Image-based Guidance for Prostate Interventions

by

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Abstract

Prostate biopsy is the gold standard for cancer diagnosis. This procedure is guided using a 2D transrectal ultrasound (TRUS) probe. Unfortunately, early stage tumors are not visible in ultrasound and prostate motion/deformations make targeting challenging. This results in a high number of false negatives and patients are often required to repeat the procedure.

Fusion of magnetic resonance images (MRI) into the workspace of a prostate biopsy has the potential to detect tumors invisible in TRUS. This allows the radiologist to better target early stage cancerous lesions. However, due to different body positions and imaging settings, the prostate undergoes motion and deformation between the biopsy coordinate system and the MRI. Furthermore, due to variable probe pressure, the prostate moves and deforms during biopsy as well. This introduces additional targeting errors. A biopsy system that compensates for these sources of error has the potential to improve the targeting accuracy and maintain a 3D record of biopsy locations.

The goal of this thesis is to provide the necessary tools to perform free-hand MR-TRUS fusion for prostate biopsy using a 3D guidance system. To this end, we have developed two novel surface-based registration methods for incorporating the MRI into the biopsy workspace. The proposed methods are the first methods that are robust to missing surface regions for MR-TRUS fusion (up to 30% missing surface points). We have validated these fusion techniques on 19 biopsy, 10 prostatectomy and 11 brachytherapy patients.

In this thesis, we have also developed methods that combine intensity-based information with biomechanical constraints to compensate for prostate motion and deformations during the biopsy. To this end, we have developed a novel 2D-3D registration framework, which was validated on an additional 10 biopsy patients. Our results suggest that accurate 2D-3D registration for freehand biopsy is feasible.

The results presented suggest that accurate registration of MR and TRUS data in the presence of partially missing data is feasible. Moreover, we demonstrate that in the presence of variable probe pressure during freehand biopsy, a combination of intensity-based and biomechanically constrained
Abstract

2D-3D registration can enable accurate alignment of pre-procedure TRUS with 2D real time TRUS images.
Preface

This thesis is primarily based on five publications, resulting from collaboration between multiple researchers. All publications have been modified to make the thesis coherent. Ethics approval for conducting this research has been provided by the Clinical Research Ethics Board, certificate numbers: H11-01789.

The study in Chapter 2 has been accepted for publication in:


The contribution of the author was in developing, implementing and evaluating the method. C. Antonio Sánchez contributed to the implementation, biomechanical modeling and mathematical derivation of the registration method. Yue Sun, Dr. Imani and Amir Khojaste Galesh Khale helped with the data collection. Drs. Romagnoli, Abdi and Chang (clinical collaborators) helped with data collection and fiducial identification to validate the registration method. All co-authors contributed to editing of the manuscript.

The study in Chapter 3 has been published in:


This chapter is the open-source release of the method published in Chapter 2 and entails further validation of our method on 11 brachytherapy patients. Dr. Fedorov developed and implemented one of the two registration
methods used in this manuscript, designed the study and conducted the experiments. The contribution of the author was in providing the second registration method and writing parts of the manuscript and editing. Dr. Tuncali performed the clinical study, collected the data and selected fiducials for quantitative validation of the registration methods. All co-authors contributed to the editing of the manuscript.

The study in Chapter 4 has been accepted for publication in:


The contribution of the author was in developing, implementing and evaluating the method. C. Antonio Sánchez contributed to the implementation and biomechanical modeling. Saman Nouranian collected the brachytherapy dataset in collaboration with Drs. Morris and Spadinger. Dr. Rasoulian provided the code for the construction of the statistical shape model. Drs. Romagnoli, Abdi and Chang (clinical collaborators) helped with data collection and fiducial identification to validate the registration method. All co-authors contributed to the editing of the manuscript.

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<th>Description</th>
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<tbody>
<tr>
<td>2D</td>
<td>2-dimensional</td>
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<tr>
<td>3D</td>
<td>3-dimensional</td>
</tr>
<tr>
<td>AUA</td>
<td>American Urological Association</td>
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<tr>
<td>AUC</td>
<td>Area Under Curve</td>
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<tr>
<td>BPH</td>
<td>Benign Prostatic Hyperplasia</td>
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<tr>
<td>BWH</td>
<td>Brigham and Women’s Hospital</td>
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<tr>
<td>CPD</td>
<td>Coherent Point Drift</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>DCE</td>
<td>Dynamic Contrast Enhanced</td>
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<tr>
<td>DRE</td>
<td>Digital Rectal Exam</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion Weighted Imaging</td>
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<tr>
<td>EM</td>
<td>Expectation Maximization</td>
</tr>
<tr>
<td>ESUR</td>
<td>European Society of Urogenital Radiology</td>
</tr>
<tr>
<td>FE</td>
<td>Finite Element</td>
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<tr>
<td>FEM</td>
<td>FE Model</td>
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<tr>
<td>FLE</td>
<td>Fiducial Localization Error</td>
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<tr>
<td>GMM</td>
<td>Gaussian Mixture Model</td>
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<tr>
<td>Gd</td>
<td>Gadolinium</td>
</tr>
<tr>
<td>GPU</td>
<td>Graphics Processing Unit</td>
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<tr>
<td>HARDI</td>
<td>High Angular Resolution Diffusion Imaging</td>
</tr>
<tr>
<td>ICP</td>
<td>Iterative Closest Point</td>
</tr>
<tr>
<td>ICP-FEM</td>
<td>ICP-based FEM</td>
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<tr>
<td>IGI</td>
<td>Image-Guided Intervention</td>
</tr>
<tr>
<td>ITK</td>
<td>Insight Toolkit</td>
</tr>
<tr>
<td>MD</td>
<td>Mean Diffusivity</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>mp-MR</td>
<td>Multi-Parametric MR</td>
</tr>
<tr>
<td>O2D</td>
<td>Orthogonal 2D</td>
</tr>
<tr>
<td>PCa</td>
<td>Prostate Cancer</td>
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<tr>
<td>Pre-op</td>
<td>Pre-operative</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
</tr>
<tr>
<td>RAS</td>
<td>Right-Anterior-Superior</td>
</tr>
<tr>
<td>RF</td>
<td>Radio Frequency</td>
</tr>
<tr>
<td>SDM</td>
<td>Statistical Deformation Model</td>
</tr>
<tr>
<td>SSM</td>
<td>Statistical Shape Model</td>
</tr>
<tr>
<td>SSD</td>
<td>Sum-of-Squared Differences</td>
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<tr>
<td>TPS</td>
<td>Thin-Plate Spline</td>
</tr>
<tr>
<td>TPS-RPM</td>
<td>TPS Robust Point Matching</td>
</tr>
<tr>
<td>TRE</td>
<td>Target Registration Error</td>
</tr>
<tr>
<td>TRUS</td>
<td>Transrectal Ultrasound</td>
</tr>
<tr>
<td>UA</td>
<td>Urethra at Apex</td>
</tr>
<tr>
<td>UB</td>
<td>Urethra at Base</td>
</tr>
<tr>
<td>UBC</td>
<td>University of British Columbia</td>
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<tr>
<td>US</td>
<td>Ultrasound</td>
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<td>VM</td>
<td>Verumontanum</td>
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Finally, I would like to thank Elmira for our ten days together in Vancouver: “So it was that he saw her whom few mortals had yet seen; Arwen, daughter of Elrond, in whom it was said that the likeness of Lúthien had come on earth again; and she was called Undómiel, for she was the Evenstar of her people.” -The Fellowship of the Ring, J. R. R. Tolkien

*When you have been in the same group for five years, the list tends to become long!
Chapter 1

Introduction

1.1 Anatomy and Histology of the Prostate

![Prostate Anatomy Diagram]

Figure 1.1: Prostate anatomy [65].

The prostate is a walnut-shaped organ that completely surrounds the urethra and is part of the male reproductive system (Figure 1.1). The physiological function of the prostate is the production of seminal fluid, which combines with sperm from the testes. Since seminal fluid is alkaline, it neutralizes the acidity of the vaginal tract, prolonging the lifespan of sperm. The prostate gland is composed of fibromuscular and glandular tissues, and contracts during ejaculation in order to secrete. It is oriented with its base angled posteriorly toward the bladder neck and its apex is angled anteriorly in continuity with the urethra. The prostate is fixed to the pubic bone via puboprostatic ligaments and sits anterior to the rectum. The prostate is composed of three primary regions along the urethra. The superior re-
1.2 Epidemiology of Prostate Cancer

Prostate Cancer (PCa) is the most commonly diagnosed noncutaneous cancer in Canadian men, with 1 in 8 males expected to be diagnosed with PCa in their lifetime. It is the leading cancer for Canadian males with 23,600 (24% of all) new cases expected in 2014 [14]. The risk of developing PCa increases with age: beginning at 8% for men in their 20s until 80% of men in their 70s harbour invasive PCa [69]. From the 40,000 expected cancer deaths in 2014, PCa is the third most common cause of mortality (10%) in males [14]. Despite its prevalence, over the past 40 years, early detection has decreased mortality rates for PCa patients without substantial changes in surgical or radiation treatment strategies [66, 128]. When PCa is diagnosed at an early and localized stage, it can be managed with hormone therapy, radiation treatment or surgical resection, to improve the patient’s survival and quality of life. [115].

Figure 1.2: Prostate zones: peripheral, central and transitional [65].
1.3 PCa Screening

1.3.1 Digital Rectal Examination
In a digital rectal examination (DRE), the urologist checks for growths, enlargements or suspicious hard areas by palpating the prostate through the rectum. Since 80-85% of all cancers arise in the peripheral zone [96], which is adjacent to the rectum, about 18% of patients with PCa can be diagnosed using a DRE [152]. Due to its lack of sensitivity to early stage cancer, the American Urological Association (AUA) does not recommend DREs for first-line screening [24]. However, this test can be used in conjunction with other diagnostic tools when screening for PCa [24].

1.3.2 Prostate Specific Antigen
The prostate specific antigen (PSA) is a protein produced by the prostate gland which can be used as a biological marker for tumors. While the antigen is present in small quantities in the serum of men with healthy prostates, elevated levels often indicate the presence of PCa. However, while PSA screening is sensitive to PCa, it lacks specificity. Only a quarter of men with high PSA actually have PCa [5]. Some men have naturally elevated PSA levels and the antigen also raises in presence of clinically insignificant tumors and benign prostatic hyperplasia (BPH) [123]. As a result, urologists evaluate PSA levels with caution to confirm or reject the cancer hypothesis.

1.4 PCa Imaging

1.4.1 X-Ray and Computed Tomography
X-ray and computed tomography (CT) have no diagnostic value in PCa, as separation from surrounding muscle is poor and the anatomy interior to the prostate is not well defined. The primary role of CT is in the detection of metastases and to plan radiation-based therapies in patients with confirmed PCa [76].

1.4.2 Magnetic Resonance
Magnetic resonance (MR) imaging provides excellent soft tissue contrast. It has shown promise as a local staging modality for identifying and localizing

\[^1\text{Benign prostate growth}\]
1.4. PCa Imaging

Potential PCa lesions within the prostate \cite{78,99,145}. Due to low contrast, the basic T1-weighted pulse sequence has limited use for PCa imaging. T2-weighted images, however, can clearly differentiate prostate zonal anatomy \cite{15}. In these images, healthy tissue in the peripheral zone appears bright, whereas cancerous regions appear as dark regions. The shortcoming of T2-weighted imaging is that signal patterns of BPH and prostatitis\footnote{Infection of the prostate} mimic malignancies in the transitional and peripheral zones, respectively \cite{93}. Due to these factors, PCa detection using T2-weighted images alone is challenging. T2-weighted MR is often used in conjunction with other MR modalities to improve detection rates \cite{50,120,150}.

Diffusion weighted imaging (DWI) is a functional imaging technique used to map and characterize the three-dimensional diffusion of water as a tensor of spatial location. It is typically formulated as a 2nd order tensor which describes the magnitude, anisotropy and orientation of fluid movement. While this formulation is the first and most popular, its shortcomings are known in regions that contain fiber-crossings. High angular resolution diffusion imaging (HARDI) techniques overcome this limitation using new reconstruction techniques based on Q-ball \cite{148} and higher order tensors \cite{106}.

Regardless of the reconstruction method used in DWI, this imaging technique is commonly used to calculate the mean diffusivity (MD), which characterizes the average random motion of hydrogen nuclei within the prostate. Healthy tissue typically exhibit a high MD, which indicates that the fluid flow is primarily in a single direction. PCa, however, tends to destroy glandular structures, which allows for unconstrained, omni-directional fluid movement. As a result, PCa appears darker compared to surrounding healthy tissue \cite{80}. However, since BPH and prostatitis also exhibit lower MD values, DWI is best in combination with other MR modalities \cite{77}.

Dynamic contrast enhanced (DCE) imaging measures blood flow through the acquisition of serial T1-weighted images before, during, and after the administration of a Gadolinium (Gd) contrast agent. Since PCa tumors are vascular, the presence of asymmetrical contrast uptake followed by a rapid wash-out is indicative of cancer \cite{44}.

The combination of T2-weighted images with functional imaging techniques is promising for high sensitivity and specificity of PCa staging. The collective information provided by multiple MR techniques is known as multi-parametric MR (mpMR). The recent European Society of Urogenital Radiology (ESUR) report \cite{4} recommends the use of T2-weighted and at least two functional acquisitions for screening patients suspicious of PCa. How-
ever, the reported results of mpMR for sensitivity and specificity vary widely across the literature, with area under curve (AUC) values ranging between 0.66-0.90 for different combinations of T2, DCE and DWI \[46, 75, 151\]. As a result, as of yet, mpMR cannot be used for the definitive diagnosis of PCa. However, it can be used to identify suspicious cancerous lesions to be targeted during a biopsy session (see Section 1.5).

1.4.3 Ultrasound Examination of the Prostate

Since the prostate is anterior to the rectum, it can be imaged using a transrectal ultrasound (TRUS) probe through the rectal wall. There are three main types of TRUS probes used in the clinic: 1) end-firing; 2) side-firing; and 3) 3D probes. End-firing and side-firing probes are commonly used in clinics for live guidance in the diagnosis and treatment of PCa. 3D probes come with enhanced functionality: they can simultaneously acquire both axial and sagittal imaging planes. They can also generate a full 3D volume using a motorized angular sweep, however, 3D-TRUS image formation is lengthier compared to 2D-TRUS. As a result, the frame rate of these probes typically lower compared to their 2D counterparts.

PCa in the peripheral zone is typically considered to appear darker compared to medium-echogenity in TRUS \[137\]. In the transitional zone, PCa does not show a specific echo pattern in appearance. Unfortunately, PCa detection is challenging using TRUS alone. TRUS-based screening has been reported with low sensitivity (35-91%) and specificity (24-81%) values for PCa detection \[34, 53, 83, 104, 127\].

1.5 PCa Diagnosis

Histopathological analysis of tissue samples, harvested using biopsy, is considered the gold standard for PCa diagnosis. The biopsy is an out-patient procedure, performed using an end-firing 2D-TRUS probe to manually image the prostate and guide the biopsy needle through the rectal wall (Figure 1.3). The current sextant protocol entails sampling of the prostate, by collecting eight to 12 cores depending on its volume and more cores at suspicious regions. The biopsy is done systematically, i.e. the cores are taken from predefined anatomical zones and are not tailored to the patient’s anatomy. Unfortunately, it is estimated that the current biopsy regimen suffers from a high (30%) false-negative rate \[107\]. Using more samples may increase cancer yield; however, there is a clinical trade-off between number of cores,
1.5. PCa Diagnosis

Figure 1.3: TRUS-guided prostate biopsy [76].

The low sensitivity of prostate biopsy is mainly due to the isoechogenic nature of small tumors. It is estimated that 40-70% of PCa tumors are invisible in TRUS, and therefore may not be sampled during the biopsy session [121]. Furthermore, 2D-TRUS images do not provide a clear spatial context of the probe with respect to the prostate, and as a result, its interpretation requires a certain level of expertise for accurate needle placement. In addition, the prostate moves and deforms during the procedure, which requires the radiologist to mentally adjust for tracking errors during systematic sampling. The cumulative effect of occult tumors and targeting errors contributes to the high number of false negatives for prostate biopsies.

When there is strong suspicion of cancer, patients with elevated PSA levels and a negative biopsy are frequently required to repeat the procedure. However, since the initial procedure was performed under 2D guidance, only a coarse record of previous biopsy locations is available for the re-biopsy. In the absence of 3D information, the radiologist is unable to maximize the cancer yield by avoiding areas that have been shown cancer-free and to re-biopsy regions prone to develop invasive cancer.

Information from prior biopsy procedures or from other 3D imaging modalities, such as MR, could be used to target suspicious areas directly. This information is best presented to the radiologist in terms of a 3D-biopsy system that enables the radiologist to plan and record biopsy locations in 3D.
Such an approach aims to combine image-specific information for improved guidance within the same systematic biopsy regimen.

## 1.6 3D Prostate Biopsy Systems

### 1.6.1 In-bore MR

In-bore systems allow the interventional radiologist to acquire MR images directly during the biopsy procedure. The architecture of the MR imaging system is either closed \([35, 79, 142]\) or open bore \([27, 31, 54]\). There is a trade-off between the strength of the magnetic field and the interventional work space for closed vs. open bore systems. Closed bore systems produce higher quality images due to the stronger magnetic field for biopsy guidance, however, the interventional workspace is much more confined. Open bore systems, provide a larger dexterous workspace compared to closed bore systems at the expense of lower quality images.

The clinical workflow for in-bore biopsy systems entails acquiring a diagnostic MR image. The image is used to identify and delineate suspicious regions to be targeted during the biopsy. These potential targets are mapped to the interventional space by registering the diagnostic MR to a 3D MR image, acquired just before the start of the procedure. Throughout the biopsy, intra-procedure MR slices are used to ensure correct needle placement.

A comparative study of in-bore systems has shown an overall improvement of 88% vs. 55% over systematic TRUS-guided biopsy \([52]\). However, in-bore systems are unlikely to replace TRUS-based biopsy. Several key disadvantages make an in-bore approach infeasible as the standard-of-care for PCa diagnosis. Since MR image formation is lengthy, the biopsy takes longer compared to the conventional TRUS-based procedure. As a result, patients are often sedated using general anesthesia to avoid involuntary motion due to discomfort. Considering the annual number of prostate biopsies, lengthy procedures and longer patient recovery time impose a huge cost burden on the healthcare system. Furthermore, using MR for image guidance requires new equipment, renovating biopsy rooms and retraining which makes integration difficult for most clinics.

### 1.6.2 MR-TRUS Fusion

A more prudent approach to allow integration of MR in the procedure room involves the registration of the diagnostic MR to real-time TRUS images, thus exploiting the advantages of each modality. Typically the clinical work-
1.6. 3D Prostate Biopsy Systems

Table 1.1: Commercial 3D-TRUS biopsy systems.

<table>
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The flow of MR-TRUS fusion systems involves the following steps. First, a diagnostic MR is acquired prior to the biopsy session. The radiologist studies the MR image to identify potential targets for biopsy. Just prior to the start of the procedure, a 3D-TRUS image is acquired to define the systematic sextant interventional space \([6, 7, 158]\). Targets from the MR image are mapped to this 3D-TRUS image using multi-modality intensity-based \([141]\) or surface-based registration \([25, 90]\). This registration needs to account for the change of coordinates between the MR and TRUS acquisitions and deformations induced due to probe pressure and endorectal coils. During the procedure, tracked 2D-TRUS images are used for real-time guidance with respect to the reference 3D-TRUS.

1.6.3 Commercial 3D-Biopsy Systems

Over the years, several solutions have been developed for MR-TRUS fusion in 3D-guided prostate biopsies. Table 1.1 is a short list of the commercially available transrectal systems and contains the probe type, tracking scheme, image acquisition, fusion technique and registration used to compensate for prostate motion and deformations during the procedure. I have excluded the Biopsee system (Pi Medical, Greece) from this list as they follow a transperineal approach, which is only used by 2% of urologists in North America \([130]\).

3D-TRUS Generation

Uronav and Artemis systems are designed to retrofit the same 2D-TRUS probe used in the conventional biopsy. In the Uronav system, a base-to-
1.6. 3D Prostate Biopsy Systems

Figure 1.4: Sagittal view of the 3D reconstructed volume following inconsistent (a) and consistent (b) probe pressure during a freehand sweep of a prostate biopsy patient.

Apex axial sweep of the prostate is acquired just before the start of the procedure [158]. The magnetically tracked 2D-TRUS images are then used to reconstruct a 3D-TRUS volume. The main disadvantage of this method of 3D-TRUS generation is the inconsistent probe pressure during the sweep. Since the prostate is an elastic organ and the probe is hand-held, the radiologist may not exert uniform probe pressure as he/she sweeps the prostate. As a result, reconstructed 3D-TRUS volumes frequently suffer from deformation artifacts which introduce additional errors in 3D guidance. Figure 1.4a is an extreme case of inconsistent probe pressure during a freehand sweep, while in Figure 1.4b the radiologist was instructed to maintain uniform probe pressure on the same patient. In practice, the quality of 3D-TRUS images will depend on the dexterity of the radiologist, tracking errors and involuntary patient motion due to discomfort.

3D-TRUS acquisition in the Artemis system is performed using a rotational sweep of the 2D-TRUS probe around its axis [7]. Since the probe is mechanically stabilized using a robotic arm, the prostate is less likely to deform during 3D-TRUS generation. The main drawback of the Artemis system is that their solution requires an additional mechanical arm, which is not part of the standard clinical hardware. As a result, their solution does not allow for freehand guidance as part of the current standard-of-care.

The Koelis system supports direct 3D acquisition using a special 3D probe. Since the average prostate is larger than the probe beam-width, three
3D volumes are typically acquired and fused together to create a panoramic volume [6]. This 3D generation method requires only three contact points and as a result, the radiologist needs to only hold his/her hand steady for a limited time. This means that deformation artifacts are less likely to appear in the panoramic 3D-TRUS.

**Fusion Scheme**

Once the 3D-TRUS volume is generated, the radiologist needs to bring the MR image into the workspace of the 3D-TRUS. However, the MR is typically collected weeks in advance, and usually in a different body position (supine vs. lateral). As a result, the fusion technique needs to account for a change of coordinates. Furthermore, MR images are frequently acquired in the presence of an endorectal coil, which causes the appearance of prostate to change due to biomechanical pressure. Finally, the 3D-TRUS is generated using an endocavity probe, which also causes the prostate to change in appearance. Fusion systems account for these effects through multi-modality rigid and deformable registration.

The fusion technique in the Uronav system is based on manual alignment of the MR and 3D-TRUS [158]. The main disadvantage of this approach, as with all manual registration techniques, is user-variability. Furthermore, since the registration transform is rigid, they do not account for prostate deformations between MR and 3D-TRUS acquisitions.

In the Artemis system, fusion is performed using a surface-based approach. Assuming that the MR has already been segmented, they perform a quick segmentation of the 3D-TRUS using a semi-automatic dynamic contour propagation approach [81]. The MR and 3D-TRUS surfaces are first aligned using a manual landmark-based approach. In order to account for deformations, they use a thin-plate spline (TPS) surface-based registration approach [12]. In addition to drawback of user-variability due to semi-automatic segmentation and manual alignment, fusion accuracy has been reported to decrease following TPS registration [25]. This result suggests that their method does not accurately account for prostate deformations between MR and 3D-TRUS acquisitions.

The Koelis system follows a surface-based approach for fusion as well. In this system, the MR and TRUS volumes are segmented using a statistical model constructed from previously segmented prostate MR images. They compensate for rigid change of coordinates and also prostate shape deformations using an elastic registration approach. However, they only provide surface errors for fusion accuracy [90]. It is unclear how accurate this method
1.6. 3D Prostate Biopsy Systems

can map potential targets inside the prostate from the MR into TRUS. They provide no values for the run-time of the registration algorithm.

One of the main shortcomings of current surface-based fusion techniques [25, 90, 154] is that these methods do not account for inaccuracies in segmentation. Manual prostate segmentation is notoriously difficult, and there is often large variability even among experts [138]. One approach to mitigate this is to use an intensity-based approach [141], thereby avoiding the need for segmentation entirely. However, this would still require a significant amount of correspondence in appearance between MR and 3D-TRUS images. This may be challenging in cases where the local appearance of the anatomy is different between the two modalities. For example, the boundary of the seminal vesicle is clearly visible in MR but not in TRUS.

Intra-procedure Registration

Once biopsy planning is completed in 3D-TRUS space, tracking the motion of the probe can be used to map the current 2D plane to the pre-procedure 3D-TRUS. The Uronav system uses magnetic sensors to track the probe [158], while the Artemis system records the 3D position and orientation of the transducer tip via the joint encoders of the mechanical arm [7]. The Koelis system does not require an additional tracker, it uses image information to track the prostate [6].

The prostate undergoes constant motion and deformation due to probe pressure during biopsy, which introduces additional errors into the tracking environment. As a result, rigid and deformable registration is required to maintain alignment of the 2D imaging plane with respect to the pre-procedure 3D-TRUS. The Uronav system accounts for the gross motion of the prostate using multi-slice intensity-based rigid registration [158]. However, Uronav does not compensate for prostate deformations even though the probe is hand held. As a result, when the prostate deformation is large, the radiologist may miss potential targets that were identified during the planning phase. Furthermore, the targeting accuracy in this system is only reported on phantom data [158].

In the Artemis system, motion compensation is performed using an intensity-based slice-to-volume registration scheme [136]. Since the probe is mechanically stabilized, the prostate is less likely to undergo deformations due to probe pressure and a rigid registration suffices. As a result, the prostate can be approximated as a rigid organ, and even its motion can be learned based on probe positions/orientations [134]. However, it has been shown that the accuracy of their system degrades with probe pressure [136]. This indicates
1.7 Required Targeting Accuracy for Prostate Biopsy Systems

that for freehand biopsies, which typically induce a larger probe pressure, rigid registration may not be sufficient to compensate for intra-procedure prostate motion/deformation. While the targeting accuracy of the Artemis system with motion correction is within clinical requirements, mechanical systems are not used in clinics. A solution for freehand 3D-guidance using 2D-TRUS probes, as part of the current standard-of-care, is highly desirable.

The Koelis system does not use any method to track ultrasound probe motion; therefore, it relies only on the image-based registration for tracking. The live 3D-TRUS volume is registered in three steps. First a global three degree-of-freedom (DOF) rigid registration, constrained using a manually delineated bounding ellipsoid that approximates the prostate shape, is performed. This registration ensures that the probe tip is in contact with the rectal wall. Then, the rigid registration is fine-tuned using a local 6-DOF rigid registration. These two steps account for the gross motion of the prostate. Finally, an elastic registration is performed to account for prostate deformations [6].

The drawback of the Koelis system is that 3D information is only available when the probe is used in 3D mode. With a long volume acquisition time of up to 5 seconds (depending on the image quality) and a total registration time of up to 10 seconds [6], this system cannot be used for live 3D guidance throughout the procedure. However, the registration time is still sufficiently low to provide feedback for targeting and to record the 3D location of biopsy cores.

1.7 Required Targeting Accuracy for Prostate Biopsy Systems

In order to avoid over-diagnosis and over-treatment, only PCa tumors larger than 0.5 cm$^3$ are considered clinically significant [36, 111]. This translates into a spherical tumor with a radius of 5 mm. If the target registration error (TRE) of the 3D biopsy system is below 2.5 mm, it can be shown that 95.4% of smallest PCa tumors can be targeted using this system [71]. Throughout this thesis, we shall use this bound as the clinical requirement for a 3D biopsy system.

1.8 Objective

The objective of this thesis is to facilitate integration of MR data in 3D freehand prostate biopsy systems to decrease the number of false negatives.
1.9 Contributions

Maintaining the freehand workflow and imaging tools of the current 2D-TRUS procedure, are the primary guidelines when designing such a system. To this end, we investigate and develop registration techniques that can bring MR data into the prostate biopsy framework. We also provide registration solutions to compensate for prostate motion and deformations during the procedure.

1.9 Contributions

This thesis is an attempt to develop techniques that are essential for MR-TRUS guided freehand 3D prostate biopsies. In the course of achieving this objective, the following contributions were made:

- Developing a novel technique for registration of two surfaces that accounts for missing points in the target surface. This is an essential step for MR-TRUS fusion in prostate biopsies, since it allows the fusion algorithm to ignore regions in the 3D-TRUS where the prostate contour has poor visibility. We denote this method as full-to-partial surface registration. We validate the method using data obtained from prostate biopsy and radical prostatectomy patients.

- Validation of full-to-partial surface registration on data obtained from prostate brachytherapy patients. The former and latter contributions suggest that the fusion method is invariant with respect to the prostate intervention and patient cohort used for validation.

- Developing a novel technique for registration of two surfaces that accounts for missing points in both MR and 3D-TRUS surfaces. This is an improvement on our full-to-partial fusion scheme, since it does not require either MR or 3D-TRUS surfaces to be fully segmented. We denote this method as partial-to-partial surface registration.

- Developing a novel 2D-3D registration technique for intra-procedure guidance during freehand prostate biopsies. This is a fundamental requirement for accurate needle placement with respect to planned targets from MR-TRUS fusion or sextant protocols.

1.10 Thesis Outline

The rest of this thesis is subdivided into five chapters as outlined below:
CHAPTER 2: BIOMECHANICALLY CONSTRAINED SURFACE REGISTRATION

In surface-based registration for image-guided interventions, the presence of missing data can be a significant issue. This often arises with real-time imaging modalities such as ultrasound, where poor contrast can make tissue boundaries difficult to distinguish from surrounding tissue. Missing data poses two challenges: ambiguity in establishing correspondences; and extrapolation of the deformation field to those missing regions. To address these, we present a novel non-rigid registration method. For establishing correspondences, we use a probabilistic framework based on a Gaussian mixture model (GMM) that treats one surface as a potentially partial observation. To extrapolate and constrain the deformation field, we incorporate biomechanical prior knowledge in the form of a finite element model (FEM). We validate the algorithm, referred to as GMM-FEM, in the context of prostate interventions. Our method leads to a significant reduction in TRE compared to similar state-of-the-art registration algorithms, with a mean TRE $\approx 2.6\text{ mm}$. We also analyze robustness of our approach, showing that GMM-FEM is a practical and reliable solution for surface-based registration.

CHAPTER 3: OPEN-SOURCE IMAGE REGISTRATION FOR MRI-TRUS FUSION

The goal of this chapter is to provide an independent validation of the GMM-FEM registration approach that was described in Chapter 2. Furthermore, this chapter is the validation of the GMM-FEM registration against a distance-based metric regularized by a B-spline transform. Our ultimate goal is to develop an open-source solution to support MRI-TRUS fusion image guidance of prostate interventions, such as targeted biopsy for prostate cancer detection and focal therapy. It is widely hypothesized that image registration is an essential component in such systems. The two non-rigid registration methods are: 1) a deformable registration of the prostate segmentation distance maps with B-spline regularization, and 2) a finite-element-based deformable registration of the segmentation surfaces in presence of partial data. We evaluate the methods retrospectively using clinical patient image data collected during standard clinical procedures. Computation time and TRE calculated at the expert-identified anatomical landmarks were used as quantitative measures for the evaluation. The presented image registration tools were capable of completing deformable registration computation within 5 minutes. Average TRE was approximately 3 mm for both methods, which
is comparable with the slice thickness in our MRI data. Both tools are available under non-restrictive open-source license. We release open-source tools that may be used for registration during MRI-TRUS guided prostate interventions. Our tools implement novel registration approaches and produce acceptable registration results. We believe these tools will lower the barriers in development and deployment of interventional research solutions, and facilitate comparison with similar tools.

CHAPTER 4: STATISTICAL BIOMECHANICAL SURFACE REGISTRATION

A common issue that arises when performing surface-based registration of images is whether or not the surfaces accurately represent the boundary of the region of interest. Image segmentation may be difficult in some regions due to either poor contrast, low slice resolution, or ambiguities. To address these concerns, we present a novel non-rigid surface registration method designed to register two partial surfaces, capable of ignoring regions where the anatomical boundary is unclear. Our approach incorporates prior geometric information in the form of a statistical shape model (SSM), as well as physical knowledge in the form of a finite element model, in a probabilistic framework. We validate results in the context of prostate interventions by registering pre-operative magnetic resonance imaging to 3D TRUS, both acquired from patients undergoing prostate biopsies. We show that both the geometric and physical priors are required in order to decrease the net TRE. Our registration approach leads to a TRE of 2.35 mm and 2.81 mm for full and partial surfaces, respectively. We investigate the robustness of the technique by varying the tunable parameters, and by removing sections from the segmented prostate surface in areas where the prostate boundary is typically difficult to discern. Results demonstrate that the proposed surface registration method is an efficient, robust, and effective technique for fusing data from multiple modalities, particularly when dealing with missing or ambiguous data.

CHAPTER 5: 2D-3D REGISTRATION FOR FREEHAND PROSTATE BIOPIES

We present a 2D to 3D registration framework to compensate for prostate motion and deformations during freehand prostate biopsies. The framework has two major components: 1) to compensate for the gross motions of the prostate, we use the trajectory of a tracked ultrasound probe to limit the
solution to the location of the live imaging plane with respect to the pre-
procedure 3D ultrasound volume; 2) to compensate for residual deformations,
we developed a non-rigid registration method that is constrained using a fi-
nite element model of the prostate and the surrounding tissue. We validate
the proposed framework on 10 prostate biopsy patients and demonstrate a
mean TRE of 4.63 mm and 3.15 mm for rigid and FEM-based components,
respectively.

CHAPTER 6: CONCLUSION AND FUTURE WORK

This chapter includes a short summary followed by a discussion of the in-
tegration of the registration algorithms into the clinical workflow. It also
includes suggestions for future work.
Chapter 2

Biomechanically Constrained Surface Registration

2.1 Introduction

The goal of an image-guided intervention (IGI) is to localize and track the position of a surgical tool with respect to a plan during the procedure. Surgical planning often requires pre-operative (pre-op) images, captured by either CT or MRI. For practicality, a different modality is often used during the procedure, typically ultrasound. One of the drawbacks of ultrasound, however, is its poor image contrast. This can lead to difficulties in distinguishing tissue boundaries of the organ of interest. A second complication in IGIs involving soft-tissue is that the tissue is flexible. Pre-operative images are usually acquired weeks in advance, and in a different body position. Thus, there can be large changes in shape and position of the anatomy between acquisitions. Most navigational assistance systems account for these changes through a combination of rigid and non-rigid image registration. However, efficient and accurate multi-modality registration is challenging, and intensity-based methods such as [58, 141, 157] still require a significant amount of correspondence in appearance between the images. These methods may fail if the local appearance differs significantly between the two modalities. For example, the seminal vesicle boundary is clearly visible in MRI but not in TRUS.

To avoid the issue of image dissemblance between modalities, we can instead rely on clinical expertise. Both the pre-operative and intra-operative images can be segmented during the clinical workflow and used in a surface-based method. However, segmentation of anatomical boundaries can also be difficult in a number of applications, including prostate interventions, where there is a high variability even among experts [138]. Part of the boundary of the anatomy may not even be visible in one or both of the
images, for example the support region during liver resection \[16, 125\], or the base and apex regions of the prostate during biopsies \[95\]. Therefore, a method that is robust to this variability, or that can handle missing data in regions where there is no clear anatomical boundary, would be highly valuable. Addressing this is the major goal of this chapter. We propose a general solution to the problem of registering two volumes when: a) the anatomy of interest undergoes mainly biomechanical deformations; and b) there is a lack of visibility in some regions of the tissue of interest. We apply our method in the context of prostate interventions through MR-TRUS fusion. In regions where the tissue boundary is not clear, we ignore the segmentation, treating these as areas where data is missing.

2.1.1 Surface-based Registration

The original surface-based registration techniques relied on manual landmark selection \[26\]. This is a tedious, time-consuming process and is subject to user variability. To automatically identify corresponding pairs of markers, a number of methods have been proposed that rely on the iterative closest point (ICP) algorithm \[9, 165\] and its variations \[9, 124, 125, 165\]. Unfortunately, ICP-based algorithms are very sensitive to initialization, noise, and outliers \[48, 92, 98, 116, 156\]. One approach to mitigate this is to map the two surfaces into a topologically equivalent space \[61, 95, 161\]. This was attempted by Moradi et al. \[95\] for MR-TRUS fusion. Its accuracy was found to still be highly sensitive to contiguous regions of missing data, such as around the apex where the prostate contour has poor visibility \[95\]. To overcome the limitations of ICP due to binary correspondences, some approaches compute probabilistic (soft) correspondences using a Gaussian-mixture model \[21, 48, 67, 92, 98, 116, 156\] or use a particle filtering approach \[101\]. These methods convert the registration into a probability-density estimation problem, maximizing the likelihood that one set of points is drawn from a probability distribution governed by the other set of points. This approach also directly accounts for having partial observations, since there is no requirement to sample any particular coverage of points.

Due to the large space of possible solutions allowed by non-rigid deformations, many algorithms require constraints on the deformation field to converge. One method of constraining deformations is with a statistical deformation model (SDM). An SDM describes the allowable set of transformations based on statistics derived from an initial population. Parameters of the transform are restricted to a linear combination of those that are present during training \[60, 94\]. The drawback of SDMs is that they re-
2.1. Introduction

quire an additional training step, and registration results are highly dependent on the quality of the training data. To generate a diverse training set, Hu et al. [60] use finite element simulations. Applied to MR-TRUS fusion for prostate interventions, they require a detailed segmentation of not only the prostate, but also the bladder and pelvic bone to create a personalized model. Subsequently, they use this model to generate an SDM to be used in a model-to-image registration framework.

Another class of constraints are in the form of regularizers, where prior knowledge is incorporated as a penalty term in a minimization problem. This approach has been followed by many to limit surface bending of a model [17, 21, 62, 71, 98, 126, 163, 166]. In the coherent point drift (CPD) algorithm [98], for example, nearby points are constrained to move “coherently” as a group by introducing a penalty on high spatial frequencies. The coherence term, however, can only penalize local variations in the deformation field; it does not consider volumetric properties such as Poisson effects or incompressibility. Other regularizers have been introduced to constrain volumetric deformation within a closed surface. These are typically based on splines, radial basis functions, or finite element (FE) techniques [16, 42, 95, 102, 103, 125, 144]. The choice of regularizer is especially important for deformable organs: in addition to guiding the minimization search, it directly governs the deformation field inside the anatomy, particularly in regions where data is missing. In many applications, the interior region is the workspace during an IGI. One drawback of surface-based regularizers is that the deformation field away from the surface is not considered during the course of registration. Instead, internal deformation is recovered via post-processing in an interpolation step.

In this chapter, we use a finite element model for regularization, since the nature of deformations is known to be mainly biomechanical during many prostate interventions, including biopsies, low-dose brachytherapy and prostatectomies. Such a model is applicable as long there is no substantial loss of mass between the two images. Deformation of the prostate is driven by pressure from surrounding organs, the pubic bone, and the TRUS probe or endorectal MR coil acting through the rectal wall. To the best of our knowledge, most existing FE-based registration techniques use explicit surface forces applied to the model to drive the deformation [16, 42, 95, 103, 125]. With the exception of [102, 144], the common thread in FE-based methods is to estimate boundary forces in a local neighborhood. These forces are typically formulated in a way that corresponding points are brought closer to each other. Correspondences are usually found based on a proximity search. This search is typically done using a variation of ICP [32, 95, 125], making it
susceptible to the drawbacks of local-search techniques. For a more detailed description of the correspondence problem, the reader is referred to a recent survey paper [149]. It is possible to use a region-based metric [102, 144] for the data-driven term to avoid the correspondence problem, however, this would require a suitable connected geometry on the target surface. This might be difficult to achieve when the target surface exhibits missing surface points. Rather than applying explicit forces based on ICP, or using a region-based approach, we combine the correspondence search and force calculation into a single framework using a global probabilistic approach. Forces arise implicitly during the minimization, and the single objective function allows for an efficient implementation.

2.1.2 Contributions

The major contribution of this work is the development of the novel registration method, GMM-FEM, that combines the ability to handle missing data using a soft-correspondence approach (GMM), with a biomechanical regularizer supplied by a FEM. We validate our registration approach on MR-TRUS images acquired from two sets of patients: one group who underwent a prostatectomy, and the other a prostate biopsy.

We compare our registration approach to three other similar surface-based methods: thin-plate spline robust point matching (TPS-RPM) [21], CPD [98], and ICP-based FEM (ICP-FEM) [42]. TPS-RPM and CPD are two popular registration methods that use soft-correspondences based on a GMM. The major difference is that TPS-RPM constrains surface deformations using thin-plate-splines, whereas CPD uses Gaussian kernels. By comparing to TPS-RPM and CPD, we isolate and evaluate the need for the FEM component of our method, since both methods use an identical correspondence scheme. ICP-FEM is a surface registration method which uses ICP to estimate surface-correspondences, then applies elastic forces on the surface of an FEM to drive the deformation. This is the point-cloud equivalent to Ferrant et al. [42]. By comparing to ICP-FEM, we isolate the GMM component of our method, since both methods use an identical FEM regularizer. This isolates the need for soft correspondences when dealing with missing data.

2.2 Method

An outline of our proposed GMM-FEM registration approach is shown in Figure 2.1. The inputs are two surfaces, referred to as the source (MR) and
2.2. Method

Figure 2.1: Overview of the registration framework. The pre-operative MR is captured before the procedure, and is segmented to create a surface representation of the anatomy (in this case, the prostate). This surface is then used to create an FE model of the volume. At the beginning of the procedure, an intra-operative (3D-TRUS) image is acquired and visible parts of the anatomy (midgland) are segmented. The GMM-FEM registration maps targets from the surface in the pre-operative plan to that of the intra-operative space.

target (TRUS). We model the surface-to-surface registration as an expectation-maximization (EM) problem. One surface is used to construct a probability density function that defines the boundary of the structure. The other surface is considered a set of observations, which may be incomplete (a partial observation). We wish to find the deformation field that maximizes the likelihood that the observations are drawn from a transformed probability distribution.

To define the probability distribution representing the complete source surface, we use a Gaussian-mixture model. These are widely used to establish soft correspondences [67, 98, 119]. A GMM is a parametric probability density function represented as a weighted sum of Gaussian densities. Vertices of the source surface are taken to be the centroids of Gaussian components, each represented by a mean and a variance. For simplicity, we take the variance to be isotropic in all directions for all components. This implies that the corresponding target point for a given Gaussian centroid is equally likely to appear in all directions. This assumption might not be correct in general, however, the method can be extended to use anisotropic GMMs [59] (also see Section 2.4). In this work, the source surface is extracted from the MRI, since the segmentation in this space is assumed to be reliable, and the target
2.2. Method

The target surface (i.e. observations) is extracted from the TRUS.

| Table 2.1: Mathematical notations |
|----------------|-------------------------------------------------|
| \(N, M, J\)   | Number of observations, GMM centroids and FEM nodes |
| \(x_n\)       | n-th point of observations                        |
| \(y_m\)       | m-th GMM centroids                                |
| \(\vec{x}_{3N\times1}\) | Vector of observations                           |
| \(\vec{y}_{3M\times1}\) | Vector of GMM centroids                          |
| \(\vec{u}_{3J\times1}\) | Vector of FEM node displacements                |
| \(\Phi_{3M\times3J}\) | FEM interpolation matrix                         |
| \(K\)         | Stiffness matrix                                  |
| \(E\)         | Young’s modulus                                   |
| \(\nu\)       | Poisson’s ratio                                   |
| \(P_{M\times N}\) | GMM posterior probabilities                      |
| \(\sigma^2\)  | Variance of Gaussian components                   |
| \(0\leq w<1\) | Estimate of noise/outliers                        |
| \(\text{diag}(\vec{v})\) | Diagonal matrix of a vector \(\vec{v}\)       |
| \(\tilde{P} = \text{kron}(P, I_{3\times3})\) | Kronecker product of matrices \(P\) and \(I\) |
| 1              | Column vector of all ones                         |

2.2.1 GMM-FEM Registration

In the derivations that follow, we use the notations listed in Table 2.1. For non-rigid registration, the Gaussian centres of the GMM \(\{y_m\}\) move with displacements \(\{v_m\}\). We then wish to maximize the likelihood that the target surface (partial observation) is drawn from this deformed probability distribution by minimizing the negative log-likelihood function:

\[
E(\theta, \sigma^2) = -\sum_{n=1}^{N} \log \sum_{m=1}^{M} P(y_m + v_m)P(x_n|y_m + v_m),
\]

where \(\theta\) is a set of parameters controlling the deformation, \(P(\cdot)\) denotes the GMM probability density function with variance \(\sigma^2\) \([98]\), \(P(\cdot|y_m + v_m)\) is a Gaussian distribution centered at \((y_m + v_m)\), and \(v_m\) represents the non-rigid displacement of the \(m\)-th point on the source surface. Similar to \([98]\), we model mis-assignments due to noise and outliers as a uniform distribution.
2.2. Method

added to the mixture model:

\[ P(x) = \frac{w}{N} + (1 - w) \sum_{i=1}^{M} \frac{1}{M} P(x|y_m + v_m). \]  \hfill (2.2)

This uniform spatial distribution accounts for points present in the observations that do not correspond well to any point on the source. The parameter \( w \) indicates the probability of an observed point being classified as an outlier. A uniform distribution is selected to prevent biasing the classification of outliers to any region of space.

The deformation field still needs to be constrained. We use a finite element model, so the parameters of the deformation are the FEM node displacements, \( u_j \), where \( j \in \{1, \ldots, J\} \) is the node index. Displacements can be concatenated into a vector \( \vec{u} = [u_{11}, u_{12}, u_{13}, \ldots, u_{J1}, u_{J2}, u_{J3}]^T \). Motion is constrained by adding a penalty term to the log-likelihood function, leading to the following objective function to be minimized:

\[ Q(\vec{u}, \sigma^2) = -\sum_{n=1}^{N} \log \sum_{m=1}^{M} P(y_m + v_m)P(x_n|y_m + v_m) + \beta \frac{1}{2} \vec{u}^T K \vec{u}. \]  \hfill (2.3)

The penalty term represents the volumetric strain energy of the FEM, scaled by a Tikhonov weight \( \beta \). This is derived from a linear stress-strain relationship, with linear stiffness matrix \( K \) \cite{11}. \( K \) is a large sparse matrix that can be systematically constructed based on the FEM mesh and a linear material model. The volumetric mesh is generated from the source surface, segmented from MR. This can be done with most FE-meshing tools, such as TetGen \cite{131}. To compute the stiffness matrix, we additionally need a constitutive material law. For linear materials, \( K \) is dependent on two parameters: Young’s modulus, \( E \), and Poisson’s ratio, \( \nu \). These are inputs to the registration.

Note that other GMM-based registration methods use a similar formulation for adding spatial regularization \cite{49, 162}. While their formulation is similar in notation, they do not use a biomechanical regularizer to constrain the deformation field inside the surface. The method by Habert et al. \cite{49} is identical to CPD registration in the use of Gaussian regularizers. The method by Zetting et al. \cite{162} is similar to TPS-RPM since it uses a TPS kernel to regularize the deformation field.

Since Equation 2.1 only involves displacements on the surface of the model, we need to relate surface locations to FEM node displacements with
2.2. Method

In our implementation, all points on the surface correspond to nodes, and internal nodes are appended to the end of the node list for the FEM. As a result, the interpolation matrix has the form, $\Phi = \begin{bmatrix} I_{3M \times 3M} & 0 \\ 0 & 0 \end{bmatrix}$. If surface points do not correspond to nodes, $\Phi$ can be derived directly from the shape functions of the FEM elements.

The unknowns, $\sigma^2$ and $\bar{u}$, are computed using an EM algorithm. Initially, the variance is estimated from the data as in Myronenko and Song [98]:

$$\sigma^2 = \frac{1}{3NM} \sum_{n=1}^{N} \sum_{m=1}^{M} \|x_n - y_m\|^2. \quad (2.5)$$

In the expectation step, we compute how likely an observation corresponds to a GMM centroid by calculating the posterior probability

$$P(y_m + v_m|x_n) = \frac{\exp\left(-\frac{1}{2\sigma^2}\|x_n - y_m - v_m\|^2\right)}{\sum_{j=1}^{M} \exp\left(-\frac{1}{2\sigma^2}\|x_n - y_j - v_j\|^2\right) + c}, \quad (2.6)$$

where $c = (2\pi\sigma^2)^{3/2} \frac{w}{1-w} \frac{M}{N}$ is the contribution related to outliers. The weight $0 \leq w < 1$ is set to zero if observations do not exhibit outliers, or up to one if there is little correspondence between observations and GMM centroids.

Ignoring constants independent of $\bar{u}$ and $\sigma^2$, we can rewrite the maximization step of Equation (2.3) as

$$Q(\bar{u}, \sigma^2) = \frac{1}{2\sigma^2} \sum_{m,n=1}^{M,N} P(y_m + v_m|x_n) \|x_n - y_m - v_m\|^2$$

$$+ \frac{3N_P}{2} \log(\sigma^2) + \frac{\beta}{2} \bar{u}^T K \bar{u}, \quad (2.7)$$

where $N_P = \sum_{m,n=1}^{M,N} P(y_m + v_m|x_n)$. Following [98], we evaluate $P(\cdot|x_n)$ based on the previously computed displacements. This allows us to separate the expectation and maximization steps in the EM algorithm. The new optimal FEM node displacements are then obtained by minimizing Equation (2.7) with respect to the vector $\bar{u}$. This yields the following sparse linear system:

$$\left[ \Phi^T \text{diag}(\tilde{P}1) \Phi + \beta \sigma^2 K \right] \bar{u} = \Phi^T \tilde{P} \bar{x} - \Phi^T \text{diag}(\tilde{P}1) \bar{y},$$

$$\quad (2.8)$$
2.2. Method

where $\bar{x}$ and $\bar{y}$ are the concatenated vectors of all observations and GMM centroids, respectively. The correspondence probability matrix $P$ is constructed by evaluating Equation (2.6) using the previous FEM node displacements. A tilde represents taking the Kronecker product, $\tilde{P} = \text{kron}(P, I_{3\times3})$, so that the matrix can be multiplied by a concatenated vector of positions. Now that we have an updated estimate of FE nodal displacements (and hence locations), we update the GMM probability distribution. The algorithm iterates between the expectation step (updating $\sigma^2$ and $\tilde{P}$) and maximization step (updating $\bar{u}$) until the variance drops below a threshold. The updated variance at each iteration is

$$
\sigma^2 = \frac{1}{3N_f} \sum_{m,n=1}^{M,N} \|x_n - (y_m + \Phi_m \bar{u})\|^2
$$

(2.9)

The subscripted $\Phi_m$ refers to only the rows of $\Phi$ that correspond to surface point $m$. The correspondence probabilities, $P$, can then be updated using the new FEM displacements $\bar{u}$ and variance $\sigma^2$.

For the biomechanical material properties, we apply a homogeneous, linearly elastic material with a constant Young’s modulus to all elements. For the prostate, we use a Young’s modulus of $E = 5$ kPa and Poisson’s ratio of $\nu = 0.49$, which are in the range of values in [72]. For other applications, material parameters should be chosen appropriately. Note that for linear materials, it can be shown that the Young’s Modulus can be factored out of the stiffness matrix, allowing it to be combined with the Tikhonov weight $\beta$. This combined parameter controls the flexibility of the model, and can be tuned to allow an appropriate level of deformation for the application. It can also be viewed as tuning the magnitude of the “implicit forces” that arise when updating the displacement field in Equation (2.8). These forces are driven by proximity between the soft-correspondences; they do not represent physical forces in the system. Reducing $\beta$ is equivalent to increasing the force of attraction between the two surfaces.

In total, there are three free parameters: $w$, which controls the fraction of outliers in the observation surface; $\nu$, the Poisson ratio of the material; and $\beta$, controlling model flexibility. For relatively smooth and reliable observations, we find that $w = 0.1$ works well in rejecting few outliers and avoiding local minima. The Poisson’s ratio should be near but not equal to 0.5 for most soft-tissues, $\nu = 0.49$ being a stable option. The final parameter, $\beta$, is tunable to fit the application. It is up to the user to decide how much force is reasonable given the context, subject to the trade-off between surface-fitting and volume-restoring regularization. We find that a value of $\beta = 0.1$
allows sufficient flexibility without over-fitting the surfaces in the context of prostate motion. If this results in an unrealistic amount of deformation, $\beta$ should be increased.

### 2.2.2 Related Registration Methods Used for Comparison

In this section, we provide a brief description of the three registration methods used as a basis for comparison. These were selected since they are the most relevant works in the field, and they allow us to isolate the importance of the two major components of our objective function. For further details on the methods, the reader is referred to [21, 42, 98].

**TPS-RPM**

This method uses a similar EM algorithm for the registration. Deterministic annealing is used in the expectation step, decreasing both a temperature, $T$, and regularization weights, $\{\lambda_1, \lambda_2\}$. The temperature in their framework corresponds to the variance of GMM centroids in ours. The weights $\lambda_1$ and $\lambda_2$ control the contributions of affine and non-rigid components, respectively, in their objective function. Its implementation is freely available[^3]. By comparing to TPS-RPM, we isolate and evaluate the contribution of the FEM component of our method, since both use a similar soft-correspondence scheme. The two methods also handle outliers and missing data differently. In TPS-RPM, outliers and source points which have no corresponding target are assigned to a separate cluster placed at the centre of mass. In GMM-FEM outliers in the observation are handled with a uniform distribution, and missing data is handled naturally by the probabilistic approach: correspondences are computed one-way, there is no requirement that every GMM centroid has a corresponding observation. The output of the algorithm is a set of surface displacements. To recover a volumetric deformation field, we use the TPS kernel to propagate the deformation field inside the prostate, as described in [132].

**CPD**

This is the closest work to the proposed GMM-FEM. The major difference is the choice of regularizer, which results in a different maximization rule. CPD has three free parameters: $w$ is an estimate of noise and outliers, $\beta$ controls smoothness, and $\lambda$ surface-to-surface fitting. By comparing to

[^3]: [http://noodle.med.yale.edu/~chui/tps-rpm.html](http://noodle.med.yale.edu/~chui/tps-rpm.html)
CPD, we isolate and evaluate the FEM component of our method, since both use an identical soft-correspondence scheme, as well as an identical approach to handling outliers and missing data. We use the open-source implementation[4] Just as with TPS-RPM, the output of the registration is a set of surface displacements. To recover the volumetric deformation field, we used the TPS kernel to propagate surface deformations inside the prostate [132].

ICP-FEM

The FE-based registration approach by Ferrant et al. [42] uses image-driven forces to deform the surface of the source object to that of the target. The system evolves by discretizing in time and using the semi-implicit update scheme:

\[(I + \tau K)u^t = u^{t-1} - \tau F^t,\]  

(2.10)

where \(\tau\) is the time step, \(F^t\) is the current estimate of surface forces, \(u^{t-1}\) are the previous nodal displacements and \(u^t\) is the next estimate of nodal displacements. Image forces are determined by a local search, driving the surface nodes of the FE-model to the nearest feature in the image. In our surface-based registration, instead of using image forces, we use ICP to estimate the nearest features in the segmentation. By comparing to ICP-FEM, we isolate the GMM component of our method, since both methods use an identical FEM regularizer.

2.3 Experiments and Results

In this section, we evaluate the proposed non-rigid registration method on MR-TRUS image pairs acquired from patients who underwent a prostate intervention. In Section 2.3.1 we discuss the data acquisition, segmentation protocol and the initialization of the registration. In Section 2.3.2, we validate our registration method using intrinsic fiducials found in the interior of the prostate on full and partial surfaces, and compare to TPS-RPM, CPD, and ICP-FEM. In Sections 2.3.3 and 2.3.4, we investigate the sensitivity of our approach to variations in the free-parameters \((\beta, \nu)\), and to the resolution of source and target surfaces.

The prostatectomy and biopsy data were segmented at two different institutes, using 3D Slicer [38] and Stradwin [147], respectively. We then used TetGen [131] to automatically create a tetrahedral volumetric mesh of the
prostate based on the MR segmentations. The models used in this study are composed of ($\approx 2000$) surface nodes and $\approx 7500$ elements. Throughout our experiments, we used a stopping condition of $\sigma^2 \leq 1e^{-4}$ mm$^2$, Young’s modulus of $E = 5$ kPa, which is in the range of values reported in [72] for the prostate, and a Poisson’s ratio of $\nu = 0.49$.

![Figure 2.2: Prostatectomy data collection protocol.](image)

(a) *In vivo* TRUS  
(b) *Ex vivo* prostate  
(c) *Ex vivo* MRI  
(d) Initial alignment

Figure 2.2: Prostatectomy data collection protocol. Prior to the prostatectomy, a volumetric US is acquired using a side-firing probe (a). Following the prostatectomy, strand-shaped fiducials are attached to the prostate to mark anatomical coordinates of the prostate in the MR. These strands are highlighted with a green circle on the prostate (b) and are visible in the *ex vivo* MRI (c). Both MR and TRUS images are segmented and brought to an initial alignment at the beginning of the registration (d).

### 2.3.1 Data

**Prostatectomy**

We acquired MR and TRUS volumes of ten patients scheduled for a prostatectomy. This data consists of *in vitro* MRI and *in vivo* TRUS. The advantage of the prostatectomy data is that we have access to a strong ground truth for *in vitro* MRI segmentation. This also helps in guiding the *in vivo* TRUS segmentation. The major steps in the data acquisition and alignment protocol
2.3. Experiments and Results

Figure 2.3: An axial slice of the T2-weighted MRI (a). An axial slice 3D-TRUS volume (b).

are outlined in Figure 2.2. The TRUS volumes were collected with an Ultrasonix Touch machine (Ultrasonix, BC, Canada) using a BPL-95/55 side firing transducer mounted on a motorized cradle. Parasagittal 2D-TRUS images were acquired at 5° intervals, beginning with a sagittal view that marks the anterior-superior plane. These slices are used to reconstruct a 3D-TRUS volume with an axial and lateral spacings of 0.12 mm, expressed in patient-centered right-anterior-superior (RAS) coordinates. Following the prostatectomy, the prostate was fixated in a 10% buffered formalin solution for preservation and MR-visible strand-shaped fiducial markers were applied to the specimen using the protocol by Gibson et al. [47]. These strand fiducials are used to mark RAS coordinates on the specimen, so that registration can be initialized with a consistent orientation. Specimens were scanned using a Discovery MR750 scanner (GE Healthcare, Waukesha, USA) at 3T, with an endorectal coil (Prostate eCoil, Medrad, Warrendale, USA) to acquire T1-weighted MR images with a 0.3 mm slice thickness.

Prostate Biopsy

The second set of data was acquired from 19 patients, each scheduled for a prostate biopsy. We acquired T2-weighted MR images from 19 patients using a 3 Tesla GE Excite HD MRI system (Milwaukee, WI, USA) with a spacing of 0.27 × 0.27 × 2.2 mm. TRUS images were acquired using a 3D-TRUS mechanical biopsy system [7] with a Philips HDI-5000 US machine and a C9-5 transducer using an axial rotation of the biopsy probe. For these
images, the rotational sweep began with an axial view of the prostate midgland, thereby defining the right-anterior plane. An example slice of both MR and TRUS is provided in Figure 2.3. These were then reconstructed into a 3D-volume with a spacing of $0.19 \times 0.19 \times 0.19$ mm. Similar to the prostatectomy data, both sets of images were acquired in a patient-centered coordinate system.

**Full and Partial Segmentation**

Both prostatectomy and biopsy MR and TRUS volumes were manually and fully segmented under the supervision of an expert clinician. For MR prostatectomy, the surgical margins and strand fiducials were not included in the segmentation. We refer to the complete segmentations as *full* surfaces. In regions where the prostate boundary was not fully visible in TRUS (e.g., near the base and apex), segmentations were completed based on prior knowledge of the full prostate shape, and by exploiting symmetries. These regions were labeled as “uncertain”, since they are not based on observed data. We then created *partial* surfaces by removing any uncertain portions from the segmentation. What remained represented the midgland, consisting of approximately 70% of the original surface. This is where segmentations are most reliable and consistent between clinicians. No points were removed from the segmented MR, since these segmentations are assumed reliable.

**2.3.2 Registration to Full and Partial Surfaces**

To initialize registration, we first oriented the MR and TRUS surfaces based on the consistent RAS coordinates. We then applied a centre-of-mass alignment, followed by a global registration to compensate for large differences in position and orientation. The global registration did not exhibit sensitivity to initialization in a range of $[-10.0, +10.0]$ mm/degrees for a 100 trials. For the prostatectomy data, we opted for an affine registration to compensate for the bulk volume loss due to the ex vivo nature of the data. The residual deformation is then assumed to be mainly biomechanically driven. For the prostate biopsy data, we used a rigid transform for the initial alignment.

**Prostatectomy**

We applied GMM-FEM, as well as the methods for comparison (TPS-RPM, CPD, and ICP-FEM), to all prostatectomy MR-TRUS pairs. We then repeated registration using the partial TRUS surfaces to see the impact of
2.3. Experiments and Results

Figure 2.4: An example of registration to full data. Registration results on prostatectomy data following surface based registration between the MR (blue) and TRUS (red) for: Rigid (a), TPS-RPM (b), CPD (c), ICP-FEM (d) and GMM-FEM (e). The estimate for missing data, \( w \), was fixed at zero for all three non-rigid methods.
2.3. Experiments and Results

(a) TRUS  (b) GMM-FEM  (c) Magnitude of the deformation field (mm)  (d) Comparison of (a) and (b)

Figure 2.5: Typical results for a prostatectomy data. The axial slice of TRUS (a) and the corresponding GMM-FEM (b) registration results. The deformation map of the non-rigid registration and the corresponding TRUS slice (dashed line) are also shown in (c). The checkerboard of (a) and (b) is shown for comparison.

ignoring uncertain regions in the segmentation. An example registration result for full TRUS surfaces is shown in Figure 2.4. For the three comparison methods, we tuned the parameters such that the best TRE was achieved. For TPS-RPM, the initial temperature was set to $T_0 = 10\, \text{mm}^2$ and the stopping condition was $T \leq 0.2\, \text{mm}^2$. For CPD, we used $\beta = 3.5$ and $\lambda = 0.1$. For ICP-FEM, we set a time step of $\tau = 0.1$, Poisson’s ratio of $\nu = 0.49$, and Young’s modulus of $E = 0.1\, \text{kPa}$. Note that this Young’s modulus is significantly lower than the value of $E = 5\, \text{kPa}$ reported in literature. The discrepancy relates to a scaling of the surface-to-surface forces, which is the role $\beta$ plays in GMM-FEM (Section 2.2.1). To visualize the result of our GMM-FEM registration in the interior of the prostate, we resampled the MR image into the space of the TRUS. The registration result in an axial slice is shown in Figure 2.5. As seen in Figure 2.5d, the boundary of the prostate matches that of the TRUS. The magnitude of the deformation field along the slice plane is shown in Figure 2.5c. Note that the majority of the correction is made near the boundary of the prostate, which is where the surface-based forces are applied.

Prostate Biopsy

To further validate our registration results, we applied the algorithms to the biopsy data described in Section 2.3.1. A typical registration result for a full-to-partial surface registration is shown in Figure 2.6. The registered images and deformation field on an axial slice are shown in Figure 2.7. Again, we
2.3. Experiments and Results

(a) Rigid

(b) TPS-RPM with $T_0 = 50$ and $\lambda_1/\lambda_2 = 1e-5$

(c) CPD with $\beta = 3.5$ and $\lambda = 0.1$

(d) ICP-FEM with $\tau = 0.1$, $E = 0.1 \text{ kPa}$ and $\nu = 0.49$

(e) GMM-FEM with $w = 0.1$, $E = 5.0 \text{ kPa}$, $\nu = 0.49$ and $\beta = 0.05$

Figure 2.6: An example of registration to missing data. Prostate biopsy results following surface based registration between the MR (blue) and TRUS (red) for: Rigid (a), TPS-RPM (b), CPD (c), ICP-FEM (d) and GMM-FEM (e).

find most of the deformation near the surface.

Quantitative Validation

To quantify the registration results, we used the Dice similarity coefficient and the TRE. Using the Dice similarity metric, we ensure that the surface-based method has converged. Furthermore, a volumetric measure such as Dice allows us to investigate volume preservation property of the registration algorithm given the Poisson’s ratio of $\nu \approx 0.5$. This property may not be easily captured using other surface-based distance measures, such as the Hausdorff distance. The TRE is used to validate the registration approach for targeting.

The Dice coefficient between two surfaces, $A$ and $B$ is defined as:

$$\text{Dice}(A, B) = \frac{2|A \cap B|}{|A| + |B|}.$$  

The Dice coefficient for the datasets in this study is
2.3. Experiments and Results

(a) TRUS  (b) GMM-FEM  (c) Magnitude of the deformation field (mm)  (d) Comparison of (a) and (b)

Figure 2.7: Typical results for a prostate biopsy data. The axial slice of TRUS (a) and the corresponding GMM-FEM (b) registration results. The deformation map of the non-rigid registration and the corresponding TRUS slice (dashed line) are also shown in (c). The checkerboard of (a) and (b) is shown for comparison.

shown in Table 2.2. Note that the Dice values are quite high (≈ 0.95), which is to be expected since we are directly optimizing for best surface fit. The one-sample Kolmogorov-Smirnov test did not reject the null hypothesis that the Dice values belonged to a normal distribution at the 95% significance level (0.21 ≤ p ≤ 0.42). Using paired t-tests, we did not observe statistically significant differences between Dice values from different surface-based registration techniques, however, the FEM-based methods (ICP-FEM and GMM-FEM) did exhibit a slightly smaller volume change (2.5 ± 0.52 vs. 3.1 ± 0.86) compared to kernel-based methods (TPS-RPM and CPD) as a result of registration. This is expected, since the FE mesh in our approach is assume to be nearly incompressible (ν = 0.49).

Note that we could have used the Dice coefficient, or any other region-based metric, to drive the registration. However, as stated in Section 2.1, this would require a suitable connected geometry on the target surface. This might be difficult to achieve for our current problem for which the target surface may exhibit missing surface points. An advantage of the proposed correspondence-based metric is that it avoids this issue entirely.

To quantify the TRE, we selected a set of intrinsic fiducials on the MR and TRUS images. For our ten prostatectomy cases, we marked up to five calcification pairs (a total of 30) in both modalities per patient. These landmarks were validated by a radiologist. While these numbers might not be adequate to validate TRE across the prostate, we were limited by landmarks that could be accurately and reliably identified by our clinical expert. For the biopsy data, we also selected up to five fiducials per patient consisting of
cysts and benign prostatic hyperplasia. This yielded a total of 93 landmarks across all subjects, distributed approximately 64.5% in the mid-gland, 21.5% in the base and 14% in the apex. An example of corresponding fiducial pairs in MR and TRUS is shown in Figure 2.8. The $L_2$ distance between corresponding fiducials was used to quantify the TRE. We did not attempt to measure the fiducial localization error (FLE). The biopsy data used in this chapter was collected as part of a separate study [71, 141], where an FLE of 0.21 mm was reported for TRUS, and 0.18 mm for MR. Given that we use the same dataset, but the landmarks are selected using a different clinician, we expect the FLE to be in the same range.

The mean and standard deviation of the TRE, and $p$-value comparisons are shown in Table 2.3. For both prostatectomy and biopsy data, the proposed GMM-FEM registration approach was found to consistently outperform TPS-RPM, CPD and ICP-FEM. Furthermore, the two FEM-based methods (ICP-FEM, GMM-FEM) led to lower TREs compared to the kernel-based ones (TPS-RPM, CPD), suggesting that there is an advantage to incorporating physical priors in the form of a finite element model.

Compared to MIND [140], the proposed GMM-FEM registration approach produces a higher TRE for full surfaces (2.72 ± 1.15 vs. 1.93 ± 0.73). Given that we do not have access to the landmarks used to validate the MIND-based approach, we are unable to draw a direct comparison. However, the lower TRE reported in their study suggests that an intensity-based approach is more suitable if similar intensity patterns are visible in both images.

Figure 2.8: Examples of fiducial pairs in MR (left column) and TRUS (right column) for prostatectomy (top row) and biopsy (bottom row) data.
2.3. Experiments and Results

Table 2.2: The Dice coefficient for prostatectomy and biopsy data following affine/rigid and non-rigid registration. For both full and partial registration, the full TRUS surface was used in the calculation of Dice.

<table>
<thead>
<tr>
<th>Method</th>
<th>Prostatectomy</th>
<th></th>
<th>Biopsy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
<td>Partial</td>
<td>Full</td>
<td>Partial</td>
</tr>
<tr>
<td>Affine</td>
<td>89.10 ± 4.45</td>
<td>88.32 ± 4.76</td>
<td>88.56 ± 5.23</td>
<td>87.01 ± 6.12</td>
</tr>
<tr>
<td>TPS-RPM</td>
<td>97.31 ± 1.23</td>
<td>96.12 ± 1.76</td>
<td>97.42 ± 1.78</td>
<td>96.28 ± 1.86</td>
</tr>
<tr>
<td>CPD</td>
<td>97.68 ± 1.48</td>
<td>96.17 ± 1.55</td>
<td>97.73 ± 1.58</td>
<td>96.78 ± 1.97</td>
</tr>
<tr>
<td>ICP-FEM</td>
<td>97.15 ± 0.88</td>
<td>96.22 ± 1.10</td>
<td>97.86 ± 0.98</td>
<td>96.23 ± 1.22</td>
</tr>
<tr>
<td>GMM-FEM</td>
<td>97.16 ± 0.92</td>
<td>96.46 ± 1.26</td>
<td>97.72 ± 1.15</td>
<td>96.91 ± 1.33</td>
</tr>
</tbody>
</table>

We found that TPS-RPM often fails to produce realistic deformation fields when dealing with partial surfaces. In Figure 2.6), we see that the two ends of the prostate are flattened after registration, where there is data missing. This leads to a large increase in TRE, since the deformation field is then interpolated inside the volume. In TPS-RPM, points in the source which cannot be matched to the target are assigned to an outlier cluster at the centre of mass. We believe this is the cause of the unrealistic inward pull. In [21], the authors acknowledge that their handling of outliers is not optimal. In ICP, points without a match can be filtered out based on proximity. The probabilistic approach in CPD and GMM-FEM eliminates the need for special handling of missing data.

To investigate statistical significance of results compared to the initial global registration (rigid/affine), we first determined whether the TRE was normally distributed. Using a one-sample Kolmogorov-Smirnov test, the TREs were found not to be normally distributed at the 95% significance level. As a result, we performed a set of Wilcoxon signed-rank tests, with the null hypothesis that the TREs of initialization versus subsequent non-rigid registration share a common median at the 95% significance level. In
2.3. Experiments and Results

Table 2.3: TRE (mm) for prostatectomy and biopsy data following affine/rigid and non-rigid registration. The star (*) denotes statistical significance at the 95% confidence interval compared to affine/rigid registration.

<table>
<thead>
<tr>
<th>Method</th>
<th>Prostatectomy</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
<td>Partial</td>
</tr>
<tr>
<td>Affine</td>
<td>3.17 ± 1.38</td>
<td>4.15 ± 1.23</td>
</tr>
<tr>
<td>TPS-RPM</td>
<td>4.19 ± 1.76*</td>
<td>5.26 ± 1.49*</td>
</tr>
<tr>
<td>CPD</td>
<td>4.02 ± 1.12*</td>
<td>4.76 ± 1.07</td>
</tr>
<tr>
<td>ICP-FEM</td>
<td>3.00 ± 1.39*</td>
<td>3.89 ± 1.24</td>
</tr>
<tr>
<td>GMM-FEM</td>
<td>2.65 ± 1.29*</td>
<td>2.89 ± 1.44*</td>
</tr>
</tbody>
</table>

Table 2.3 results for which this hypothesis was rejected (and hence are statistically significant) are indicated with a star (*), each resulting in \( p < 10^{-4} \). Note that in some cases, TPS-RPM and CPD led to an increase in TRE compared to initialization. The increase in TRE for TPS kernels has been previously reported in the literature [25].

To investigate the statistical significance of the proposed algorithm over TPS-RPM, CPD and ICP-FEM, we performed additional Wilcoxon signed-rank tests (Table 2.4). Results show that GMM-FEM does lead to statistically significant improvements in TRE over CPD, TPS-RPM, and ICP-FEM when applied to partial surface observations \( (p \leq 10^{-6}) \), as well as over CPD and TPS-RPM when applied to full surfaces \( (p \leq 10^{-6}) \). When comparing to ICP-FEM for fully segmented TRUS surfaces, however, although the TRE is reduced, the signed-rank test fails to reject the null hypothesis. Hence, the improvement is not statistically significant if full segmentations of both MR and TRUS are available.

Finally, to investigate the statistical significance of registration using full versus partial segmentations, we performed four additional sets of Wilcoxon signed-rank tests. Results of are shown in Table 2.5. For TPS-RPM, CPD
2.3. Experiments and Results

Table 2.4: \( P \)-values from Wilcoxon signed-rank between different registration methods.

<table>
<thead>
<tr>
<th>Test</th>
<th>Prostatectomy</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
<td>Partial</td>
</tr>
<tr>
<td>GMM-FEM vs. TPS-RPM</td>
<td>( 10^{-9} )</td>
<td>( 10^{-12} )</td>
</tr>
<tr>
<td>GMM-FEM vs. CPD</td>
<td>( 10^{-9} )</td>
<td>( 10^{-9} )</td>
</tr>
<tr>
<td>GMM-FEM vs. ICP-FEM</td>
<td>0.45</td>
<td>10^{-6}</td>
</tr>
</tbody>
</table>

Table 2.5: \( P \)-values from Wilcoxon signed-rank between different registration methods for full vs. partial data.

<table>
<thead>
<tr>
<th>Method</th>
<th>Prostatectomy</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPS-RPM</td>
<td>( 10^{-9} )</td>
<td>( 10^{-8} )</td>
</tr>
<tr>
<td>CPD</td>
<td>( 10^{-7} )</td>
<td>( 10^{-7} )</td>
</tr>
<tr>
<td>ICP-FEM</td>
<td>( 10^{-6} )</td>
<td>( 10^{-3} )</td>
</tr>
<tr>
<td>GMM-FEM</td>
<td>0.28</td>
<td>0.42</td>
</tr>
</tbody>
</table>

and ICP-FEM, the increase in the TRE is significant, suggesting that these methods are not suitable when the TRUS is only partially segmented. However, for GMM-FEM, the test fails to reject the hypothesis. This implies that, for our method, a full segmentation of the prostate is not necessary: a partial surface (with up to 30% missing points) registration leads to a comparable TRE. This can help speed-up the segmentation process, which must take place during the clinical procedure.

2.3.3 Sensitivity to Biomechanical Parameters

The final deformation field in GMM-FEM is affected by the values of the two FEM material parameters (Young’s modulus and Poisson’s ratio), and by the regularization weight. Since it can be shown that \( E \) can be factored out of the stiffness matrix, there are only two free parameters controlling deformation: 1) the product of the regularization weight and elasticity, \( \beta E \); and 2) Poisson’s ratio, \( \nu \). To investigate the sensitivity of our registration method to these parameters, we perturbed the values for one of our prostatectomy patients and examined the resulting deformation fields. We refer to the \( L_2 \) distance between fields produced by perturbed parameters versus optimal as robustness, shown in Figure 2.9.

As seen in Figure 2.9a, the result of GMM-FEM registration can be some-
2.3. Experiments and Results

(a) Regularization weight.  (b) Poisson’s ratio.

(c) Left to right: Spatial distribution of robustness when regularization weight is changed to 0.05, 0.5 and 1.0, respectively.
(d) Left to right: Spatial distribution of robustness when Poisson’s ratio is changed to 0.40, 0.45 and 0.48, respectively.

Figure 2.9: Robustness of GMM-FEM registration for different regularization weights (a) and Poisson’s ratios (b). Biomechanical parameters are perturbed around parameters which provided the best surface overlap ($E = 5.0$ kPa, $\nu = 0.49$ and $\beta = 0.1$). For better visualization, distances larger than 5 mm are shown with the same color.
what sensitive to the regularization weight, $\beta$. Varying the value by orders of magnitude leads to three distinct behaviors. For large values (e.g. $\beta \geq 1.0$), the FEM acts essentially rigid, allowing no deformation. For small weights (e.g. $\beta \leq 0.01$), the FEM provides little regularization, allowing the surface to move freely. For moderate values (e.g. $\beta \approx 0.1$), the level of deformation varies, balancing resistance to internal strain with the surface-to-surface fitting. This parameter, $\beta$, should be tuned for the application, taking into consideration the level of deformation expected given the context.

Figure 2.9b shows the sensitivity of the internal deformation field to Poisson’s ratio. The registration is much less sensitive to perturbations in this parameter compared to the regularization weight. A value of $\nu = 0.49$ leads to the nearly-incompressible behavior of soft-tissues while avoiding the singularity at 0.5.

2.3.4 Sensitivity to Number of Surface Points

The number of points on the segmented surface may affect both the robustness of the correspondence scheme, and the fidelity of the finite-element model. To establish a ground truth deformation field, we performed the registration with 10,000 surface nodes in both MR and TRUS surfaces. Next, we systematically decimated both surfaces down to 1,200 points and computed the resulting internal deformation fields following registration. We found that GMM-FEM is not sensitive to the number of surface points up a to minimum resolution: differences in the TRE and internal deformations stay below 1.0 mm when the surface resolution drops from 10,000 to 1,800 points (Figure 2.10). This seems to be an appropriate lower bound on surface resolution. If the surfaces are further decimated to 1,200 points, we begin to see artifacts. At this level, we find that the surface no longer well-approximates the original shape.

The number of surface nodes on the source surface, and the resolution of the FEM are intimately related. Theoretically, a higher resolution FEM would result in a more accurate representation of the deformation field up to a point of convergence. However, errors due to lack of convergence given the current FEM resolution are expected to be much lower than errors caused by inaccuracies in segmentation and in the estimated soft correspondences. Thus, the resolution of the FEM should be chosen such that it is able to produce an adequate deformation field for the particular application. We consider the current resolution of our prostate surfaces to be a lower limit for this. For computational efficiency, the number of surface points (and hence FEM nodes) should be chosen to be the minimum such that the nature of
2.3. Experiments and Results

(a) TRE across all prostatectomy patients for different surface resolutions.

(b) Left to right: Spatial distribution of robustness for one sample prostatectomy patient when number of surface points are reduced to 1200, 1800 and 8600 points, respectively.

Figure 2.10: Robustness of GMM-FEM registration for different surface resolutions. Biomechanical parameters are tuned for best TRE ($E = 5.0 \text{ kPa}$, $\nu = 0.49$ and $\beta = 0.1$).
2.4. Discussion and Conclusions

Table 2.6: Time (seconds) required for each component of GMM-FEM registration reported across all patients.

<table>
<thead>
<tr>
<th>Component</th>
<th>Time (±)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FE-meshing</td>
<td>0.64 ± 0.22</td>
</tr>
<tr>
<td>Stiffness Matrix</td>
<td>1.03 ± 0.27</td>
</tr>
<tr>
<td>Average Iteration</td>
<td>0.15 ± 0.01</td>
</tr>
<tr>
<td>Total Time</td>
<td>9.34 ± 3.63</td>
</tr>
</tbody>
</table>

the surface is sufficiently captured and the deformation field is sufficiently smooth.

2.3.5 Registration Time and Computational Complexity

We implemented GMM-FEM in Matlab (MathWorks, MA) with C++ mex code to interface with TetGen [131]. Timings were recorded on a PC with a 3.4 GHz Intel Core i7 processor and 8.00 GB of RAM. Average times for each step, across all patients, is summarized in Table 2.6. The total times encapsulate all steps, including mesh generation and stiffness matrix computation. In all cases, the algorithm converged within 100 iterations.

The proposed registration algorithm converges on average within ten seconds on a regular desktop PC. This efficiency is achieved due to the linearity assumption of the FEM, and the sparse nature of the equations involved. Since the stiffness matrix does not change between iterations in a linear material model, it only needs to be computed once given the original volumetric mesh. For the size of models considered in this work, this step takes on average 1.03 seconds. The next most computationally expensive step is the matrix solve in Equation (2.8) for updating the FEM displacements. Since the system is sparse, it can be solved quite efficiently in Matlab. Such sparse solves can typically be computed with complexity between $O(M^{1.5})$ and $O(M^2)$, where $M$ is the number of FEM nodes.

2.4 Discussion and Conclusions

In this chapter, we presented a novel non-rigid surface-based registration approach that handles missing data up to 30% and accounts for volumetric deformation effects known to be present in soft tissues. We applied the method to MR-TRUS fusion for prostate interventions, where a full segmentation from MR was fit to a potentially partial segmentation from TRUS.

In Section 2.3.2, we validated the algorithm on data from both prostatectomies and prostate biopsies. We compared the TRE against three other
non-rigid registration methods: TPS-RPM, CPD, and ICP-FEM. The proposed GMM-FEM was found to outperform both TPS-RPM and CPD in all cases. This improvement is shown to be statistically significant. Since the only effective difference between these registration methods is in the regularization scheme (FEM-based vs. Gaussian/TPS-based), we conclude that the FEM component is responsible. Compared to ICP-FEM, our method did not lead to statistically significant improvements when a full TRUS segmentation was available. However, if only a partial segmentation is available, then the improvement was found to be significant. Since the only effective difference between the two methods is in the correspondence scheme (soft vs. binary assignments), we conclude that the GMM component of the proposed framework is responsible.

While there are some techniques that focus on partial-surface registration, most do not consider volumetric properties (e.g. Poisson effects, incompressibility) during the registration, only surface bending. A 3D deformation field would then need to be interpolated internally based on the fitted surface, as a post-processing step. Physically, it is the internal volume that resists deformation, affecting the shape of the surface. Our method better reflects this. By comparing to CPD, which requires post-processing to recover a 3D field, we show that keeping the FE-regularizer in-loop leads to improved results.

For a tumor to be considered clinically significant, its radius should be no less than 5 mm. The TRE, as a root-mean-square error, provides an estimate of the standard deviation for biopsy targets. A standard deviation given by a TRE of 2.5 mm yields a confidence interval in which 95.4% of targets fall within the clinically significant 5 mm radius [71]. The current results (2.61 mm) of our GMM-FEM registration bring us closer to these bounds.

In Section 2.3.3, we investigated the robustness of the internal deformation field to perturbations in biomechanical parameters. GMM-FEM seems to be quite robust to perturbations in Poisson’s ratio, however, it can be sensitive to changes in the biomechanical regularization weight ($\beta$). This parameter controls the trade-off between model flexibility and the ability to perform surface-to-surface fitting. It must be tuned to allow an appropriate level of deformation, given the context of the involved anatomy.

We also examined robustness to surface resolution (Section 2.3.4), since this may affect both surface correspondences, and FEM resolution. Fortunately, we found that GMM-FEM does not seem sensitive to the number of surface points. This holds true as long as the prostate surfaces adequately represents the anatomy. Based on our findings, we consider 2000 surface
nodes to be sufficient for our registration pipe-line. For surfaces with higher curvature or a more complex shape, however, more points will be required.

In this chapter, we used an isotropic GMM to model the source surface. This implies that for a given source point, its observation is equally likely to appear in all directions. This assumption is not true in general. For example, points near the TRUS probe tip are more likely to move in the direction which the probe is pushing. A possible research direction is to extend GMM-FEM registration to use anisotropic GMMs using a similar approach to Horaud et al. [59].

In our GMM-FEM registration, we used a tetrahedral mesh to create an FE model of the prostate. We note that tetrahedral meshes are prone to mesh locking behavior, however, we did not encounter this issue in our dataset. However, should this issue arise in other datasets, one workaround is to relax the Poisson’s ratio to a lower value, given that the deformation field is less sensitive to this parameter. Another solution is to use a different element type such as a hexahedron, which is less susceptible to mesh locking.

The EM algorithm is known to be susceptible to local minima for point cloud registration [67]. These local minima usually arise in the presence of large global motion, symmetries, or transformation models with high degrees of freedom [67]. In our application, we typically have a priori knowledge of the general location and orientation of the prostate. This allows for a reasonable initialization that will prevent any large mis-assignments. Due to the smooth and unique curvatures of the prostate shape, we have not encountered such convergence to local minima given the full or 70% partial surface observations used in this study. If more data is missing (e.g., 50%+), and if the observation does not contain unique features, then local minima will be unavoidable. In such a case, we would recommend combining the method with other optimization heuristics, such as a multi-resolution approach, or having multiple starting points [67]. If too much of the surface segmentation is deemed unreliable, then a surface-based registration approach may not be appropriate.

One shortcoming of our algorithm is that it requires the MR and TRUS to be segmented prior to the registration. While the MR can be segmented ahead of time, the 3D-TRUS needs to be segmented within minutes due to clinical requirements. Since the presented method is designed to be robust to missing data, we suggest to only segment regions in which the boundary of the anatomy can be clearly distinguished, such as in the mid-gland for prostate interventions. This can help speed up the segmentation process. Where the anatomical boundary is clearly visible, we recommend using fast semi-automated segmentation methods (e.g., [114]).
2.4. Discussion and Conclusions

In this chapter, we used a linear, homogeneous material to create the finite element model of the prostate. We did not take into account that the calcification, cysts, and cancerous regions typically have different stiffness within the normal tissue. These spatially-varying properties can easily be incorporated into finite-element-based techniques, affecting computation of the stiffness matrix. However, this would require having an expert classify regions of tissue and assigning appropriate relative stiffness parameters. The definition of spatially-varying properties could potentially be automated by combining with elastography, should it become part of the prostate biopsy protocol. Note that with other, non FEM-based interpolators, homogeneity is also implicitly assumed.

The presented method, GMM-FEM, is shown to be both efficient and robust. It was designed to handle cases where visibility can limit accuracy of boundary segmentation in some regions of an organ, leading to the need to handle missing data. However, the method also performs well when full segmentations are available. It was shown to outperform current state-of-the-art surface-registration techniques: TPS-RPM, CPD, and ICP-FEM. We believe this makes it a strong candidate for use in image-guided interventions.
Chapter 3

Open-source Image Registration for MRI-TRUS fusion

3.1 Introduction

Prostate cancer is a leading cause of cancer-related deaths in males in the USA and Canada [133]. Accurate and early diagnosis of aggressive PCa is critical for adequate patient management. TRUS and MRI are complementary imaging modalities in visualizing anatomy of the prostate and characterizing the tissue for cancer presence. While MRI is the ideal imaging tool for PCa staging and characterization [55], TRUS is the most widely used modality due to its real-time nature, low-cost and ubiquity. It is also the primary modality used for interventional applications such as biopsy and brachytherapy. In this chapter we present and compare two practical software tools that can be used for non-rigid registration of prostate TRUS and MRI data to enable joint use of these modalities.

The concept of MRI-TRUS fusion targeted prostate biopsy was first introduced in 2002 by Kaplan et al. [70]. MRI is typically acquired weeks prior to the biopsy, with the patient in a different position (supine vs. lateral decubitus) and often with an endorectal coil, leading to substantial differences in prostate shape between the MR and TRUS volumes. This leads to the need for a non-trivial technique to consolidate the data. Image registration can be used to bring these two modalities in alignment.

Over the last decade, MRI-TRUS fusion biopsy has evolved and several solutions have been implemented in commercial products [85]. Strong evidence exists that targeted prostate biopsy, enabled in particular by such fusion systems, improves accuracy of PCa sampling [85]. In a recent study Puech et al. conclude that software-based image registration does not cur-
3.1. Introduction

Currently offer any advantages over cognitive registration done by visual re-identification of the biopsy targets between the two modalities [113]. In contrast, a study of Delongchamps et al. confirmed the utility of software registration but produced no evidence that deformable registration leads to any tangible improvements over rigid registration [30]. Most commercial MRI-TRUS fusion products implement linear registration only [85]. Further studies are needed to evaluate the overall clinical value of software registration as well as specific registration methods.

Comparison studies of image registration algorithms for the purposes of targeted prostate biopsy are challenging. Commercial tools are typically constrained to the manufacturer-specific registration algorithms, which are often not described in sufficient detail, and do not allow exporting of the registration results. Numerous registration algorithms have been proposed in the literature for MRI-TRUS fusion [60, 95, 141], but very few academic chapters are accompanied by a software implementation (the study by Moradi et al. [95] is the only study known to us that uses a publicly available registration tool) that could be easily used in a comparison study, or considered for translation into clinical research setting. Therefore, we believe open-source solutions that could readily be applied to MRI-TRUS fusion studies would greatly benefit the community.

MRI-TRUS registration approaches of prostate images can be categorized into intensity-based and segmentation-based methods. Efficient and accurate 3D non-rigid MRI-TRUS registration is inherently challenging because of the inter-modality nature of the problem and the low signal-to-noise ratio of TRUS. To the best of our knowledge, the only fully intensity-based approach for MRI-TRUS fusion is the method by Sun et al. [141]. All other methods rely on TRUS segmentation [60, 95, 100]. Similar to all intensity-based approaches, the method proposed by Sun et al. [141] requires homologous anatomical features to appear in both images. The challenge with MRI-TRUS fusion is that since the imaging physics are substantially different between the two modalities, there may be parts of the anatomy that can be visible in one image but not the other.

MRI can be segmented in advance of the procedure without sacrificing the procedure time. TRUS images are typically segmented during brachytherapy workflow. In the biopsy workflow, manual segmentation of the prostate gland is considered acceptable in the commercial fusion tools. Therefore, we can bypass difficulties associated with multi-modal intensity-based registration using a method that relies on the availability of the prostate gland segmentation. However, especially for prostate interventions, even experts are prone to over- and under-segmentation of the anatomy, as discussed in [138]. This
3.2. Methods

is also evident in the results presented in this chapter. The discrepancy can be attributed to the poor visibility of the prostate boundary near the base and apex in TRUS. Therefore a method that is robust to this potential variability, or that can handle missing data in regions where the prostate boundary is not clear, would be highly valuable, as mid-gland segmentation can be done robustly [138].

3.1.1 Contributions

The goal of this chapter is to provide an independent validation of the GMM-FEM (see Chapter 2) registration method against a signed distance map approach described in Section 3.2.2. This method represents the deformation field interior to the prostate using B-splines. Both methods are validated and compared independent of the author using data collected for 11 PCa patients who underwent standard MRI and TRUS imaging as part of their clinical care at Brigham and Women’s Hospital (BWH). While this chapter can be added to Section 2.3 as another dataset, I feel that since Chapters 2 and 3 have been published in different journals, it might not be suitable to combine them into a single chapter.

The group at BWH has made the signed distance approach available as an open-source tool to facilitate development and evaluation of registration methodologies, and to support clinical research in image-guided prostate interventions.

3.2 Methods

The registration approaches we propose consider clinical setup consisting of the two stages:

1. Pre-processing (planning) stage: the MRI exam of the patient is analyzed to identify the planned biopsy targets. The prostate gland can be contoured in MRI, and post-processing of the segmentation can be applied to recover a smooth surface.

2. Intra-procedural stage: a volumetric sweep of the prostate gland with TRUS is obtained, followed by reconstruction of a volumetric image. The prostate is segmented on the volumetric image and it is used to generate a smooth surface of the gland. The MRI and TRUS surfaces are then set as input to either of the registration methods described further to compute displacements that can be used for target position computation or fused MRI-TRUS display.
In this section we describe image acquisition and the various processing steps in detail, and discuss our approach to the retrospective evaluation of the registration techniques.

3.2.1 Image Acquisition and Pre-processing

The imaging data used in this evaluation was collected as part of a HIPAA-compliant prospective study that was approved by the institutional review board of the Brigham and Women’s Hospital. The author was not involved in the acquisition and processing of this dataset, which is described in this section. Clinical indication for both MRI and TRUS imaging was histologically confirmed prostate cancer, with low dose rate radiation brachytherapy as a preferred treatment option. TRUS image acquisition was performed during brachytherapy prostate volume studies, with the goal of confirming suitability of the patient for the procedure (volume of the prostate gland is within the clinically acceptable range, and there is no interference of the pubic arch with the brachytherapy needle insertion plan). Per standard clinical protocol, no anesthesia was administered to the patient during either MRI or TRUS imaging.

Multiparametric MRI data was collected using the standard imaging protocols established at our institution [55]. All MR imaging exams were performed on a GE Signa HDx 3.0T system (GE Healthcare, Waukesha, WI) with the patient in a supine position using a combination of 8-channel abdominal array and endorectal coils (Medrad, Pittsburgh, PA). The imaging study included anatomical T2-weighted imaging (T2WI) (FRFSE sequence, TR/TE = 3500ms/102ms over a 16 cm$^2$ FOV, reconstructed pixel size 0.3×0.3×3 mm), which was the series used for registration experiments presented in this work. The total time of the multiparametric MRI exam was about 45 minutes.

TRUS imaging was done in a separate session, with the patient in a lithotomy position. Per standard clinical setup, the TRUS probe (BK 8848) was attached to a motorized mover (Nucletron EndoCavity Rotational Mover (ECRM)) and mounted on a rigid stand with the enclosure for the TRUS probe (Nucletron OncoSelect stepper). Imaging was performed using the sagittal array of the probe rotated by the ECRM. Camera link and OEM research interfaces of the BK ProFocus US scanner (BK Medical) were used to collect radiofrequency (RF) TRUS concurrently with the clinical image acquisition. A position tracking device equipped with accelerometer, magnetometer and gyroscope (Phidget Spatial 3/3/3) was attached to the handle of the probe to track sagittal array orientation during motorized sweep. Syn-
3.2. Methods

Chronous collection of the RF and tracking data was performed using Public Library for UltraSound research (PLUS) \[82\] on a workstation equipped with a camera link interface (Dalsa X64 CL Express). The total time of the TRUS image collection was less than 5 minutes.

The following pre-processing steps were applied to prepare the data before applying the registration procedure. PLUS was used for converting RF TRUS data into B-mode images and for 3D reconstruction of the TRUS volumes from the tracked data using the gyroscope sensor tracking information. Volumetric TRUS images were reconstructed at 0.2 mm isotropic voxel size. TRUS and axial T2WI MRI volumes were brought into initial alignment by rigidly registering three fiducial points (left-most, right-most and anterior points identified on the mid-gland axial slice of the prostate) placed manually in reconstructed volumes using 3D Slicer \[39\], and were aligned with the T2WI MRI images. The prostate gland was contoured manually in both TRUS and T2WI volumes using the 3D Slicer Editor module. For the purposes of simplifying the segmentation procedure, TRUS volumes were resampled to the resolution of the T2WI dataset (3 mm slice thickness). The manually segmented masks were resampled back to the 0.2 mm isotropic spacing and smoothed by applying a recursive Gaussian image filter with $\sigma = 3$. The resulting masks were then used as input for the two registration tools we describe next. The group at BWH has made three of the datasets used in the evaluation publicly available.

3.2.2 Registration of Signed Distance Maps with B-spline Regularization

The BRAINSFit \[68\] registration module of 3D Slicer was used to perform non-rigid registration between MR and TRUS pairs, which was earlier adapted to prostate MRI intensity-based hierarchical registration \[37\] at BWH. Over the last few years, this module has been used to support clinical trials of MRI-guided in-bore transperineal prostate biopsy at BWH \[110\]. To apply this registration approach to MRI-TRUS registration, the BWH group implemented additional pre-processing of the segmentations, and modified the registration parameters as follows. First, the isotropic segmentation masks were cropped using a fixed size ($\approx$10 mm) margin around the bounding box of the segmentation to reduce computation time of the subsequent steps. Maurer signed distance transformation \[91\] as implemented in Insight Toolkit (ITK) was applied to the smooth segmentations of the prostate gland.

\[\text{See } \text{http://www.spl.harvard.edu/publications/item/view/2718}\]
3.2. Methods

in both MRI and TRUS. The BWH group chose Maurer implementation of the distance transformation due to its improved (linear time) performance as compared to other implementations available. The resulting distance maps were registered using the standard BRAINSFit module of 3D Slicer (v4.3.1) with affine and B-spline (isotropic grid of six control points) registration stages applied in sequence. The SPL group used the mean squared difference similarity metric with a fixed number of 10000 samples. All of the processing was done either in 3D Slicer, or using standard classes of ITK. This approach was developed by the team at the BWH, and thus will be further referred as such in the text.

The registration tool implementing the approach above is available as a module within ProstateIGT extension of 3D Slicer software.

3.2.3 GMM-FEM Registration

The second method in this chapter is the GMM-FEM registration method that was previously introduced in Chapter 2. For brevity, I refrain from duplicating the description of the method, which has already been discussed in Section 2.2.1. For the purpose of evaluating the capabilities of the GMM-FEM method in registering partial data, a partial surface datasets were created for each case by cropping the full surface 10 mm from the end points using planes perpendicular to the prostate gland main axis. The choice of data to be discarded was motivated by the practical difficulties in accurate segmentation of the prostate at apex and base.

3.2.4 Evaluation Setup

The two registration tools described above were applied to the MRI and TRUS datasets collected for prostate cancer patients at BWH. The author of this thesis was not involved in the evaluation setup. Identical parameters were used for each of the algorithms across the datasets used in the evaluation. Quantitative assessment was done based on the observed computation time and TRE. Computation time was measured for each of the processing steps. The accuracy of registration was evaluated using the TRE measured between the corresponding landmarks identified by an interventional radiologist specializing in abdominal image-guided interventions with over 10 years of experience in both MRI and ultrasound guided procedures. The landmarks were localized independently from the process of gland segmentation. The landmarks used in the evaluation included anatomical landmarks that

6The source code and license are available at [https://github.com/SlicerProstate](https://github.com/SlicerProstate).
could be consistently identified in each patient (entry of the urethra at base (coded as UB) and apex (coded as UA) of the prostate gland, and verumontanum (coded as VM)) as well as patient-specific landmarks (calcifications or cysts). The landmarks were marked using a setup where both MRI and volume reconstructed TRUS images were shown to the operator side by side using 3D Slicer to facilitate consistent identification.

Normality testing was performed using Shapiro-Wilk test, statistical comparisons were done using paired t-test. Statistical analysis and plotting were performed using R version 3.0.1. Registration experiments were performed on a MacBook Pro laptop (early-2011 model, 2.3 GHz Intel Core i7, 8GB RAM, SSD, OS X 10.9.5). C++ code was compiled using XCode 6.1 clang-600.0.54 compiler in Release mode. Matlab version 2013b was used for the GMM-FEM registration tool.

3.3 Results

Evaluation was conducted using imaging data collected for 11 patients. Volumes of the segmented prostate gland for the cases used in the evaluation are shown in Table 3.1. The volume of the gland segmented in TRUS was typically smaller than the one in MRI, the difference exceeded 20% in 4 out of 11 cases.

Computation time was as follows. BWH registration pre-processing took on average 35 sec (range 31-51 sec), while registration (including resampling) took 40 sec (range 32-56 sec). Pre-processing for the GMM-FEM method was comparable and on average took 40 sec (range 23-64 sec). Average registration time for the GMM-FEM method was 93 sec (range 33-248 sec) while using the full surface data, and 60 sec (range 19-137 sec) when partial data was used. No statistically significant correlation was observed between the volume of the prostate gland segmentation and the registration time. A representative example of a registration result is shown in Fig. 3.1. Visualization of the displacement fields obtained with both methods for the same case is in Fig. 3.2.

The total of 48 landmarks across all cases were identified for the purposes of TRE assessment. In the majority of the cases (6 out of 11) the landmarks corresponding to the UA and/or UB anatomical locations were outside the gland segmentation (also see Fig. 3.4 showing landmarks located outside the gland segmentation). Only landmarks that were inside the gland in both MRI and TRUS segmented volumes (the total of 37) were considered in

\[^7\]http://www.r-project.org/
3.3. Results

Figure 3.1: Example of the registration result for case 10 using BWH method. The green outline corresponds to the smoothed surface of the segmented prostate gland in the US image (both rows). Top row shows views of the TRUS volume, bottom row corresponds to the registered MRI volume for the same case. Annotations show examples of the landmarks used in the evaluation: urethra entry at base (red arrow) and apex (yellow arrow).
3.3. Results

<table>
<thead>
<tr>
<th>Case ID</th>
<th>$V_{MR}$, mL</th>
<th>$V_{US}$, mL</th>
<th>Percent difference, %</th>
</tr>
</thead>
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<td>9</td>
<td>33.1</td>
<td>30.7</td>
<td>7.1</td>
</tr>
<tr>
<td>10</td>
<td>27.1</td>
<td>26.9</td>
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</tbody>
</table>

Table 3.1: Volumes of the prostate gland segmentation in MRI ($V_{MR}$) and US ($V_{US}$). Large discrepancies were observed in a number of cases, which is attributed to the difficulties of accurately localizing prostate apex and base in US. Percent difference is calculated as $(V_{MR} - V_{US})/V_{MR} \times 100$.

Figure 3.2: Visualization of the deformation field for case 10 using both BWH (top row) and GMM-FEM (bottom row) methods. The green outline corresponds to the MR surface before registration, and the purple outline is the intersection of the TRUS prostate surface with the image plane. Note that for the GMM-FEM method deformation is restricted to the inside the gland segmentation, while BWH method produces continuous smooth deformation field that extends beyond the prostate segmentation.
3.3. Results

<table>
<thead>
<tr>
<th></th>
<th>Init.</th>
<th>BWH-aff</th>
<th>BWH-bspline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>7.8±4</td>
<td>3.7±1.8</td>
<td>3.8±1.8</td>
</tr>
<tr>
<td>Range</td>
<td>[1.7-15.4]</td>
<td>[0.5-7.3]</td>
<td>[1.1-7.8]</td>
</tr>
<tr>
<td>CPD-aff</td>
<td>GMM-FEM-full</td>
<td>GMM-FEM-part</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>3.5±1.7</td>
<td>3.5±1.7</td>
<td>3.6±1.5</td>
</tr>
<tr>
<td>Range</td>
<td>[0.3-7.1]</td>
<td>[0.5-7.3]</td>
<td>[0.7-6.6]</td>
</tr>
</tbody>
</table>

Table 3.2: Summary statistics in mm of the initial TRE (Init.), TRE following affine registration using BWH (BWH-aff) and UBC (CPD-aff) methods, and using deformable registration using BWH (BWH-bspline) and GMM-FEM methods with full (GMM-FEM-full) and partial (GMM-FEM-part) surface information. Significant reduction in TRE was observed as a result of affine registration, deformable registration component did not produce improvements.

the quantitative evaluation, to ensure the same set of landmarks is used in evaluating both methods. Among those landmarks, mean initial TRE was 7.8 mm (range 1.7-15.3 mm). The detailed summary of the TRE statistics is shown in Table 3.2.

There was no sufficient evidence to reject the hypothesis about the normality of the observed errors based on Shapiro-Wilk test (p>0.05). Both GMM-FEM and BWH led to significantly smaller TREs as a result of an affine registration step (p<0.0001), leading to mean residual TRE of about 3.5 mm (range 0.1-7.3 mm) (the CPD-affine step refers the “affine” version of [98]). The deformable component of the registration did not result in a statistically significant improvement of mean TRE. Comparison of the registration results obtained using BWH and full surface GMM-FEM methods do show a statistically significant difference between them (p<0.05). However, the difference between the means was only 0.3 mm. A detailed summary of the GMM-FEM and BWH registration results for each landmark is shown in Fig. 3.4. No significant difference was observed between the TREs corresponding to the registration results obtained with the GMM-FEM method while comparing full and partial surface registration results. At the same time, we observed that visually the results can be noticeably different, as illustrated in Fig. 3.3.
3.4 Discussion

In this chapter two software tools were presented that I believe are practical for MRI-TRUS fusion in clinical research concerned with prostate interventional applications. The first tool was presented in The results of this chapter are an independent validation of the GMM-FEM registration approach presented in Chapter 2. The implemented approaches both rely on the availability of the prostate gland segmentation, but are quite different in the methodology and capabilities. The BWH approach has been implemented based on the easily accessible “off-the-shelf” components of 3D Slicer and ITK. The GMM-FEM approach has the benefit of utilizing a biomechanical model, which has the potential to lead to a more realistic displacement field and can handle partial surface information. However its implementation required significantly more custom code development.

To the best of our knowledge, only two of the currently available commercial tools, Urostation (Koelis) and Artemis (Eigen), support elastic registration [85]. While both of these operate on segmented prostate gland, none is using distance map representation or biomechanical model for registration, or is capable of handling partial surface data. Numerous MRI-TRUS approaches have been presented in academic literature, but most are not accompanied with reliable implementations for testing. We are aware of only one publication that has an open-source implementation [95]. A major in-
3.4. Discussion

Figure 3.4: Summary of the TREs for the datasets used in the evaluation. Each point corresponds to a single landmark (“UA” is urethra at apex, “UB” - urethra at base, “VM” - verumontanum, “Other” corresponds to case-specific landmarks identified for calcifications or cysts), with the BWH method TRE plotted on the vertical axis, and GMM-FEM method (using full surface data in the top, and partial data in the bottom panel). Red points correspond to the landmarks that were marked outside the gland segmentation. Note that GMM-FEM TREs for the landmarks located outside the gland include only the affine registration component, since the deformation can only be estimated inside the tetrahedral mesh. For this reason, only those landmarks that were located inside the gland in both MRI and TRUS were considered in the quantitative evaluation.
novation of our work is in streamlining translation of the MRI-TRUS fusion capability into the clinical research workflows. Possibly the closest work to ours in terms of developing an open-source translational system for prostate interventions is by Shah et al. [129]. Our work is complementary in that while Shah et al. investigate system integration, we focus solely on software registration tools.

Once image data is collected and the prostate gland is segmented, all the processing steps for both methods can be completed without user interaction in under 5 minutes. The mean error observed by the BWH group is in the order of 3 mm, which is the slice thickness for the MRI data. We also note that the BWH group did not attempt to quantify the error in localization of the anatomical landmarks, as they did not have resources to conduct a multi-reader study. Such study would require clinical experts that are familiar with both MRI and TRUS appearance of the prostate. This expertise is rare at both UBC and BWH institutes, since clinical reads of prostate MRI is done by the radiology department, while most of the TRUS-guided prostate procedures are done by either radiation oncology or urology departments. Overall, we (UBC and BWH) believe our tools are suitable for prospective evaluation in the context of clinical research prostate biopsy applications.

The BWH group did not observe a significant differences between the two approaches in terms of TRE that are of practical value. The evaluation was complicated by the possible inconsistencies in the segmentation of the prostate gland, and the difficulties in placement of some of the anatomical landmarks that resulted in UA/UB points being located outside the prostate gland. Accurate and consistent segmentation of the prostate is challenging in TRUS, especially at the apex and base of the gland [97, 138]. Note that the differences between the prostate volumes estimated from 3D TRUS and MR have been recognized earlier in a number of studies. The average TRUS/MR volume ratio that the BWH group observed was 0.87, which is similar to Smith et al. [138] who reported average ratio of 0.9. While the BWH group cannot with absolute certainty determine the sources of variability, there are several factors that could have contributed to the difference. First, TRUS images have poor contrast at apex and base, potentially leading to under-segmentation of these areas. Second, the actual physical volumes of the gland could be affected by the compression of the prostate gland, to a different degree by both endorectal MR coil and ultrasound probe. Heijmink et al. observed average reduction of 17% in prostate volume due to the use of endorectal MR coil [56].

The BWH group adopted 3D Slicer for implementing the BWH approach presented here. 3D Slicer includes a variety of registration tools and in-
3.5 Conclusions

We (UBC and BWH) proposed open-source tools that can be used as a component of a system for MRI-TRUS fusion guided prostate interventions. The registration tools implement novel registration approaches and produce acceptable registration results, aiming to reduce the barriers in development and deployment of interventional research solutions for prostate image-guided interventions, and facilitate comparison with similar tools.
Chapter 4

Statistical Biomechanical Surface Registration

4.1 Introduction

Image guided interventions often require the registration of pre-operative images to intra-operative data. Pre-operative imaging, usually either CT or MRI, provides high-resolution information about the patient anatomy that is invaluable for assessing the location and extent of disease. Intra-operative imaging, on the other hand, must be fast and portable to be practical for guidance. The most popular choice is ultrasound, which is a low-cost, real-time and radiation-free modality, widely used for abdominal and urological interventions. Registration of pre-operative and intra-operative images is inherently challenging: the anatomy undergoes motion and deformation due to changes in body positions posture, and in response to external pressures such as from an ultrasound probe. As a result, registration is needed to compensate. If the structure is highly rigid, the transform may involve only rotation and translation. For non-rigid deformations, a larger parameter space is required to account for changes in shape.

Intensity-based registration of multimodal images is an active field of research (e.g. [112, 139]). Techniques typically involve maximizing a similarity metric. When comparing separate modalities, it is important to consider varying image properties due to the different imaging physics being exploited. One method of particular note attempts to account for this by defining a feature set, based on denoising literature, called the modality independent neighborhood descriptor (MIND) [58]. This technique has been successfully applied to multi-modal prostate registration [141]. However, just as with all intensity-based approaches, MIND still requires a sufficient number of anatomical features to appear in both images [58]. This may be challenging when parts of the anatomy are only visible in one image. For example, in
TRUS, the boundary of the prostate is not easily distinguished at its base, making it difficult to see where the prostate ends and the seminal vesicles begin.

If both pre-operative and intra-operative images are segmented during the clinical workflow, we can use these for a surface-based registration technique, avoiding the issue of finding intensity-based correlations. Instead, we rely on clinical expertise. The trade-off is that we then heavily rely on segmentation accuracy. Smith et al. [138] found that for prostate interventions, there was a high variability in segmentations, even when they were completed by clinical experts. The primary cause of inconsistencies were mainly due to tissue ambiguities or lack of visibility of the boundary, forcing clinicians to rely on prior knowledge of prostate shape and symmetries. To address this, we have developed a technique that allows for ambiguous or missing data. We propose that the surfaces be segmented only where the anatomical boundary is clear. This leads to the need to register two or more partial surfaces. The main topic and contribution of this chapter is to present a technique to register two partial surfaces in an efficient and robust way.

4.1.1 Related Work

Surface-based registration of a source surface, \( Y \), and a target surface, \( X \), is often presented as the minimization of an objective function of the form

\[
E(X, T(Y, \Theta)) + R(\Theta).
\] (4.1)

The first term, \( E(\cdot) \), is a distance metric between source and target surfaces. The source surface is transformed by a mapping, \( T(\cdot) \), parameterized by a collection of inputs, \( \Theta \), that bring it closer to the target. The second term, \( R(\cdot) \), represents regularization that seeks to constrain properties in the transform parameters. The goal is to find the optimal set of inputs, \( \Theta \). Regularization terms are often used to guarantee convergence. For non-rigid registration, they can also dictate the nature of the transformation by restricting the solution space.

The distance metric in surface-based techniques is typically formulated as a summation of distances between corresponding points. Thus, the metric and the correspondence scheme are intimately related. The iterative closest point algorithm [9, 165], one of the most popular approaches, assigns correspondences based on proximity. However, ICP requires accurate initialization, and is sensitive to noise, outliers, and missing data. To address this, soft-correspondences have been proposed based on the Gaussian Mixture
4.1. Introduction

Model \([21, 59, 67, 98, 153]\). Rather than treating correspondences as binary assignments, the source is interpreted as a probability density function consisting of a mixture of Gaussian probabilities. Registration is then cast as a likelihood maximization problem: find the transform that maximizes the likelihood that the target points are drawn from the transformed source distribution. These methods are robust to missing points on the target, but they assume a complete source surface for defining the GMM. When both surfaces are only partially segmented, more informed priors are required to tackle the under-determined nature of the problem.

A standard approach in gathering prior knowledge of surface geometry is through statistical modeling of a population. A statistical shape model \([57]\), describes shape statistics based on a set of training data. It consists of a mean shape, plus a combination of variational modes. Surface-based SSMs have been widely used in the literature (e.g., see \([20, 28, 32, 117]\)). Originally, correspondences between points in the training data were assigned manually \([26]\). This is a tedious, time-consuming process, and subject to user variability. Automatic pair-wise construction techniques have since been proposed, where one shape is arbitrarily chosen as the mean, and is registered to all other shapes in the training set. Correspondences are then estimated based on proximity. Unfortunately, this approach is inherently biased towards the selected mean shape, which may reduce the generality of the resulting SSM. To remove this bias, group-wise registration techniques have been developed \([3, 117]\), where both the mean shape and its pair-wise transformations to the training data are considered unknown. They are concurrently estimated by registering the entire group together at once.

Statistical shape models have been extended to multiple modalities. Chowdhury et al. \([19]\) investigate the concurrent segmentation of the prostate in MR and CT using a linked-SSM. This linked-SSM has two separate mean shapes: one for MRI and one for CT. Fitting the SSM to a new MRI predicts the corresponding prostate boundary in CT due to the linkage. The implicit assumption is that changes in shape between modalities is predictable. This may hold in CT and MRI, as long as imaging conditions are consistent for all subjects. Unfortunately, the assumption breaks down for TRUS, where the probe location, orientation, and pressure will inevitably vary across subjects.

When dealing with a collection of observations of a shape, each with missing sections of data, it may not be clear what the full target shape should be; it is like piecing together a puzzle without having a complete reference image. A reference for the full 3D structure would naturally simplify the process. A surface-based SSM for the anatomy of interest could be used to find an intermediate shape to help piece multiple partial surfaces together.
4.1. Introduction

By applying an approach similar to the group-wise registration framework of Rasoulian et al. [117], we find the single surface geometry generated by the SSM that most closely matches two incomplete observations. Once this intermediate shape is registered to both partial surfaces, we use it to construct a map between the two. In statistical shape modeling, the registration transform between shape instance and target is usually considered to be rigid (e.g., see [2, 8]). Its purpose is to compensate for differing coordinate systems. However, more complex transforms can be used. For instance, if the SSM does not capture a certain behavior, such as physical deformation, then a non-rigid transformation function might be desired (e.g., see [118]). In the literature, the combination of SSMs and non-rigid transformations is also used to generate synthetic data [13, 51].

Non-rigid transformation models can be separated into one of three groups: 1) Geometric-inspired; 2) Interpolation-inspired; and 3) Knowledge-based models.

Geometric-inspired models provide a minimal set of conditions that are common when mapping together similar objects. Such conditions may include inverse consistency [22], topology preservation [61, 95, 161] and isometry [166]. To the best of our knowledge, the only geometric-inspired approach for prostate interventions is the method by Moradi et al [95], which enforces a preservation of topology in establishing correspondences, and leverages finite element methods to model non-rigid deformations. However, they do not account for uncertainties in segmentation. As a result, they found that registration accuracy degraded in the apex area, where the prostate contour has poor visibility.

In interpolation-inspired models, there is an assumption of “smoothness” of the displacement field. Deformation is controlled by a set of control points or modes, and the full field is interpolated from these. Examples of important families of interpolation strategies include radial basis functions [21], free-form deformations [153] and Gaussian basis functions [98]. These methods have been used for statistical shape analysis [1, 117, 164] and prostate interventions [87, 88]. However, in most methods, only surface displacements are regularized during the registration process. Internal, volumetric deformations are then computed post-registration. This may result in unnatural changes in volume and shape, since the interior deformation field is not directly considered during the course of the registration.

Knowledge-based transformation models are typically used in scenarios involving a well-defined procedure or task. Introducing knowledge regarding the deformation may be achieved in two ways: statistical analysis, and biomechanical modeling. Similar to SSMs, statistical deformation models
4.1. Introduction

capture statistical information about deformation fields across a population. For a new deformation instance, the registration strives to find a linear combination of SDM basis transforms that minimizes an objective function \[60, 94\]. The drawback of SDMs is that they require an additional training step, and their capture range is limited to previously-observed deformations \[60\].

The main motivation behind biomechanical modeling is the premise that physically consistent models allow a more accurate and compact description of complex tissue behaviors. Finite element models can represent the deformable nature of soft tissue. FEM-based registration is typically driven using a combination of surface forces and boundary conditions \[16, 42, 95, 102, 103, 125, 144\]. A variation of ICP is generally used to compute the surface forces that drive the registration \[42, 95, 125\]. This method is susceptible to the drawbacks of local-search techniques. Rather than using ICP, we apply a probabilistic framework to estimate surface-to-surface correspondences, and forces are implicitly applied through an expectation maximization framework.

4.1.2 Contributions

In this work, we aim to improve the accuracy of IGIs by developing a non-rigid surface-based registration method, referred to as SSM-FEM, that considers both the geometric statistics and biomechanical nature of the deformation between pre-operative and intra-operative acquisitions. The method is designed with the consideration that boundaries of the desired anatomy may not be visible in regions of one or both images. To compensate for difficulties in segmentation, we propose to segment each image only where the boundary can be reliably and precisely traced. This results in two partial segmentations, which are then concurrently fused with the help of an SSM through a group-wise approach (similar to \[118\]). Since the anatomy may exist in different biomechanical states in the two images, a finite element model is used to define a deformation between the SSM and each observation. This adds flexibility to the SSM. We combine both the geometric (SSM) and biomechanical (FEM) priors into a single framework using a probabilistic approach.

We validate our algorithm in the context of MR-TRUS fusion on 19 patients who underwent prostate biopsies. By modifying it to remove either the geometric or biomechanical priors and contrasting the results, we demonstrate the need for both the SSM and FEM when dealing with the registration of deformable bodies with missing data.
4.2 Method

4.2.1 Clinical Workflow

An outline of the proposed MR-TRUS fusion is shown in Figure 4.1. The MR image can be acquired any time prior to the biopsy. It is subsequently contoured in axial slices by tracing the boundary of the prostate only where it can be reliably segmented, as determined by a clinician. We refer to the partial MR segmentation as the *MR observation*.

At the beginning of the biopsy procedure, the radiologist acquires a sweep of the prostate gland using tracked 2D-TRUS. We used an axial rotation along the probe with a mechanical system [7] to acquire this sweep, however, other trackers/sweep protocols [158] should perform just as well. These tracked slices are then used to generate a 3D-TRUS volume [41]. The prostate is subsequently segmented where its boundary can be reliably traced. We refer to partial TRUS segmentation as the *US observation*. We then perform the proposed SSM-FEM registration to map the MR image into the space of TRUS. Throughout the procedure, mono-modality 2D/3D TRUS registration is used to compensate for intra-procedure motions and
4.2. Method

dehormations [136].

4.2.2 Partial Surface to Partial Surface Registration

We treat the registration problem as two coupled SSM to partial-surface registrations, which are solved concurrently using an expectation-maximization approach. The SSM is used to construct two probability density functions that define the boundary of the structure, one for solving the registration problem for each modality. This probability density function is transformed using two separate spatial transformations that maps to each modality. For these transformations, we wish to find:

- a. The single set of SSM modes that best fit both partial observations
- b. Two non-rigid transformations (one for each modality) that map the SSM to each observation

Note that the SSM modes are shared between observations, while the non-rigid transformations are not. The reason is that we assume the SSM to capture inter-subject variability among patients. This implies that a single instance of the SSM represents the prostate “at rest”. The two non-rigid transformations are biomechanical deformations that map the SSM instance to observations in each modality.

To construct the SSM, we use a group-wise GMM approach. This has been shown to provide a generally applicable, anatomically specific, and compact representation of surfaces [117]. Details of the training are provided in Section 4.3.1. The result is a linear SSM model where shapes can be generated by adding a combination of modes of variation to a mean shape. The linear weights, hereafter referred to as shape parameters, along with the modes of variation, define a single instance of the SSM. Parameters that control the rigid transformation of an instance are referred to as pose parameters. During registration, instances of the SSM are used to create a finite element model of the prostate, which is used to compute and limit internal deformations. Note that to form a FEM given a surface, we need to generate a volumetric mesh which often includes additional nodes interior to the volume. This can be done automatically with most meshing tools [131].

From an SSM instance, we create a single Gaussian mixture model to represent the anatomical boundary of interest. Vertices define the Gaussian centres, each with a common mean and variance. We then construct a pair of composite transforms that deforms the SSM surface to fit each of the observations. These involve a rigid component to account for a change
in coordinates, and FEM-based interpolation to govern prostate deformation. The key idea is that the surfaces in US and MR represent deformed observations of a single common shape. Hence, the solution to the SSM shape parameters depends on both. Since the two images are acquired at different times and under different contexts, any deformations are considered independent. We therefore compute two separate deformation fields, one for each modality. The shape parameters and deformation fields are combined in a single framework, where the goal is to minimize net deformation and surface-to-surface errors.

4.2.3 Probabilistic SSM-FEM

SSM-FEM is based on an expectation-maximization framework. It is constrained by Tikhonov regularization of shape parameters (to control the intermediate shape instance) and of the volumetric strain energy of a finite element model (to limit deformation). The algorithm involves fitting the SSM to all observations simultaneously, constructing a simple FEM of the prostate based on the SSM instance, then allowing the model to deform to fit each observation independently. There are no explicit boundary conditions applied to the FEM; instead, the boundary is allowed to move freely. Registration is driven by implicit surface-to-surface forces that arise by minimizing a global objective function.

Following Equation (4.1), we can define a separate distance measure between the SSM and each independent observation. These consist of a modality-dependent surface error, $E_{md}$, and regularization term, $R_{md}$, which both involve modality-specific transform parameters, $\Theta_{md}$. By summing errors across modalities, we form a unified objective function:

$$E = \sum_{md \in \{MR, US\}} E_{md}(\sigma_{md}^2, \Theta_{md}) + R_{md}(\Theta_{md}).$$  \hspace{1cm} (4.2)

The surface error, $E_{md}$, also depends on a Gaussian variance, $\sigma_{md}^2$, which parameterizes the Gaussian mixture models. This can be interpreted as controlling the capture radius of each point on the SSM when computing correspondences.

For each modality, a transformed version of the SSM is used to define the GMM representing the complete anatomical boundary. We wish to find the set of transform parameters, $\Theta_{md}$, that maximizes the likelihood that the observed partial surface is drawn from that model. This motivates us to define the modality-dependent surface error using the negative log-likelihood
4.2. Method

Table 4.1: Mathematical notations

<table>
<thead>
<tr>
<th>Variables: scalars, vectors and matrices</th>
</tr>
</thead>
<tbody>
<tr>
<td>( md \in { \text{US, MR} } )</td>
</tr>
<tr>
<td>( N_{md} )</td>
</tr>
<tr>
<td>( X_{md} )</td>
</tr>
<tr>
<td>( M, L )</td>
</tr>
<tr>
<td>( Z_{M \times 3} )</td>
</tr>
<tr>
<td>( Y_{M \times 3} )</td>
</tr>
<tr>
<td>( \Psi_{3M \times L} )</td>
</tr>
<tr>
<td>( b_{L \times 1} )</td>
</tr>
<tr>
<td>( R_{md}, t_{md}, s_{md} )</td>
</tr>
<tr>
<td>( J )</td>
</tr>
<tr>
<td>( U_{md} )</td>
</tr>
<tr>
<td>( V_{md} )</td>
</tr>
<tr>
<td>( \Phi_{M \times J} )</td>
</tr>
<tr>
<td>( K_{3J \times 3J} )</td>
</tr>
<tr>
<td>( E )</td>
</tr>
<tr>
<td>( \nu )</td>
</tr>
<tr>
<td>( P_{md} )</td>
</tr>
<tr>
<td>( \sigma_{md}^2 )</td>
</tr>
<tr>
<td>( w_{md} \in [0, 1] )</td>
</tr>
<tr>
<td>( I_{3 \times 3} )</td>
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<tr>
<td>( \bar{I}_{3 \times 3M} )</td>
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<tr>
<td>1</td>
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<table>
<thead>
<tr>
<th>Operators</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{diag}(\vec{v}) )</td>
</tr>
<tr>
<td>( \bar{v}_{2N \times 1} )</td>
</tr>
<tr>
<td>( \bar{P} = \text{kron}(P, I) )</td>
</tr>
</tbody>
</table>

function:

\[
\mathcal{E}_{md}(\sigma_{md}^2, \Theta_{md}) = -\sum_{n=1}^{N_{md}} \log \sum_{m=1}^{M} P_{md}(z_m)P_{md}(x_{n}^{md}|T(z_m, \Theta_{md})), \tag{4.3}
\]

where \( P_{md}(\cdot) \) denotes the GMM probability density function, \( z_m \) is the lo-
4.2. Method

cation of the $m$-th vertex in the SSM mean, and $T(z_m, \Theta_{md})$ represents the ideal transformed location. This transform involves:

- SSM modes for determining the intermediate shape
- FEM deformation to provide flexibility
- Rigid transform parameters for gross alignment

Following the notations defined in Table 2.1, we can write the net transform as

$$T(z_m, \Theta_{md}) = s_{md} R_{md} \left[ (z_m + \Psi_m b) + v_m^{md} \right] + t_{md}. \tag{4.4}$$

The term $(z_m + \Psi_m b)$ represents the $m$-th instance vertex, given shape parameters $b$ and corresponding modes of variation in the columns of $\Psi$ (with $\Psi_m$ consisting of only the three rows of $\Psi$ pertaining to vertex $m$). The shape instance is then deformed by adding the FEM displacement field, $v_m^{md}$. Finally, the rigid transform is applied, with rotation, translation, and scale given by $\{R_{md}, t_{md}, s_{md}\}$. It is important that the residual deformation between the shape instance and observation, $v_m^{md}$, is computed in the SSM coordinate space. This reduces rotational artifacts when using a linear material model for the FEM. Since the SSM is only a surface model while the FEM is volumetric, we need an interpolation matrix, $\Phi$, to relate surface displacements to FEM node displacements:

$$v_m^{md} = \Phi_m U_{md}, \tag{4.5}$$

where $U_{md}$ is the $J \times 3$ matrix of all FEM node displacements, and $\Phi_m$ the $m$th row of $\Phi$. In our implementation, all points on the surface correspond to FE nodes, and internal nodes are appended to the end of the node list. As a result, the interpolation matrix has the form,

$$\Phi = \begin{bmatrix} I_{M \times M} & 0 \\ 0 & 0 \end{bmatrix}. $$

In the general case, $\Phi$ is a sparse matrix which can be computed directly from the FE mesh via its shape functions (e.g., see [11]). With this substitution, we can expand Equation (4.4) as

$$T(z_m, \Theta_{md}) = s_{md} R_{md} (z_m + \Psi_m b + \Phi_m U_{md}) + t_{md}. \tag{4.6}$$

This transform completes the definition of the negative log-likelihood objective functions in Equation (4.3). For each modality, we have $\Theta_{md} = \ldots$
4.2. Method

\{R_{\text{md}}, t_{\text{md}}, s_{\text{md}}, U_{\text{md}}, b\}, noting that the shape parameters \( b \) are shared. The set of unknowns \( \{\sigma^2_{\text{md}}, \Theta_{\text{md}}\} \) are solved using an EM algorithm. An initial GMM variance is estimated directly from the data as in Myronenko and Song [98],

\[
\sigma^2_{\text{md}} = \frac{1}{3MN_{\text{md}}} \sum_{n=1}^{N_{\text{md}}} \sum_{m=1}^{M} \left\| x^\text{md}_n - z_m \right\|^2. \tag{4.7}
\]

In the expectation step, we compute how likely it is that an observation corresponds to a GMM centroid by calculating the posterior probability

\[
P_{\text{md}}(z_m|x^\text{md}_n) = \frac{\exp \left( -\frac{1}{2} \left\| x^\text{md}_n - T(z_m, \Theta_{\text{md}}) \right\|^2 / \sigma^2_{\text{md}} \right)}{\sum_{j=1}^{M} \exp \left( -\frac{1}{2} \left\| x_n - T(z_j, \Theta_{\text{md}}) \right\|^2 / \sigma^2_{\text{md}} \right)} + c, \tag{4.8}
\]

where

\[
c = \left(2\pi \sigma^2_{\text{md}}\right)^{3/2} \frac{w_{\text{md}}}{1 - w_{\text{md}}} \frac{M}{N_{\text{md}}} \tag{4.9}
\]

is the contribution of an additional uniform distribution to account for noise and outliers. The scalar weight \( w \in [0, 1) \) controls the probability that a given point is classified as an outlier, set to zero if observations do not exhibit any noise or outliers. A value of one implies that no correspondence between observed points and GMM centroids can be made. Ignoring terms independent of \( \sigma^2_{\text{md}} \) and \( \Theta_{\text{md}} \), we can rewrite the negative log-likelihood function of Equation (4.3) as

\[
\mathcal{E}_{\text{md}}(\sigma^2_{\text{md}}, \Theta_{\text{md}}) = \frac{3N_{\text{md}}}{2} \log(\sigma^2_{\text{md}}) + \frac{1}{2\sigma^2_{\text{md}}} \sum_{m,n=1}^{M,N_{\text{md}}} P_{\text{md}}(z_m|x^\text{md}_n) \left\| x^\text{md}_n - T(z_m, \Theta_{\text{md}}) \right\|^2, \tag{4.10}
\]

where \( N_{\text{md}} = \sum_{m,n=1}^{M,N_{\text{md}}} P_{\text{md}}(z_m|x^\text{md}_n) \). To constrain the SSM shape parameters and the FE nodal displacements, we add two Tikhonov regularizers:

\[
\mathcal{R}_{\text{md}}(\Theta_{\text{md}}) = \frac{\mu}{4} b^T \Lambda b + \frac{\beta}{2} \bar{u}_{\text{md}}^T K \bar{u}_{\text{md}}. \tag{4.11}
\]

This adds two free parameters: \( \mu \) and \( \beta \). The first, \( \mu \), limits the shape parameters, with \( \Lambda \) the diagonal matrix of inverted SSM eigenvalues. This is scaled by 1/4 since the term is split equally between the two observations.
For registering to \( n \) surfaces, the fraction would be \( 1/2n \). The parameter \( \beta \) controls the trade-off between tightness of the fit and biomechanical regularization. This term represents the total linearized strain energy of the FEM [11]. It involves the stiffness matrix, \( K \), and a rasterized vector of FEM nodal displacements, \( \vec{u} \). The stiffness matrix is a large sparse matrix that can be systematically constructed based on the FEM mesh and properties of the material. For simplicity, we assume a linear stress-strain relationship. More complex material models can be applied, but the linearized strain-energy will then include an additional forcing term dependent on the current deformation state. In the current implementation, whenever the SSM is updated, we remesh the FEM to ensure a high mesh quality.

To perform the registration, we need to minimize the total objective function in Equation (4.2) using the distance metric and regularization terms defined in Equations (4.10) and (4.11). Unfortunately, due to the coupling between the rigid transforms, FEM deformation, and shape parameters, finding the optimal solution to this objective function directly is non-trivial. Instead, we propose a simple alternating minimization strategy. First, we assume that the FEM deformation and SSM shape parameters are fixed, and solve for the pose parameters of each observation: \( \{R_{md}, t_{md}, s_{md}\} \). Since the transformation is independent between observations, this results in two rigid registration problems between pairs of surfaces. These are trivially solved by minimizing Equation (4.10) for each modality, which can be interpreted as an orthogonal Procrustes problem. This aligns the current best estimate of each deformed model to its corresponding observation.

The next step is to update the intermediate SSM shape instance. This requires finding the optimal shape parameters, \( b \), to fit both observations. The solution given a single observation is outlined in [117]. By extension, (see Appendix A) the optimal shape parameters provided two observations is the solution to the following set of linear equations:

\[
\Gamma_{SSM} b = \Upsilon_{SSM},
\]

with

\[
\Gamma_{SSM} = \mu \Lambda + \sum_{md} \frac{s_{md}^2}{\sigma_{md}^2} \Psi^T \text{diag}(\tilde{P}_{md}1) \Psi,
\]

\[
\Upsilon_{SSM} = \sum_{md} \frac{s_{md}}{\sigma_{md}^2} \left[ \Psi^T \tilde{P}^T_{md} \tilde{P}_{md} \bar{x}_{md} \right. \\
- \Psi^T \text{diag}(\tilde{P}_{md}1) \left( s_{md}(\tilde{z} + \bar{v}_{md}) + \tilde{I} R^T_{md} t_{md} \right) \left. \right].
\]
4.2. Method

This is a dense system that can be solved with numeric complexity $O(L^3)$, where $L$ is the number of SSM modes. Fortunately, we use a small number of modes (i.e. 50), so $b$ can be computed quite quickly. The resulting shape instance can be thought of as a common “starting shape”, from which we will determine further biomechanical deformation for each observation.

Finally, we compute FEM nodal displacements, keeping the pose and shape parameters fixed. A single finite element model is automatically generated from the SSM shape instance. For this, we use TetGen [131], and assume a linear material model. Given the FEM, displacements can be solved independently for each input modality. Minimizing Equation (4.2) with respect to the rasterized vector $\vec{u}_{md}$ yields the following system:

$$\Gamma_{\text{FEM}} \vec{u}_{md} = \Upsilon_{\text{FEM}},$$  \hspace{1cm} (4.15)

where

$$\Gamma_{\text{FEM}} = \beta \sigma_{md}^2 K + s_{md} \Phi^T \text{diag}(P_{md}) \Phi$$  \hspace{1cm} (4.16)

$$\Upsilon_{\text{FEM}} = s_{md} \Phi^T \tilde{P}_{md}^T \tilde{P}_{md} \tilde{x}_{md} - \Phi^T \text{diag}(P_{md}) (s_{md} \tilde{y} + s_{md} \tilde{R}_{td}^T t_{md}).$$

Full details of the derivation are provided in Appendix B. This is a sparse linear system that can be solved efficiently with complexity between $O(J^{1.5})$ and $O(J^2)$, where $J$ is the number of FE-nodes. The nodal displacements, $\vec{u}_{md}$, can be easily computed using any sparse linear solver. At the end of this step, we have now updated all unknown parameters required by the transformation function (4.6).

With the transformation from the SSM to each observation known, we recalculate the estimated variances:

$$\sigma_{md}^2 = \frac{1}{N_{md}} \sum_{m,n=1}^{M,N_{md}} \|x_{n}^{md} - T(z_m, \Theta_{md})\|^2.$$  \hspace{1cm} (4.17)

With this new variance estimate, we update the GMM probability distributions (Equation (4.8)), and repeat the process.

The registration algorithm iterates between the expectation step (updating GMM distributions) and maximization step (updating the transform parameters) until the variances drop below a certain threshold. The complete algorithm for the proposed SSM-FEM registration is summarized in Algorithm 1.

Once the SSM-FEM registration has converged, we can propagate the FEM using the transform parameters $\{\Theta_{md}\}$ into the space of the TRUS.
4.2. Method

Require: $E, \nu, \mu, \beta, Z, \Psi, X_{md}$ and $w_{md}$;
Initialize: $b, s_{md}, R_{md}, t_{md}, \bar{u}_{md}$ and $\sigma^2_{md}$;
where $md \in \{\text{MR, US}\}$;
while not converged do
  E-Step:
  for $md \in \{\text{MR, US}\}$ do
    Update $P_{md}$ using Equation (4.8);
  end
  M-Step:
  for $md \in \{\text{MR, US}\}$ do
    Rigid registration between $X_{md}$ and $Y + \Phi U_{md}$;
    Update pose: $s_{md}, R_{md}$ and $t_{md}$;
  end
  Shape registration using Equation (4.12);
  Update $b$ which updates $Y$;
  for $md \in \{\text{MR, US}\}$ do
    Biomechanical registration using Equation (4.15);
    Update $U_{md}$;
  end
  for $md \in \{\text{MR, US}\}$ do
    Update $\sigma^2_{md}$ using Equation (4.17);
  end
end

Algorithm 1: SSM-FEM registration

and MR images. This enables us to express voxels in either modality using the natural coordinates of the FEM (similar to barycentric coordinates). Thus, for voxels inside the prostate in one modality, it is possible to find its corresponding voxel in the other.

For material properties, we apply a homogeneous elastic material with a constant Young's modulus to all elements. The models used in this study are composed of $\approx 7500$ elements. Throughout our experiments, we used a stopping condition of $\sigma^2 \leq 10^{-4}$ mm$^2$, Young's modulus of $E = 5$ kPa, which is in the range of values reported in [72] for the prostate, and a Poisson's ratio of $\nu = 0.49$ to maintain near incompressibility.

In total, there are five free parameters in the proposed method: $\mu, \beta, w$, and the two FEM-specific material parameters $E$ and $\nu$. The first two parameters are tunable. The first, $\mu$, controls the impact of SSM modes. If set
too high, the SSM will be restricted to the mean shape. If too low, the SSM may produce unlikely instances. For our model, a value of $\mu = 400$ allowed reasonable variations from the mean. The second parameter, $\beta$, controls the balance between implicit surface-to-surface forces and internal resistance provided by the FEM. It should be tuned to allow for “reasonable” flexibility of the model. We found $\beta = 10$ to be sufficient for this prostate application. This parameter can be viewed as scaling external forces acting on the prostate to fall within a reasonable range. The fraction of outliers, $w$, is a property of the quality of the data. For high-quality data, we set $w = 0$. If over-fitting to extraneous points is observed, then $w$ should be increased, but remain low. For linear materials, the Young’s modulus, $E$, can be factored out of the stiffness matrix in Equation (4.11). This allows it to be combined with $\beta$. Thus, the actual value for Young’s modulus has no impact on the registration as long as $\beta$ is scaled appropriately. However, we still recommend keeping a reasonable value for consistency. Finally, Poisson’s ratio $\nu$ controls Poisson’s effects in the volume: when compressed along one dimension, how much the material expands perpendicularly. For incompressible materials, $\nu \approx 0.5$, although this value results in a singularity. Most soft tissues, including the prostate, are considered nearly incompressible, so we set $\nu = 0.49^{[72]}$.

4.2.4 Registration Methods Used for Comparison

The proposed SSM-FEM registration method consists of two priors: 1) Geometric (SSM); and 2) Biomechanical (FEM). To highlight the importance of each component, we remove each a priori piece of information and compare results.

Keeping only the geometric prior, we implicitly assume that the SSM, TRUS and MR surfaces are in the same biomechanical state. The concurrent registration of a SSM to both TRUS and MR surfaces without the biomechanical component is equivalent to a group-wise rigid SSM registration. Henceforth, we refer to this approach as SSM registration.

If a full surface of the prostate is available, e.g. through a full segmentation of the MRI, then there is no need for the geometric prior. In this case, we can treat the fully segmented MR surface as the source shape instance rather than relying on the SSM. We solve only for the coordinate transform and biomechanical deformations between source and target surfaces using Equation (4.15). We refer to this approach as GMM-FEM registration (Chapter 2), which is only presented here for continuity. The displacements
in this case can be determined by solving the linear system:

\[ \Gamma \vec{u} = \Upsilon, \]

(4.18)

where \( P, \sigma^2 \) describes a GMM that corresponds to the fully segmented source surface and

\[ \begin{align*}
\Gamma &= \beta \sigma^2 K + s^2 \tilde{\Phi}^T \text{diag}(\tilde{P}1) \tilde{\Phi} \\
\Upsilon &= s \tilde{\Phi}^T \tilde{R}^T \tilde{\Phi}_{\text{target}} \\
&\quad - \tilde{\Phi}^T \text{diag}(\tilde{P}1) \left( s^2 \tilde{y}_{\text{source}} + s \tilde{I} R^T t \right).
\end{align*} \]

(4.19)

GMM-FEM registration is performed exactly as SSM-FEM registration, but replacing the role of the statistical shape model with the fully segmented MR surface. In the E-step, using Equation (4.8), we compute the posterior probabilities between source and target surfaces. The M-step is substituted by Equation (4.18) for updating FEM nodal displacements.

4.3 Experiments and Results

We evaluate the proposed registration method on MR-TRUS image pairs acquired from patients who underwent a prostate intervention. The data acquisition protocol was approved by our respective institutional ethics boards, and all patients provided written consent to be included in the study. The rest of this section is divided into five subsections. In Section 4.3.1, we discuss the training population used for SSM construction. In Section 4.3.1, we discuss the biopsy data acquisition, segmentation protocol, and initialization. We then validate the accuracy of our registration in Section 4.3.2, by measuring the target registration error between pairs of intrinsic fiducials in the prostate. To highlight the importance of the SSM, we compare the outcome of the combined SSM-FEM registration with the similar registration that excludes either the SSM or FEM components. Finally, we investigate sensitivity of the method to errors in segmentation (Section 4.3.3), missing data (Section 4.3.4), and to variations in the two tunable parameters controlling regularization (Section 4.3.5).

4.3.1 Data

SSM Construction

To construct a statistical model that represents inter-subject variation of prostate shapes, we require a large set of training data. A suitable source is a
4.3. Experiments and Results

Figure 4.2: Graphical representation of the prostate shapes described by the SSM after varying weights corresponding to the first three principal modes of variation by three standard deviations ($\pm 3\sqrt{\lambda}$). The mean shape is shown with a green model in the middle column. The amount of variation in the left and right column is color coded for each mode.

A large population of prostate images acquired in a single modality. The choice of modality is important, since the technique may affect the prostate shape (e.g., forces from end-firing probes or endorectal coils). Ideally, the prostates should be in the same mechanical state so that differences in appearance are mostly due to inter-subject variations. Finally, for surface-based SSMs, the prostate needs to be accurately and reliably segmented.

Brachytherapy volumes are routinely acquired and segmented in large clinics and interventional centers. We used a dataset of images acquired from 290 brachytherapy patients in the construction of our SSM. Each TRUS volume consists of 7 to 14 parallel equally spaced (5 mm apart) axial B-mode images of the prostate, captured using a side-firing transrectal probe. The in-plane resolution of these images was (0.16,0.16) mm. For each B-mode image, the prostate gland is delineated using Variseed (Varian Medical Systems, Palo Alto, CA, USA) and a contouring plug-in. This plug-in is based on the semi-automatic prostate segmentation method presented by Mahdavi et al. [86]. Contours are manually corrected by an expert clinician,
4.3. Experiments and Results

Figure 4.3: Two brachytherapy prostates from the SSM training set. Slices from each patient is colored by black and blue, respectively. Even though each patient is sampled coarsely (5.0 mm out-of-plane resolution), the set of both prostates is a finer sampling of the mean-shape than each prostate alone.

and subsequently used as the SSM training population.

For construction of the SSM, we used the group-wise GMM method of Rasoulian et al. [117]. This resulted in a SSM with a mean shape consisting of 1000 vertices and 1996 faces. The mean and primary modes of variation are depicted in Figure 4.2. As seen in the figure, the first two modes control the scale, whereas the third mode controls the curvature of the prostate.

The choice of the number of modes is governed by the compactness of the SSM. Compactness simply measures the cumulative variance of the model as modes are added in descending order of eigenvalues [57]. A popular rule is to keep the first $L$ modes that span 95% of the total variation. For our SSM, this results in a model with 50 principal modes. After this point, each additional mode contributes negligibly to the cumulative variation ($< 0.1\%$).

Although the slice thickness is relatively thick, 5.0 mm, we are able to create a higher resolution SSM along the base-apex axis due to varying slice positions among subjects. Since the location of slices are random between patients, the training data represents a fine statistical sampling of the prostate anatomy. This is demonstrated graphically in Figure 4.3. Two segmented
4.3. Experiments and Results

brachytherapy prostates, from different patients in the SSM training set, are represented by blue and black slices. Even though each individual prostate is coarsely sampled, under the assumption that the prostate is smooth, the combination allows for a finer out-of-plane resolution than the individual ensembles.

Note that this method of SSM construction implicitly assumes that the mean shape is a GMM and training examples are spatially transformed observations of this GMM. However, during SSM construction, the GMM is decoupled when the mean shape is updated, i.e. the means shape is simply the average of the back-projected training examples under a spatial smoothness constraint. Since the focus of this thesis is not construction of SSMs, we will not tackle this issue. However, it would be interesting to see how the results vary if the GMM and mean shape are updated simultaneously.

Prostate Biopsy

Validation data was acquired from 19 patients scheduled for a prostate biopsy. In Figure 4.4, a typical example of an MR and TRUS image pair is shown. The T2-weighted MR images were acquired using a 3 Tesla GE Excite HD MRI system (Milwaukee, WI, USA) with a spacing of $0.27 \times 0.27 \times 2.2$ mm. Slices from base, mid-gland and apex are shown in Figures 4.4a, 4.4b and 4.4c respectively. The TRUS images were acquired using a 3D-TRUS mechanical biopsy system [7] with a Philips HDI-5000 US machine and a C9-5 transducer using an axial rotation of the biopsy probe. The TRUS images were reconstructed into a 3D-volume with a spacing of $0.19 \times 0.19 \times 0.19$ mm. Figures 4.4d, 4.4e and 4.4f show slices from base, mid-gland and apex, respectively. In each modality, areas around the mid-gland (e.g. Figures 4.4b and 4.4e) were segmented where the prostate boundary could be reliably and accurately traced, as determined by an expert clinician. We refer to these contours as a partial segmentation. Additionally, we segmented regions of the prostate where the boundary was not clearly visible based on symmetries and prior knowledge of the general prostate shape. White arrows in Figure 4.4 indicate examples of these uncertain regions. These added contours are referred to as uncertain data. The combination of both uncertain and partial data make up the full segmentations. Example segmentations of MR and TRUS volumes are shown in Figures 4.4g and 4.4h respectively. For the data used in this study, the partial segmentations of MR represent approximately 80% of the full surface, and the partial segmentations of TRUS approximately 70%. All segmentations were performed manually using Stradwin (Cambridge University, UK).
4.3. Experiments and Results

Figure 4.4: Axial slices from MR (top-row) and TRUS (middle-row) volumes. Typically, the prostate boundary can be accurately and reliably segmented in the mid-gland, i.e. (b) and (e). White arrows highlight regions where the true prostate boundary is ambiguous. (g) and (h) depict the resulting segmentation of MR and TRUS, respectively. Partial segmentations are color coded in green, uncertain contours are in red.

Note that even though the prostate boundary is typically more visible in MR than TRUS, it is still prone to segmentation error [138]. For example, since axial MR slices are typically very thick, it may be ambiguous where
the prostate ends and the bladder begins, as the prostate may terminate between slices. Another source of MR segmentation error, specifically at the base, is the potential inclusion of the seminal vesicles, as this varies between experts [138].

Figure 4.5: An example of SSM-FEM registration with $w = 0.0$, $\mu = 400$, $\beta = 10.0$, $E = 5.0$ kPa and $\nu = 0.49$ to full data (TRUS on the left, MR on the right). Following center of mass initialization (a), the SSM mean is evolved to target surfaces (b). The target surfaces are shown in red, the current SSM instance is shown in green, and the result of SSM-FEM registration is shown in blue.
4.3. Experiments and Results

4.3.2 Registration of Full and Partial Surfaces

We used the biopsy data to validate our registration pipeline using both the pairs of full surfaces, and the pairs of partial surfaces. To initialize translation, we use a center of mass alignment between SSM-mean and target surfaces, as seen in Figures 4.5a and Figure 4.6a. For the initial rotation, we simply matched the right-anterior-superior coordinates of SSM-mean and target surfaces. Within a range of $[-10.0, +10.0]$ mm/degrees, we did not observe sensitivity to initialization for SSM, GMM-FEM and SSM-FEM registration in 100 trials.
4.3. Experiments and Results

Figure 4.6: An example of SSM-FEM registration with $w = 0.2$, $\mu = 400$, $\beta = 10.0$, $E = 5.0$ kPa and $\nu = 0.49$ to partial data (TRUS on the left, MR on the right). Following center of mass initialization (a), the SSM mean is evolved to target surfaces (b). The target surfaces are shown in red, the current SSM instance is shown in green, and the result of SSM-FEM registration is shown in blue.

Following initialization, we apply the SSM-FEM algorithm until registration converges. A typical result for full MR-TRUS surfaces is shown in Figure 4.5b. The Tikhonov regularization weights were tuned to allow sufficient flexibility while still resulting in plausible prostate shapes. This resulted in a choice of $\mu = 400$ and $\beta = 10$. Since the quality of data was quite high and the surfaces sufficiently smooth, we set the estimate of outliers, $w_{md}$, to
4.3. Experiments and Results

zero. For a fair comparison, we used the same parameters for SSM and for GMM-FEM registration methods as well.

The same experiment was applied to the partial MR and TRUS surfaces. A typical SSM-FEM registration result for a partial MR-TRUS surface pair is shown in Figure 4.6. We used the same Tikhonov regularization weights as for the full data. However, since partial surfaces exhibit missing points, we set the estimate of noise and outliers to $w_{md} = 0.2$. As demonstrated by Myronenko and Song [98], this helps avoid falling into local minima due to poor initialization. The same parameters were used for SSM and GMM-FEM registration methods.

Figure 4.7: Examples of fiducial pairs in MR (left column) and TRUS (middle column) images. The composite image following SSM-FEM registration is shown in the right column. The segmented prostate boundary for MR and TRUS is shown in blue and red, respectively.

Quantitative Validation

To quantify the registration results, we asked an expert radiologist to select five intrinsic fiducials per patient consisting of cysts and benign prostatic hyperplasia. While we did not follow a strict protocol regarding the precise anatomical location of these landmarks, we did ask our clinical collaborator to only draw samples interior to the prostate. This resulted in a total of 93 landmarks from the cohort of 19 patients. The spatial distribution of these
4.3. Experiments and Results

landmarks was: 64.5% in the mid-gland, 21.5% in the base and 14% in the apex. An example of corresponding fiducial pairs in MR and TRUS, as well as the fused MR-TRUS image following SMM-FEM registration, is shown in Figure 4.7. The $L_2$ distance between these fiducial pairs was used to quantify the TRE. The fiducial localization error is approximately $0.21$ mm for TRUS and $0.18$ mm for MR, as reported in a previous study [71, 141]. This suggests that the FLE is not likely to dominate.

Table 4.2: TRE for registration algorithms. The $p$-values reflect Wilcoxon signed-rank tests compared to initialization. Partial data represents $\approx 70\%$ of the TRUS and $\approx 80\%$ of the MR surfaces, respectively.

<table>
<thead>
<tr>
<th>Method</th>
<th>TRE (mm)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
<td>Partial</td>
</tr>
<tr>
<td>Initial</td>
<td>4.86 ± 1.43</td>
<td>4.53 ± 1.35</td>
</tr>
<tr>
<td>SSM</td>
<td>3.86 ± 1.26</td>
<td>3.95 ± 1.26</td>
</tr>
<tr>
<td>GMM-FEM</td>
<td>2.72 ± 1.15</td>
<td>4.89 ± 1.46</td>
</tr>
<tr>
<td>SSM-FEM</td>
<td>2.35 ± 0.81</td>
<td>2.81 ± 0.66</td>
</tr>
</tbody>
</table>

The mean and standard deviation of the TREs, as well as corresponding $p$-values when compared to initialization, are shown in Table 4.2. To investigate the statistical significance, we first check whether or not the TRE distributions are normally distributed. Using a one-sample Kolmogorov-Smirnov test, the TREs were found not to be normally distributed at the 95% significance level ($p \leq 10^{-4}$). As a result, we performed a set of Wilcoxon signed-rank tests, which are robust to deviations from normality. The null hypothesis is that the TREs of the initialization and the subsequent registration method share a common median at the 95% significance level.

For full surfaces, all three methods (SSM, GMM-FEM and SSM-FEM) significantly decrease the TRE compared to the initial rigid registration. The mean TRE improvement for SSM, GMM-FEM and SSM-FEM registration methods is 1.00 mm, 2.14 mm and 2.51, respectively. The mean TRE for SSM-FEM registration is 1.51 mm lower compared to SSM registration alone. This suggests that the transformation between MR and TRUS surfaces is not rigid: substantial deformations exist. For partial surfaces, SSM led to a decrease in mean TRE by 0.58 mm, and GMM-FEM to an increase by 0.36 mm. However, these differences are deemed not significant at the 95% level. The $1.72$ mm decrease in TRE of the proposed SSM-FEM, however, is significant at the 95% level ($p < 10^{-4}$).

Table 4.3 shows the TRE following SSM-FEM registration for fiducials
4.3. Experiments and Results

Table 4.3: TRE for SSM-FEM registration at base, mid-gland and apex for full and partial data. Partial data represents $\approx 70\%$ of the TRUS and $\approx 80\%$ of the MR surfaces, respectively.

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Mid-gland</th>
<th>Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>2.87 ± 0.75</td>
<td>1.95 ± 0.61</td>
<td>2.53 ± 0.91</td>
</tr>
<tr>
<td>Partial</td>
<td>3.12 ± 0.65</td>
<td>2.21 ± 0.45</td>
<td>3.05 ± 0.76</td>
</tr>
</tbody>
</table>

Table 4.4: Wilcoxon signed-rank tests between methods. Partial data represents $\approx 70\%$ of the TRUS and $\approx 80\%$ of the MR surfaces, respectively.

<table>
<thead>
<tr>
<th>Test</th>
<th>p-value</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
<td>Partial</td>
<td></td>
</tr>
<tr>
<td>GMM-FEM vs. SSM</td>
<td>$10^{-4}$</td>
<td>$10^{-3}$</td>
<td></td>
</tr>
<tr>
<td>SSM-FEM vs. SSM</td>
<td>$10^{-6}$</td>
<td>$10^{-5}$</td>
<td></td>
</tr>
<tr>
<td>SSM-FEM vs. GMM-FEM</td>
<td>0.45</td>
<td>$10^{-4}$</td>
<td></td>
</tr>
</tbody>
</table>

at the base, mid-gland and apex, separately. Errors in the mid-gland are consistently lower compared to those in the base and apex for both full and partial data. The reason for this is likely that prostate segmentations here are more reliable compared to the base and apex, leading to fewer assumptions when reconstructing the deformation field.

To compare the methods, we performed additional Wilcoxon signed-rank tests on the paired TREs, the $p$-values of which are reported in Table 4.4. From these tests, we see that GMM-FEM significantly outperforms SSM alone when the full segmentations are available ($p < 10^{-4}$), but SSM is the better of the two when only partial segmentations are available ($p < 10^{-4}$). Upon inspection, we observed that the increased error in GMM-FEM is mainly due to a mis-assignment of the base to apex regions (i.e. flipping). The SSM component is able to mitigate this, providing enough additional information to prevent flips caused by a lack of corresponding surface features. Comparing SSM to SSM-FEM, we see that the flexibility added by the finite element model leads to significant reductions in TRE for both full and partial surfaces ($p < 10^{-5}$). Finally, comparing SSM-FEM to GMM-FEM, we find that the difference in TRE is not significant at the 95% level when full surfaces are available. However, when applied to partial segmentations, SSM-FEM does significantly outperform GMM-FEM ($p < 10^{-4}$).

Finally, we investigate the impact on TREs of using full versus partial segmentations. For GMM-FEM, there is a significantly large increase in TRE of 2.1 mm ($p < 10^{-3}$) when applied to partial TRUS data. The soft-
correspondences alone are found not sufficient for handling uncertainties in segmentations. For SSM, the difference in TRE between full and partial surfaces is minor (0.39 mm, \( p = 0.25 \)). Similarly, for SSM-FEM, there is no statistically relevant difference in TRE (0.46 mm, \( p = 0.33 \)). This suggests that for SSM and SSM-FEM, a full segmentation of the prostate is not necessary: registration based on partial surfaces produces similar TREs.

Computation times for the SSM, GMM-FEM and SSM-FEM methods are provided in Table 4.5. Timings are reported on a regular desktop PC with a 3.4 GHz Intel Core i7 CPU with 8.00 GB of RAM. Due to the increased computational complexity of both the FEM and SSM components, it is not surprising that the SSM-FEM algorithm is the slowest. However, the mean total computation time is still under one minute when applied to both full and partial surfaces, making it practical for clinical use.

<table>
<thead>
<tr>
<th>Method</th>
<th>Time (s)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full</td>
<td>Partial</td>
<td></td>
</tr>
<tr>
<td>SSM</td>
<td>5.72 ± 0.53</td>
<td>5.51 ± 0.42</td>
<td></td>
</tr>
<tr>
<td>GMM-FEM</td>
<td>9.54 ± 3.26</td>
<td>8.69 ± 2.21</td>
<td></td>
</tr>
<tr>
<td>SSM-FEM</td>
<td>50.61 ± 6.82</td>
<td>29.34 ± 2.55</td>
<td></td>
</tr>
</tbody>
</table>
4.3. Experiments and Results

(a) Box-plot distribution of TREs (mm) with different magnitudes of Gaussian noise.

(b) Box-plot distribution of TREs (mm) with different Gaussian kernel widths. A value of zero refers to a segmentation without any added noise.

Figure 4.8: The effect of Gaussian noise on TRE (mm) values with registration parameters $E = 5.0$ kPa, $\mu = 400$, $\beta = 10.0$, and $\nu = 0.49$.  

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4.3.3 Sensitivity to Errors in Segmentation

Segmentation of MR and TRUS images will inevitably contain intra-observer and inter-observer variability. Here, we explore the sensitivity of SSM-FEM to such errors. We synthetically perturbed both TRUS and MR full segmentations using a Gaussian kernel to simulate an additive Gaussian noise. This kernel has two parameters: 1) width ($\sigma$), which controls the locality of segmentation errors; and 2) magnitude ($\alpha$). Our protocol for creating noisy surfaces is as follows:

1. Select a random seed face.
2. Calculate the normal ($\vec{n}$) and center ($c$) of the seed face.
3. For every point ($x$) on the segmented prostate, add the following Gaussian noise: $\alpha \vec{n} \exp(\|x - c\|^2 / 2\sigma^2)$

For every combination of $\alpha \in [-10.0, 10.0]$ mm and $\sigma^2 \in [5.0, 50.0]$, we generated 1000 noisy MR and TRUS surfaces. These surfaces were used to investigate the sensitivity of the TRE in the presence of Gaussian noise. Figures 4.8a and 4.8b illustrate the sensitivity of the TRE to the magnitude and width of the Gaussian noise.

Figure 4.8a shows the sensitivity of the TRE to the magnitude of Gaussian noise with a constant kernel width ($\sigma^2 = 25.0$ mm$^2$). The general trend in this figure is that the TRE increases with the magnitude of the additive Gaussian noise. The mean TRE stays below 3.0 mm for Gaussian noise magnitudes between $[-5.0, 5.0]$ mm. This value provides a rough confidence interval for segmentation accuracy.

Figure 4.8b shows the sensitivity of the TRE to the kernel width given a constant noise magnitude ($\alpha = 7.5$ mm). The general trend, again, is that the TRE increases with the width of the Gaussian kernel. At small kernel widths ($\sigma^2 \leq 10.0$ mm$^2$), the TRE seems to be unaffected with the added noise, even though its magnitude is large ($\alpha = 7.5$ mm). We believe the main contributor to this behavior is the soft-correspondence approach, since probabilistic solutions to point cloud registration are known to be robust to outliers [21, 98].
4.3. Experiments and Results

(a) Box-plot distribution of robustness as observations are removed

(b) Left to right: Spatial distribution of robustness for SSM-FEM registration when 10%, 20% and 40% of observations are removed.

Figure 4.9: Distribution of robustness as different percentages of observations are removed with $E = 5.0$ kPa, $\mu = 400$, $\beta = 10.0$, and $\nu = 0.49$. Sagittal slice of robustness for SSM-FEM registration when different amounts of observations are removed. For better visualization, distances larger than 6 mm are shown in the same color.

4.3.4 Sensitivity to Missing Surface Points

Until now, the partial surfaces were defined based on a visibility criterion: if the prostate boundary is unclear in certain regions of the images, those sections of the segmentations were removed. What remained represented approximately 80% of the original MR surfaces, and 70% of the TRUS surfaces. Here, we investigate robustness of our method to missing data by systematically removing points (i.e. rows of $X_{md}$) from both the base and apex (from 2.5% to 20% from each). Subsequently, we applied our algorithm to the cropped observations. To quantify performance, we compared the internal deformation computed using partial surfaces to that using the full surfaces, measuring the $L_2$ distance between the displacement fields. Intuitively, this evaluates the method’s ability to recover the same deformations in the presence of missing data.

Results of this experiment are shown in Figure 4.9 for a typical biopsy patient. The majority of the deformation stays below 2.0 mm when 10% of the observations are removed. The crosses in Figure 4.9a correspond to points that fall outside the 1.5×interquartile-range. These are mostly concentrated along boundary of the prostate, seen as green–red in Figure 4.9b. The robustness of SSM-FEM registration progressively declines as
more points from the base and apex are removed.

As seen in Figure 4.9b, the deformation field in the centre (interior) of the prostate is more robust to missing data compared to near the surface. Removing surface data most strongly affects results in the immediate vicinity. The effect, however, rapidly drops-off as we move away from the surface. This is a consequence of the FE model: forces are propagated from the boundaries, inward, and begin to balance each other.

Figure 4.10: Robustness of SSM-FEM registration for different regularization weights. (a) varying the SSM scale factor, \( \mu \). (b) varying the FEM scale factor, \( \beta \). Weights are perturbed around parameters which provided the best surface overlap (\( E = 5.0 \) kPa, \( \nu = 0.49, \mu = 400 \) and \( \beta = 10.0 \)). For better visualization contrast, distances larger than 6 mm are shown with the same color.

### 4.3.5 Sensitivity to Regularization Parameters

There are two tunable parameters that control the regularization: \( \mu \) and \( \beta \). To examine the sensitivity to these values, we perturbed \( \mu \in [200, 700] \), and \( \beta \in [0.1, 1000] \). Results are shown in Figure 4.10 for a typical fully segmented
4.4 Discussion and Conclusions

Sensitivity of the deformation field to $\mu$, controlling SSM shape parameters, is shown in Figure 4.10a. The registration seems not to be sensitive to these perturbations. For small values, $\mu \leq 200.0$, the registration becomes unstable; the SSM is not sufficiently constrained, so it produces unrealistic shapes. For large Tikhonov values, $\mu \geq 550.0$, the SSM is restricted to instances very close to the mean. For values between the two extremes, the search space is restricted to reasonable SSM instances. As seen in Figure 4.10c, changes in $\mu$ mostly affect the boundary of the prostate; regions interior are less sensitive to these perturbations.

SSM-FEM is more sensitive to the biomechanical regularization weight, $\beta$ (Figure 4.10b). When tuning this parameter, the registration exhibits three distinct behaviors. For large values, $\beta \geq 50.0$, the FEM is essentially rigid, allowing no further deformation. For very small weights (e.g. $\beta \leq 2.5$), the FEM does not resist any deformation: the surface is allowed to move freely, independently of interior nodes. For values between the two extremes, the parameter allows a trade-off between surface-fitting and deforming. A spatial distribution of robustness for the three different behaviors is shown in Figure 4.10d. This parameter should be tuned for the application. We found a value of $\beta = 10$ is a good starting point for allowing reasonable deformations. If this leads to a model that is overly flexible, the value should be increased.

4.4 Discussion and Conclusions

In this chapter, we presented a novel non-rigid surface-based registration approach that is robust to missing data. The method uses a statistical shape model as an intermediary to help co-register two partial surfaces. The SSM introduces geometric prior knowledge, allowing for varying shapes across a population. To account for physical deformations, we introduce a finite-element based regularizer. This adds flexibility to the SSM, accounting for differences in biomechanical states between the observed partial surfaces.

The proposed registration algorithm converges within a minute on a regular desktop PC. We showed the internal deformation found through our method to be robust up to 2.0 mm when 10% of the surfaces are removed. A great advantage of the algorithm is that it estimates point-correspondences, nodal displacements, shape, and pose parameters in a single minimization framework. This is one of the contributing factors to the efficiency. We also obtain a full volumetric deformation field as a by-product of the regulariza-
tion. This is in contrast to many existing surface-based approaches, where deformations need to be estimated from the surface in a post-processing step.

In Section 4.3.2, we investigated the performance of our method using intrinsic fiducial pairs. We compare to two alternatives: group-wise SSM, where the influence of the biomechanical (FEM) prior is removed; and GMM-FEM, where the influence of the geometric (SSM) prior is removed. SSM-FEM yields a statistically significant improvement compared to SSM registration alone (by 1.51 mm for full surfaces, 1.14 mm for partial). This indicates that the FEM component plays an important role, accounting for differences in deformation states of the prostate in the two observations. When comparing to GMM-FEM, the difference in TRE was only found to be statistically significant when partial surfaces are used (2.0 mm, \( p < 10^{-4} \)). In this case, we saw that GMM-FEM sometimes resulted in mis-assignments of the base and apex. The SSM adds sufficient information to prevent this.

We did not compare SSM-FEM to other methods that combine a SSM and FEM, such as that by Hu et al. [60]. While both use an EM algorithm to maximize a similar functional, the role of the SSM and FEM are different. The approach by Hu et al. requires full segmentations of the MR, including not only the prostate, but also the surrounding anatomy. Thus, it is assumed all tissues boundaries are clearly visible. Based on the segmentations, a personalized FEM is created and used to train a subject-specific SSM, which is then used to register directly to a new image. The training process must be repeated for every new subject, since it is a personalized model. In SSM-FEM, the SSM represents variations in prostate shapes across subjects. The FEM then adds flexibility to account for additional deviations and deformations.

In Section 4.3.3, we investigated the sensitivity of SSM-FEM to errors in segmentation of the MR and TRUS surfaces. For ambiguities within ±5.0 mm, we found the TRE to be insensitive to segmentation variability. It has been previously reported that expert inter-subject variation of prostate contours falls in the range of [0.7, 2.5] mm [138]. Since the TRE for our registration method seems to be insensitive to variations in contouring within this range, we infer that errors caused by inter-subject variations will be negligible.

The most time-consuming portion of the registration method is the finite-element mesh creation, which is repeated every time a new SSM shape instance is generated. Efficiency can be improved by meshing only when the SSM instance differs significantly from the previous iteration. Another shortcoming of our algorithm is that it requires both the MR and TRUS to be segmented prior to the registration. While the MR can typically be seg-
mented ahead of time, the 3D-TRUS needs to be segmented within minutes due to the clinical requirements. Since our algorithm is designed to handle partial surfaces and is robust to missing data, we suggest to only segment regions in which the boundary of the anatomy can be clearly distinguished (such as the mid-gland). This can help expedite the segmentation process. For the regions that have clear boundaries, a semi-automatic segmentation method can also be useful [114].

While the improvement in the TRE seems small (on the order of a millimeter), it should be compared to the acceptable error bounds of a targeted biopsy system. A clinically significant tumor has a radius of at least 5 mm [71]. A TRE of 2.5 mm would lead to a confidence interval in which 95% of targets fall within that radius. Our values of $2.35 \pm 0.81$ mm and $2.81 \pm 0.66$ mm for full and partial surfaces respectively, brings us close to these bounds.

In this chapter, the method was limited to surfaces segmented from two modalities. However, it can be trivially extended to concurrently register more than two surfaces. Such a situation may arise when the patient is scheduled for a re-biopsy, and it is desirable to simultaneously register MR, the previous TRUS, and the current TRUS. This would enable the radiologist to avoid areas that in the previous biopsy were found to be cancer-free, and enable re-sampling suspicious areas. The extension is accomplished by simply modifying the objective function in Equation (4.2) to sum over further observations.

The implicit assumption when using the SSM as a “starting shape” for computing biomechanical deformations is that it represents the prostate “at rest”. This assumption is not true in general, since there will always be some biomechanical forces present in the training population (e.g. pressure from the bladder, gravity, probes/endorectal coils). Ideally, the training images would be acquired under conditions where these forces are minimized. The training population in our study is a compromise in size, segmentation accuracy, and initial biomechanical forces. To account for errors caused by existing deformations in the training data, an initial strain field can be estimated. This can be accomplished by measuring or estimating any external forces (e.g. from a force sensor on a transrectal probe), and back-solving for the initial strain [108].

We currently assume a homogeneous linear material model for the FEM. The homogeneity assumption is similar to uniform smoothness of the interpolation field in other surface-to-surface registration techniques. An advantage of the FEM framework is that including spatially varying properties, such as a localized stiff region caused by a tumor, is possible as long as the ap-
4.4. Discussion and Conclusions

Appropriate data is available. Such data may be defined manually, or obtained via elastography and registered to the model. The only step modified in the registration algorithm is the computation of the stiffness matrix, $K$. It is also possible to incorporate non-linear material models, such as the Mooney-Rivlin material [122]. This requires modifying the strain energy term used in the regularization, linearizing about the current deformation state. This will introduce a synthetic force to be added to the objective function.

While the application in this chapter is MR-TRUS fusion for prostate biopsies, the proposed method is not limited to this context. It is applicable as long as the following conditions are met: 1) a statistical shape model of inter-subject variability is available; and 2) each observation surface represents a snapshot of the deformed anatomy. A free-hand ultrasound probe may be used if it is tracked to allow for 3D image reconstruction prior to segmentation. However, the second condition may fail if motion of the probe induces significantly different deformations between slices. In that case, the reconstructed image would not represent a single consistent deformation state.

Our probabilistic algorithm is based on very simple concepts: soft correspondences via Gaussian mixture models, geometric prior knowledge provided by a statistical shape model, and biomechanical regularization based on a linearized finite element model. The soft correspondences make the method robust to noise and missing data points; the SSM provides geometric information when boundaries of anatomical regions are not clear in images; and the FEM adds flexibility, allowing the shape to deform to account for soft-tissue motion between acquisitions. The method is general and robust, able to co-register any set of full or partial segmented surfaces.
Chapter 5

2D-3D Registration for Freehand Prostate Biopsies

5.1 Introduction

Prostate biopsy is the gold standard for prostate cancer diagnosis. This is typically performed freehand using 2D TRUS guidance. Unfortunately, the current systematic biopsy approach is prone to false negatives [84], and patients are frequently asked to repeat the procedure. To improve the cancer yield, 3D biopsy systems have been developed [6, 135, 159]. In these systems, biopsy locations are planned and recorded with respect to a 3D-TRUS reference volume acquired just prior to the procedure. However, the prostate moves and deforms during the biopsy process, in a way which cannot be compensated for using passive tracking alone [6, 135, 159]. Without motion and deformation compensation through slice-to-volume registration, the live ultrasound image will deviate more with respect to the reference volume, making it infeasible for the radiologist to accurately sample planned targets. As a result, slice-to-volume registration is required to maintain alignment of the 2D imaging plane with respect to the pre-procedure 3D-TRUS. The goal of this chapter is to provide the registration tools to perform such freehand 3D-guided prostate biopsies.

5.1.1 Related Work

2D-3D registration in the literature can refer to the alignment of 3D images to a single tomographic or projective slice. In the first case, each pixel from the 2D slice image is assumed to have a corresponding voxel in the 3D image. In this case, 2D-3D registration is an extreme case of 3D-3D registration, where one of the images spans a single slice. Examples of tomographic 2D-3D registration include the alignment of interventional MRI slices and pre-procedure 3D MRI [40] or 2D-US and CT [23, 63, 155].
In the second case, for projective slices, the one-to-one correspondence between 3D and 2D data is no longer valid and therefore a different approach is required. Methods for projective 2D-3D registration incorporate either a projection \[10, 105\], or a reconstruction \[43\] operator. Using a projective operator, the 3D data is transformed into the 2D domain such that the projections and 2D data until the best match is obtained. With a reconstruction operator, the 2D projections are back-projected into the 3D domain until the reconstructed data is aligned with the 3D image.

Both tomographic and projective 2D-3D methods formulate the registration problem as a minimization of a metric with respect to a set of transformation parameters. This transformation dictates the spatial mapping between the 2D slice and the 3D volume. Common metrics for 2D-3D registration problems include sum-of-squared differences (SSD) \[18\], normalized cross correlation (NCC) \[135\] and mutual information (MI) \[167\].

2D-3D registration for prostate biopsy falls into tomographic 2D-3D registration. As a result, we assume that the 2D slice is a 3D image with a single frame and treat 2D-3D registration similar to 3D-3D registration (see Section 5.2.2). However, robust 2D-3D TRUS registration in a freehand environment is still a challenging task. First, an accurate volume representing the prostate “at rest” must be generated. For freehand biopsies, this volume is typically acquired using a tracked axial sweep from base to apex \[74, 159\]. Unfortunately, due to patient discomfort and inconsistent probe pressure, resulting volumes suffer from deformation artifacts. To reduce these, systems have been developed that use mechanical stabilization \[135\] or 3D probes \[6\], ensuring consistent probe pressure. The second challenge relates to the nature of the 2D-3D registration problem. The limited 2D spatial information, low signal-to-noise ratio of TRUS, and varying probe-induced pressures, all make motion and deformation compensation difficult. When the probe is mechanically stabilized, De Silva et al. \[134, 135\] show that rigid 2D-3D registration is sufficient for 3D guidance. They approximate the prostate as rigid, and its motion is learned based on probe positions/orientations \[134\]. Systems that use 3D probes \[6\] avoid the 2D-3D registration issue, since the additional out-of-plane information can be used to increase accuracy and robustness \[29, 74\]. However, neither mechanical systems nor 3D probes are widely used in clinics. A solution for freehand 3D-guidance using 2D-TRUS probes, as part of the current standard-of-care, is highly desirable.

In this chapter, we provide a solution for freehand TRUS-guided prostate biopsies using a combined rigid and non-rigid 2D-3D registration. The closest works to ours, involving slice-to-volume registration on freehand TRUS data, are by Xu et al. \[159\] and Khallaghi et al. \[74\]. The shortcoming
5.2. Methods

5.2.1 Data Acquisition

The TRUS images in this study were acquired using a magnetically tracked EC9-5/10 probe with a custom data collection software running on a Sonix Touch machine (Ultrasonix Inc., Canada). Prior to the procedure, the probe was calibrated at a depth of 6.0 cm with an N-wire phantom using fCal [82] (calibration accuracy of $0.45 \pm 0.2$ mm). At the start of the procedure, we asked an interventional radiologist to perform a freehand axial sweep of the prostate gland, from base to apex. We refer to the tracked probe’s tip along the sweep as the trajectory. This trajectory is shown graphically
5.2. Methods

Figure 5.1: Clinical workflow. **Pre-procedure:** The radiologist takes a free-hand sweep of the prostate gland from base to apex (frame stack shown in gray). This sweep is used to construct a probe tip trajectory and a 3D volume (sagittal view). This volume is segmented to create a FEM consisting of two regions: the prostate, and the surrounding soft tissue. **Intra-procedure:** The 2D-TRUS is registered using a rigid transform constrained by the trajectory. Subsequently, a FEM-based non-rigid registration is used to compensate for residual deformations.

with red/green/blue axes in Figure 5.1. Each sweep was obtained at 20 frames/second (≈ 500 frames total), and used to reconstruct a 3D volume of the prostate and surrounding tissue. To account for small fluctuations in probe pressure during the pre-procedure sweep, a moving average with window length of 65 was applied to the transforms. Since the prostate is known to be stiffer than the surrounding tissue [72], we manually segmented the prostate in the 3D-TRUS and created a simplified FEM consisting of two regions: prostate, and the surrounding tissue (see Section 5.2.2). If desired, segmentation can be automated [160], or skipped and a single homogeneous FEM can be used [89]. Note that commercial 3D-TRUS systems, such as UroNav (Invivo Co., USA) and Artemis (Eigen Inc., USA) already incorporate intra-operative segmentation of the prostate on TRUS images. If elastography becomes part of the prostate biopsy protocol, spatially-varying material properties can also easily be incorporated into the FEM.

Throughout the procedure, tracked TRUS images were obtained continuously at 20 frames/second. At each biopsy location, we asked the radiologist to press a foot-pedal to tag the TRUS image associated with the core. The 2D-TRUS at each biopsy core was used then for off-line validation of our
5.2. Methods

framework. The two major components are the rigid registration, and the FEM-based deformable registration methods, which are discussed in Section 5.2.2. We refer to the pre-procedure 3D-TRUS and the intra-procedure 2D-TRUS as source and target images, respectively. A full workflow is presented in Figure 5.1.

5.2.2 2D-3D Registration

We treat the 2D images in this chapter as 3D images with a single slice. This facilitates the linear algebra in our implementation since the calibration and magnetic tracking transforms are recorded using homogeneous transforms of type $\begin{bmatrix} R_{3 \times 3} & t_{3 \times 1} \\ 0_{1 \times 3} & 1 \end{bmatrix}$, where $R_{3 \times 3}$ is the rotation and scale component of the transformation and the $t_{3 \times 1}$ represents the translation.

The 2D-3D registration is framed as the minimization of an objective functional between the planar 2D target image, $F(x) : \mathbb{R}^3 \to \mathbb{R}$, and the 3D source, $M(x) : \mathbb{R}^3 \to \mathbb{R}$, where $x \in \Omega$ refers to grid points on the target slice. We denote the number of points in $\Omega$ by $N$ and concatenate them into a single $3N \times 1$ vector, $\vec{x}$. Since the problem is mono-modal, we used the SSD for the intensity metric. Other intensity-based metrics, such as NCC, mutual information, and MIND can also be used. However, it has been previously shown that the Demons registration method works well for ultrasound registration of elastic organs [73]. Since Demons is derived using SSD [109], we chose this metric for the image-based component of our framework. For rigid registration, the transform is constrained using the probe trajectory. For FEM-based registration, the objective functional is regularized using the total strain energy of the FEM.

**Trajectory-based Rigid Registration:** We formulate the rigid registration as the minimization of the objective functional:

$$Q_r(s, \theta_1, \theta_2, \theta_3) = \frac{1}{2N} \|F(\vec{x}) - M(T_r(s, \theta_1, \theta_2, \theta_3, \vec{x}))\|^2,$$

where $T_r(s, \theta_1, \theta_2, \theta_3, x)$ is a rigid transform. The translation component is restricted to the probe tip trajectory parameterized by $s \in [0, 1]$. This trajectory approximates the rectal wall in the 3D volume, on which the probe tip in the live 2D imaging plane should also fall. We did not constrain this parameter in our implementation, however, a quadratic penalty such as $s^2$ can be applied if rigid registration is trapped in local minima in future datasets. Rotation around the probe tip is controlled by the three Euler angles $(\theta_1, \theta_2, \theta_3)$. Euler angles are susceptible to the Gimbal lock issue,
5.2. Methods

however, we only expect the amount of correction in rotation to be small since the position and orientation of the probe is already tracked.

To initialize the location parameter \( s \), we project the tracked probe tip to the trajectory. The rotation is initialized using the orientation from magnetic tracking. We then used the “pattern search” optimizer in Matlab (Math-Works, USA) to find the optimal rigid parameters \((s, \theta_1, \theta_2, \theta_3)\).

**FEM-based Registration:** Central to the deformable registration is a FEM, constructed from the 3D image volume using a \( 8 \times 8 \times 8 \) grid of hexahedral elements. For simplicity, we use a linear material, which depends on a Young’s Modulus, \( E \), and Poisson’s ratio, \( \nu \). Since the prostate more stiff than the surrounding tissue, we increase the Young’s Modulus within this region. Similar to [89], we do not assume any boundary conditions; the FEM is freely able to move based on image-driven forces. We systematically compute the stiffness matrix of the FEM, \( K_{3J \times 3J} \), where \( J \) is the number of FEM nodes in the hexahedral grid. We formulate the objective functional as a regularized SSD metric:

\[
Q_{\text{FEM}}(\vec{u}) = \frac{1}{2N} \left\| F(\vec{x}) - M(\vec{x} - \Phi \vec{u}) \right\|^2 + \frac{\alpha}{2} \left\| \vec{u} - \vec{u}^{(p)} \right\|^2 + \frac{\beta}{2} \vec{u}^T K \vec{u},
\]

(5.2)

where \( \vec{u}_{3J \times 1} = (u_{11}, \ldots, u_{13}, \ldots, u_{J3})^T \) is the vector of FEM node displacements. A damping term is added for stability, scaled by a coefficient \( \alpha \), that limits deviation from the displacement values in the previous iteration, \( \vec{u}^{(p)} \). Deformation is controlled by the strain energy, scaled by regularization weight \( \beta \). The interpolation matrix, \( \Phi_{3N \times 3J} \), is used to represent spatial coordinates \( \vec{x} \) in terms of the FEM node locations. It is constructed by detecting which deformed element contains each point, \( \vec{x} \), and computing interpolation coefficients based on the element’s shape functions (similar to computing barycentric coordinates). Differentiating Equation (5.2) with respect to the \( l \)th coordinate of node \( k \), \( u_{kl} \), yields

\[
\frac{\partial Q}{\partial u_{kl}} = \frac{1}{N} \sum_{n=1}^{N} \left[ F_n(\vec{x}) - M_n(\vec{y}) \right] \sum_{m=1}^{3} \frac{\partial M_n(\vec{y})}{\partial y_{nm}} \left( \Phi_{nk} + \sum_{j=1}^{J} \frac{\partial \Phi_{nj}}{\partial u_{kl}} u_{jm} \right) \\
+ \alpha \left( u_{kl} - u_{kl}^{(p)} \right) + \beta \sum_{j=1}^{J} \sum_{m=1}^{3} K(3k+l)(3j+m) u_{jm},
\]

(5.3)

where \( \vec{y} = \vec{x} - \Phi \vec{u} \) are the mapped coordinates in the moving image volume, \( n \) loops over all pixels in the fixed image plane, \( m \) loops over the three dimensions, and \( j \) loops over all FEM nodes. The derivative of the shape functions
5.3 Experiments and Results

with respect to nodal displacements, $\partial \Phi_{nj}/\partial u_{kl}$, can be derived based on the FEM shape functions. We use standard linear shape functions, which are typically defined in terms of isoparametric (or ‘natural’) coordinates $(\xi, \eta, \mu)$. In such a case, one can derive the following expression:

$$
\frac{\partial \Phi_{nj}}{\partial (u_{k0}, u_{k1}, u_{k2})} = -\Phi_{nj}(J^{-1}) \frac{\partial \Phi}{\partial (\xi, \eta, \mu)},
$$

(5.4)

where $J$ is the Jacobian matrix of the element containing point $x$. Details of the derivation are given in Appendix C. By differentiating Equation (5.2) for all coordinates $(k, l)$, we arrive at the sparse linear system:

$$(\Gamma + \alpha I + \beta K) \vec{u} = \Upsilon + \alpha \vec{u}^{(p)},$$

(5.5)

where $\Upsilon$ and $\Gamma$ are defined by collecting the appropriate terms from Equation (5.3). For the implementation, it is useful to note that if a point $\vec{x}_n$ falls in an element, then $\Phi_{nk} = \partial \Phi_{nk}/\partial u_{kl} = 0$ for all nodes $i$ not belonging to that element. Still, computation of $\Upsilon$ and $\Gamma$ is the most time-consuming portion of our registration. For each point $x$, it requires finding the element containing that point, and determining its interpolation functions and their derivatives within the element. We use a bounding volume hierarchy to accelerate the element-detection component. To further improve efficiency, $\Upsilon$ and $\Gamma$ can be computed in parallel per pixel.

For linear materials, it can be shown that the stiffness matrix scales linearly with the Young’s modulus. As a result, the Young’s modulus can be factored out and combined with $\beta$ to create a single free parameter. This means that the proposed registration method has four free parameters: damping coefficient ($\alpha$), relative soft tissue to prostate elasticity ($E_t/E_p$), scaled prostate elasticity ($\beta E_p$) and Poisson’s ratio ($\nu$). Throughout the experiments, we used the following values: $\alpha = 1.0$, $\beta E_p = 0.25 \times 5.0$ kPa [72], $E_t/E_p = 0.2$ [72], $\nu = 0.49$ [89]. The damping parameter, $\alpha$, prevents large gradients from inducing too strong a force. It should be set large enough to maintain stability, but not too large or it will reduce the convergence rate. The scale parameter, $\beta$, controls the relative influence of the image-driven forces and the restoring energy of the FEM. We tuned this parameter to allow realistic deformations. The same parameter values were used for all subjects.

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The proposed 2D-3D registration was evaluated on 10 patients. The systematic sextant biopsy protocol in our hospital requires the acquisition of
5.3. Experiments and Results

Figure 5.2: Example of a calcification (a) and a cyst (c) on the target slice. The corresponding fiducial on the source volume is shown in (b) and (d), respectively.

8–12 distributed cores, with extra cores in suspicious regions. For the patients in this study, this yielded a total of 10 pre-procedure TRUS volumes and 115 2D TRUS slices at biopsy cores. To quantify registration error, we computed the Euclidean distance between intrinsic fiducials, consisting of micro-calcifications and cysts (Figure 5.2). A total of 65 fiducials were identified by the author.

Figure 5.3 shows registration results for three patients. In the top-row, rigid registration performs well, however, there is a slight improvement near the prostate boundary following FEM-based registration. The middle-row shows an example where FEM-based registration corrects for the boundary and brings additional structures into the registration plane. In the bottom-row, FEM-based registration is required to correctly identify the calcification.

As seen in Table 5.1, rigid and FEM-based registration reduce the mean TRE from the initial 6.31 mm down to 4.63 mm and 3.15 mm, respectively. This suggests that substantial biomechanical deformations exist and can be compensated for using our FEM-based approach. To investigate the statistical significance of TRE reduction, we first checked if the TREs were normally distributed. Using the one-sample Kolmogorov-Smirnov test, we found that the distribution of the TRE is not normal at the 5% significance level for initial, rigid and FEM-based methods ($p < 10^{-4}$). Therefore, we performed a signed Wilcoxon rank sum test. The $p$-value from this experiment is also shown in Table 5.1. The test rejected the hypothesis that TREs for initial vs. rigid and rigid vs. FEM-based methods belong to a distribution with equal medians. Therefore, the improvements in mean TRE following rigid and FEM-based registration are statistically significant.
5.4 Discussion and Conclusions

We presented a novel registration framework for motion and deformation compensation during a freehand TRUS-guided prostate biopsy. The improvement in the TRE using the FEM-based registration should be compared to the acceptable error bounds of a 3D prostate biopsy system. A TRE of 2.5 mm yields a confidence interval in which 95\% of registered targets come within the smallest clinically significant tumor [71]. The result of our FEM-based registration (3.15 mm) brings us closer to this acceptable error bound. In our study, no instructions were given to the radiologist to control the probe pressure. If the biopsy protocol is slightly modified to maintain a low probe pressure, it should be possible to decrease the error closer to a clinically acceptable range [71].

The explicit assumption when using the pre-procedure volume is that

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<thead>
<tr>
<th>Target</th>
<th>Initial</th>
<th>Rigid</th>
<th>FEM-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 5.3: Typical registration results for three patients (top, middle and bottom rows). The first column denotes the live 2D-TRUS (target) images. The next three columns show the initial alignment using the trajectory, rigid registration, and FEM-based registration results, respectively. White arrows indicate locations where the registration framework shows improvements.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.1: Registration results and $p$-values.

<table>
<thead>
<tr>
<th>TRE, mean ± s.d. (mm)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Rigid</td>
</tr>
<tr>
<td>6.31 ± 1.86</td>
<td>4.63 ± 1.05</td>
</tr>
</tbody>
</table>
5.4. Discussion and Conclusions

it represents the prostate “at rest”. This assumption is not true in general, since there will always be some biomechanical forces present during the sweep (e.g. pressure from the probe, the bladder, and gravity). Ideally, the sweep would be acquired under conditions where these forces are minimized. To account for errors caused by existing deformations in the sweep, a possible solution is to use a super resolution approach similar to [45] that is capable of compensating for deformations between slices in the freehand sweep.

Our next steps aim to increase the accuracy of the proposed framework. Given that the landmarks used to calculate the TRE in this study were acquired using the author, a more extensive validation using landmarks selected by expert clinicians is warranted. Furthermore, since the quality of the pre-procedure volume directly affects registration results [74], we wish to tackle challenges associated with deformation artifacts due to breathing and inconsistent probe pressure, including estimating a “rest shape” of the prostate using shape statistics, and validating the reconstructed volume against magnetic resonance images. Another direction is to perform multi-slice registration, which has been shown to improve the TRE [29, 74], and compare our non-rigid registration approach to other methods [74].

The current run-times of the rigid and FEM-based components of our framework are in the order of ≈30 seconds and ≈10 minutes, respectively. Decreasing the registration time can be accomplished by calculating the terms in Equation (5.3) in parallel per pixel on a graphics processing unit, by adopting a multi-resolution approach, using a boundary element method [64], through a partial differential equation formulation [102] and by performing registration continuously during the procedure [29].

There are four plausible scenarios for the execution time once we have a GPU implementation. If the registration can be done in less than one second, then our method can be readily used for live guidance. If the execution time is between 1-10 seconds, similar to [6], then continuous FEM-based registration is not feasible. However, we might still be able to use a Kalman filter to estimate the deformation state of the prostate [89], such that we only require FEM-based registration every 10 seconds. If the FEM-based run-time is between 10-30 seconds, then we most likely have to rely on rigid registration for guidance throughout the procedure and use FEM-based registration only at biopsy targets. If the execution time is above 30 seconds, our FEM-based registration is not suitable for prostate biopsies.

Given that Baumann et al. [6] achieve a non-rigid registration time of 7 seconds for 3D-3D registration, and their volumes are larger than our single slice, we believe an expected execution time of 1-10 seconds is most likely feasible using a more efficient implementation of our method. This would
5.4. Discussion and Conclusions

allow us to integrate the registration framework into the biopsy procedure, so it can be validated on a larger cohort of patients.
Chapter 6

Conclusions and Future Work

The work in this thesis is intended to decrease the high number of false negatives in freehand TRUS-guided prostate biopsies. There are two major challenges that hinder accurate targeting of prostate tumors: 1) lack of visibility in TRUS; and 2) intra-procedure prostate motion and deformations.

In order to overcome these challenges, we have developed methods that were presented throughout this thesis. Since PCa is more visible in MRI, Chapters 2, 3 and 4 address the issues of tumor visibility in TRUS, by providing the registration tools for MR-TRUS fusion. The salient feature of these surface-based methods is their ability to ignore regions where the prostate boundary cannot be reliably traced. This is important, since the accuracy of surface-based MR-TRUS fusion methods is known to decrease in the presence of segmentation errors [95]. In Chapter 5, we tackled the challenges associated with tracking the prostate during the biopsy session. To this end, we extended our FEM-based surface registration framework to intensity-based registration. This provided us with a framework to compensate for prostate motion and deformations due to variable probe pressure in a freehand biopsy session.

6.1 Contributions

The contributions of this thesis are summarized as follows:

- A novel technique, i.e. GMM-FEM, was developed for the registration of two surfaces. The method requires the source surface to be complete, however, the target surface need not be fully segmented. The registration is considered as a probability density estimation problem in the presence of a biomechanical regularizer. The points in the source surface are assumed to be the centroids of an isotropic GMM, and the points on the target surface are the observations. The registration is driven by surface-based forces, which maximize the likelihood of the GMM generating the observations. Additionally, the points on the source surface are forced to move in a physically realistic manner by
adding a total strain energy. We validated this method against three other state of the art surface-based methods on MR/TRUS surfaces from prostate biopsy patients.

• Further validation of the GMM-FEM method on MR/TRUS surfaces from brachytherapy patients and its open-source implementation. While the improvement in the TRE was small compared to affine registration on this dataset (0.3 mm), the TRE in our method does not degrade in the presence of missing data. Note that the experiments in this chapter were done independently at BWH, and the UBC group did not have direct access to the brachytherapy surfaces used in this study.

• A novel technique for the registration of two partial surfaces, i.e. SSM-FEM registration. The technique utilizes a geometrical prior (SSM) as a reference for the complete shape, thereby casting the partial-surface-to-partial-surface registration problem into two full-surface-to-partial-surface problems. Given that the two partial surfaces and the SSM are in different deformation states, the method uses a FEM to compensate for deformations present in both partial surfaces.

• A novel framework for 2D-3D intensity-based registration is developed to compensate for prostate motion and deformations in a freehand biopsy procedure. The framework has two components: 1) trajectory-based rigid registration; and 2) FEM-based non-rigid registration. The first component compensate for the bulk motion of the prostate during a biopsy session using the prostate pre-procedure sweep trajectory. This constraint is necessary to avoid local minima, given the limited spatial information in a 2D slice and the low signal-to-noise ratio of TRUS. The second component accounts for off-trajectory motion and probe-induced biomechanical deformations.

6.2 Future Work

Novel methods have been presented in this thesis for MR-TRUS fusion and intra-procedure motion and deformation compensation. A number of interesting areas of research can be suggested as follows:

• In Chapter[2] I validated the GMM-FEM registration approach against three other surface-based registration techniques. These techniques were chosen to highlight specific components of the proposed method. However, there are a multitude of other methods in the literature for
MR-TRUS fusion that were not considered in our validation [60, 102, 140, 144, 154]. As a result, a more extensive validation of the GMM-FEM method against other MR-TRUS fusion methods is warranted.

- GMM-FEM and SSM-FEM registration have only been validated under the assumption of homogeneous elasticity, with a single Young’s modulus used for different patients. However, it is known that the prostate has inhomogeneous elasticity and that the Young’s modulus varies across subjects. Theoretically, spatially varying elasticity can be incorporated into the registration methods, affecting the computation of the stiffness matrix. Should elastography be available, a natural extension of our surface-based methods is to incorporate inhomogeneous elasticity as part of the MR-TRUS fusion workflow. It would be especially interesting to compare the GMM-FEM and SSM-FEM methods with FEM-based methods in the literature that are validated using knowledge of inhomogeneous of material properties [102, 144].

- The EM algorithm used in GMM-FEM and SSM-FEM registration methods is known to be susceptible to local minima. In our MR-TRUS fusion application, we did not observe this issue for the selected parameters over a wide range of datasets. However, if the problem of local minima arises in other datasets, the method needs to be extended with other optimization heuristics, such as a multi-resolution approach, or having multiple starting points [67].

- Note that the SSM construction method [119] used Chapter [1] implicitly assumes that the mean shape is a GMM and training examples are spatially transformed observations of this GMM. However, during SSM construction, the GMM is decoupled when the mean shape is updated, i.e. the mean shape is simply the average of the back-projected training examples under a spatial smoothness constraint. Since the focus of this thesis is not construction of SSMs, we did not tackle this issue. However, it would be interesting to see how the results vary if the GMM and mean shape are updated simultaneously. This can be an interesting direction for future research.

- The 2D-3D registration framework for prostate motion and deformation compensation requires the generation of a pre-procedure 3D-TRUS volume. Due to inconsistent probe pressure, this 3D-TRUS contains deformation artifacts. Since our 2D-3D registration is intensity-based, these artifacts push the optimizer away from the true solution, which
6.2. Future Work

has an adverse effect on the final TRE. Estimating a “rest” shape of the prostate from the deformed 3D-TRUS may improve the TRE in 2D-3D registration. A possible solution to this problem is to use a super-resolution approach similar to [45] that is capable of compensating for deformations between slices in the freehand sweep.

• A limitation of the work presented in this thesis is the lack of independent TRE measurements. This issue is partially addressed for GMM-FEM registration during an independent validation at BWH. However, especially for the 2D-3D registration framework presented in Chapter [5] TRE measurements were only performed using landmarks selected by the author. As a result, a more extensive validation by clinical experts needs to be performed.

• The proposed MR-TRUS fusion (GMM-FEM and SSM-FEM) and 2D-3D registration methods need to be integrated into the clinical workflow. Given that GMM-FEM registration is a special case of SSM-FEM registration, and simpler to implement, we recommend this method as a starting point. While the run-time of GMM-FEM registration is well within clinical requirements, the run-time of our 2D-3D registration needs to be improved by two orders of magnitude. This speed-up should be possible using the approaches discussed in Section [5.4]
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Appendix A

Derivation of Shape Parameters

To minimize Equation (4.2) w.r.t. shape parameters, conditioned by observations in both modalities, we first ignore terms independent of $b$:

$$
\mathcal{E}(b) = \sum_{md} \frac{1}{2\sigma_{md}^2} \sum_{m,n=1}^{M,N_{md}} P_{md} \left\| x_{mn} - s R \left( z_{mn} + \Psi_{m} b \right) - t \right\|^2_2 \\
+ \frac{\mu}{2} b^T \Lambda b, \tag{A.1}
$$

where $md \in \{MR, US\}$, $P_{md} = P(z_{m} | x_{md})$ and $z_{md}^m = z_{m} + v_{md}$. We can expand Equation (A.1) and re-write it in a rasterized form:

$$
\mathcal{E}(b) = \sum_{md} \frac{1}{2\sigma_{md}^2} \left[ N_{p} r_{md}^T \hat{t}_{md} + \hat{x}_{md}^T \text{diag}(\hat{P}_{md}^T) \hat{x}_{md} \\
- 2 \hat{t}_{md}^T \hat{I} \text{diag}(\hat{P}_{md}^T) \hat{x}_{md} \\
+ \hat{z}_{md}^T \left( \hat{z}_{md} + \Psi b \right)^T \text{diag}(\hat{P}_{md}^T) \left( \hat{z}_{md} + \Psi b \right) \\
+ 2s_{md} \hat{t}_{md}^T \hat{P}_{md} \hat{I} \text{diag}(\hat{P}_{md}^T) \left( \hat{z}_{md} + \Psi b \right) \\
- 2s_{md} \hat{x}_{md}^T \hat{P}_{md} \hat{I} \text{diag}(\hat{P}_{md}^T) \left( \hat{z}_{md} + \Psi b \right) \\
+ \frac{\mu}{2} b^T \Lambda b \right], \tag{A.2}
$$

where $\hat{I} = [I_{3 \times 3} \cdots I_{3 \times 3}]_{3 \times 3N}$. The matrix $\hat{P}_{md} = \text{kron}(P_{md}, I_{3 \times 3})$ is the Kronecker-delta product of the correspondence probability matrix with an identity matrix, so it can be applied to a concatenation of all $(x, y, z)$.
coordinates of input points. Differentiation w.r.t. $b$ results in:

\[
\frac{\partial E(b)}{\partial b} = \mu \Lambda b + \sum_{md} \frac{1}{2\sigma^2_{md}} \left[ 2s^2_{md} \Psi^T \text{diag}(\tilde{P}_{md1}) \Psi b \\
+ 2s^2_{md} \Psi^T \text{diag}(\tilde{P}_{md1}) \tilde{z}_{md} \\
+ 2s_{md} \Psi^T \text{diag}(\tilde{P}_{md1}) \tilde{R}_{md}^T I_{md} \tilde{t}_{md} \\
- 2s_{md} \Psi^T \tilde{R}_{md} \tilde{P}_{md} \tilde{x}_{md} \right].
\] (A.3)

Setting Equation (A.3) to zero yields the set of linear equations described in Equation (4.12).
Appendix B

Derivation of FE Nodal Displacements

Minimization of Equation (4.2) w.r.t. nodal displacements in each modality is equivalent to registering the SSM instance to each observation independently. To avoid clutter, we drop the modality subscript, \( m_d \), throughout this section.

Limiting to a single modality and ignoring terms independent of \( U \), Equation (4.2) can be written as:

\[
\mathcal{E}(U) = \frac{1}{2\sigma^2} \sum_{m,n=1}^{M,N} P(z_m|x_n) \| x_n - sR(y_m + \Phi_m U) - t \|^2 + \beta \frac{1}{2} \vec{u}^T K \vec{u},
\]

(B.1)

where \( \vec{u} = (u_{11}, \ldots, u_{13}, \ldots, u_{J3})^T \) is the rasterized representation of \( U \). Written in matrix form, this is equivalent to

\[
\mathcal{E}(U) = \frac{1}{2\sigma^2} \left[ NPt^Tt + \text{tr} \left( X^T \text{diag}(P^T 1) X \right) - 2 t^T X^T P 1 \right.
\]

\[
+ s^2 \text{tr} \left( (Y + \Phi U)^T \text{diag}(P 1) (Y + \Phi U) \right) + 2s t^T R (Y + \Phi U)^T P 1
\]

\[
- 2s \text{tr} \left( X^T P^T (Y + \Phi U) R^T \right) \left. \right]
\]

\[
+ \beta \frac{1}{2} \vec{u}^T K \vec{u},
\]

(B.2)

where \( \text{tr}(\cdot) \) denotes the trace of a square matrix. To simplify the derivation,
we can rewrite Equation (B.2) in a rasterized form:

\[
E(\vec{u}) = \frac{1}{2\sigma^2} \left[ N_p \vec{t}^T \vec{t} + \vec{x}^T \text{diag}(\vec{P}^T \vec{x}) - 2t^T \vec{R} \text{diag}(\vec{P}^T \vec{x}) \right] \\
+ s^2 (\vec{y} + \Phi \vec{u})^T \text{diag}(\vec{P}^T \vec{y}) + 2s t^T R \text{diag}(\vec{P}^T \vec{t}) + 2s^2 (\vec{y} + \Phi \vec{u})^T \\
- 2s \vec{x}^T \vec{P} \vec{R} (\vec{t} + \Phi \vec{u}) \right] + \frac{\beta}{2} \vec{u}^T K \vec{u},
\] (B.3)

where \( \vec{R} = [I_{3 \times 3} \cdots I_{3 \times 3}]_{3 \times 3N} \). Excluding terms independent of \( \vec{u} \), this reduces to

\[
E(\vec{u}) = \frac{s^2}{2\sigma^2} \vec{u}^T \Phi^T \text{diag}(\vec{P}^T \Phi \vec{u}) + \frac{\beta}{2} \vec{u}^T K \vec{u}
\] (B.4)

Differentiating with respect to \( \vec{u} \) results in:

\[
\frac{\partial E(\vec{u})}{\partial \vec{u}} = \left[ \frac{s^2}{\sigma^2} \Phi^T \text{diag}(\vec{P}^T \Phi) + \beta K \right] \vec{u}
\] (B.5)

Setting \( \partial E(\vec{u})/\partial \vec{u} = 0 \) results in the system of equations described in Equation (4.15).
Appendix C

Derivative of the Interpolation Matrix

Throughout this appendix, we use the following notations:

- Let \( \vec{y} \) be a spatial coordinate independent of the FEM.
- Let \( \vec{x} \) be an Eulerian coordinate of a point in the FEM.
- Let \( \vec{X} \) be the Lagrangian spatial coordinate of \( vx \) within the FEM. \( vX \) moves with the FEM, so its representation remains unchanged.
- Let \( \vec{v}_i \) be the Eulerian position of the \( i \)th FEM node. \( v_{ij} \) denotes the \( j \)th coordinate of \( \vec{v}_i \).
- Let \( \vec{u}_i \) be the Eulerian displacement of the \( i \)th FEM node. \( u_{ij} \) denotes the \( j \)th coordinate of \( \vec{u}_i \).

For a particular point within the FEM (e.g. the centre of an element), its Lagrangian coordinate remains fixed as the FEM moves, but the Eulerian coordinate changes. If the FEM hasn’t moved, then the Eulerian and Lagrangian coordinates coincide (i.e. \( \vec{X} = \vec{x}(0) \)). This leads to the expression:

\[
\vec{x}(t) = \sum_i \phi_i(\vec{x}(0)) \vec{v}_i = \sum_i \phi_i(\vec{X}) \vec{v}_i(t) \quad (C.1)
\]

\[
\vec{x}(t) = \vec{x}(0) + \sum_i \phi_i(\vec{X}) \vec{u}_i(t) \quad (C.2)
\]

which says nothing more than that locations inside the material are interpolated based positions (C.1) or displacements (C.2) of the FEM nodes. The interpolation functions \( \phi_i \) are called shape functions in FEM literature, and are defined on the material (Lagrangian) coordinates \( \vec{X} \). To actually express the shape functions, a set of “natural coordinates” \((\xi, \eta, \mu)\) within elements
Appendix C. Derivative of the Interpolation Matrix

are often introduced. The material coordinates are then interpolated within the element as

\[
\vec{X}(\xi, \eta, \mu) = \sum_i \phi_i(\xi, \eta, \mu) \vec{X}_i
\]

\[= \sum_i \phi_i(\xi, \eta, \mu) \vec{v}_i(0),
\]  

(C.3)

where \(\vec{X}_i\) is the Lagrangian coordinate of the \(i\)th FEM node. This holds everywhere within the material, particularly at time \(t = 0\). From Equation (C.1), this means that:

\[
\vec{x}(0) = \sum_i \phi_i(\vec{X}) \vec{v}_i(0)
\]

\[\Rightarrow \vec{X} = \sum_i \phi_i(\vec{X}) \vec{v}_i(0)
\]

\[\Rightarrow \phi_i(\vec{X}) = \phi_i(\xi, \eta, \mu)
\]

This is just a complicated way of defining a separate set of “natural coordinates” within elements and express the shape functions in terms of these coordinates. For tetrahedral elements, the natural coordinates are barycentric coordinates. For hexahedral elements, they are derived by warping a size \(2 \times 2 \times 2\) cube to the hex.

Normally in the FEM framework, we are interested only in how the original material moves in space. The shape functions remain fixed for a given point in Lagrangian (i.e. material) coordinates. In Chapter 5, we ask a different question. We have a point in spatial (Eulerian) coordinates from the slice, \(\vec{y}\), which happens to fall within the FEM volume. At a given point in time, \(\vec{y}\) corresponds to a particular point in the material, \(\vec{y} = \vec{x}_1(t)\), which in turn corresponds to a fixed material (Lagrangian) coordinate in the FEM, \(\vec{X}_1\). If the FEM moves, the same spatial coordinate will correspond to a different point in the material, \(\vec{y} = \vec{x}_2(t)\). The new Lagrangian coordinate, \(\vec{X}_2\), will have different interpolation coefficients. How do the shape functions change at a given spatial coordinate as the FEM nodes move?

At a given time \(t\), we know all FEM node positions \(\{\vec{v}_i\}\). We also know we are interpolating with the elements based on natural coordinates. From Equation (C.1), and given \(\vec{y} = \vec{x}(t)\), we have

\[
\vec{y} = \sum_i \phi(\xi, \eta, \mu) \vec{v}_i(t).
\]  

(C.4)
Appendix C. Derivative of the Interpolation Matrix

Based on knowledge of the node positions and functional form of $\phi$ in terms of the natural coordinates, we can invert this expression to determine the natural coordinates $(\xi, \eta, \mu)$. For tetrahedral elements, this is a linear inversion problem. For other element types, it typically requires a few numerical iterations to solve. To compute the desired derivative terms, we start with Equation (C.4) and differentiate with respect to the $l$th coordinate of $\vec{u}_k$:

$$
\frac{\partial y_j}{\partial u_{kl}} = \sum_i \frac{\partial}{\partial u_{kl}} [\phi_i(\xi, \eta, \mu) v_{ij}(t)], \quad j = \{1, 2, 3\}, \quad k = \{1, \ldots, N\}, \quad l = \{1, 2, 3\}
$$

$$
= \sum_i \phi_i(\xi, \eta, \mu) \frac{\partial v_{ij}(t)}{\partial u_{kl}} + \frac{\partial \phi_i(\xi, \eta, \mu)}{\partial u_{kl}} v_{ij}(t)
$$

$$
= \sum_i \phi_i(\xi, \eta, \mu) \frac{\partial [v_{ij}(0) + u_{ij}]}{\partial u_{kl}} + \frac{\partial (\xi, \eta, \mu)}{\partial u_{kl}} \frac{\partial \phi_i(\xi, \eta, \mu)}{\partial (\xi, \eta, \mu)} v_{ij}(t)
$$

$$
= \sum_i \phi_i(\xi, \eta, \mu) \delta_{kl} \delta_{lj} + \frac{\partial (\xi, \eta, \mu)}{\partial u_{kl}} \frac{\partial \phi_i(\xi, \eta, \mu)}{\partial (\xi, \eta, \mu)} v_{ij}(t)
$$

$$
= \delta_{lj} \phi_k(\xi, \eta, \mu) + \sum_i \frac{\partial (\xi, \eta, \mu)}{\partial u_{kl}} \frac{\partial \phi_i(\xi, \eta, \mu)}{\partial (\xi, \eta, \mu)} v_{ij}(t), \quad (C.5)
$$

where $\delta_{ij}$ denotes the Kronecker delta. The location $\vec{y}$ is fixed in space, so $\frac{\partial y_j}{\partial u_{kl}} = 0$. We can express the above system of equations in matrix form for a fixed $k \in \{1, \ldots, N\}$:

$$
0 = \begin{bmatrix}
\phi_k & 0 & 0 \\
0 & \phi_k & 0 \\
0 & 0 & \phi_k
\end{bmatrix}
+ \begin{bmatrix}
\frac{\partial \xi}{\partial u_{k1}} & \frac{\partial \eta}{\partial u_{k1}} & \frac{\partial \mu}{\partial u_{k1}} \\
\frac{\partial \xi}{\partial u_{k2}} & \frac{\partial \eta}{\partial u_{k2}} & \frac{\partial \mu}{\partial u_{k2}} \\
\frac{\partial \xi}{\partial u_{k3}} & \frac{\partial \eta}{\partial u_{k3}} & \frac{\partial \mu}{\partial u_{k3}}
\end{bmatrix}
\begin{bmatrix}
\frac{\partial \phi_1}{\partial \xi} & \cdots & \frac{\partial \phi_N}{\partial \xi} \\
\frac{\partial \phi_1}{\partial \eta} & \cdots & \frac{\partial \phi_N}{\partial \eta} \\
\frac{\partial \phi_1}{\partial \mu} & \cdots & \frac{\partial \phi_N}{\partial \mu}
\end{bmatrix}
\begin{bmatrix}
v_{11} & v_{12} & v_{13} \\
v_{N1} & v_{N2} & v_{N3}
\end{bmatrix}
$$

For every $k$, this is a linear system of nine equations with nine unknowns, which has a unique solution as long as the element is not degenerated (inverted). In such a case, we have:

$$
\frac{\partial (\xi, \eta, \mu)}{\partial \vec{u}_k} = - \begin{bmatrix}
\phi_k & 0 & 0 \\
0 & \phi_k & 0 \\
0 & 0 & \phi_k
\end{bmatrix}
\begin{bmatrix}
\frac{\partial \phi_1}{\partial \xi} & \cdots & \frac{\partial \phi_N}{\partial \xi} \\
\frac{\partial \phi_1}{\partial \eta} & \cdots & \frac{\partial \phi_N}{\partial \eta} \\
\frac{\partial \phi_1}{\partial \mu} & \cdots & \frac{\partial \phi_N}{\partial \mu}
\end{bmatrix}
^{-1}
\begin{bmatrix}
v_{11} & v_{12} & v_{13} \\
v_{N1} & v_{N2} & v_{N3}
\end{bmatrix}
$$

(C.6)
Appendix C. Derivative of the Interpolation Matrix

To recover $\frac{\partial \phi_i}{\partial \vec{u}_k}$, we simply use the chain rule which results in Equation (5.4):

$$
\frac{\partial \phi_i(\xi, \eta, \mu)}{\partial \vec{u}_k} = \frac{\partial \phi_i}{\partial \vec{u}_k} \left[ \begin{array}{ccc}
\frac{\partial \phi_1}{\partial \xi} & \cdots & \frac{\partial \phi_N}{\partial \xi} \\
\frac{\partial \phi_1}{\partial \eta} & \cdots & \frac{\partial \phi_N}{\partial \eta} \\
\frac{\partial \phi_1}{\partial \mu} & \cdots & \frac{\partial \phi_N}{\partial \mu}
\end{array} \right]^{-1} \left[ \begin{array}{c}
v_{11} v_{12} v_{13} \\
v_{N1} v_{N2} v_{N3}
\end{array} \right]
$$

$$
= - \begin{bmatrix}
\phi_k & 0 & 0 \\
0 & \phi_k & 0 \\
0 & 0 & \phi_k
\end{bmatrix}
\begin{bmatrix}
\frac{\partial \phi_1}{\partial \xi} & \cdots & \frac{\partial \phi_N}{\partial \xi} \\
\frac{\partial \phi_1}{\partial \eta} & \cdots & \frac{\partial \phi_N}{\partial \eta} \\
\frac{\partial \phi_1}{\partial \mu} & \cdots & \frac{\partial \phi_N}{\partial \mu}
\end{bmatrix}
\begin{bmatrix}
v_{11} v_{12} v_{13} \\
v_{N1} v_{N2} v_{N3}
\end{bmatrix}
$$

$$
\begin{bmatrix}
\frac{\partial \phi_1}{\partial \xi} \\
\frac{\partial \phi_1}{\partial \eta} \\
\frac{\partial \phi_1}{\partial \mu}
\end{bmatrix}
$$

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