculated with the second Paden-Kahan sub-problem approach, as follows.

The axes of the robot are

$$\begin{align*}
\xi_1 &= (\sin \phi, 0, -\cos \phi)^T \\
\xi_2 &= (0, 1, 0)^T  \\
\xi_3 &= (0, 0, 1)^T
\end{align*}$$

(3.5)

where $\phi = 60^\circ$ is a constant offset angle. The needle insertion depth $L$ required to place the needle point at the target $\vec{p}$ is

$$L = L_e + L_p + \tau$$

(3.6)
where $L_e$ is a constant distance between the entry point of the needle-guide and the RCM point in the direction of the axis $\xi_3$, and $L_p$ is a distance between the RCM point and the target point $\vec{p}$ in the direction of the axis $\xi_3$ such that:

$$L_p = \sqrt{\vec{p}^T \vec{p} - \vec{o}^T \vec{o}}$$  \hfill (3.7)

When the robot is in zero position as shown in Figure 3.9a, the needle tip $\vec{q}_1$ is given by:

$$\vec{q}_1 = (o_x, o_y, -L_p)^T$$  \hfill (3.8)

and when rotated by $\theta_3$ is:

$$\vec{q}_2 = e^{\xi_3 \theta_3} \vec{q}_1$$  \hfill (3.9)

where $\xi_3$ is the cross-product matrix of $\xi_3$.

Figure 3.9: Inverse kinematics of the robot: (a) for a given target point $\vec{p}$ and rotation angle $\theta_3$, (b) find the rotation angles $\theta_1$ and $\theta_2$
Then, $\theta_1$ and $\theta_2$ satisfy:

$$e^{\xi_1 \theta_1} e^{\xi_2 \theta_2} \vec{q}_2 = \vec{p}$$

(3.10)

where $\hat{\xi}_1$ and $\hat{\xi}_2$ are the cross-product matrices of $\xi_1$ and $\xi_2$, respectively. If $\vec{q}_3$ is a point such that:

$$\vec{q}_3 = e^{\hat{\xi}_2 \theta_2} \vec{q}_2 = e^{-\hat{\xi}_1 \theta_1} \vec{p}$$

(3.11)

then:

$$\vec{q}_3 = \alpha \xi_1 + \beta \xi_2 + \gamma (\xi_1 \times \xi_2)$$

(3.12)

where:

$$\alpha = \frac{(\xi_1^T \xi_2) \xi_2^T \vec{q}_2 - \xi_1^T \vec{p}}{(\xi_1^T \xi_2)^2 - 1}$$

$$\beta = \frac{(\xi_1^T \xi_2) \xi_1^T \vec{p} - \xi_2^T \vec{q}_2}{(\xi_1^T \xi_2)^2 - 1}$$

$$\gamma = \pm \sqrt{\frac{\vec{q}_2^T \vec{q}_2 - \alpha^2 - \beta^2 - 2\alpha \beta \xi_1^T \xi_2}{(\xi_1 \times \xi_2)^T (\xi_1 \times \xi_2)}}$$

(3.13)

Finally, $\theta_1$ and $\theta_2$ can be found by solving:

$$e^{\hat{\xi}_2 \theta_2} \vec{q}_2 = \vec{q}_3$$

and $e^{-\hat{\xi}_1 \theta_1} \vec{p} = \vec{q}_3$

(3.14)

as:

$$\theta_2 = \text{atan2} \left( \xi_2^T (\vec{q}_3' \times \vec{q}_3'), \vec{q}_2^T \vec{q}_3' \right)$$

$$\vec{q}_2' = \vec{q}_2 - \xi_2 \xi_2^T \vec{q}_2$$

(3.15)

$$\vec{q}_3' = \vec{q}_3 - \xi_2 \xi_2^T \vec{q}_3$$
\[
\theta_1 = -\arctan\left(\xi_1^T (\vec{p}' \times \vec{q}_3'') \right)
\]

\[
\vec{p}' = \vec{p} - \xi_1 \xi_1^T \vec{p}
\]

\[
\vec{q}_3'' = \vec{q}_3 - \xi_1 \xi_1^T \vec{q}_3
\]

From the hardware joint limits of the robot, the range of \(\theta_2\) is \(-17.0^\circ \leq \theta_2 \leq 46.0^\circ\). Therefore, \(\theta_1\) and \(\theta_2\) are unique since \(\vec{q}_3\) is unique (\(\gamma < 0\)).

For a given target \(\vec{p}\) and \(\theta_3\), a unique solution \((\theta_1, \theta_2)^T\) that aligns the needle on target is calculated by solving the inverse kinematics (IK) problem as shown above:

\[
(\theta_1, \theta_2)^T = I(\vec{p}, \theta_3)
\]  

For example, the blue curves in Figure 3.10 show \(\theta_1\) and \(\theta_2\) as a function of \(\theta_3\) for a target \(p = (10, 10, -100)^T\) and scan position \((\theta_1^s, \theta_2^s) = (0, 0)\).

The optimal approach of the TRUS probe to a target is one that minimizes the movements of the \(\theta_1\) and \(\theta_2\) from their scan positions \(\theta_1^s\) and \(\theta_2^s\):

\[
\theta_3^{opt} = \arg\min_{\theta_3} [(\theta_1 - \theta_1^s)^2 + (\theta_2 - \theta_2^s)^2]
\]  

Figure 3.10: Example of optimizing the approach angles for target point \(\vec{p} = (10, 10, -100)^T\) and scan
For example, the red curve in Figure 3.10 shows the sum of squared values for all $\theta_3$ angles, and the green line shows the optimal value.

The optimal $\theta_1$ and $\theta_2$ angles are:

\[
\begin{pmatrix} \theta_{1\text{opt}}^\top, \theta_{2\text{opt}}^\top \end{pmatrix} = T(p, \theta_3^{\text{opt}})
\]  

(3.18)

A gradient descent algorithm was used to determine the minimum solution. Given the shapes of the curves, the global minimum was found by starting the minimization from each limit and the center of the $\theta_3$ range and retaining the lowest solution.

### 3.3.6.2 Optimizing the Order of the Biopsy Cores

Once the optimal approach angles are calculated for a set of $n$ biopsy points, the order of the biopsies can also be optimized to minimize the travel of the probe, a problem known as the travelling salesman problem (TSP). The TSP is to find the shortest route that starts from the initial scan position, visits each biopsy point once, and returns to the initial scan position $\vec{s}_0 = (\theta_1^0, \theta_2^0, 0)^T$. The optimal approach of biopsy point $i = 1, \ldots, n$ is $\vec{s}_i = (\theta_1^i, \theta_2^i, \theta_3^i)^T$. The squared distance between a pair of points is:

\[
d(\vec{s}_i, \vec{s}_j) = (\vec{s}_i - \vec{s}_j)^T(\vec{s}_i - \vec{s}_j) \text{ for } i \neq j
\]

(3.19)

Figure 3.11: Example of the location of 12 biopsy cores in (a) joint and (b) Cartesian coordinates

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The goal is to find an ordering $\pi$ that minimizes the total distance:

$$D = \sum_{i=0}^{n-1} d(s_{\pi(i)}, s_{\pi(i+1)}) + d(s_{\pi(n)}, s_{\pi(0)})$$  \hspace{1cm} (3.20)

The solution of the TSP is found using a classic 2-step algorithm [173]. Figure 3.11 shows an example of $n = 12$ biopsy points, represented in robot joint coordinates (Figure 3.11a) and Cartesian space of the prostate (Figure 3.11b).

### 3.3.7 Rotation Axes and RCM Check

#### 3.3.7.1 Materials and Methods

A bench test was performed to verify some kinematic parameters of the robot, such as angles between the rotational and translational axes and distances between the rotational axes at the RCM point. An optical localizer (Polaris, NDI, Canada) was used to measure the 3D position of a reflective marker on a light and rigid rod attached to the robot, as shown in Figure 3.12b. The manufacturer-stated RMS error of the localizer is 0.35 \[mm\]. The distance between the reflective marker and the RCM point was about 250 \[mm\] and the optical localizer was approximately located 1100 \[mm\] away from the marker. The accuracy of the localizer can be improved in this environment up to 0.078 \[mm\] [98].

![Figure 3.12: Experimental setup for robot joint accuracy test](image)
In the measurement, each joint of the robot moved one at a time with an increment of 5 [deg] for \( \theta_1, \theta_2, \) and \( \theta_3 \), and 5 [mm] for \( \tau \). The movement ranges were \(-80 [deg] \leq \theta_1 \leq 80 [deg], -15 [deg] \leq \theta_2 \leq 40 [deg], -80 [deg] \leq \theta_3 \leq 80 [deg], \) and \(-45 [mm] \leq \tau \leq 45 [mm], \) respectively. The 3D positions of the marker were measured for 500 frames and averaged for each position.

In the analysis, the rotational axes (\( \xi_1, \xi_2, \) and \( \xi_3 \)) and the translation axis (\( \xi_4 \)) were estimated using the obtained 4 sets of the mean points. To estimate a rotational axis, first, a plane was fitted to the point set using a least square technique and a normal vector of the plane was found. Second, the point set was projected onto the plane. Third, a circle was fitted to the projected point set using a least square technique and a center point was found. The rotational axis was defined with the center point of the circle and the normal vector of the plane. To estimate a translational axis, first, a PCA was applied to the point set. Second, a mean point of the point set was calculated. The translational axis was defined with the mean point and the first principal axis of the point set. The estimated 4 axes were used to check the kinematic parameters mentioned above.

### 3.3.7.2 Results

Figure 3.13 shows a 3D plot of the rotational (\( \xi_1, \xi_2, \xi_3 \)) and translational (\( \xi_4 \)) axes estimated using the measured points. The angles between the axes and the distances between the rotational axes at the RCM point are presented in Table 3.1. Angular error between the rotational axes, such as \( \xi_1-\xi_2, \xi_1-\xi_3, \xi_2-\xi_3, \xi_1-\xi_4, \xi_2-\xi_4, \) and \( \xi_3-\xi_4, \) were 1.67, 0.03, 0.45, 0.06, 0.89, and 0.45 [deg], respectively. Distance errors between the rotational axes, such as \( \xi_1-\xi_2, \xi_1-\xi_3, \) and \( \xi_2-\xi_3, \) were 0.70, 0.35, and 0.21 [mm], respectively.

<table>
<thead>
<tr>
<th>Axis</th>
<th>Angle [deg]</th>
<th>Distance [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \xi_1-\xi_2 )</td>
<td>91.67</td>
<td>0.70</td>
</tr>
<tr>
<td>( \xi_1-\xi_3 )</td>
<td>59.97</td>
<td>0.35</td>
</tr>
<tr>
<td>( \xi_2-\xi_3 )</td>
<td>90.45</td>
<td>0.21</td>
</tr>
<tr>
<td>( \xi_1-\xi_4 )</td>
<td>60.06</td>
<td>-</td>
</tr>
<tr>
<td>( \xi_2-\xi_4 )</td>
<td>90.89</td>
<td>-</td>
</tr>
<tr>
<td>( \xi_3-\xi_4 )</td>
<td>0.45</td>
<td>-</td>
</tr>
</tbody>
</table>
3.3.8 Joint Accuracy Test

3.3.8.1 Materials and Methods

An additional bench test was performed to verify the joint accuracies of the robot. The point set data obtained in the previous test was used for this test. The rotational errors of $\theta_1$, $\theta_2$, and $\theta_3$ were measured by calculating the angles between the lines that connect the projected points and the center point of the estimated circle. The translational errors of $\tau$ were measured by calculating the distances between the points projected onto the first principal axis of the point set.

3.3.8.2 Results

Figure 3.14 shows 2D plots of the data points, which were used for the joint accuracy test. The joint accuracies and precisions of the robot were presented in Table 3.2.

<table>
<thead>
<tr>
<th>Joint</th>
<th>Accuracy</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\theta_1$ [deg]</td>
<td>0.112</td>
<td>0.079</td>
</tr>
<tr>
<td>$\theta_2$ [deg]</td>
<td>0.021</td>
<td>0.028</td>
</tr>
<tr>
<td>$\theta_3$ [deg]</td>
<td>0.040</td>
<td>0.033</td>
</tr>
<tr>
<td>$\tau$ [mm]</td>
<td>0.015</td>
<td>0.013</td>
</tr>
</tbody>
</table>
3.3.9 Robot Space Set Point Test

3.3.9.1 Materials and Methods

A supplemental bench test was performed to verify the virtual needle-tip positing accuracy. All the experimental setups were equivalent to the previous tests except marker attachment location. For this test, a reflective marker with a slender rod was placed at the virtual needle tip position through the needle-guide, approximately 142 [mm] apart from the RCM point, 55 [mm] apart from the probe tip (Figure 3.15).
In the measurement, \( \theta_1 \) was moved from -45 [deg] to 45 [deg] with an increment of 5 [deg]. For each position, \( \theta_2 \) moved from -15 [deg] to 40 [deg] with an increment of 5 [deg]. The 3D positions of the marker were measured for 300 frames at each position. The measurement was repeated 7 \((N_k)\) times for different positions of \( \theta_3 = \{-90, -60, -30, 0, 30, 60, 90 [deg] \}\) and a fixed position of \( \tau = 0 \). By averaging the measured points for each position, the actual point sets were obtained \( \vec{p}_{i,j,k}, i = 1,2, ..., N_i, j = 1,2, ..., N_j, k = 1,2, ..., N_k \) \((N_i = 19, N_j = 12, N_k = 7)\). Then, by solving the forward kinematics problems of the robot, the set point set was generated \( \vec{q}_{i,j,k}, i = 1,2, ..., N_i, j = 1,2, ..., N_j, k = 1,2, ..., N_k \) \((N_i = 19, N_j = 12, N_k = 7)\). The transformation \( F \) from the optical localizer coordinate system to the robot coordinate system was estimated with a rigid point cloud registration technique [99]. The virtual needle-tip positioning error \( e_v \) was then evaluated as

\[
e_v = \frac{1}{N_i N_j N_k} \sum_{i,j,k} \| F \cdot \vec{p}_{i,j,k} - \vec{q}_{i,j,k} \| \tag{3.21}
\]

The accuracy and precision were calculated as the average and standard deviation of the errors, as usual.

**3.3.9.2 Results**

Figure 3.16 shows an example of the set point test results \((\theta_3 = 0 [deg])\). The accuracy and precision of the virtual needle tip positioning were 0.56 [mm] and 0.30 [mm], respectively. The maximum error was 1.47 [mm].

![Figure 3.16: Robot set point test results (\( \theta_3 = 0 [deg] \))](image-url)
3.3.10 Ultrasound Probe Calibration Check

3.3.10.1 Materials and Methods

An imaging test was performed to verify the result of the ultrasound probe calibration. A 5-by-5 grid mock-up was built with thin strings (Ø0.4 [mm]). The grids were 10 [mm] apart from each other. In the experiment, the grid mock-up was submerged and imaged with a 3D rotary scan. The 25 intersection points of the grid were then picked from the 3D volume image, as shown in Figure 3.17b. The picked 25 points were registered to the ideal grid point set using a Horn’s method [99]. The errors were calculated as a distance between two corresponding points. The test was repeated for different depth settings of the ultrasound scanner (See Figure 3.17a, \( d = 50, 65, 85, 110, 125 [mm] \)).

3.3.10.2 Results

The accuracies and precisions of the 25 points with 5 different depth settings are presented in Table 3.3.

Table 3.3: 3D imaging geometric accuracy results

<table>
<thead>
<tr>
<th>Depth Setting ( d ) [mm]</th>
<th>Accuracy [mm]</th>
<th>Precision [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.48</td>
<td>0.26</td>
</tr>
<tr>
<td>65</td>
<td>0.51</td>
<td>0.20</td>
</tr>
<tr>
<td>85</td>
<td>0.47</td>
<td>0.19</td>
</tr>
<tr>
<td>110</td>
<td>0.51</td>
<td>0.27</td>
</tr>
<tr>
<td>125</td>
<td>0.44</td>
<td>0.23</td>
</tr>
<tr>
<td>Total</td>
<td>0.48</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Figure 3.17: Ultrasound probe calibration check; (a) depth setting of the scanner and (b) 25 grid points picked from volume image
3.3.113-Dimensional TRUS Imaging Test

3.3.11.1 Materials and Methods

An additional imaging test was performed to verify the effectiveness of the two techniques proposed for 3D TRUS imaging. A prostate mock-up (M053, CIRS, VA) was imaged with and without the proposed techniques, such as applying a small lateral motion prior to the rotary motion during the 3D scan and calculating a maximum angular velocity of $\theta_3$ ahead of the 3D scan.

3.3.11.2 Results

The results of the 3D TRUS imaging check were presented in Figure 3.18. It includes axial and coronal images of the prostate mock-up generated without and with the proposed method.

![Figure 3.18: 3D ultrasound imaging; axial and coronal images of the prostate mockup (a)(c) before and (b)(d) after applying the proposed techniques. Red and blue arrows show the empty voxels caused by the non-aligned image plane and the fast rotation speed of the probe, respectively.](image)
3.3.12 Targeting Test with Grid Mockup

3.3.12.1 Materials and Methods

A targeting test was performed using the same grid mockup used in the ultrasound probe calibration check. The aim of this test was to verify the targeting accuracy of the system under idealized conditions. The experimental environment was the same as the ultrasound probe calibration check. The grid mock was submerged and imaged with a 3D rotary scan, as shown in Figure 3.19a. The 25 intersection points were then picked from the volume image, as shown in Figure 3.19b. The robot was then sent to each point and a biopsy needle (Ø1.0 [mm]) was inserted through the needle-guide. The test was repeated for different depths of the grid mock-up, such as 20, 40, and 60 [mm] (Figure 3.19b, c, d). The errors were measured based on the pre-defined criteria, as shown in Table 3.4 and Figure 3.19e, f, g.

Figure 3.19: Targeting experiment with grid mock-up; (a) experimental setup, (b) criterion (i) (e≤0.5), (c) criterion (ii) (0.5<e≤1.0), (d) criterion (iii) (1.0<e≤1.5), 25 grid points in different depths (e) 20, (f) 40, (g) 60 [mm]
### 3.3.12.2 Results

The results of the targeting test with the grid mock-up were presented in Table 3.5. For the grid depth of 20 [mm], the number of experiments with targeting errors ≤0.5, ≤1.0, and >1.0 [mm] were 18, 6, and 1 respectively. For the grid depth of 40 [mm], the corresponding numbers were 21, 3, and 1, respectively. For the grid depth of 60 [mm], the corresponding numbers were 20, 5, and 0. The two cases when the errors were >1.0 [mm] appeared to be ≤1.5 [mm]. Examples of these cases are shown in Figure 3.19g.

#### Table 3.5: Targeting results with grid mockup

<table>
<thead>
<tr>
<th>Grid Depth [mm]</th>
<th>Number of criterion (i)</th>
<th>Number of criterion (ii)</th>
<th>Number of criterion (iii)</th>
<th>Number of criterion (iv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>18</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>21</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>20</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>14</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

### 3.3.13 Targeting Test with Prostate Mockup

#### 3.3.13.1 Materials and Methods

An additional targeting test was performed with a prostate mock-up. The aim of this test was to verify the effectiveness of the optimization methods and the targeting accuracy of the system using a deformable and displaceable prostate mock-up. A deformable prostate-mimicking mock-up (M053, CIRS, VA) was fixed on the table using an elastic rope to simulate its movability, as shown in Figure 3.20a.

---

Table 3.4: Criteria for targeting error evaluation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Error (e) [mm]</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i)</td>
<td>$e \leq 0.5$</td>
<td>Tip of the needle is on the grid point (Figure 3.19e).</td>
</tr>
<tr>
<td>(ii)</td>
<td>$0.5 &lt; e \leq 1.0$</td>
<td>Distance between the centerline of needle and the grid point is shorter than the needle diameter (Ø1.0 [mm]) (Figure 3.19f).</td>
</tr>
<tr>
<td>(iii)</td>
<td>$1.0 &lt; e \leq 1.5$</td>
<td>Distance between the outline of needle and the grid point is shorter than the needle diameter (Ø1.0 [mm]) (Figure 3.19g).</td>
</tr>
<tr>
<td>(iv)</td>
<td>$e &gt; 1.5$</td>
<td>Distance between the outline of needle and the grid point is farther than the needle diameter (Ø1.0 [mm]).</td>
</tr>
</tbody>
</table>
In the experiment, a rotary 3D scan was performed to obtain a 3D volume image after adjusting the translation of the ultrasound probe so that the probe barely touches the simulated rectal wall and the central sagittal view of the simulated prostate is clearly visible. Next, an extended 12-cores biopsy plan was established after completing the prostate segmentation. Then, the robot aimed at each target, and the biopsy needle (length of sample notch: 1.8 [cm], gauge size: 18 gauge, needle length: 25 [cm], penetration depth: 22 [mm], MC1825, Bard Medical, GA) was inserted under the guidance of the navigation screen. A real-time ultrasound image was saved at each aimed position. At last, a post-biopsy 3D scan was performed for evaluation purpose.

Figure 3.20: Targeting experiment with prostate mock-up; (a) experimental setup, (b) 2D displacement and deformation

Figure 3.21: Schematic of (a) prostate displacement and (b) prostate deformation measurements
In the analysis, a prostate contour was manually identified from each real-time ultrasound image saved at each aimed position, as shown in Figure 3.20b. 2D displacements of the prostate, $d_{p,i}, i = 1, ... , 12$, were calculated as the distances between the center points of the pre-acquired prostate contours, $c_{1,i}, i = 1, ... , 12$, and the corresponding center points of the real-time prostate contours, $c_{2,i}, i = 1, ... , 12$, as shown in Figure 3.21a. To measure the 2D deformations of the prostate, the pre-acquired contours were translated by $(c_{2,i} - c_{1,i})$ so that the two contours have a same center point, as shown in Figure 3.21b. 2D deformations of the prostate, $d_{f,i}, i = 1, ... , 12$, were then calculated as the mean distances of two-points sets where the two contours intersect with a line that rotates uniformly ($\phi = 15 [deg]$) about the center point, as shown in Figure 3.21b. Subsequently, the needle insertion errors $e_{n,i}, i = 1, ... , 12$ were measured as distances between the center of the biopsy needle imaged on the ultrasound image and the corresponding target points, as shown in Figure 3.23a. The targeting errors $e_{t,i}, i = 1, ... , 12$ were then calculated as a sum of the needle insertion errors and the 2D displacements of the prostate such that $e_{t,i} = e_{n,i} + d_{p,i}, i = 1, ... , 12$. Furthermore, 3D displacement $D_p$ and deformation $D_f$ of the prostate were measured from the two prostate surface models generated from the pre- and post-biopsy ultrasound volumes, respectively. $D_p$ was calculated as a distance between the centroids of the two surface models. To measure the 3D deformation, the pre-biopsy prostate surface model was translated so that the two surface models have a same centroid. $D_f$ and $D_f^{\max}$ were then calculated as a mean and maximum value of the distances from vertices of the pre-biopsy prostate surface model to the corresponding closest point on the post-biopsy prostate surface model.

An additional experiment was performed to visually observe the motion of the TRUS probe about the prostate and how the probe deforms the prostate. The prostate mockup was made of a soft-boiled chicken.

![Image](image.png)

Figure 3.22: Probe motion test (a) experimental setup and (b) corresponding image guidance screen
egg, peeled shell, and placed on 4 vertical poles support, as shown in Figure 3.22a. The support was made to gently hold the egg so that the egg could be easily unbalanced and pushed off, to see if a biopsy can be performed on the egg without dropping it. A limitation of this experiment is that the egg mockup is unrealistic in many respects. We have derived it to visualize the motion of the probe about the prostate, which is calculated by algorithms and is difficult to observe with closed, more realistic mockups.

### 3.3.13.2 Results

The results of the targeting test with the prostate mock-up were presented in Table VI. The times required for aiming at the 12 targets with the optimal and normal sequences were 61 and 137 [sec], respectively. The 3D displacement $D_p$ and deformation $D_f$ of the prostate were 0.58 and 0.20 [mm], respectively. The maximum deformation distance $D_f^{max}$ was 0.89 [mm]. The biopsy on the egg experiment performed the 3D scan and positioned the probe for biopsy without pushing the egg off the support.

<table>
<thead>
<tr>
<th>Target Number</th>
<th>Target Position</th>
<th>Errors [mm]</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$d_p$</td>
<td>$d_f$</td>
<td>$e_n$</td>
<td>$e_t$</td>
</tr>
<tr>
<td>1</td>
<td>RAM</td>
<td>1.21</td>
<td>0.71</td>
<td>0.79</td>
</tr>
<tr>
<td>2</td>
<td>RAL</td>
<td>0.38</td>
<td>0.46</td>
<td>0.41</td>
</tr>
<tr>
<td>3</td>
<td>RML</td>
<td>0.48</td>
<td>0.30</td>
<td>0.60</td>
</tr>
<tr>
<td>4</td>
<td>RBL</td>
<td>0.26</td>
<td>0.41</td>
<td>0.70</td>
</tr>
<tr>
<td>5</td>
<td>RBM</td>
<td>1.13</td>
<td>0.37</td>
<td>0.80</td>
</tr>
<tr>
<td>6</td>
<td>RMM</td>
<td>0.88</td>
<td>0.45</td>
<td>0.70</td>
</tr>
<tr>
<td>7</td>
<td>LBL</td>
<td>0.77</td>
<td>0.39</td>
<td>0.40</td>
</tr>
<tr>
<td>8</td>
<td>LML</td>
<td>1.03</td>
<td>0.71</td>
<td>0.31</td>
</tr>
<tr>
<td>9</td>
<td>LAL</td>
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<td>0.57</td>
<td>0.69</td>
</tr>
<tr>
<td>10</td>
<td>LBM</td>
<td>0.76</td>
<td>0.42</td>
<td>0.60</td>
</tr>
<tr>
<td>11</td>
<td>LMM</td>
<td>0.97</td>
<td>0.41</td>
<td>0.51</td>
</tr>
<tr>
<td>12</td>
<td>LAM</td>
<td>1.26</td>
<td>0.36</td>
<td>0.31</td>
</tr>
<tr>
<td>Max</td>
<td></td>
<td>1.26</td>
<td>0.71</td>
<td>0.80</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td>0.78</td>
<td>0.46</td>
<td>0.57</td>
</tr>
<tr>
<td>Precision</td>
<td></td>
<td>0.37</td>
<td>0.13</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Clinical Trials

3.3.14.1 Materials and Methods

An FDA/IRB-approved clinical study was conducted to verify the feasibility of the robotic prostate biopsy system. Figure 3.24 shows the system setup for the clinical study. The study was carried out on five men with an elevated PSA level (≥4 [ng/ml]) and/or abnormal DRE. In the study, the TRUS probe is cleaned and disinfected, as usual, mounted in the robot, and covered with a condom as usual. The patient is positioned in the left lateral decubitus position and periprostatic local anesthesia are performed as usual. With the support arm unlocked, the TRUS probe mounted in the robot is transrectally placed and adjusted to show a central sagittal view of the prostate. The support arm is locked for the duration of the procedure. The minimal level
of probe insertion is adjusted under joystick control. A 3D rotary scan is then performed under the software control. The PCS and biopsy plan are made by the urologist. The software then optimizes the approach to each core and core order. Sequentially, the robot moves automatically to each core position. The urologist inserts the biopsy needle (length of sample notch: 1.8 [cm], gauge size: 18 gauge, needle length: 25 [cm], penetration depth: 22 [mm], MC1825, Bard Medical, GA) through the needle-guide up to the depth overlaid onto the real-time ultrasound (Figure 3.5b), and samples the biopsy manually, as usual. Ultrasound images are acquired with the needle inserted at each site for confirmation. All data, including the ultrasound images and configurations, A-B points, PCS, targets, and confirmation images are saved automatically.

Needle insertion errors $e_n$ were calculated as described in the previous section. Needle targeting accuracy and precision were calculated as the average respectively standard deviation of the errors, as usual. Partial and overall procedure times were also recorded.

### 3.3.14.2 Results

The robot allowed 3D imaging of the prostate, 3D size measurements, and volume estimation. The results are presented in Table 3.7. The robot also enabled hands-free TRUS operation for prostate biopsy and all 5 procedures were successful from the first attempt. No adverse effects due to the robotic system were reported by the patients. The biopsy procedures took 13 minutes on average. Slight patient motion at the time of biopsy firing was occasionally observed. No remnant prostate shift was observed. There were no adverse effects due to the robotic system. Three of the five patients had a malignant tumor with biopsy Gleason Scores of 3+3, 3+4, and 3+3. Numerical results are presented in Table 3.8.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prostate Size [mm]</th>
<th>Prostate Volume [cm³]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Superior-Inferior</td>
<td>Anterior-Posterior</td>
</tr>
<tr>
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<td>38.85</td>
<td>30.32</td>
</tr>
<tr>
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<td>52.78</td>
<td>40.45</td>
</tr>
<tr>
<td>5</td>
<td>50.81</td>
<td>43.85</td>
</tr>
<tr>
<td>Average</td>
<td>49.65</td>
<td>38.49</td>
</tr>
</tbody>
</table>
3.3.15 Discussion

In this section, a novel robotic prostate biopsy system was reported. The system includes a compact and precise robotic manipulator and integrated software. The robotic manipulator precisely guides a biopsy needle to the designated target with a safety feature of the RCM mechanism. It also provides the urologists with freedom in his/her hand. Furthermore, the software possesses extensive abilities, such as 3D TRUS imaging, prostate segmentation, biopsy target planning, robot control, and needle insertion navigation. In addition, the software enables accurate biopsy using special optimization techniques.

Image registration is a commonly required step of clinical procedures that are guided by medical images [58, 59]. This step must normally be performed during the procedure and adds to the overall time. With the TRUS robot, and also with fusion biopsy devices [16, 18], intra-procedural registration is not required. Instead, a calibration is performed only once for a given probe [169]. The probe adapter was designed to mount it repeatedly at the same position when removed for cleaning and reinstalled, to preserve the calibration.

Bench positioning tests show that the robot itself can point a needle with submillimeter accuracy and precision. The geometric accuracy and precision of 3D imaging were submillimetric. Combined, image-guided targeting errors in a water tank (no deformations) were submillimetric in 97.3% of the tests and <1.5 [mm] overall. Experiments on a prostate mockup showed that changes in the position and deformation of the prostate at the time of the initial scan and biopsy were submillimetric. The results of the targeting test with

| Number of ultrasound images for 3D reconstruction | 238 |
| Average Time [min] | 3D image scan | 0.48 |
| | PCS and biopsy plan | 6.26 |
| | Biopsy sampling | 4.42 |
| | Total procedure | 13.02 |
| Needle Targeting* [mm] | Accuracy | 0.51 |
| | Precision | 0.17 |
| Cancer Diagnosis | 3/5 patients |

* Over 4 patients (we missed recording all confirmation images on a patient)
the prostate mock-up showed 1.35±0.39 [mm] targeting accuracy. This accuracy does not include the error result from the prostate deformation. However, considering the amount of 2D prostate deformation (0.46±0.13 [mm]) and the size of clinically significant PCa (≥0.5 [cm³], radius 4.924 [mm]), the system would be sufficiently accurate. Moreover, the biopsy on the egg experiment showed that the robot can operate the TRUS probe gently, with minimal pressure.

Preserving prostate deformations at the time of the 3D scan and biopsy was achieved by using primarily rotary motion about the axis of the probe and minimizing lateral motion. A similar approach may be intuitively made with the Artemis (Eigen) [25] system, which uses a passive mechanical arm to manipulate the TRUS probe. Here, the optimal approach angles are derived mathematically.

One of the challenging problems encountered in the validation tests was to measure the amounts of the prostate displacement and deformation during the biopsy. Since the displacement and deformation of the prostate are directly related to the targeting accuracy, they were considered as the important evaluation factors of the study. The novel segmentation technique, which will be introduced in Chapter 4.2, was used to segment the prostate after the 3D scan and before the biopsy. Using the pre-acquired prostate surface model, the displacement and deformation of the prostate were able to be measured. The mockup test with this evaluation method validated the algorithms developed to minimize the prostate deformation.

In the experiments, it is observed that optimal solutions were uncommon, unintuitive, and not ergonomic to freehand. Figure 3.25a shows the way that a physician would normally freehand the probe to a site. Instead, Figure 3.25b shows the optimal approach to the same site, which is not ergonomic and difficult to freehand. A freehand biopsy is often suboptimal because turning the probe upside down is not ergonomic. The upside down TRUS operation is feasible with the robot.

A coordinate system associated with the prostate (PCS) and a method to formulate a systematic biopsy plan were also presented. Several prostate biopsy systems [146] use intraoperative methods to locate a system that is similar to the PCS, by manually positioning the probe centrally to the prostate. In our approach, the

Figure 3.25: Example of free handing the probe to a site: (a) common and (b) optimal
PCS is derived in the 3D image, possibly making it more reliable, while the two methods were not directly compared here.

The results of the clinical trial show that robot-assisted prostate biopsy was safe and feasible. Needle targeting accuracy was on the order of 1 [mm]. Additional possible errors such as errors caused by patient motion should be further evaluated and minimized. No significant patient movement was observed during our limited initial trial, and no loss of ultrasound coupling was experienced. The development of leg support to help the patient maintain the position and additional algorithms to correct for the motion are in progress.

The TRUS robot and the Artemis device [25] are the only systems that manipulate the probe about an RCM fulcrum point. With the other systems that freehand the probe the fulcrum is floating [26], [85], [145], [157]–[159]. Patient discomfort related to fixing the fulcrum has not been observed yet. Performing a biopsy with minimal probe pressure and motion could ease the discomfort and help the patient to hold still. The Artemis has a passive probe support arm, while the TRUS robot has an active arm. The passive arm helps to reduce deformations, but its manual operation leads to variability among urologists. On the other hand, the active probe manipulation of the TRUS robot enables hands-free and skill-independent prostate biopsy.

Clinically, our robot is for transrectal biopsy and the other approach is transperineal [86], [156]. Traditionally, a transperineal biopsy was uncommon because requires higher anesthesia and an operating room setting, but offered the advantage of lower infection rates [14]. New transperineal approaches for systematic biopsy and cognitive targeted biopsy are emerging with less anesthesia and at the clinic [15]. Yet, the mainstream prostate biopsy is transrectal. Several methods reported herein, such as the PCS and TRUS imaging with reduced prostate deformations could apply as well to transperineal biopsy.

3.3.16 Conclusion

In this section, a novel robotic system was presented to takes transrectal prostate biopsy one step further, with an actuated TRUS manipulation arm. The robot enables the performance of hands-free, skill-independent prostate biopsy. The work discussed in this section includes the robotic system, the methods used to reduce prostate deformations (at 3D image scan and at biopsy), comprehensive pre-clinical test results, and the outcome of the first 5-patient clinical trial. Hands-free TRUS operation and transrectal TRUS-guided prostate biopsy with minimal prostate deformations are novel approaches.
Comprehensive mockup experiments and safety and feasibility clinical trials are presented. In preclinical experiments, the accuracy of image-based needle targeting was on the order of 1 [mm]. Clinically, targeting accuracy is substantially lower than the 5 [mm] required to target clinically significant PCa [8, 30]. In the clinical trials, the biopsy procedure took approximately 13 [min], and all cases were successfully completed, showing that the robotic approach is feasible. The approach can be used with systematic and targeted biopsies. Trials of clinical significance are needed to determine if more accurate biopsy targeting correlates with higher detection of clinically significant PCa.

3.4 Cohesive TRUS Probe-Robot for Prostate Biopsy

The main goal of the work involved in this section was to develop and evaluate a robotic system, the cohesive TRUS probe-robot, to assist urologists in performing prostate biopsy under TRUS guidance.

3.4.1 Personal Contributions

The design of the robot was done by Dr. Dan Stoianovici and the manufacturing of the robot was done by Dr. Dan Stoianovici and Dr. Doru Petrisor. Those works are not discussed in detail here.

My personal contribution includes:

- System integration.
- Formulation and analysis of the robot kinematics.
- Design and implementation of the ultrasound calibration algorithm described here.
- Design, implementation, and debug of the robot control and image guidance software.
- Design, execution, and analysis of all the experiments discussed here.

3.4.2 Robot Structure

Figure 3.26 shows the cohesive ultrasound probe-robot. A commercial ultrasound probe (EUP-U533, Hitachi Medical Corporation, Japan) has been disassembled and the linear sensor of the probe is used to build the robot. The body of the robot was 3D printed (Form 2, formlabs, MA) and the linear side-fire ultrasound sensor (EUP-U533L) has been integrated with the robotic components, as shown in Figure 3.26.
The robot has 2 DoF consisting of two revolute joints, such that probe drive and needle-guide drive, as shown in Figure 3.26. The probe drive rotates the whole robot about the axis \( \xi_1 \) and the needle-guide drive rotates the needle-guide about \( \xi_2 \). A harmonic gear is used for the probe drive and a three-links mechanism is used for the needle-guide drive. The robot is attached to a passive support arm (7-DoA, GR9000, HoldIt, Noga, Israel), which can be mounted to the patient bed. The robot is controlled by the custom-written software presented in Section 3.2.

### 3.4.3 Forward Kinematics

Forward kinematics problem of the robot is to calculate the position of the biopsy needle tip \( \vec{p}_t \in \mathbb{R}^3 \) for a given motor counts \([\text{cnt}_1, \text{cnt}_2] \) and needle length \( L \). Figure 3.27 shows a schematic diagram of the robot kinematics at the zero position. The robot is designed so that the angle \( (\theta_2) \) between the needle-guide and the probe axis \( \xi_1 \) becomes zero when the robot is at the zero position, as shown in Figure 3.27. The needle-guide rotates about the fixed point \( \vec{p}_1 \) and the angle from the probe axis \( \theta_2 \) is controlled by the needle-guide drive located at the fixed point \( \vec{p}_4 \). The needle-guide and the needle-guide drive are connected by three links. The lengths of the needle-guide and the three links are \( l_1, l'_1, l_2, l_3 \), respectively. The two joints of the three links are movable and defined as \( \vec{p}_2 \) and \( \vec{p}_3 \), respectively. The distance between the fixed point \( \vec{p}_1 \) and the probe axis is defined as \( d_1 \). The needle-guide and the first link have a constant offset angle of \( \theta'_2 \) and the
two offset distances at the edges of the needle-guide and the first link are defined as $d_2$ and $d_3$, respectively. The horizontal and vertical offset distances between $\vec{p}_1$ and $\vec{p}_4$ are defined as $d_4$ and $d_5$, respectively.

The forward kinematics problem of the robot is solved as:

First, the distance between $\vec{p}_1$ and $\vec{p}_4$, $D_1$, is calculated as:

$$D_1 = dist(\vec{p}_1, \vec{p}_4) = \sqrt{d_4^2 + d_5^2}$$

(3.22)

Then, the angle between the first and the second links, $\alpha$, is computed as:

$$\alpha = \pi - \cos^{-1}\left(\frac{l_1'^2 + (l_2 - l_3)^2 - D_1^2}{2l_1' (l_2 - l_3)}\right)$$

(3.23)

The angle between the first link and the probe axis, $\beta$, is computed as:

$$\beta = \tan^{-1}\left(\frac{d_2 + d_3}{l_1'}\right)$$

(3.24)

Therefore, the angle between the third link and the probe axis $\xi_1$ at the zero position, $\gamma$, is computed as:

Figure 3.27: Schematic of robot kinematics (zero position)
\[
\gamma = \alpha + \beta = \pi - \cos^{-1}\left(\frac{\left(l_1'\right)^2 + \left(l_2 - l_3\right)^2 - D_1^2}{2l_1'(l_2 - l_3)}\right) + \tan^{-1}\left(\frac{d_2 + d_3}{l_1}\right)
\]  

Figure 3.28: Schematic of robot kinematics (stretched position)

\[
\lambda = \pi - \psi - \omega + \gamma
\]

where

\[
\omega = \tan^{-1}\left(\frac{d_5}{d_4}\right)
\]

\[
\psi = \cos^{-1}\left(\frac{D_1^2 + (l_2 + l_3)^2 - l_1'^2}{2D_1(l_2 + l_3)}\right)
\]

Next, using the transmission ratios of the robot \([tr_1, tr_2]\), the joint angles \([\theta_1, \theta_2]\) of the robot are calculated for a given motor counts \([cnt_1, cnt_2]\). Figure 3.29 shows a schematic of the robot forward kinematics. Since the unit of the transmission ratio is given by \([\text{counts/turn}]\), the first joint angle of the robot \(\theta_1\) and the rotation angle of the third link \(\theta_5\) are calculated as:

\[
\theta_1 = 2\pi \frac{cnt_1}{tr_1}
\]
\[ \theta_5 = 2\pi \frac{c_{nt_2}}{tr_2} \]

The lengths of the first link and the needle-guide have a relationship of

\[ l'_1 = \sqrt{l_1^2 + (d_2 + d_3)^2} \tag{3.28} \]

Also, the angles from the probe axis \( \xi_1 \) to the first link and the needle-guide have a relationship of

\[ \theta'_2 = \theta_2 - \tan^{-1} \left( \frac{d_2 + d_3}{l_1} \right) \tag{3.29} \]

If a 2D coordinate system is defined at the fixed point \( \vec{p}_4, \vec{p}_1 \) and \( \vec{p}_3 \) are defined as:

\[ \vec{p}_1 = (d_4, -d_5)^T \]
\[ \vec{p}_3 = (l_3 \cos(\theta_5 + \pi - \gamma), l_3 \sin(\theta_5 + \pi - \gamma))^T \tag{3.30} \]

The distance between \( \vec{p}_1 \) and \( \vec{p}_3 \), \( D_2 \), is calculated as:

\[ D_2 = \text{dist}(\vec{p}_1, \vec{p}_3) = \sqrt{(l_3 \cos(\theta_5 + \pi - \gamma) - d_4)^2 + (l_3 \sin(\theta_5 + \pi - \gamma) + d_5)^2} \tag{3.31} \]
The two angles $\rho$ and $\sigma$ defined in Figure 3.30 are calculated as:

$$\rho = \text{sign} \left( \sin(\theta_5 + \omega - \gamma) \right) \cos^{-1} \left( \frac{D_1^2 + D_2^2 - l_3^2}{2D_1D_2} \right)$$

$$\sigma = \cos^{-1} \left( \frac{D_2^2 + l_1'^2 - l_2^2}{2D_2l_1'} \right)$$

(3.32)

Therefore, the angle between the needle-guide and the probe axis, $\theta_2$, is calculated using the equation (3.29).

$$\theta_2 = \theta_2' + \tan^{-1} \left( \frac{d_2 + d_3}{l_1} \right) = \rho + \sigma - \omega + \tan^{-1} \left( \frac{d_2 + d_3}{l_1} \right)$$

(3.33)

Now, we have corresponding joint angles of the robot $[\theta_1, \theta_2]$ for a given motor counts $[\text{cnt}_1, \text{cnt}_2]$.

Subsequently, the target point $\mathbf{p}_t$ is calculated for a given joint angles $[\theta_1, \theta_2]$ and needle length $L$. The robot coordinate system $\Sigma_R$ is defined at the point $\mathbf{p}_0$ with the orientation shown in Figure 3.26. The needle length $L$ is measured from the tip of the needle-guide to the tip of the biopsy needle. Each transformation matrix from the robot coordinate system to the tip position of the biopsy needle is then given by:
\[ R_x(\theta_1) = \begin{bmatrix} \cos \theta_1 & -\sin \theta_1 & 0 & 0 \\ \sin \theta_1 & \cos \theta_1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]

\[ T_x(d_1) = \begin{bmatrix} 1 & 0 & 0 & d_1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]

\[ R_y(-\theta_2) = \begin{bmatrix} \cos(-\theta_2) & 0 & \sin(-\theta_2) & 0 \\ 0 & 1 & 0 & 0 \\ -\sin(-\theta_2) & 0 & \cos(-\theta_2) & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]  \hspace{1cm} (3.34)

\[ T_x(d_2) = \begin{bmatrix} 1 & 0 & 0 & d_2 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]

\[ T_z(-L) = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & -L \\ 0 & 0 & 0 & 1 \end{bmatrix} \]

Therefore, the tip position of the biopsy needle, \( \mathbf{\hat{p}_t} \), is calculated as:

\[ T_t = \begin{bmatrix} R_t \\ 0 \\ \mathbf{\hat{p}_t} \end{bmatrix} = R_x(\theta_1)T_x(d_1)R_y(-\theta_2)T_x(d_2)T_z(-L) \]

\[ = \begin{bmatrix} \cos \theta_1 \cos \theta_2 & -\sin \theta_1 & -\cos \theta_1 \sin \theta_2 & \cos \theta_1 (d_2 \cos \theta_2 + L \sin \theta_2) + d_1 \cos \theta_1 \\ \sin \theta_1 \cos \theta_2 & \cos \theta_1 & -\sin \theta_1 \sin \theta_2 & \sin \theta_1 (d_2 \cos \theta_2 + L \sin \theta_2) + d_1 \sin \theta_1 \\ \sin \theta_2 & 0 & \cos \theta_2 & d_2 \sin \theta_2 - L \cos \theta_2 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]  \hspace{1cm} (3.35)

\[ \mathbf{\hat{p}_t} = \begin{bmatrix} \cos \theta_1 (d_2 \cos \theta_2 + L \sin \theta_2) + d_1 \cos \theta_1 \\ \sin \theta_1 (d_2 \cos \theta_2 + L \sin \theta_2) + d_1 \sin \theta_1 \\ d_2 \sin \theta_2 - L \cos \theta_2 \end{bmatrix} \]  \hspace{1cm} (3.36)

### 3.4.4 Inverse Kinematics

Inverse kinematics problem of the robot is to calculate the motor counts \([cnt_1, cnt_2]\) and needle length \(L\) for a given position of the biopsy needle tip \(\mathbf{\hat{p}_t} \in \mathbb{R}^3\). Figure 3.31 and Figure 3.32 show schematic diagrams of the robot inverse kinematics.
First, the joint angles of the robot $[\theta_1, \theta_2]$ is calculated for a given target point $\vec{p}_t = (t_x, t_y, t_z)^T$. Figure 3.31 shows a schematic diagram for this calculation. As shown in Figure 3.31a, the rotation angle of the probe drive $\theta_1$ is calculated as:

$$\theta_1 = \begin{cases} 
\tan^{-1}\left(\frac{t_y}{t_x}\right), & \text{if } t_x \geq 0 \\
\tan^{-1}\left(\frac{t_y}{t_x}\right) + \pi, & \text{if } t_x < 0 \text{ and } t_y < 0 \\
\tan^{-1}\left(\frac{t_y}{t_x}\right) - \pi, & \text{if } t_x < 0 \text{ and } t_y \geq 0
\end{cases} \quad (3.37)$$

Next, the rotation angle of the needle-guide $\theta_2$ is calculated. First, the target point $\vec{p}_t$ is rotated about the probe axis $\xi_1$ (Z-axis) with an amount of $-\theta_1$ to obtain a point $\vec{p}'_t$ that placed on the XZ plane (Figure 3.31b) as:

$$\vec{p}'_t = R_z(-\theta_1)\vec{p}_t$$

Then, $\vec{p}'_t$ is translated to the negative X direction with an amount of $d_1$ to obtain $\vec{p}''_t$ as:

$$\vec{p}''_t = \vec{p}'_t - \begin{bmatrix} d_1 \\ 0 \\ 0 \end{bmatrix} \quad (3.39)$$
The point $\vec{p}_p$ that is placed on the needle insertion path and corresponds to the $\vec{p}_i''$ when the needle-guide is rotated with an amount of $\theta_2$ is calculated (Figure 3.31c) as:

$$\vec{p}_p = \begin{bmatrix} d/2 \\ 0 \\ -L \end{bmatrix}$$  \hspace{1cm} (3.40)

where $L$ is the needle length such that

$$L = \sqrt{||\vec{p}_i''||^2 - d_2^2}$$  \hspace{1cm} (3.41)

Using the two points $\vec{p}_i''$ and $\vec{p}_p$, the rotation angle of the needle-guide $\theta_2$ is calculated as:

$$\theta_2 = sign \left( \begin{bmatrix} 0 \\ 1 \end{bmatrix} : [\vec{p}_p \times \vec{p}_i''] \right) \tan^{-1} \left( \frac{||\vec{p}_p \times \vec{p}_i''||}{\vec{p}_p \cdot \vec{p}_i''} \right)$$  \hspace{1cm} (3.42)

Subsequently, we compute the motor counts $[cnt_1,cnt_2]$ for a given joint angles $[\theta_1,\theta_2]$. Figure 3.32 shows a schematic diagram for this calculation. If a 2D coordinate system is defined at the fixed point $\vec{p}_1$, $\vec{p}_2$ and $\vec{p}_4$ are defined as:

$$\vec{p}_2 = (l'_1 \cos(\theta'_2 + \pi), l'_1 \sin(\theta'_2 + \pi))^T$$  \hspace{1cm} (3.43)

$$\vec{p}_4 = (-d_4, d_5)^T$$

where $l'_1$ and $\theta'_2$ are calculated by equation (3.28) and (3.29), respectively.

The distance between $\vec{p}_2$ and $\vec{p}_4$, $D_3$, is calculated as:

$$D_3 = \text{dist}(\vec{p}_2, \vec{p}_4) = \sqrt{(l'_1 \cos(\theta'_2 + \pi) + d_4)^2 + (l'_1 \sin(\theta'_2 + \pi) - d_2)^2}$$  \hspace{1cm} (3.44)
The two angles $\delta$ and $\mu$ defined in Figure 3.32 are calculated as:

$$\delta = \cos^{-1}\left(\frac{D_3^2 + l_3^2 - l_2^2}{2D_3l_3}\right)$$

$$\mu = \cos^{-1}\left(\frac{D_1^2 + D_3^2 - l_1^2}{2D_1D_3}\right)$$

(3.45)

The rotation angle of the third link (rotation angle of the second motor) $\theta_5$ is calculated as:

$$\theta_5 = \begin{cases} \pi - \delta - \mu - \omega + \gamma, & \text{if } 0 \leq \theta_5 < \lambda, \text{first solution} \\ \delta + \mu + \omega + \gamma, & \text{if } \lambda - 2\pi \leq \theta_5 < 0, \text{second solution} \end{cases}$$

(3.46)

where $\gamma$ and $\omega$ are calculated by equation (3.25) and (3.26), respectively.

Finally, using the transmission ratios of the robot [$tr_1, tr_2$], the motor counts of the robot [$cnt_1, cnt_2$] are calculated as (the unit of the transmission ratio is given by [counts/turn]):

$$cnt_1 = \frac{\theta_1}{2\pi} tr_1$$

$$cnt_2 = \frac{\theta_5}{2\pi} tr_2$$

(3.47)

Figure 3.32: Schematic of kinematics; inverse kinematics step2
3.4.5 Parameter Identification

3.4.5.1 Materials and Methods

Since the body parts of the robot were 3D printed, the original design kinematic parameters of the robot may have manufacturing errors. This could particularly make a considerable error on the second axis $\xi_2 (\theta_2)$ as the axis is composed of multiple links and fixed on the 3D printed parts. Therefore, parameter identifications were performed to estimate the real kinematic parameters of the second axis. First, the home position of the axis was identified. In the design of the robot, the home position of the second axis was set at the position that the needle-guide is parallel to the probe axis $\xi_1$. However, in some cases, this position may cannot be obtained due to the manufacturing error of the axis. Therefore, the position, which minimizes the angle between the needle-guide and the probe axis, has been identified to be set as a home position. Second, the kinematic parameters described in Section 3.4.3 and 3.4.4, such as $d_2$, $d_3$, $d_4$, $d_5$, $L_1$, $L_2$, and $L_3$ were identified. Lengths and relative position of the links are the important kinematic parameters that determine the accuracy of the axis, while their real values are unknown.

An optical localizer (Polaris, NDI, Canada) was used to measure the 3D position of a reflective marker on a straight needle attached to the needle-guide, as shown in Figure 3.33. The distance between the center point of the reflective marker and the tip point of the needle-guide was about 117 [mm] and the optical localizer was approximately located 1100 [mm] away from the marker. The accuracy of the localizer can be improved in this environment up to 0.078 [mm] [98].

![Figure 3.33: Experimental setup for parameter identification](image)
In the measurement for the home position identification, the second axis ($\xi_2$, needle driver) was rotated in the rage of the motor counts \{-11000, 16000\} with an increment of 180 [counts]. For each position, the 3D positions of the optical marker were measured for 200 frames and averaged to obtain a point set $\vec{p}_i, i = 1, ..., 150$.

In the home position analysis, a plane is fitted to the point set $\vec{p}_i$ and the point set $\vec{p}_i$ was projected onto the plane. A circle was then fitted to the projected points and the center point was estimated. Rotational angles of the projected points about the center point were measured from an arbitrary datum line and plotted with the corresponding motor counts, as show in Figure 3.34. A polynomial was then fitted to the plotted points and the minima was found using a gradient descent technique. Finally, the motor count corresponds to the minima was used to calculate the home position.

After updating the home position, the measurement was repeated for the kinematic parameter identification. In the measurement, the first axis ($\xi_1$, probe driver) was rotated in the range of the joint angle \{0, 180\} with an increment of 5 [deg] and the second axis ($\xi_2$, needle driver) was rotated in the rage of the motor counts \{-11000, 16000\} with an increment of 180 [counts]. For each position, the 3D positions of the optical marker were measured for 200 frames and averaged to obtain two point set $\vec{q}_i, i = 1, ..., 37$ and $\vec{r}_j, j = 1, ..., 150$, respectively.

![Figure 3.34: Experimental results of home position identification](image)
In the kinematic parameter identification, a plane was fitted to the point set $\hat{q}_i$ and the point set was projected to the plane. A circle was then fitted to the projected point set and the rotation axis $\xi_1$ passing through the center point of the circle and normal to the plane was estimated. Next, a plane was fitted to the point set $\hat{r}_j$ and the point set $\hat{r}_j$ and the estimated rotation axis $\xi_1$ are projected to the plane. A circle was then fitted to the projected points. Rotation angles of the projected points about the center point were measured from the projected rotation axis with the corresponding motor counts, as shown in Figure 3.35 (red curve).

To identify the kinematic parameters of the axis, a nonlinear optimization using simplex search method of Lagarias el al. [175] was performed so that the curve obtained with the kinematic calculation (green curve in Figure 3.35) get closer to the curve obtained in the previous step (red curve in Figure 3.35).

### 3.4.5.2 Results

The motor count offset for the home position was 359 [counts]. Table 3.9 shows the original and identified kinematic parameters of the second axis $\xi_2 (\theta_2)$. 
### Motivation and Objective

An ultrasound probe calibration is a procedure to estimate a constant homogeneous transformation $T_{PI} \in SE(3)$ between the trackable probe coordinate system $\Sigma_p$ to the image coordinate system $\Sigma_i$, as shown in Figure 3.36a. However, common calibration approaches only work with a freehand ultrasound probe (6-DoF) [134, 135] or a manipulator with multiple DoF [169]. Since these calibration methods assume the movements of the ultrasound probe with multiple-DoF, an ultrasound probe manipulator such as the cohesive TRUS probe-robot cannot be calibrated using these methods. Therefore, a novel method to calibrate an ultrasound probe manipulator with 1-DoF is presented here. The calibration method estimates the constant calibration matrix $T_{PI}$ based on the evaluation of 3D volume images of the object with known feature points.

### Table 3.9: Kinematic parameter identification results

<table>
<thead>
<tr>
<th>Kinematic parameters</th>
<th>Original design values [mm]</th>
<th>Identified values [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d_2$</td>
<td>1.5</td>
<td>1.583</td>
</tr>
<tr>
<td>$d_3$</td>
<td>5.0</td>
<td>5.550</td>
</tr>
<tr>
<td>$d_4$</td>
<td>111.993</td>
<td>109.326</td>
</tr>
<tr>
<td>$d_5$</td>
<td>15.0</td>
<td>14.649</td>
</tr>
<tr>
<td>$L_1$</td>
<td>85.0</td>
<td>83.218</td>
</tr>
<tr>
<td>$L_2$</td>
<td>56.6</td>
<td>56.282</td>
</tr>
<tr>
<td>$L_3$</td>
<td>28.3</td>
<td>28.018</td>
</tr>
</tbody>
</table>

### 3.4.6 Ultrasound Probe Calibration

3.4.6.1 Motivation and Objective

3.4.6.1 Motivation and Objective

An ultrasound probe calibration is a procedure to estimate a constant homogeneous transformation $T_{PI} \in SE(3)$ between the trackable probe coordinate system $\Sigma_p$ to the image coordinate system $\Sigma_i$, as shown in Figure 3.36a. However, common calibration approaches only work with a freehand ultrasound probe (6-DoF) [134, 135] or a manipulator with multiple DoF [169]. Since these calibration methods assume the movements of the ultrasound probe with multiple-DoF, an ultrasound probe manipulator such as the cohesive TRUS probe-robot cannot be calibrated using these methods. Therefore, a novel method to calibrate an ultrasound probe manipulator with 1-DoF is presented here. The calibration method estimates the constant calibration matrix $T_{PI}$ based on the evaluation of 3D volume images of the object with known feature points.

Figure 3.36: (a) Ultrasound probe manipulator with 1 DoF, (b) 3D scanning results of 5-by-5 grid
3.4.6.2 Materials and Methods

Forward Projection:

Figure 3.37 shows a schematic diagram for the forward and inverse projection problems of the feature point in the ultrasound probe manipulator with 1-DoF. The forward projection problem is to calculate a feature point $\vec{p} \in \mathbb{R}^3$ defined in the robot coordinate system $\Sigma_R$ for a given feature point $\vec{g} \in \mathbb{R}^2$ defined in the image coordinate system $\Sigma_I$, and rotation angle of the ultrasound manipulator $\theta \in \mathbb{R}$, and constant calibration matrix $T_{PI} \in SE(3)$. The forward projection problem is calculated as:

First, $T_{RP}, T_{PI} \in SE(3), \vec{p}, \vec{g} \in \mathbb{R}^4$ are defined as:

\[
T_{RP} = \begin{pmatrix}
\cos \theta & -\sin \theta & 0 & 0 \\
\sin \theta & \cos \theta & 0 & 0 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 1
\end{pmatrix},
T_{PI} = \begin{pmatrix}
r_{11} & r_{12} & r_{13} & t_1 \\
r_{21} & r_{22} & r_{23} & t_2 \\
r_{31} & r_{32} & r_{33} & t_3 \\
0 & 0 & 0 & 1
\end{pmatrix},
\]

\[
\vec{p} = \begin{pmatrix}
p_x \\
p_y \\
p_z \\
1
\end{pmatrix},
\vec{g} = \begin{pmatrix}
g_x \\
g_y \\
0 \\
1
\end{pmatrix}
\]

(3.48)
From Figure 3.37, for a given joint angle $\theta$, constant calibration matrix $T_{PI}$, and feature point $\vec{g}$ defined in the image coordinate system $\Sigma_I$, the corresponding feature point $\vec{p}$ defined in robot coordinate systems $\Sigma_R$ can be calculated as:

$$\vec{p} = T_{RP}T_{PI}\vec{g}$$

$$= \begin{pmatrix} \cos\theta & -\sin\theta & 0 & 0 \\ \sin\theta & \cos\theta & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix} \begin{pmatrix} r_{11} & r_{12} & r_{13} & t_1 \\ r_{21} & r_{22} & r_{23} & t_2 \\ r_{31} & r_{32} & r_{33} & t_3 \end{pmatrix} \begin{pmatrix} g_x \\ g_y \\ 0 \\ 1 \end{pmatrix}$$

(3.49)

Inverse Projection:

The inverse projection problem is to calculate a feature point $\vec{g} \in \mathbb{R}^2$ defined in the image coordinate system $\Sigma_I$ and rotation angle of the ultrasound probe manipulator $\theta \in \mathbb{R}$ for a given feature point $\vec{p} \in \mathbb{R}^3$ defined in the robot coordinate system $\Sigma_R$ and constant calibration matrix $T_{PI} \in SE(3)$. The inverse projection problem is calculated as:

Three equations are given from Eq. (3.55) as:

$$\left( r_{11}g_x + r_{12}g_y + t_1 \right) \cos\theta - \left( r_{21}g_x + r_{22}g_y + t_2 \right) \sin\theta = p_x$$

(3.50)

$$\left( r_{11}g_x + r_{12}g_y + t_1 \right) \sin\theta + \left( r_{21}g_x + r_{22}g_y + t_2 \right) \cos\theta = p_y$$

(3.51)

$$r_{31}g_x + r_{32}g_y + t_3 = p_z$$

(3.52)

These simultaneous equations are solved for $\theta$, $g_x$, and $g_y$.

Eq. (3.50)$\times \cos\theta$ + Eq. (3.51)$\times \sin\theta$ gives:

$$r_{11}g_x + r_{12}g_y + t_1 = p_x \cos\theta + p_y \sin\theta$$

(3.53)
\[ r_{21}g_x + r_{22}g_y + t_2 = p_y \cos \theta - p_x \sin \theta \] (3.54)

Eq. (3.53) \times p_x + Eq. (3.54) \times p_y gives

\[ (r_{11}p_x + r_{21}p_y)g_x + (r_{12}p_x + r_{22}p_y)g_y + p_xt_1 + p_yt_2 = (p_x^2 + p_y^2) \cos \theta \] (3.55)

Eq. (3.53) \times p_y - Eq. (3.54) \times p_x gives

\[ (r_{11}p_y - r_{21}p_x)g_x + (r_{12}p_y - r_{22}p_x)g_y + p_yt_1 - p_xt_2 = (p_x^2 + p_y^2) \sin \theta \] (3.56)

Eq. (3.56) / Eq. (3.55) gives

\[ \frac{(r_{11}p_y - r_{21}p_x)g_x + (r_{12}p_y - r_{22}p_x)g_y + p_xt_1 - p_yt_2}{(r_{11}p_x + r_{21}p_y)g_x + (r_{12}p_x + r_{22}p_y)g_y + p_xt_1 + p_yt_2} = \tan \theta \] (3.57)

Eq. (3.56)\(^2 \) + Eq. (3.55)\(^2 \) gives

\[ (p_x^2 + p_y^2)^2 = (r_{11}p_x + r_{21}p_y)g_x + (r_{12}p_x + r_{22}p_y)g_y + p_xt_1 + p_yt_2] \]
\[ + (r_{11}p_y - r_{21}p_x)g_x + (r_{12}p_y - r_{22}p_x)g_y + p_yt_1 - p_xt_2] \] (3.58)

The simultaneous equations (Eq. (3.52) and Eq. (3.58)) are solved for \( g_x \) and \( g_y \).

The Mathematica [178] gives:
\[ g_x = \left( -r_{32}^2 (r_{11}t_1 + r_{21}t_2) + (r_{12}^2 + r_{22}^2)r_{31} \right) (p_x - t_3) \\
+ r_{32} \left( -p_x (r_{11}r_{12} + r_{21}r_{22}) + r_{12} (r_{31}t_1 + r_{11}t_3) + r_{22} (r_{31}t_2 + r_{21}t_3) \right) \\
/ \left( (r_{12}^2 + r_{22}^2)r_{31}^2 - 2(r_{11}r_{12} + r_{21}r_{22})r_{31}r_{32} + (r_{11}^2 + r_{21}^2)r_{32}^2 \right) \\
\pm \sqrt{4 \left( p_x (r_{12}^2 + r_{22}^2)r_{31} - (r_{11}r_{12} + r_{21}r_{22})r_{32} \right) \\
+ r_{32} \left( r_{12}r_{31}t_1 + r_{22}r_{31}t_2 - r_{32}(r_{11}t_1 + r_{21}t_2) \right) \\
+ (-r_{12}^2 + r_{22}^2)r_{31}^2 + (r_{11}r_{12} + r_{21}r_{22})r_{32}t_3 \right)^2} \tag{3.59}
\]

\[ g_y = \left( r_{32}^2 (p_x (r_{11}^2 + r_{21}^2) + r_{31}(r_{11}t_1 + r_{21}t_2) - (r_{11}^2 + r_{21}^2)t_3) \\
- r_{31}r_{32} (p_x (r_{11}r_{12} + r_{21}r_{22}) + r_{31}(r_{12}t_1 + r_{22}t_2) - (r_{11}r_{12} + r_{21}r_{22})t_3) \right) \\
/ \left( (r_{12}^2 + r_{22}^2)r_{31}^2 - 2(r_{11}r_{12} + r_{21}r_{22})r_{31}r_{32} + (r_{11}^2 + r_{21}^2)r_{32}^2 \right) \\
\pm r_{31} \sqrt{4 \left( p_x (r_{12}^2 + r_{22}^2)r_{31} - (r_{11}r_{12} + r_{21}r_{22})r_{32} \right) \\
+ r_{32} \left( r_{12}r_{31}t_1 + r_{22}r_{31}t_2 - r_{32}(r_{11}t_1 + r_{21}t_2) \right) \\
+ (-r_{12}^2 + r_{22}^2)r_{31}^2 + (r_{11}r_{12} + r_{21}r_{22})r_{32}t_3 \right)^2} \tag{3.60}
\]

Then, by substituting \( g_x \) and \( g_y \) into Eq. (3.57), \( \theta \) is determined as:

\[
\theta = \tan^{-1} \left( \frac{(r_{11}p_y - r_{21}p_x)g_x + (r_{12}p_y - r_{22}p_x)g_y + p_y t_1 - p_x t_2}{(r_{11}p_x + r_{21}p_y)g_x + (r_{12}p_x + r_{22}p_y)g_y + p_x t_1 + p_y t_2} \right) 
\tag{3.61}
\]

We have two solutions as above. However, one of the two solutions can be eliminated from the fact that the manipulator has limits on its rotation angle \( \theta \) for the 3D scan. Therefore, a unique solution can be obtained.
Ultrasound probe calibration based on image distortion evaluation:

If the ultrasound image plane is misaligned with respect to the probe manipulator coordinates (bad calibration results; \( T^p_I \in SE(3) \)), the 3D scanning results of a 5-by-5 grid made with thin strings will be distorted as shown in Figure 3.36b. By defining a distortion error \( e(H), H \in SE(3) \), the calibration matrix \( T^p_I \) can be estimated as

\[
T_{PI} = \text{argmin}_H e(H)
\]

Detailed steps are as follow:

Step 1: Submerge a 5-by-5 grid mockup made with thin strings and perform a 3D scan.

Step 2: Reconstruct a volume image of the grid mockup using the initial calibration matrix \( T^{(j)}_{PI}, j = 0 \).

Step 3: Pick grid points \( \tilde{p}_i^{(j)}, i = 1, \ldots, 25, j = 0 \) from the volume image, as shown in Figure 3.36b.

Step 4: By solving the inverse projection problem, calculate the corresponding grid points \( \tilde{g}_i, i = 1, \ldots, 25 \), which are defined in the image coordinate system \( \Sigma_I \), and the corresponding rotation angles of the manipulator \( \theta_i, i = 1, \ldots, 25 \). Note that the grid points \( \tilde{g}_i \) are invariant regardless of the calibration matrix \( T_{PI} \) because they are defined in the image coordinate system \( \Sigma_I \).

Step 5: Perform a point cloud registration [99] using the grid points \( \tilde{p}_i^{(j)} \) and the corresponding model grid points \( \tilde{q}_i \) (ideal grid points in 3D space) and estimate a registration matrix such that \( \tilde{p}_i^{(j)} = F^j_{reg} \tilde{q}_i \).

Step 6: Evaluate the distortion error \( e(T^{(j)}_{PI}) \) such that

\[
e(T^{(j)}_{PI}) = \sum_{i=1}^{25} \| \tilde{p}_i^{(j)} - F^j_{reg} \tilde{q}_i \|
\]

Step 7: Update \( T^{(j)}_{PI} \) to \( T^{(j+1)}_{PI} \) using a gradient descent technique on \( SE(3) \), described in Appendices (A.2).

Step 8: Calculate \( \tilde{p}_i^{(j+1)} \) by solving the forward projection problem using \( T^{(j+1)}_{PI}, \tilde{g}_i, \theta_i \).

Step 9: Repeat from Step 5-Step 8 until the distortion error \( e(T^{(j)}_{PI}) \) converges and find the corresponding \( T_{PI} \).
Experiment: A validation experiment was performed using a 5-by-5 grid. The grid was made with thin strings (Ø0.4 \( \text{mm} \)) and placed in the water tank and imaged by the robot with two different depths, as shown in Figure 3.38a. The initial calibration matrix was modified to be misaligned on purpose. 3D volumes were reconstructed and visible grid points (23 points) were selected, as shown in Figure 3.38b,c. For the two sets of the grid points, the proposed algorithm was applied to estimate the best calibration matrix \( T_{pl} \) such that

\[
T_{pl} = \arg\min_{H} [E_1(H) + E_2(H)]
\]

\[
E_j(H) = \sum_{i=1}^{23} \| \tilde{p}_i^{(j)} - F_{reg}^{(j)} \tilde{q}_i \|, j = 1, 2
\]

(3.64)

where \( \tilde{p}_i^{(j)} \) is the grid points of the volume image at the jth depth, \( F_{reg}^{(j)} \) is the corresponding registration matrix, and \( \tilde{q}_i \) is the model grid points.

3.4.6.3 Results

The cost value was converged, as shown in Figure 3.39a. The corresponding error was converged to 0.35 [\( \text{mm} \)], as shown in Figure 3.39b. Translation and rotational components along and about the probe axis (\( \xi_1 \)) cannot be determined. However, the translation component can be determined by aligning the needle position imaged on the real-time ultrasound image and calculated from the robot kinematics, as shown in Figure 3.41. The rotational component cannot be determined. However, the error for the component could be minimized in the robot assembly process by rotating the ultrasound sensor about its axis so that the whole
needle is clearly visible in the real-time ultrasound image. The volume reconstruction with the estimated calibration matrix shows that the distortion of the grid has been corrected, as shown in Figure 3.41a,b.

Figure 3.39: (a) cost value and (b) mean error change

Figure 3.40: Volume images with the (a) initial and (b) estimated calibration matrixes

Figure 3.41: Translational component calibration along the probe axis
3.4.7 Joint Accuracy Test

3.4.7.1 Materials and Methods

A bench test was performed to validate the joint accuracies of the robot. An optical localizer (Polaris, NDI, Canada) was used to measure the 3D position of a reflective marker on a straight needle attached to the needle-guide, as shown in Figure 3.42. The manufacturer-stated RMS error of the localizer is 0.35 [mm]. The distance between the center point of the reflective marker and the tip point of the needle-guide was about 117 [mm] and the optical localizer was approximately located 1100 [mm] away from the marker. The accuracy of the localizer can be improved in this environment up to 0.078 [mm] [98].

In the measurement, each joint of the robot moved one at a time with an increment of 5 [deg] for $\theta_1$ and $\theta_2$. The movement ranges were $-90 [deg] \leq \theta_1 \leq 90 [deg]$ and $-45 [deg] \leq \theta_2 \leq -5 [deg]$, respectively. The 3D positions of the marker were measured for 500 frames and averaged for each position. The measurement was repeated for the positive and negative rotational directions of the needle-guide drive. Moreover, the robot kinematics problem was solved for $\theta_2$ using two different sets of the robot kinematic parameters such as the original design parameters from the CAD model and the optimal parameter estimated in Section 3.4.5.

In the analysis, the rotational axes ($\xi_1$ and $\xi_2$) were estimated using the obtained 2 sets of the mean points. To estimate a rotational axis, first, a plane was fitted to the point set using a least square technique and a normal vector of the plane was found. Second, the point set was projected onto the plane. Third, a circle

Figure 3.42: Experimental setup for set point test
was fitted to the projected point set using a least square technique and a center point was found, as shown in Figure 3.43. The rotational axis was defined with the center point of the circle and the normal vector of the plane. The rotational errors of \( \theta_1 \) and \( \theta_2 \) were measured by calculating the angles between the lines that connect the projected points and the center point of the estimated circle, as shown in Figure 3.43.

### 3.4.7.2 Results

Table 3.10 shows the final joint accuracies of the robot for each joint. Figure 3.43 shows 3D plots of the measured point sets, the point sets projected onto the plane, the estimated circles, etc. Table 3.11 and Table 3.12 show the accuracy test results of the axis \( \xi_2 (\theta_2) \) with the original design kinematic parameters and the optical kinematic parameter estimated in Section 3.4.5, respectively.

![Figure 3.43: Analysis results; Top: \( \xi_1 (\theta_1) \), Bottom: \( \xi_2 (\theta_2) \)](image-url)
Materials and Methods

An additional bench test was performed to verify the virtual needle-tip positing accuracy. All the experimental setups were equivalent to the previous tests except the number of measurement points.

In the measurement, $\theta_1$ was moved from $-45\ [deg]$ to $45\ [deg]$ with an increment of $5\ [deg]$. For each position, $\theta_2$ moved from $-45\ [deg]$ to $-5\ [deg]$ with an increment of $5\ [deg]$. The 3D positions of the marker were measured for 300 frames at each position. By averaging the measured points for each position, the actual point sets were obtained $\vec{p}_{i,j}$, $i = 1, 2, ..., N_i$, $j = 1, 2, ..., N_j$ ($N_i = 19$, $N_j = 9$). Then, by solving the

\begin{table}[h]
\centering
\caption{Joint accuracy test results}
\begin{tabular}{|c|c|c|}
\hline
Axis (rotation angle) & Accuracy [deg] & Precision [deg] \\
\hline
$\xi_1 (\theta_1)$ & 0.086 & 0.057 \\
$\xi_2 (\theta_2)$ & 0.060 & 0.073 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Accuracy test results of axis $\xi_2$ ($\theta_2$) (with initial kinematic parameters)}
\begin{tabular}{|c|c|c|c|}
\hline
Rotation direction & Test & Accuracy [deg] & Precision [deg] \\
\hline
Positive & 1 & 0.538 & 0.466 \\
 & 2 & 0.531 & 0.468 \\
 & Total & 0.534 & 0.467 \\
Negative & 1 & 0.451 & 0.627 \\
 & 2 & 0.449 & 0.626 \\
 & Total & 0.450 & 0.627 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Accuracy test results of axis $\xi_2$ ($\theta_2$) (with optimal kinematic parameters)}
\begin{tabular}{|c|c|c|c|}
\hline
Rotation direction & Test & Accuracy [deg] & Precision [deg] \\
\hline
Positive & 1 & 0.134 & 0.174 \\
 & 2 & 0.135 & 0.171 \\
 & Total & 0.134 & 0.173 \\
Negative & 1 & 0.061 & 0.073 \\
 & 2 & 0.059 & 0.073 \\
 & Total & 0.060 & 0.073 \\
\hline
\end{tabular}
\end{table}

\section{Robot Space Set Point Test}

\subsection{Materials and Methods}

An additional bench test was performed to verify the virtual needle-tip positing accuracy. All the experimental setups were equivalent to the previous tests except the number of measurement points.

In the measurement, $\theta_1$ was moved from $-45\ [deg]$ to $45\ [deg]$ with an increment of $5\ [deg]$. For each position, $\theta_2$ moved from $-45\ [deg]$ to $-5\ [deg]$ with an increment of $5\ [deg]$. The 3D positions of the marker were measured for 300 frames at each position. By averaging the measured points for each position, the actual point sets were obtained $\vec{p}_{i,j}$, $i = 1, 2, ..., N_i$, $j = 1, 2, ..., N_j$ ($N_i = 19$, $N_j = 9$). Then, by solving the
forward kinematics problems of the robot, the set point set was generated \( \vec{q}_{i,j}, i = 1, 2, \ldots, N_i, j = 1, 2, \ldots, N_j \) \((N_i = 19, N_j = 9)\). The transformation \( F \) from the optical localizer coordinate system to the robot coordinate system was estimated with a rigid point cloud registration technique [99]. The virtual needle-tip positioning error \( e_v \) was then evaluated as:

\[
e_v = \frac{1}{N_iN_j} \sum_{i,j} \| F \cdot \vec{p}_{i,j} - \vec{q}_{i,j} \|
\]  

(3.65)

The accuracy and precision were calculated as the average and standard deviation of the errors, as usual.

### 3.4.8.2 Results

Figure 3.42 shows the result of the set point test. The accuracy and precision of the virtual needle tip positioning were 0.56 [\text{mm}] and 0.23 [\text{mm}], respectively. The maximum error was 1.37 [\text{mm}].

![Figure 3.44: Results of robot space set point test](image)
3.4.9 Targeting Test with Grid Mockup

3.4.9.1 Materials and Methods

A targeting test was performed using a 5-by-5 grid mock-up built with thin strings (Ø0.4 [mm]). The grids were 10 [mm] apart from each other. The aim of this test was to verify the targeting accuracy of the system under idealized conditions. The grid mock was submerged and imaged with a 3D scan, as shown in Figure 3.45. The 25 intersection points were then picked from the volume image, as shown in Figure 3.46a. The robot was sent to each point and a biopsy needle (Ø1.0 [mm]) was inserted through the needle-guide. The errors were measured based on the pre-defined criteria, as shown in Table 3.4 and Figure 3.19e, f, g.

Figure 3.45: Experimental setup for targeting test with grid mockup

Figure 3.46: (a) Virtual reality environment, (b) Real-time 2D ultrasound image (aiming target #1)
3.4.9.2 Results

Figure 3.47 shows targeting results for 25 grid points. All the targeting results were satisfied with the criterion (i) \(e \leq 0.5 [\text{mm}]\) in Table 3.4. Therefore, we can conclude that the overall targeting accuracy of the cohesive TRUS probe-robot is less than 0.5 [\text{mm}] in the ideal environment.

Figure 3.47: Grid targeting result (25 targets)
3.4.10 Targeting Test with Prostate Mockup

3.4.10.1 Materials and Methods

An additional targeting test was performed with a prostate mock-up. The aim of this test was to verify the targeting accuracy of the system using a deformable and movable prostate mock-up. A deformable prostate-mimicking mock-up (Model 066, CIRS, VA) was put on the table without fixation to simulate its movability, as shown in Figure 3.48.

In the experiment, a 3D scan was performed to obtain a 3D volume image after adjusting the ultrasound probe so that the probe barely touches the simulated rectal wall and the central sagittal view of the simulated prostate is clearly visible. Next, an extended 12-cores biopsy plan was established after completing the prostate segmentation, as shown in Figure 3.49. Then, the robot aimed at each target, and the biopsy needle (length of sample notch: 1.8 [cm], gauge size: 18 gauge, needle length: 25 [cm], penetration depth: 22 [mm], MC1825, Bard Medical, GA) was inserted under the guidance of the navigation screen. A real-time ultrasound image was saved at each aimed position. After finishing targeting for 25 grid points, a post-biopsy 3D scan was performed for evaluation purpose. The time required for each procedure was also measured.

In the analysis, a prostate contour was manually identified from each real-time ultrasound image saved at each aimed position, as shown in Figure 3.50b. 2D displacements of the prostate, \( d_{p,i} = 1, \ldots, 12 \), were calculated as the distances between the center points of the pre-acquired prostate contours, \( c_{1,i} = 1, \ldots, 12 \), and the corresponding center points of the real-time prostate contours, \( c_{2,i} = 1, \ldots, 12 \), as shown in Figure 3.21a. To measure the 2D deformations of the prostate, the pre-acquired contours were translated by \( (c_{2,i} - c_{1,i}) \)
so that the two contours have a same center point, as shown in Figure 3.21b. 2D deformations of the prostate, $d_{fi}, i = 1, \ldots, 12$, were then calculated as the mean distances of two-points sets where the two contours intersect with a line that rotates uniformly ($\varphi = 15$ [deg]) about the center point, as shown in Figure 3.21b. Subsequently, the needle insertion errors $e_{ni}, i = 1, \ldots, 12$ were measured as distances between the center of the biopsy needle imaged on the ultrasound image and the corresponding target points, as shown in Figure 3.50a. The targeting errors $e_{ti}, i = 1, \ldots, 12$ were then calculated as a sum of the needle insertion errors and the 2D displacements of the prostate such that $e_{ti} = e_{ni} + d_{pi}, i = 1, \ldots, 12$. Furthermore, 3D displacement $D_p$ and deformation $D_f$ of the prostate were measured from the two prostate surface models generated from the pre- and post-biopsy ultrasound volumes, as shown in Figure 3.51. $D_p$ was calculated as a distance between the centroids of the two surface models. To measure the 3D deformation, the pre-biopsy prostate surface model was translated so that the two surface models have a same centroid. $D_f$ and $D_f^{\text{max}}$ were then calculated as a mean and maximum value of the distances from vertices of the pre-biopsy prostate surface model to the corresponding closest point on the post-biopsy prostate surface model.
3.4.10.2 Results

Table 3.13 shows the time required for the biopsy with the prostate mockup. Figure 3.50 shows an example of measurements for needle insertion, prostate displacement, and prostate deformation errors. Table 3.14 shows targeting accuracy for 25 grid points. The accuracy and precision were calculated as the average and standard deviation of the errors, as usual. The 3D displacement $D_p$ and deformation $D_f$ of the prostate were 0.24 and 0.17 $[mm]$, respectively. The maximum deformation distance $D_f^{max}$ was 0.68 $[mm]$.

Table 3.13: Time required for the biopsy with prostate mockup

<table>
<thead>
<tr>
<th></th>
<th>Time [min]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation time</td>
<td>10.0</td>
</tr>
<tr>
<td>Scanning time</td>
<td>0.5</td>
</tr>
<tr>
<td>Planning time</td>
<td>3.0</td>
</tr>
<tr>
<td>Biopsy time</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>18.5</strong></td>
</tr>
</tbody>
</table>

Figure 3.50: Measurements of (a) needle insertion, (b) displacement, and deformation errors (Target10)
Table 3.14: Experimental results for targeting with prostate mockup

<table>
<thead>
<tr>
<th>Target Number</th>
<th>Target Position</th>
<th>Error [mm]</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$d_p$</td>
<td>$d_f$</td>
<td>$e_n$</td>
</tr>
<tr>
<td>1</td>
<td>RBL</td>
<td>0.40</td>
<td>0.44</td>
<td>0.54</td>
</tr>
<tr>
<td>2</td>
<td>RBM</td>
<td>0.39</td>
<td>0.28</td>
<td>0.68</td>
</tr>
<tr>
<td>3</td>
<td>RML</td>
<td>0.68</td>
<td>0.43</td>
<td>0.53</td>
</tr>
<tr>
<td>4</td>
<td>RMM</td>
<td>0.40</td>
<td>0.38</td>
<td>0.33</td>
</tr>
<tr>
<td>5</td>
<td>RAL</td>
<td>0.55</td>
<td>0.51</td>
<td>0.37</td>
</tr>
<tr>
<td>6</td>
<td>RAM</td>
<td>0.33</td>
<td>0.40</td>
<td>0.44</td>
</tr>
<tr>
<td>7</td>
<td>LBL</td>
<td>0.48</td>
<td>0.42</td>
<td>0.74</td>
</tr>
<tr>
<td>8</td>
<td>LBM</td>
<td>0.54</td>
<td>0.24</td>
<td>0.80</td>
</tr>
<tr>
<td>9</td>
<td>LML</td>
<td>0.91</td>
<td>0.91</td>
<td>0.89</td>
</tr>
<tr>
<td>10</td>
<td>LMM</td>
<td>0.35</td>
<td>0.30</td>
<td>0.56</td>
</tr>
<tr>
<td>11</td>
<td>LAL</td>
<td>0.46</td>
<td>0.47</td>
<td>0.65</td>
</tr>
<tr>
<td>12</td>
<td>LAM</td>
<td>0.42</td>
<td>0.20</td>
<td>0.57</td>
</tr>
<tr>
<td>Max</td>
<td></td>
<td>0.91</td>
<td>0.91</td>
<td>0.89</td>
</tr>
<tr>
<td>Accuracy</td>
<td></td>
<td>0.49</td>
<td>0.41</td>
<td>0.59</td>
</tr>
<tr>
<td>Precision</td>
<td></td>
<td>0.16</td>
<td>0.18</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Figure 3.51: Segmented prostate models with (a) intra- and (b) post-biopsy scans, (c) Deformation result
3.4.11 Discussion

One of the challenging problems encountered in the development of the robot was to remove the noise on the ultrasound images. Since the ultrasound probe sensor was disassembled and integrated with robotic components, electromagnetic interferences occurred between the robotic components and the ultrasound sensor. To remove this interference problem, the spaces for the robotic components and the ultrasound sensor are completely separated and the inner surface of each space was sprayed with conductive materials (Nickel) or covered with thin copper foil tapes.

The ultrasound probe calibration method presented in this section (Subsection 3.4.6) could be potentially applied not only to the ultrasound probe manipulator with 1-DoF but also to the ultrasound probe manipulator with multiple-DoF by applying the method for each DoF. In this case, all components of the calibration matrix can be determined.

The results of the joint accuracy test show that the joint accuracy with the identified kinematic parameters (positive direction: 0.134±0.173 [deg], negative direction: 0.060±0.073 [deg]) was significantly improved compared to the joint accuracy with the original design parameters (positive direction: 0.534±0.467 [deg], negative direction: 0.450±0.627 [deg]). Also, the joint accuracy was higher when the needle-guide driver was rotated in the negative direction. This is because the needle-guide driver has a longer stroke in the negative direction.

The cohesive TRUS probe-robot inherits the advantages of the TRUS robot as it is, enabling hands-free and skill-independent prostate biopsy. In addition to these advantages, the robot also significantly improves the TRUS-guided robotic prostate biopsy in two aspects as follows.

First, the cohesive TRUS probe-robot minimizes the prostate deformation by design, while the prostate deformations are minimized using the software algorithms in the TRUS robot. The transrectal prostate biopsy is commonly performed using an end-fire ultrasound probe. However, the cohesive TRUS probe-robot uses a side-fire ultrasound probe for prostate biopsy. The side-fire ultrasound probe has a long linear sensor array at the side of the probe, while the end-fire ultrasound probe has a short circular sensor array at the end of the probe. The side-fire ultrasound probe is known to have multiple benefits over the end-fire ultrasound probe. The first benefit is in the capability of minimizing the prostate deformation. The side-fire probe facilitates
preserving the prostate shape during its operation, as it has a line-contact to the rectal wall while the end-fire probe has a point-contact. The second benefit is in the capability of acquiring images with better quality. Since the side-fire probe commonly has long linear sensor array and the acoustic beam does not expand as the depth changes, the image quality with the side-fire probe is superior to the image quality with the end-fire probe in general.

Second, the cohesive TRUS probe-robot has 2-DoF, while the TRUS robot has 4-DoF. Having lower DoF for the same task is preferred for multiple reasons. The first benefit is in the capability of obtaining a higher targeting accuracy. In practice, the targeting accuracy with the cohesive TRUS probe-robot \((1.08\pm0.28 \text{ [mm]})\) was higher than the targeting accuracy with the TRUS robot \((1.35\pm0.39 \text{ [mm]})\) in the mockup test. The second benefit is in the capability of building a compact and light system. Since prostate biopsy is commonly performed in a small clinic room by a urologist, the size and weight of the robot could be an important factor to be considered.

### 3.4.12 Conclusion

In this section, a novel robot for TRUS-guided prostate biopsy was presented. An ultrasound probe was incorporated into the robot. The robot enables accurate, hands-free, skill-independent prostate biopsy. The work discussed in this section includes the robotic system, the calibration method for the ultrasound probe manipulator with 1-DoF, and comprehensive pre-clinical test results. The cohesive TRUS probe-robot and the image-model based calibration method are novel approaches.

Comprehensive mockup experiments are presented. In preclinical experiments, the accuracy of image-based needle targeting was on the order of 0.5 \([\text{mm}]\). Clinically, targeting accuracy is substantially lower than the 5 \([\text{mm}]\) required to target clinically significant PCa [8, 30]. In the prostate mockup study, the robot showed its superiorities in targeting accuracy and reducing prostate deformation compared to the results with the TRUS robot presented in the previous section (3.3.12). In future work, clinical trials are required to validate the feasibility and effectiveness of the robotic system.
3.5 Chapter Summary

This chapter presented the work in developing the TRUS-guided robotic system for prostate biopsy. First, a concept of the robotic system for TRUS-guided transrectal prostate biopsy was introduced together with its background, motivation, and system overview.

Second, the software for robot control and image navigation was developed to be used for the robotic prostate biopsy system. A detailed explanation about a new 3D TRUS imaging algorithm, a novel prostate biopsy planning method based on the PCS, and unique techniques for robot control and biopsy navigation were presented.

Third, the TRUS robot for TRUS-guide robotic prostate biopsy system was presented. The structure and calibration procedure of the robot were briefly described first. The TRUS robot moves the probe with the same 4 DoF that is closely replicating its movement by hand. Novel techniques to minimize the prostate deformation were then presented. Comprehensive validation tests including bench tests, mockup tests, and FDA/IRB-approved clinical trials showed the feasibility of the proposed techniques and robotic system.

Last, the cohesive TRUS probe-robot for TRUS-guided robotic prostate biopsy system was presented. The structure of the robot was briefly described first. The cohesive TRUS probe-robot has only 2-DoF, while it carries out the same task as the TRUS robot. The forward and inverse kinematics of the robot was then presented in detail. A novel calibration method for the ultrasound probe manipulator with 1-DoF was presented, and its feasibility was confirmed in the mockup test. Finally, validation tests including bench tests and mockup tests showed an improvement in targeting accuracy and reducing prostate deformation.

3.6 Conclusion

A concept of the robotic system for TRUS-guided transrectal prostate biopsy was proposed. The robotic system takes transrectal prostate biopsy one step further, with an actuated TRUS probe manipulation robot and a custom-written software for robot control and image navigation. Like no other, the system enables minimization of the prostate deformation and accurate, hands-free, skill-independent prostate biopsy.
The TRUS robot was developed to assist urologists in performing prostate biopsy under TRUS guidance. The TRUS robot moves an ultrasound probe with the same 4 DoF that is used manually in transrectal procedures, closely replicating its movement by hand. In addition to the TRUS robot, novel techniques for minimizing the prostate deformation during the biopsy were presented. By applying the techniques uniquely designed for the TRUS robot, it is possible to minimize the movement of the ultrasound probe during the biopsy, reducing the prostate deformation and increasing the targeting accuracy. The robotic system was validated in comprehensive tests including bench, mockup tests, and clinical trials for 5 patients, showing the feasibility of the system.

The cohesive TRUS probe-robot was developed to assist urologists in performing prostate biopsy under TRUS guidance. While the robot carries out the same transrectal prostate biopsy as the TRUS robot does, the robot has only 2-DoF, 1-DoF for rotating the ultrasound probe and 1-DoF for rotating the needle-guide. The lower DoF enables not only performing accurate needle targeting but also developing a compact and light system. As prostate biopsy is commonly performed in a small clinic room by a urologist, the size and weight of the robotic system is an important factor to be considered. The robotic prostate biopsy system including the software and the robot would be potentially integrated into the ultrasound machine, making the system even more compact and simple. The robotic system was validated in bench and mockup tests.

### 3.7 Contributions

The scientific contribution of this chapter includes:

- **TRUS Robot**, a novel ultrasound-guided robot for prostate biopsy, which enables minimization of the prostate deformation and accurate, hands-free, skill-independent prostate biopsy.

- **Cohesive TRUS Probe-Robot**, a novel ultrasound-guided robot for prostate biopsy, which is accurate, compact, light and designed to minimize the prostate deformation.

- **Custom-written software** for 3D TRUS imaging, biopsy planning, robot control, and navigation.

- **Novel algorithms** to minimize the prostate deformation during the biopsy.

- **In-vitro experiments** evaluating the mechanical performance of the robots.

- **A preclinical study** demonstrating the effectiveness of the TRUS-guided robotic prostate biopsy.

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- FDA/IRB-approved clinical trials demonstrating the feasibility of the TRUS-guided robotic prostate biopsy system.

The design of the robot was done by Dr. Dan Stoianovici and the fabrication of the robot was done by Dr. Doru Petrisor.

My personal contribution to the work described in this chapter includes:

- System integration.
- Formulation and analysis of the robot kinematics.
- Design, implementation, and debug of the robot control and imaging software.
- Design and implementation of the optimization algorithms described in this chapter.
- Design and implementation of the ultrasound calibration algorithm described in this chapter.
- Design, execution, and analysis of all the experiments discussed in this chapter.
Chapter 4 is organized as follows. Section 4.1 presents the background and motivation of the personalized robotic prostate biopsy. Section 4.2 presents a novel method for prostate segmentation. Section 4.3 presents several advanced approaches for geometric systematic biopsy plan optimization. Section 4.4 presents the results of the FDA/IRB-approved clinical trials. Section 4.6 and Section 4.7 presents a summary and a conclusion of Chapter 4, respectively. At last, Section 4.8 presents a list of the contributions involved in this chapter.

4.1 Background and Motivation

PCa is one of the most common cancers in Northern America, Australasia, Northern Europe, and Western Europe [7]. In 2019, 174,650 cases of PCa were estimated to be diagnosed and 31,620 of deaths from PCa are expected in the United States alone [8]. PSA blood test and DRE are commonly performed as preliminary screening tests of PCa [9], [10]. If one of these test results is abnormal, a prostate biopsy is advised to confirm the diagnosis of PCa. In a prostate biopsy, a thin needle is inserted into the prostate and tissue samples are withdrawn under the guidance of freehand TRUS probe.

A general freehand TRUS-guided prostate biopsy samples prostate tissues systematically over the prostate gland since cancerous tissue cannot be differentiated from benign prostate tissue in ultrasound images. An extended sextant (12-cores) prostate biopsy plan is widely used to diagnose PCa and has been shown its validity [16]. However, the 12-cores biopsy plan is defined on a 2D plane and identical for all patients regardless of their prostate size and shape. It is also subjective to urologist’s interpretation.

Moreover, a freehand biopsy is highly inaccurate. The freehand biopsy samples do not follow the systematic schema (plan for 12 biopsy cores). They cluster or miss regions [17]. Furthermore, the freehand biopsy samples vary significantly depending on operator [18]. Therefore, a freehand TRUS-guided prostate biopsy includes limitations such as an under-sampling problem and an over-sampling problem [19].

If the 12-cores biopsy plan could be geometrically optimized based on the patient-specific information such as prostate sizes and shape, the detection probability of clinically significant PCa would be increased.
The main idea of the geometric optimization of the biopsy plan using the capsule model [17] was introduced in our previous work [179]. The work showed that optimizing the geometric distribution of the biopsy cores increases the detection probability of PCa. However, the validation tests were performed in a strictly controlled environment and they were not applied clinically.

The previous work [179] includes two limitations. The first limitation is the absence of an efficient, robust, and functional prostate segmentation method. Most of the prostate segmentation methods are performed based on the axial images of the prostate [180], [181]. Although several methods were improved in efficiency-wise [92], [182], the prostate segmentation is still a time-consuming procedure. Moreover, as boundaries of the prostate and urethra are commonly blurred in ultrasound images, the segmentation results vary depending on the image quality. Thus, an efficient, robust, and functional method for prostate segmentation is required for clinical practice. The second limitation is that the capsule used in the capsule model had a constant radius $R = 4.924 [mm]$, which was determined based on the size of clinically significant PCa [17]. If the volume of the prostate is relatively bigger than the union volume of the capsules, the capsules cannot be uniformly distributed over the prostate due to the constant capsule size, yielding clustered biopsy cores and missed regions. Several novel methods and algorithms were developed to resolve these limitations and presented in this chapter.

Meanwhile, the robotic needle guidance in TRUS-guided prostate biopsy showed outstanding accuracy results in Chapter 3. The robotic prostate biopsy approach could enable the optimized plan to be executed precisely, with hands-free TRUS guidance that makes the procedure less dependent on the urologist’s skills. Accordingly, a patient-specific optimization on the geometrical distribution of the biopsy cores followed by robotic needle guidance could potentially increase the detection probability of clinically significant PCa. Eventually, these would increase the detection rate of clinically significant PCa as well.

In this chapter, we present a personalized robotic prostate biopsy. The robotic prostate biopsy system, which was presented in Chapter 3, was integrated with the methods and algorithms for the geometric optimization of the 12-cores biopsy plan. In details, we introduce a novel and efficient prostate segmentation method, advanced algorithms for the geometric optimization of the 12-cores biopsy plan, its validation test, and FDA/IRB-approved clinical trials. In the rest of the chapter, the feasibility test of the MRI-ultrasound fusion based, targeted, robotic prostate biopsy was presented.
4.2 Prostate Segmentation

The main goal of the work involved in this section was to develop a functional prostate segmentation method to be used in the practical biopsy procedure. The method has been reported in a conference proceeding [183].

4.2.1 Personal Contributions

I developed the method for prostate segmentation under the supervision of Dr. Dan Stoianovici. I was also exclusively responsible for implementing the method into the software.

4.2.2 Orthogonal-Planes Based Prostate Segmentation

We present a novel prostate segmentation method. In our method, the prostate is represented by 26 control nodes, as shown in Figure 4.1g. By aligning only 5 Bézier curves on the five orthogonally resliced image planes on the PCS (axial, sagittal, coronal, and two paraxial planes, Figure 4.1a-e), the prostate segmentation is efficiently acquired. With our method, the prostate segmentation becomes simpler and more efficient compared to the conventional approach that requires numerous segmentations of the prostate in the axial direction [180], [181]. A concept of the PCS, which was introduced in our previous research [36], is used in the segmentation. The origin of the PCS is defined at a mid-point of the urethra center point at the apex (A in Figure 4.1b) and the farthest point at the base of the prostate (B in Figure 4.1b). The direction of the PCS is then aligned to the direction of the A-B axis and the central sagittal plane of the prostate, as shown in Figure 4.1. The PCS follows a standard anatomic system (Left-Posterior-Superior coordinate).

A region of the prostate is segmented based on the PCS. In details, it is segmented by defining 7 closed Bézier curves, namely central-axial (CA) curve, central-sagittal (CS) curve, central-coronal (CC) curve, left-sagittal (LS) curve, right-sagittal (RS) curve, apex-axial (AA) curve, and base-axial (BA) curve, as shown in Figure 4.1. These 7 closed curves are controlled by its 26 intersection nodes including the A and B points.

The steps for the prostate segmentation and surface model reconstruction are as follows.

Step1: Initialize three closed curves on three orthogonal planes, such as the CA plane, the CS plane, the CC plane (See Figure 4.1a-c).
Step 2: Adjust nodes of the orthogonal curves so that the curves place on the prostate boundary (See Figure 4.1a-c).

Step 3: Based on the orthogonal curves, initialize four additional closed curves, such as the LS curve, the RS curve, the AA curve, and the BA curve (See Figure 4.1g).

Step 4: Adjust nodes on the AA and BA curves so that the curves place on the boundary (See Figure 4.1d-e).

Step 5: Update the CS, CC, LS, and RS curves based on the adjusted nodes in the step 4.

Step 6: Interpolate axial curves using the CS, CC, LS, and RS curves (See Figure 4.1f).

Figure 4.1: Orthogonal-planes based prostate segmentation; (a) central-axial curve, (b) central-sagittal curve and urethra curve, (c) central-coronal curve, (d) apex-axial curve, (e) base-axial curve, (f) interpolated axial curves, and (g) prostate and urethra surface models generated based on the PCS.
Step 7: Generate a surface model of the prostate using the interpolated axial curves (See Figure 4.1g).

A region of the urethra is segmented based on the urethra curve (red line) on the CS plane, as shown in Figure 4.1b. An endpoint of the urethra curve is fixed at the A point, and four control points of the urethra curve are adjustable. Once the curve is aligned along the urethra path, the diameter of the urethra is measured, as shown in Figure 4.1b. The surface model of the urethra is then generated by sweeping a circle with the urethra diameter along the urethra curve, as shown in Figure 4.1g.

### 4.2.3 Average Prostate and Urethra Model

A prostate segmentation is performed after the 3D scan and before the biopsy planning. During this process, the patient needs to retain their position. Unexpected movements of the patient occurred during this process could make a negative impact on biopsy results or a repeated 3D scan. Hence, reducing the time required for the segmentation is required.

We present a method to make the proposed segmentation approach even simpler. An averaged prostate and urethra models are built based on the accumulated patient data set in advance and used as an initial shape of the prostate and urethra models in the segmentation. The average model could potentially decrease the time for aligning the control nodes to the prostate boundary. Eventually, it could potentially reduce the time for segmentation. Figure 4.2 shows a schematic diagram of the average model. The average prostate model consists of the averaged 24 control nodes and is generated as follows.

The $i^{th}$ control node of the $m^{th}$ data set $\vec{c}_{lm} \in \mathbb{R}^3$ is normalized based on the distance between the apex and base points $d^S$, and averaged as follows:

\[
\vec{u}_i = \frac{1}{N_D} \sum_{m=1}^{N_D} \frac{1}{d^S_m} \vec{c}_{lm}, i = 1, \ldots, N_C
\]

where $N_D$ is the total number of the data set, $d^S_m$ is the distance between the apex and base points of the $m^{th}$ data set, and $N_C$ is the total number of the control nodes ($N_C = 24$).

The new control nodes for a new data set $k$ are then calculated as:
\[ \mathbf{c}_{ik} = d_k \mathbf{u}_i, \quad i = 1, \ldots, N_C \]  

where \( d_k \) is the distance between the apex and base points of the data set \( k \).

The average urethra model is also generated in the same way. Figure 4.2 shows an average prostate model built using the patient data obtained from the clinical trials in Section 3.3.14.

### 4.2.4 Discussion and Conclusion

A novel method for prostate segmentation was presented. In the method, the prostate is segmented based on the 26 control nodes and 7 Bézier curves which are defined on the orthogonal planes.

Most of the prostate segmentation methods have been performed based on the axial images of the prostate [180], [181]. While several methods were developed to improve segmentation efficiency [92], [182], the prostate segmentation remains a time-consuming procedure. Furthermore, since boundaries of the prostate and urethra are not clearly visible in ultrasound images, the automatic segmentation methods are not usually functional and require fine adjustments at last.
On the other hand, in the orthogonal-planes based segmentation method, the prostate can be represented using only 26 nodes controlled under the supervision of the urologist, enabling expedited, robust, and functional prostate segmentation for clinical practice. Moreover, an average model of the prostates can be generated based on the 26 node points and used to expedite the segmentation even further.

### 4.3 Optimization of Systematic Prostate Biopsy Plan

The main goal of the work involved in this section was to develop a method to maximize the cancer detection probability (CDP) in robotic biopsy planning. Part of the main idea was originally published in journal articles [80, 140]. However, the previous method has been significantly advanced to be practically used in the clinical trials of the robotic prostate biopsy and it has been reported in a conference proceeding [183].

#### 4.3.1 Personal Contributions

The work discussed in this section was done under the supervision of Dr. Dan Stoianovici.

**My personal contribution** includes:

- Development and implementation of the algorithms described here.
- Design, running, and analysis of all the experiments discussed here.

#### 4.3.2 Capsule Model and Biopsy Plan Optimization

In our previous publication [17], the capsule model was introduced to define the sampling volume of a biopsy core needle. Figure 4.3 shows a schematic diagram of the capsule model. In the capsule model, a tumor was assumed to have a spherical shape with radius \( R \). If the distance from the needle specimen notch to the tumor center is closer than \( R \) (\( \leq R \)), the tumor is considered as sampled. Otherwise (\( > R \)), the tumor is considered as not sampled. The length \( L = 18 \) [\( mm \)] and radius \( R = 4.924 \) [\( mm \)] of the capsule correspond with the specimen notch length of the regular prostate biopsy needle (MC1825, Bard Medical, GA) and the minimum size of the clinically significant PCa (\( \leq 0.5 \) [\( cm^3 \)]).
The capsule model is originally used to define the CDP in our previous publication [179]. The CDP $P^R$ is defined as the ratio of the prostate volume that was included within the capsules with radius $R$ over the total prostate volume such that:

$$P^R = \frac{V_p \cap (V_{C,1}^R \cup V_{C,2}^R \cdots \cup V_{C,n}^R)}{V_p}$$

(4.3)

where $V_p$ is the volume of the prostate and $V_{C,n}^R$ is the volume of the $n^{th}$ capsule with radius $R$.

The CDP $P^R$ is a function of the position and orientation of the biopsy cores.

Meanwhile, in our robotic TRUS-guided prostate biopsy system, the orientations of the biopsy cores are dependently determined by their positions $(p_{ix}, p_{iy}, p_{iz}), i = 1, ..., n$ during the optimization process [133]. Therefore, a biopsy plan for $n$ cores can be defined as a state matrix $\Omega \in \mathbb{R}^{n \times 3}$ such that:

$$\Omega = \begin{bmatrix} p_{1x} & p_{1y} & p_{1z} \\ \vdots & \vdots & \vdots \\ p_{nx} & p_{ny} & p_{nz} \end{bmatrix}$$

(4.4)

The patient-specific biopsy plan optimization problem is then defined to find the state matrix $\Omega$ that maximizes the CDP $P^R$.

![Figure 4.3: Capsule model; a spherical tumor (green) is considered as sampled ($d \leq R$), a spherical tumor (red) is considered as not sampled ($d > R$).](image)
\[ \Omega^{opt} = \arg\max_{\Omega} P^R(\Omega) \] (4.5)

A pattern search algorithm [185] was implemented to solve the optimization problem and find the best biopsy plan.

### 4.3.3 Adaptive Capsule Radius

In this section, we present two advanced methods to distribute the capsules evenly over the prostate gland. The first method is the adaptive capsule radius approach that change the radius of the capsules depend on the prostate size.

In the optimization problem shown in Equation (4.5), the union volume of the capsules needs to be equal to the certain percentage of the prostate volume in order to evenly distribute the capsules over the prostate gland. If the capsules are excessively small compare to the prostate size, the capsules stop to spread out when the intersecting portions between the capsules are disappeared, as shown in Figure 4.4a. If the capsules are excessively large, the CDP stays at maximum (\(= 1\)), and the capsules stay in their positions. From these facts, a cubic equation is derived to find the best capsule radius for the optimization as:

\[
\left( L \pi R_a^2 + \frac{4}{3} \pi R_a^3 \right) n = \rho V_p
\] (4.6)

where \(n\) is the number of the capsules, \(L\) is the length of the capsules, \(R_a\) is the best radius of the capsules, \(V_p\) is the volume of the prostate, \(\rho\) is an adjustment factor. \(\rho\) is experimentally selected as 0.6.

The best capsule radius \(R_a\) is then calculated as a unique solution of the cubic equation \((R_a > 0)\) as:

\[
R_a = \sqrt[3]{h + \sqrt{h^2 - g^6}} + \sqrt[3]{h - \sqrt{h^2 - g^6}} + g
\] (4.7)

where:
$g = -\frac{1}{4} L$

$h = g^3 + \frac{3\alpha V_p}{8\pi n}$

Based on the capsules with the radius of $R_a$, the CDP function $P^{R_a}(\Omega)$ is calculated as:

$$P^{R_a}(\Omega) = \frac{V_e N_c^{R_a}}{V_p}$$  \hspace{1cm} (4.8)$$

where $V_e$ is the volume of a unit voxel element, $V_p$ is the volume of the prostate, $N_c^{R_a}$ is the number of voxel elements inside of the prostate and the capsules with radius $R_a$.

The capsules can be uniformly distributed over the prostate based on the optimal biopsy plan $\Omega^{opt}$ that maximize the CDP $P^{R_a}$, as shown in Figure 4.4b.

### 4.3.4 Uniformity + Cancer Detection Probability

The second method is the uniformity + CDP approach that considers the uniformity of the biopsy core distribution together with the CDP.
To make the capsules with a constant radius $R (= 4.924 \text{ mm})$ spread out over the prostate region evenly, a new cost value function is required, such as a function that evaluates the uniformity of the core distribution over the prostate. The uniformity value function $U(\Omega)$ of the capsule distribution can be defined as

$$U(\Omega) = -\sigma^2 = -\frac{1}{N_p} \sum_{i=1}^{N_p} (d_i - \mu)^2$$  \hspace{1cm} (4.9)

where $N_p$ is the number of voxels inside of the prostate, $d_i$ is the distance between $i^{th}$ voxel center and the closest core, $\mu$ and $\sigma^2$ are the mean and the variance of the distances $d_i$, respectively.

If the uniformity value function $U(\Omega)$ is used as a cost value function in the optimization shown in Equation (4.5), it acts like an expansion force that disperses the capsules over the prostate region, as shown in Figure 4.5a. However, the uniformity value function alone does not guarantee keeping the capsules inside of the prostate region, as shown in Figure 4.5a. Adding an additional CDP term can compensate for this defect. The additional CDP term acts like a contraction force that keeps the capsules inside of the prostate, as shown in Figure 4.5b. Consequently, the combined cost value function $C(\Omega)$ for the optimization is defined as:

$$C(\Omega) = U(\Omega) + \alpha P^R(\Omega)$$  \hspace{1cm} (4.10)

where $\alpha(>0)$ is a balancing factor.

Figure 4.5: Uniformity + CDP approach; (a) expansion force (uniformity), and (b) contraction force (CDP).
4.3.5 Safety and Detection Probability Improvements

During a prostate biopsy, avoiding a urethra region is very important in terms of safety. If a biopsy needle penetrates and invades a urethra, it may cause clinically significant infectious complications, such as urinary tract infection (UTI) and sepsis [186]. Therefore, it is vital to keep the biopsy plan away from the urethra region during the optimization process. Here, we present a method to avoid the urethra region during the biopsy plan optimization.

First, the safety distance $S$ measured from the urethra region to the biopsy needle is defined as:

$$ S = \gamma R_N $$

(4.11)

where $\gamma$ is a safety factor and $R_N$ is the radius of the biopsy needle. The safety factor $\gamma$ is empirically selected as 5.

For each voxel element inside of the urethra region, the distance from each voxel center to the needle insertion axis of the closest core is calculated. If the distance is closer than the safety distance $S$, it increases the count of perilous urethra voxels $N_U$.

The penalty function $X(\Omega)$ is then defined as:

$$ X(\Omega) = -\beta N_U $$

(4.12)

where $\beta$ is a penalty factor.

Meanwhile, the peripheral zone of the prostate, predominantly located in the posterior region of the prostate, is known as the place where the majority of PCa are found (68% [94]). If the capsules can cover more regions of the peripheral zone of the prostate, the detection probability of PCa could be improved. Here, we present a method to put a weight to the posterior region of the prostate during the biopsy plan optimization.

The weighted CDP function $P_\beta^w(\Omega)$ is defined as:
\[ P_w^R(\Omega) = \frac{V_E}{V_p} \{ N_{CA}^R (1 - w) + N_{CP}^R (1 + w) \} \] (4.13)

where \( V_E \) is the volume of a unit voxel element, \( V_p \) is the volume of the prostate, \( N_{CA}^R \) is the number of voxels inside of the capsules with radius \( R \) and the anterior region of the prostate, \( N_{CP}^R \) is the number of voxels inside of the capsules with radius \( R \) and the posterior region of the prostate, \( w \) is the posterior weight factor (\(-1 \leq w \leq 1\)).

The weighted uniformity value function \( U_w(\Omega) \) is then defined as:

\[ U_w(\Omega) = -\frac{1}{2} \{ \sigma_A^2 (1 - w) + \sigma_P^2 (1 + w) \} \] (4.14)

where \( \sigma_A^2 \) and \( \sigma_P^2 \) are the variances of the distances measured from each voxel center to the closest core in the anterior and posterior regions of the prostate, respectively.

The cost function \( C(\Omega) \) for the adaptive capsule radius approach is defined as:

\[ C(\Omega) = P_w^{Ra}(\Omega) + X(\Omega) \] (4.15)

The cost function \( C(\Omega) \) for the uniformity + CDP approach is defined as:

\[ C(\Omega) = U_w(\Omega) + \alpha P_w^R(\Omega) + X(\Omega) \] (4.16)

where \( \alpha(> 0) \) is a balancing factor. \( \alpha \) is experimentally selected as 350.

### 4.3.6 Improved Initial Core Positions

The biopsy plan optimization is carried out after the prostate segmentation and prior to the tissue sampling. Since the patient needs to keep their position during this process, reducing a computation time for the optimization is required as much as possible.
Meanwhile, since a pattern search algorithm, which is used to solve the optimized problem, is a heuristic algorithm, initial positions of the biopsy cores (initial state matrix $\Omega_{init}$) play an important role in determining a computation time for the optimization. If the initial positions of the biopsy cores ($\Omega_{init}$) are adjacent to the corresponding final positions of the biopsy cores ($\Omega_{opt}$), it could decrease the computation time for the optimization.

Here, we present a method to calculate an improved initial state matrix. The improved initial state matrix $\Omega_{init}^*$ is calculated by averaging the optimal core positions calculated from the accumulated patient data set in advance. The improved initial state matrix $\Omega_{init}^*$ is calculated as below.

The center of the $j^{th}$ biopsy core of the $m^{th}$ data set $\vec{p}_{j,m} \in \mathbb{R}^3$ is normalized based on the normalizing vector of the $m^{th}$ data set $\vec{s}_m \in \mathbb{R}^3$, and averaged as follow:

\[
\vec{u}_j = \frac{1}{N_D} \sum_{m=1}^{N_D} \vec{s}_m \circ \vec{p}_{j,m}, j = 1, \cdots, n
\]  

(4.17)

where $\circ$ is the entry-wise product, $N_D$ is the number of the data set, $n$ is the number of the biopsy cores, and $\vec{s}_m$ is the normalization vector of the $m^{th}$ data set such that:

\[
\vec{s}_m = \left( \frac{1}{d_{mL}} \frac{1}{d_{mP}} \frac{1}{d_{mS}} \right)^T
\]  

(4.18)

$d_{mL}, d_{mP}, d_{mS}$ are the distances between the two farthest control nodes in each direction of the PCS in the $m^{th}$ data set, as shown in Figure 4.2.

The improved initial core positions for a new data set $k$ are then estimated as:

\[
\vec{p}_{j,k} = \vec{r}_k \circ \vec{u}_j, j = 1, \cdots, N_c
\]

where:

\[
\vec{r}_k = \left( d_{kL}^2 d_{kP}^2 d_{kS}^2 \right)^T
\]  

(4.19)
The improved initial state matrix $\Omega^{\text{init}*}_k$ is obtained as:

$$\Omega^{\text{init}*}_k = \begin{bmatrix} \vec{p}_{1,k}^T \\
\vdots \\
\vec{p}_{n,k}^T \end{bmatrix}$$

(4.20)

4.3.7 Experiments

4.3.7.1 Adaptive Capsule Radius vs. Uniformity + CDP

Methods:

A validation test was performed to check the feasibility of the two proposed algorithms for capsule saturation. One of the patient image data (Patient 2) obtained from the clinical trial in Section 3.3.14 was used. The prostate and urethra were segmented from the ultrasound images using the orthogonal-planes based segmentation method, as shown in Figure 4.6a. Prostate volume was 74.77 $[\text{cm}^3]$. For the same prostate and urethra model, the adaptive capsule radius and uniformity + CDP approaches were applied for the optimization, respectively. CDP was measured before and after the optimization. Time required for the optimization was also measured. In addition, to evaluate a uniformity improvement of the capsule distribution, distances from each voxel center inside of the prostate model to the closest core were measured and analyzed.

Results:

Figure 4.6 and Figure 4.8 show the results of the optimized biopsy plan using each approach. The figures show (a) urethra region avoidance ($w = 0\%$), (b) anteriorly weighted plan ($w = -70\%$), (c) zero-weight plan ($w = 0\%$), and (d) posteriorly weighted plan ($w = 70\%$). Table 4.1 shows the CDPs before and after the optimization and time required for the optimization. Figure 4.7 shows histograms created based on the distances, which were measured from each voxel center to the closest core.
Table 4.1: Geometric optimization results of the systematic biopsy plan

<table>
<thead>
<tr>
<th>Weight [%]</th>
<th>Adaptive Capsule Radius</th>
<th>Uniformity + CDP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CDP [%]</td>
<td>Time [sec]</td>
</tr>
<tr>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>-70</td>
<td>20.3</td>
<td>27.8</td>
</tr>
<tr>
<td>0</td>
<td>20.3</td>
<td>29.3</td>
</tr>
<tr>
<td>70</td>
<td>20.3</td>
<td>28.2</td>
</tr>
<tr>
<td>Average</td>
<td>20.3</td>
<td>28.4</td>
</tr>
</tbody>
</table>

Figure 4.6: Optimized biopsy plans with adaptive capsule radius approach showing (a) urethra region avoidance (w = 0%), (b) anteriorly weighted plan (w = -70%), (c) zero-weight plan (w = 0%), and (d) posteriorly weighted plan (w = 70%)
Figure 4.7: Histograms showing uniformity improvements in both approaches

Figure 4.8: Optimized biopsy plans with uniformity + CDP approach showing (a) urethra region avoidance (w = 0%), (b) anteriorly weighted plan (w = -70%), (c) zero-weight plan (w = 0%), and (d) posteriorly weighted plan (w = 70%)
### 4.3.7.2 Validation test for Improved Initial Core Positions

**Methods:**

A validation test was performed to check the utility of the improved initial core position approach. The five patient image data obtained from the clinical trial in Section 3.3.14 were used. In the experiment, the improved initial state matrix $\Omega_{k}^{init*}$ (averaged optimal core positions) was calculated and used for the optimization as initial core positions. The image data for the evaluation subject was excluded from the data set for the improved initial state matrix calculation. For example, image data from patient 1 to 4 were used to calculate an initial state matrix $\Omega_{k}^{init*}$, and it is used to verified with image data from patient 5. The initial state matrix calculation and evaluation was repeated for each image data. For each evaluation, the optimization was performed for two times based on the general initial 12-core positions, which is defined in a 2D plane, and the improved initial state matrix $\Omega_{k}^{init*}$. The optimization was performed using both optimization approaches such as the adaptive capsule radius approach and the uniformity + CDP approach. CDPs before and after the optimization were measured together with time required for the optimization. The improvement in optimization time was then calculated in percentage.

**Results:**

Table 4.2 and Table 4.4 show the results of the validation test using the adaptive capsule radius approach and the uniformity + CDP approach, respectively. The tables show prostate volumes, CDPs before and after the optimization, time required for the optimization, and time improvement. Overall, the time for the optimization was improved about 23 [%] with the improved initial core positions on average.

Table 4.2: Validation results of the improved initial core positions (Adaptive Capsule Radius)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prostate Volume [cm$^3$]</th>
<th>2D Initial Position</th>
<th>Averaged-Optimal Position</th>
<th>Optimization Time Improvement [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CDP [%]</td>
<td>Optimization Time [sec]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>1</td>
<td>27.33</td>
<td></td>
<td>57.27</td>
<td>68.62</td>
</tr>
<tr>
<td>2</td>
<td>85.05</td>
<td></td>
<td>23.74</td>
<td>25.25</td>
</tr>
<tr>
<td>3</td>
<td>39.24</td>
<td></td>
<td>40.93</td>
<td>52.28</td>
</tr>
<tr>
<td>4</td>
<td>83.66</td>
<td></td>
<td>22.73</td>
<td>25.99</td>
</tr>
<tr>
<td>5</td>
<td>81.43</td>
<td></td>
<td>23.67</td>
<td>26.47</td>
</tr>
<tr>
<td>Average</td>
<td>63.34</td>
<td></td>
<td>33.67</td>
<td>39.72</td>
</tr>
</tbody>
</table>
4.3.7.3 Discussion

Two algorithms were presented for the geometric optimization of the systematic biopsy plan, which evenly distributes the capsules over the prostate gland. From the results (Table 4.1), it was confirmed that both algorithms improve the CDP by uniformly distribute the capsule. There was about 8 [%] improvement in CDP after the optimization. In time-wise, however, the uniformity + CDP approach was superior to the adaptive capsule radius approach. The time required for the optimization was about two times faster with the uniformity + CDP approach, while both algorithms showed similar optimization performance in terms of CDP and uniformity of the capsule distribution.

One of the challenging problems encountered in the validation test of the two optimization algorithms was how to evaluate each algorithm to show its performance effectively. The CDP is not increasing once it reaches the maximum value, even if the biopsy cores are more evenly distributed. As such, CDP was not able to be used to evaluate the performance of the algorithms properly. Therefore, the uniformity of the biopsy cores was directly measured. The distances from each voxel center inside of the prostate model to the closest biopsy core were measured and used to draw a histogram. A decrease in the variance of the histogram curve means an increase in the uniformity of the biopsy cores. The histograms (Figure 4.7) show that variances of the histogram curves were decreased in both cases after the optimization. From this, it was concluded that the uniformity of the biopsy core distribution was improved in both cases after the optimization.

From the validation results of the improved initial core positions (Table 4.2 and Table 4.4), the efficiency of the method was confirmed. Time for the optimization was improved about 23 [%] on average with the improved initial core positions in both optimization approaches such as the adaptive capsule radius.
and the uniformity + CDP. This would decrease the time for biopsy planning, potentially reducing the risk of the patient movement during the planning procedure.

### 4.3.8 Discussion and Conclusion

Several novel algorithms were developed for the geometric optimization of the systematic biopsy plan based on the prostate and urethra segmentation results.

The main idea of the geometric optimization of the biopsy plan was introduced in our previous works [17], [179]. Yet, the validation tests were performed in a strictly controlled environment. The previous work had several limitations to be used in clinical practice. In particular, the radius of the capsule was determined as $R = 4.924 [\text{mm}]$ based on the size of clinically significant PCa and applied for all prostates regardless of its size [17], [179]. This may cause a significant problem in clinical practice. For instance, if the volume of the prostate is relatively bigger than the union volume of the capsules, due to the constant capsule size, the capsules cannot be uniformly distributed over the prostate, yielding a clustered biopsy cores and missed regions.

The uniquely designed algorithms enable uniform distribution of the biopsy targets over the prostate, avoidance of the urethra region, and weighted coverage of the peripheral zone where the majority of prostate tumors are found (68% [94]). This could potentially increase the detection probability of clinically significant PCa and decrease the infection risk of the patients.
4.4 Clinical Trials

The main goal of the work involved in this section was to evaluate and validate the feasibility of the TRUS-guided robotic prostate biopsy system in clinical trials. The work has been reported in a conference proceeding [183].

4.4.1 Personal Contributions

Most of the clinical work and protocol design was done by Dr. Misop Han and Dr. Dan Stoianovici. My personal contribution includes:

- Design, debugging, and implementation of the software for 3D TRUS imaging, biopsy planning, robot control, and navigation.
- Manipulation of the software in the clinical trials.
- Analysis of the experimental data.

4.4.2 Methods

An FDA/IRB-approved clinical study was conducted to verify the feasibility of the robotics prostate biopsy system. Figure 4.10 shows the system setup for the clinical trial. The study was carried out on seven men with an elevated PSA level (≥4ng/ml) and/or abnormal DRE. In the clinical trial, a patient is positioned in the left lateral decubitus position (lying on the left side) on the patient bed. This position allows for easier...

![Image of robotic prostate biopsy setup]  
Figure 4.9: Personalized robotic prostate biopsy: robot handles TRUS probe and urologist handles needle
insertion of the rectal ultrasound probe. After performing periprostatic local anesthesia, the rectal probe mounted on the robot manipulator is advanced into the rectum and its position is adjusted so that the central sagittal plane of the prostate is clearly visible. Once the initial position of the robot manipulator is determined, the translation of the probe is adjusted from the software so that the probe barely touches the rectal wall without deforming or displacing the prostate. A 3D rotary scan is then performed under the control of the software. If the images of the prostate are successfully acquired, the prostate and urethra are segmented, and their 3D surfaces are generated. Then, a set of uniformly distributed 12 targets is established by the geometric optimization of the biopsy plan. Once the software sends the robot to the target, the urologist inserts a biopsy needle (length of sample notch: 1.8 [cm], gauge size: 18 gauge, needle length: 25 [cm], penetration depth: 22 [mm], MC1825, Bard Medical, GA) through the needle-guide under the guidance of the navigation screen (Figure 3.5b) and take tissue samples. After finishing all the biopsy procedures, all the data including the ultrasound images and its configurations, the 3D surface model of the prostate, the 12 target positions, the AB points, and the PCS are automatically saved.

Needle insertion errors $e_n$ were calculated as described in Section 3.3.13. Needle targeting accuracy and precision were calculated as the average respectively standard deviation of the errors, as usual. Partial and overall procedure times were also recorded.

**4.4.3 Results**

In two cases, the patients moved at the time of biopsy needle firing, and the urologists decided to retract the robotic biopsy and performed a general freehand TRUS biopsy. There were no adverse effects due to the robotic system. A case was retracted because of software failure. In the other four cases, the robot allowed 3D imaging of the prostate, 3D size measurements, and volume estimation. The results are presented in Table 4.4. The robot also enabled hands-free TRUS operation for prostate biopsy and all four procedures were successful. No adverse effects due to the robotic system were reported by the patients. The biopsy procedures took 12.33 minutes on average. Two of the four patients had a malignant tumor with biopsy Gleason Scores of 3+4, and 3+4. Numerical results are presented in Table 4.5.
Discussion and Conclusion

FDA/IRB-approved clinical trials were conducted to check the feasibility of the personalized robotic prostate biopsy. During the trials, a software failure occurred because of a memory management problem in the optimization. The problem was fixed after the trial. To prevent similar potential problems, an additional safety feature was added to the software. The software automatically saves all the data at each step of the procedures and the data can be immediately recovered once a software failure occurred.

Two patients moved at the time of biopsy needle firing. One of the challenging problems encountered in the clinical trials was minimizing the patient’s movements during the biopsy. The devices that support the patient’s leg and back may help to minimize the patient movements during the prostate biopsy.

### Table 4.4: Prostate size and volume

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prostate Size [mm]</th>
<th>Prostate Volume [cm³]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Superior-Inferior</td>
<td>Anterior-Posterior</td>
</tr>
<tr>
<td>1</td>
<td>41.46</td>
<td>30.65</td>
</tr>
<tr>
<td>2</td>
<td>45.12</td>
<td>34.85</td>
</tr>
<tr>
<td>3</td>
<td>57.15</td>
<td>47.65</td>
</tr>
<tr>
<td>4</td>
<td>36.88</td>
<td>27.18</td>
</tr>
<tr>
<td>Average</td>
<td>45.15</td>
<td>35.08</td>
</tr>
</tbody>
</table>

### Table 4.5: Clinical trial results

| Number of ultrasound images for 3D reconstruction | 341 |
| Average Time [min] | 0.50 | 5.93 | 3.90 | 12.33 |
| Needle Targeting [mm] | 0.79 | 0.28 |
| Cancer Diagnosis | 2/4 patients |

### 4.4.4 Discussion and Conclusion
The software includes an ability to compensate for the translational movement of the prostate by re-aligning the pre-acquired prostate contour to the real-time prostate contour together with the target points. However, it is limited in a small translational movement in 2D. For a large movement, a repeated 3D prostate scan is currently required. However, since a repeated scan delays the biopsy procedure significantly, it is not practical. A technique that guarantees an immediate 3D compensation of prostate movement is necessary.

The needle targeting error consists of multiple error components, such as error for needle insertion, error from unexpected patient movements, and error from prostate deformation. The errors from patient movement and prostate deformation were not able to be measured this time.

Currently, a 12-cores prostate biopsy plan is most commonly used for patients with PCa regardless of their prostate size [16]. While CDP of clinically significant PCa was able to be maximized from the geometric optimization in the 12-cores biopsy plan, it varies for different sizes of the prostate with the same number of the biopsy cores. Bigger prostate needs more biopsy cores to achieve the same CDP of smaller prostate with 12-cores. Accordingly, a patient-specific optimization on the number of biopsy cores is necessary and it could potentially increase the CDR of clinically significant PCa.

In future work, further trials are needed to determine if uniformly distributed biopsy plan and its precise execution using robotic guidance correlate with a higher detection rate of clinically significant PCa.

### 4.5 MRI-Ultrasound Fusion Prostate Biopsy

#### 4.5.1 Methods

While mpMRI has 5%–15% false-negative clinically significant CDR, it has been known that CSR is visible in mpMRI [135]. The biggest benefit of the MRI-ultrasound fusion is to bring targets identified in MRI space to the real-time ultrasound space so that the urologist can directly target the CSR under the real-time ultrasound guidance. This technique has been showing its advantage in sampling efficiency, increases CDR of clinically significant cancers, and reduces CDR of clinically insignificant cancers [19], [28].

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A novel method for MRI-ultrasound fusion is developed based on the PCS. Figure 4.10 shows a schematic diagram of the method. Using this method together with the robotic prostate biopsy system presented in Chapter 3, a target selected on the MR image can be precisely targeted under the robotic real-time ultrasound guidance.

The MRI-ultrasound fusion based on the PCS is achieved as follows. The robot coordinate system $\Sigma_R$ is defined at the RCM point of the robot as shown in Figure 4.10. The locations of the PCSs $\Sigma_P$ are determined in the robot $\Sigma_R$ and MR image $\Sigma_M$ coordinates during the segmentations using the ultrasound images and MR images, respectively. From this, the transformation from the robot coordinates $\Sigma_R$ to the PCS of the prostate model segmented from the ultrasound images, $T_{RP}$, and the transformation from the MRI coordinates $\Sigma_M$ to the PCS of the prostate model segmented from the MR images, $T_{MP}$, are determined. The transformation from the robot coordinates $\Sigma_R$ to the MR image coordinates $\Sigma_M$, $T_{RM}$, is calculated as:

$$T_{RM} = T_{RP} T_{MP}^{-1}$$  \hspace{1cm} (4.21)
Figure 4.11 shows a schematic diagram of MRI-ultrasound fusion. The transformation $T_{RM}$ allows transforming a target point $\vec{p}$ defined in the MRI space to the point $\vec{p}'$ defined in the robot space as:

$$\vec{p}' = T_{RM} \vec{p}$$  \hspace{1cm} (4.22)

The desired motor counts and joint values are calculated by solving the inverse kinematics problem of the robots as described in Section 3.3.6 and 3.4.4.

A simple test was performed to check the feasibility of the MRI-ultrasound fusion based on the PCS. Patient data from the clinical trial (Section 4.4) was used. The patient took an MRI scan before the biopsy. Since the MRI result was PCa negative, the patient underwent the robotic prostate biopsy with an optimized systematic biopsy plan. The ultrasound images obtained during the biopsy and the MRI data were used for the experiment.

In the experiment, the prostate and urethra were segmented from the MRI and the ultrasound images using the orthogonal-planes based segmentation method. The MRI-ultrasound fusion was then performed based on the PCSs, which were determined in the MRI space and the robot space during each segmentation, respectively (Figure 4.10). The distances between two prostate surface models and the volumes of the two prostate models were measured.

Figure 4.11: Schematic diagram for MRI-ultrasound fusion
4.5.2 Results

Figure 4.12 shows the results of the MRI-ultrasound fusion showing the prostate urethra models segmented from the ultrasound (Figure 4.12a) and MR (Figure 4.12b) images, respectively. Figure 4.12c shows the superimposed of two prostate and urethra surface models. Figure 4.12d shows a color map showing distances from the vertices on the prostate surface model generated from the ultrasound images to the prostate surface model generated from the MRI. Average and max distances were 1.51 and 6.07 [mm], respectively. The volumes of the prostate models from ultrasound and MRI were 89.38 and 93.42 [cm$^3$], respectively.

4.5.3 Discussion and Conclusion

The feasibility test of the MRI-ultrasound fusion, targeted prostate biopsy showed that the prostate was deformed in the ultrasound image compared to the shape in the MRI. This could shift the target selected on MRI during the biopsy, missing a sample on CSR. A fusion method using a deformable prostate model may circumvent the potential issue.

Figure 4.12: MRI-ultrasound fusion results
4.6 Chapter Summary

This chapter presented the work in developing the methodology for personalized robotic prostate biopsy. Several novel methods and algorithms were developed for the personalized robotic prostate biopsy. A novel method for prostate segmentation was developed. Also, a method to generate an average model of the prostate and urethra was developed to reduce the time required for segmentation. Based on the segmentation results, a method for the geometrical optimization of the systematic prostate biopsy plan was then developed. The capsule model was utilized for maximizing the CDP by evenly distributing the capsules over the prostate gland. Two novel algorithms to uniformly distribute the capsules over the prostate were presented and evaluated for their functionalities. Algorithms for improving the safety, detection probability, and computation efficiency of the method were also presented. The TRUS-guided robotic prostate biopsy system with the proposed methodologies integrated was validated in clinical trials with seven patients. In addition, the feasibility of the MRI-ultrasound fusion based, targeted, robotic prostate biopsy was tested using patient image data.

4.7 Conclusion

In this chapter, a novel methodology for personalized robotic prostate biopsy was presented. The personalized robotic prostate biopsy has the potential to increase the CDR of clinically significant PCa with systematic biopsy. Novel methods and algorithms for geometric optimization of the 12-cores biopsy plan were developed and integrated with the robotic prostate biopsy system, which was presented in Chapter 3.

A novel method for prostate segmentation was developed. The prostate is segmented based on the 26 control nodes and 7 Bézier curves, which are defined on the orthogonal planes. The orthogonal-planes based segmentation enables expedited, robust, and functional prostate segmentation for clinical practice. With this method, the prostate is able to be represented using only 26 nodes. Moreover, it is possible to expedite the segmentation even further using an averaged prostate model, which is generated based on the PCS and used as an initial placement of the control nodes.
Novel algorithms were developed for the geometric optimization of the systematic biopsy plan. The optimization could potentially increase the CDP of clinically significant PCa and decrease the infection risk. The algorithms are used to evenly distribute the biopsy plan over the prostate, avoid the urethra, and cover the peripheral zone where the majority of prostate tumors are found (68% [94]). FDA/IRB-approved clinical trials showed that optimizing the systematic biopsy plan for each patient is feasible using the novel algorithms. To the best of our knowledge, this is the first report of personalized systematic prostate biopsy in men.

The geometric optimization of the 12-cores biopsy plan maximizes the probability of sampling significant PCa for the patient. Moreover, the robotic biopsy approach enables the optimized plan to be executed precisely, with hands-free TRUS guidance that makes the procedure less dependent on the urologist’s skills. Together, these have the potential to increase the CDR of clinically significant PCa with systematic biopsy, independent or in addition to targeted biopsy.

An MRI-ultrasound fusion technique based on the PCS was presented and its feasibility was validated in a simple test. The MRI-ultrasound fusion based, targeted prostate biopsy is a fast-growing current trend in prostate biopsy. Integration of the fusion technology and the robotic guidance technology could take the current fusion biopsy one step further. Further researches in developing an MRI-ultrasound fusion based, targeted robotic prostate biopsy are ongoing.

### 4.8 Contributions

The scientific contribution of this chapter includes:

- Personalized robotic prostate biopsy, a novel concept for prostate biopsy, which enables a patient-specific optimal biopsy plan that maximizes the detection probability of PCa.
- A novel prostate segmentation method, which is efficient, robust, and functional in clinical practice.
- A novel algorithm to maximize the detection probability of PCa by enabling a uniform distribution of the systematic biopsy plan over the prostate gland.
- FDA/IRB approved clinical trials demonstrating the feasibility of the personalized robotic prostate biopsy system.
- A novel MRI-ultrasound fusion technique based on the prostate associated coordinate system.
The work discussed in this chapter was done under the supervision of Dr. Dan Stoianovici.

My personal contribution to the work described in this chapter includes:

- Development and implementation of the prostate segmentation method.
- Development and implementation of the biopsy plan optimization algorithms.
- Design, debugging, and implementation of the software for 3D TRUS imaging, biopsy plan optimization, robot control, and navigation.
- Manipulation of the software in the clinical trials.
- Analysis of the experimental data discussed in this chapter.
5 Summary, Conclusion, and Future Work

5.1 Summary of Work

Chapter 1 surveyed background information about the main medical applications involved in this dissertation, such as CNB, pediatric bone biopsy, and prostate biopsy. The chapter also reviewed the previous researches in MRI- and ultrasound-guided robotic interventions. In the rest of the chapter, scientific contributions, and significance of the work discussed in this dissertation were summarized.

Chapter 2 presented the work in developing the MRI-guided robotic system for CNB. A novel MRI-compatible robot was developed. The robot is MR Safe according to the ASTM standard [62] and has a parallelogram-based RCM mechanism. In addition to the robot, two software programs for the image guidance and the robot control were developed in C/C++. The image guidance software is capable of performing a marker segmentation, image-robot registration, and targeting simulation. The robot control software includes a special structure designed for safety. The first clinical application of the MRI-guided robotic system was for pediatric bone biopsy. A novel workflow to minimize trauma and eliminate radiation exposure in children with bone cancer and infection was proposed. The feasibility of the robotic system was validated in the mockup and cadaver studies. The second clinical application of the robotic system was for stereotactic brain biopsy. Intraoperative MRI-guided robotic needle insertion tests on a skull mockup showed the feasibility of the robotic approach.

Chapter 3 presented the work in developing the TRUS-guided robotic system for CNB. A concept of the robotic system for TRUS-guided transrectal prostate biopsy was presented. The software for robot control and image navigation was developed. The software enables 3D TRUS imaging, prostate biopsy planning, robot control, and biopsy navigation. In addition to the software, two different robots were developed. The TRUS robot moves the probe with the same 4 DoF that closely replicate the movement by hand. The robot works based on novel algorithms to minimize prostate deformations. Comprehensive validation tests including bench tests, mockup tests, and FDA/IRB approved clinical trials showed the feasibility of the system. The cohesive TRUS probe-robot has only 2-DoF, while it carries out the same task as the TRUS
robot. A novel calibration method for the robot was presented, and the feasibility of the robotic system was confirmed in the mockup tests.

Chapter 4 presented the work in developing the methodology for personalized robotic prostate biopsy. A novel method for prostate segmentation was developed. Based on the segmentation results, a method for the geometrical optimization of the systematic prostate biopsy plan was also developed. The capsule model was employed for maximizing cancer detection probability by evenly distributing the capsules over the prostate gland. Two algorithms to uniformly distribute the capsules over the prostate were presented and evaluated for their functionalities. Algorithms for improving the safety, detection probability, and computation efficiency of the method were also presented. The TRUS-guided robotic prostate biopsy system with integrated methodologies was validated in clinical trials. Last, the feasibility of the MRI-ultrasound fusion based, targeted, robotic prostate biopsy was tested using the patient image data.

5.2 Conclusion

In this dissertation, several image-guided robotic systems for CNB were presented. Integration of the information from medical images and the precise robotic technologies enables reliable biopsy planning and accurate execution of interventional CNB. This dissertation presented several novel robotic systems, uniquely designed algorithms, and important experimental data that may have significant clinical effects.

The MR Safe RCM robot was entirely made of nonconductive, nonmetallic, and nonmagnetic materials. Moreover, to work within the MR scanner, the robot was designed and developed to be compact, stiff, accurate, safe to operate in the MRI, and not to deteriorate the image quality. Together with the robot, the custom-written software enables accurate image-guided robotic targeting. The robotic system can be utilized to be a part of an improved clinical workflow in which pediatric bone biopsy can be performed ideally within the diagnostic MRI scan session. Since the robot enables the bone biopsy to be performed in the MRI scanner, the time needed to schedule a separate biopsy procedure in the operating room or CT scanner is eliminated. Performing the biopsy with MRI guidance would also allow more precise sampling, especially for bone marrow lesions that are best seen with MRI. Furthermore, the use of the MR Safe robot to perform MRI-
guided bone biopsy would eliminate the radiation exposure from CT guidance for both the patient and the physician.

A second and most promising application of the MR Safe robot is for stereotactic brain biopsy with an intraoperative MRI scanner. The system would allow neurosurgeons to formulate surgical plans based on most recent images, utilize continuous imaging for direct feedback, and maintain the operative rhythm by eliminating the common in-out moves of the patient bed into the scanner. Furthermore, the robotic system could be potentially used not only for brain biopsy, but also for numerous neurosurgical procedures that require deep brain access such as DBS, ventriculoperitoneal shunting, and laser ablation of the hippocampus.

The TRUS-guided robotic prostate biopsy system takes transrectal prostate biopsy one step further, with an actuated TRUS probe manipulation robot and custom-written software for robot control and image navigation. Like no other, the system enables minimization of the prostate deformation and accurate biopsy targeting. The proposed system also enables hands-free, skill-independent prostate biopsy. Novel algorithms for minimizing prostate deformations at imaging and biopsy were also developed. By applying the algorithms uniquely designed for the TRUS robot, the movement of the probe is minimized during the biopsy, reducing the prostate deformation and increasing targeting accuracy.

The second TRUS robot, the cohesive TRUS probe-robot, has only 2-DoF. While in the TRUS robot prostate deformations are controlled in software, in the new 2-DoF design these are controlled by design, in a compact and light system.

The personalized robotic prostate biopsy has the potential to increase cancer detection rates of clinically significant PCa at systematic biopsy. Novel methods and algorithms for geometric optimization of the 12-cores biopsy plan were developed and integrated with the robotic prostate biopsy system. The orthogonal-planes based segmentation enables expedited, robust, and functional prostate segmentation for clinical practice. With this method, the prostate can be represented using only 26 nodes. The averaged prostate model generated based on the node points further expedites the segmentation.

The novel algorithms developed for the geometric optimization of the systematic biopsy plan could potentially increase the detection probability of clinically significant PCa and decrease the risk of infection. The algorithms are used to evenly distribute the biopsy plan over the prostate, avoid the urethra, and cover the peripheral zone where the majority of prostate tumors are found (68% [94]). FDA/IRB approved clinical
trials showed that optimizing the systematic biopsy plan for each patient is feasible. The geometric optimization of the 12-cores biopsy plan maximizes the sampling probability of significant PCa. Furthermore, a robotic biopsy approach enables the optimized plan to be executed precisely, with hands-free TRUS guidance that makes the procedure less dependent on the urologist’s skills. Together, these have the potential to increase the CDR of clinically significant PCa with systematic biopsy, independent or in addition to targeted biopsy. To the best of our knowledge, this is the first report of personalized systematic prostate biopsy.

The main contributions of the work discussed in this dissertation are in the development of integrated image-guided robotic systems for interventional CNB. The development includes novel robotic systems, uniquely designed algorithms, novel software, and clinically significant experimental data. While the research was validated for specific clinical applications, the technologies developed extend to other medical fields.

### 5.3 Future Work

While the feasibility of the MR Safe robotic system was verified pre-clinically for bone biopsy, the robotic system could also be used for other procedures such as a probe placement for ablations of bone and soft tissue tumors, or percutaneous screw placement for traumatic bone fractures. Moreover, the robotic system could be potentially used for numerous neurosurgical procedures that require deep brain access such as stereotactic brain biopsy, DBS, ventriculoperitoneal shunting, and laser ablation of the hippocampus. Future researches may address the validation of the robotic system in various medical applications.

Although the accuracy and feasibility tests of the MRI-guided robot showed outstanding results in the mockup and cadaver studies, there were some limitations. These were *in-vitro* and *ex-vivo* experiments. Clinical trials of the MR robot are required to validate the system.

With the TRUS-Robot, validation was taken all the way to clinical trials. *In-vitro* tests and clinical trials showed outstanding accuracy results for robotic prostate biopsy. Further clinical trials are needed to determine the impact of biopsy sampling accuracy on clinical outcomes, in the detection of clinically significant PCa.
Most patients with PCa are undergoing the same extended 12-cores prostate biopsy regardless of their prostate shape [16]. Detection probability of clinically significant PCa would vary for different sizes of the prostate with the same number of the biopsy cores. Patient-specific optimizations on the number of the biopsy cores could increase CDR of clinically significant PCa. Future work may include optimized biopsy schemata with varying numbers of cores.

MRI-ultrasound fusion based, targeted prostate biopsy is a fast-growing current trend in prostate biopsy. Integration of the fusion with the robotic guidance technology could take the current fusion biopsy one step further. Future steps may also combine the optimization of systematic biopsy cores in addition to the targeted cores.
Appendices

A.1 Paden-Kahan subproblems

Subproblem 1. Rotation about a single axis

Problem:

Given a line $L(\vec{\omega}, \vec{r})$, which directs to $\vec{\omega}$, $\|\vec{\omega}\| = 1$ and passes a point $\vec{r} \in \mathbb{R}^3$, and two points $\vec{p}, \vec{q} \in \mathbb{R}^3$, find a rotation angle $\theta$ such that

$$e^{i\theta} \vec{p} = \vec{q}$$  \hspace{1cm} (A.1)

Solution:

As shown in Figure A.1, let $\vec{u}, \vec{v}, \vec{u}', \vec{v}' \in \mathbb{R}^3$ be vectors such that

$$\vec{u} = \vec{p} - \vec{r}$$
$$\vec{v} = \vec{q} - \vec{r}$$
$$\vec{u}' = \vec{u} - (\vec{\omega} \cdot \vec{u})\vec{\omega}$$
$$\vec{v}' = \vec{v} - (\vec{\omega} \cdot \vec{v})\vec{\omega}$$  \hspace{1cm} (A.2)

The problem has a solution only if the projections of $\vec{u}$ and $\vec{v}$ onto the axis $\vec{\omega}$ and the plane perpendicular to the axis $\vec{\omega}$ has the same lengths such that

Figure A.1: Paden-Kahan subproblem1
\[(\vec{\omega} \cdot \vec{u}) = (\vec{\omega} \cdot \vec{v}); \|\vec{u}'\| = \|\vec{v}'\|\]  

(A.3)

Using the cross and dot products between \(\vec{u}'\) and \(\vec{v}'\) such that

\[\vec{u}' \times \vec{v}' = \vec{\omega} \sin\|\vec{u}'\|\|\vec{v}'\|\]  

\[\vec{u}' \cdot \vec{v}' = \cos\|\vec{u}'\|\|\vec{v}'\|\]  

(A.4)

The rotation angle \(\theta\) is determined as

\[\theta = \tan^{-1} \frac{\vec{\omega} \cdot (\vec{u}' \times \vec{v}')}{{\|\vec{u}'\|}{\|\vec{v}'\|}}\]  

(A.5)

**Subproblem 2: Rotation about two subsequent axes**

**Problem:**

Given two lines \(L_1(\vec{\omega}_1, \vec{r})\) and \(L_2(\vec{\omega}_2, \vec{r})\), which pass a same point \(\vec{r} \in \mathbb{R}^3\) and direct to \(\vec{\omega}_1, \vec{\omega}_2, \|\vec{\omega}_1\| = \|\vec{\omega}_2\| = 1\), respectively, and two points \(\vec{p}, \vec{q} \in \mathbb{R}^3\), find rotation angles \(\theta_1, \theta_2\) such that

\[e^{\vec{\omega}_1 \theta_1} e^{\vec{\omega}_2 \theta_2} \vec{p} = \vec{q}\]  

(A.6)

**Solution:**

As shown in Figure A.2, let \(\vec{c}\) be a point such that

\[e^{\vec{\omega}_2 \theta_2} \vec{p} = \vec{c} = e^{-\vec{\omega}_1 \theta_1} \vec{q}\]  

(A.7)

Then, we have similar relations for \(\vec{u} = \vec{p} - \vec{r}, \vec{v} = \vec{q} - \vec{r}, \vec{\ell} = \vec{c} - \vec{r}\) such that

\[e^{\vec{\omega}_2 \theta_2} \vec{u} = \vec{\ell} = e^{-\vec{\omega}_1 \theta_1} \vec{v}\]  

(A.8)
From Eq. (A.3), we have

\[(\vec{\omega}_2 \cdot \vec{u}) = (\vec{\omega}_2 \cdot \vec{r}); (\vec{\omega}_1 \cdot \vec{v}) = (\vec{\omega}_1 \cdot \vec{r})\]  \hspace{1cm} (A.9)

Since \(\vec{\omega}_1, \vec{\omega}_2,\) and \((\vec{\omega}_1 \times \vec{\omega}_2)\) are linearly independent, \(\vec{r}\) can be expressed as

\[\vec{r} = \alpha \vec{\omega}_1 + \beta \vec{\omega}_2 + \gamma(\vec{\omega}_1 \times \vec{\omega}_2)\]  \hspace{1cm} (A.10)

By substituting Eq. (A.10) into (A.9), we have two equations such that

\[\vec{\omega}_1 \cdot \vec{c} = \alpha + \beta(\vec{\omega}_1 \cdot \vec{\omega}_2) = \vec{\omega}_1 \vec{q}\]  \hspace{1cm} (A.11)
\[\vec{\omega}_2 \cdot \vec{c} = \alpha(\vec{\omega}_1 \cdot \vec{\omega}_2) + \beta = \vec{\omega}_2 \vec{p}\]

Solving for \(\alpha\) and \(\beta\) gives

\[\alpha = \frac{(\vec{\omega}_1 \cdot \vec{\omega}_2)(\vec{\omega}_1 \cdot \vec{p}) - (\vec{\omega}_2 \cdot \vec{q})}{(\vec{\omega}_1 \cdot \vec{\omega}_2)^2 - 1}\]  \hspace{1cm} (A.12)
\[
\beta = \frac{\langle \bar{\omega}_1 \cdot \bar{\omega}_2 \rangle \langle \bar{\omega}_1 \cdot \bar{\theta} \rangle - \langle \bar{\omega}_2 \cdot \bar{\theta} \rangle}{(\bar{\omega}_1 \cdot \bar{\omega}_2)^2 - 1}
\]

From Eq. (A.10), we have

\[
\|\vec{t}\|^2 = \alpha^2 + \beta^2 + 2\beta\alpha\langle \bar{\omega}_1 \cdot \bar{\omega}_2 \rangle + \gamma\|ar{\omega}_1 \times \bar{\omega}_2\|^2
\]  
(A.13)

Solving this equation using the fact that \(\|\vec{t}\|^2 = \|\vec{u}\|^2\) gives

\[
\gamma^2 = \frac{\|\vec{u}\|^2 - \alpha^2 - \beta^2 - 2\alpha \beta \langle \bar{\omega}_1 \cdot \bar{\omega}_2 \rangle}{\|ar{\omega}_1 \times \bar{\omega}_2\|^2}
\]  
(A.14)

\(\vec{c}\) can be obtained from \(\alpha, \beta, \gamma, \theta_1\) and \(\theta_2\) are then determined by solving two subproblems such that

\[
\vec{c} = e^{-\bar{\omega}_1 \theta_1} \bar{q}; \quad \vec{c} = e^{\bar{\omega}_2 \theta_2} \bar{p}
\]  
(A.15)
A.2 Gradient descent on SE(3)

A gradient descent technique can be applied on SE(3) as follows.

Step 1: For a given cost function $f(H), H \in SE(3)$ such that $f: SE(3) \to \mathbb{R}$, choose $H_0$.

Step 2: For $i = 0$, compute the differential as

$$
(\tilde{E}_k f)(H_{i-1}) \equiv \left. \frac{d}{dt} f(H_{i-1} \circ \exp(t E_k)) \right|_{t=0} \\
\approx \frac{f(H_{i-1} \circ \exp(e E_k)) - f(H_{i-1})}{ε} 
$$

(A.16)

where elements of SE(3) $E_k, k = 1, ..., 6$ are given as

$$
E_1 = \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & -1 & 0 \\
0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix};
E_2 = \begin{pmatrix}
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 \\
-1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix};
E_3 = \begin{pmatrix}
0 & -1 & 0 & 0 \\
1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix};
E_4 = \begin{pmatrix}
0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix};
E_5 = \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix};
E_6 = \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0
\end{pmatrix}
$$

(A.17)

Step 3: For $i = i + 1$, update $H_i$ as

$$
H_i = H_{i-1} \circ \exp \left( -ε \sum_{k=1}^{6} (\tilde{E}_k f)(H_{i-1}) E_k \right) 
$$

(A.18)

Step 4: Repeat Step2 and Step3 until the cost $f(H_i)$ converges or $i$ is greater than or equal to the maximum number of iterations.
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JOURNAL PAPERS


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Patents

- D. Stoianovici, **S. Lim,** M. Han: “Device and Methods for Transrectal Ultrasound-Guided Prostate Biopsy,” Application No.: 62/774,559, U.S. Patent Pending.
- D. Stoianovici, D. Petrisor, C. Jun, **S. Lim:** “Remote Center of Motion Robot,” Application No.: 16/098,284, U.S. Patent Pending.
- D. Lee, S. Park, **S. Lim,** and S. Lee: “Visualization apparatus for vein,” U.S. Patent Issued (Patent No.: 9522240, Issue Date: 12/20/2016), South Korea Patent Issued (Patent No.:10-1503838-00-00, Issue Data: 03/12/2015).