Haptic Simulation of Prostate Cancer Based on Magnetic Resonance Elastography

BY

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THESIS

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This thesis is dedicated to my parents, Marco and Mildre, and to my brother Daniel for their continuous and unconditional support throughout my life. They are my motivation and inspiration for improving in all aspects of my life every day and without whom I would never be what I am today.
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DEZ
Contribution of Authors

Dr. Cristian Luciano: Supervised the development of the MRE-based augmented reality application and continuously provided support in the implementation of the haptic portion of the project.

Dr. Simone Crivellaro: Provided invaluable feedback from a specialized urologist’s perspective for the two procedures presented in this thesis: prostate biopsy and radical prostatectomy. Dr. Crivellaro was responsible for providing the ex-vivo prostate specimens used in the second study.

Dr. Steven Kearney: was responsible for the scanning of the prostate phantom and the ex-vivo prostates. He provided the processed MRE volumetric datasets used in both studies.

Dr. Dieter Klatt and Dr. Thomas Royston: Actively supported and collaborated with the implementation of the MRE experiments. They assisted in the determination of the best imaging parameters. Dr. Klatt and Dr. Royston are the creators of SLIM-MRE sequence used in both MRE portion of this study.

Kathleen Tetzlaff: Created the medical illustrations of the prostate anatomy presented in the introductory chapter of this thesis.
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<table>
<thead>
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<th>Description</th>
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<tbody>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>ACS</td>
<td>American Cancer Society</td>
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<tr>
<td>API</td>
<td>Application Programming Interface</td>
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<tr>
<td>CaP</td>
<td>Prostate Cancer (PCa also used)</td>
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<td>BPH</td>
<td>Benign Prostatic Hyperplasia</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
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<td>DRE</td>
<td>Digital Rectal Examination</td>
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<tr>
<td>FLTK</td>
<td>Fast Light Toolkit</td>
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<tr>
<td>GUI</td>
<td>Graphical User Interface</td>
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<tr>
<td>I/O</td>
<td>Input/Output</td>
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<tr>
<td>MRE</td>
<td>Magnetic Resonance Elastography</td>
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<td>MPMRI</td>
<td>Multi-parametric Magnetic Resonance Imaging</td>
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<tr>
<td>PSA</td>
<td>Prostate Specific Antigen</td>
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<tr>
<td>SDK</td>
<td>Software Development Kit</td>
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<td>TRUS</td>
<td>Transrectal Ultrasound</td>
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<td>VRML</td>
<td>Virtual Reality Modeling Language</td>
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SUMMARY

As with any type of cancer, screening for prostate cancer (CaP), becomes fundamental since early detection represents better possibilities for treatment. The goal of this project was an innovative integration between magnetic resonance elastography and haptics for the virtual simulation of prostate cancer.

MRE can be defined as a non-invasive assessment of variations in tissue stiffness. The term ‘elastography’ means ‘elasticity imaging’. MRE is an innovative and relatively new technique that uses the principles and applications of magnetic resonance imaging (MRI) and mechanical wave theory to calculate the mechanical properties of tissues. The resulting shear modulus maps or elastograms, are a quantitative measure of these properties. These offer the potential for improved differentiation between pathological and healthy tissue as well as precise tumor localization.

In the first study, a prostate phantom was used to validate a methodology to generate haptic force feedback using the information provided by MRE. Polygonal meshes (3D models) of each of the phantom components were extracted from the MRI magnitude image. The phantom MRE volume was used to develop a mathematical model for the calculation of a viscoelastic haptic effect. This demonstrated the feasibility of performing MRE experiments on a prostate phantom in an ultra-high magnetic field. Moreover, this study presented the implementation and rendering of haptic force feedback based on two different methods: the collision detection, used for the polygonal meshes of the different anatomical components of the phantom prostate extracted from the MRI scans and the custom haptic effect created to generate haptic feedback from the MRE volumetric dataset.

In the second study, the implementation of an isosurface haptic rendering algorithm was discussed. One of its advantages was the ability to interact with the volume directly, without the
need of creating polygonal meshes for each shape. By doing so, necessary steps such as segmentation or optimization could be disregarded. In terms of haptic rendering stability and operability, this algorithm provided a better way to generate haptic cues from the MRE volumetric data. The creation of 3 isosurface layers, each with unique haptic properties allowed for the haptic computation and rendering of a stiffness varying effect.

The results of this preliminary study suggest the feasibility of using a novel combination of magnetic resonance imaging, elastography, and haptic technologies on prostates to better identify tumor locations and sizes, and more accurately perform cancer staging. This methodology tested with the plastic prostate phantom and the MRI/MRE ex-vivo prostate datasets of patients with prostate cancer presents the first step in determining the potential of improving pre-surgical planning of biopsy and radical prostatectomy.
I. INTRODUCTION

Prostate cancer (CaP) can be defined as an abnormal growth of cells in the prostate gland, leading to the formation of tumors [22]. It is the most common non-cutaneous cancer in American men; and its mortality falls second only to lung cancer [22]. The American Cancer Society (ACS) estimates there will be about 180,890 new diagnoses of prostate cancer with about 26,120 deaths from this disease for the year 2016. This means that about 1 man in 39 will die of prostate cancer. This epidemiological indicators, have made the prostate a vital and challenging organ to study for clinicians as well as translational researchers. Screening, which refers to testing to find a disease in people that do not present any symptoms becomes fundamental since early cancer detection can translate to individualized treatment approaches and better patient outcomes.

Presentation of prostate cancer is varied. “As 70% of prostate cancers are in the peripheral zones of the prostate away from the urethra, most men will not have symptoms until the disease progresses. Therefore, a lesion in the peripheral zone may produce no symptoms (Nash, 1997)” [3]. Early detection methods includes digital rectal examination (DRE) and testing the amount of prostate-specific antigen (PSA) in the blood. However, there are many limitations in these procedures as they are not completely accurate. Abnormal results can occur in these tests even when the cancer is not present (false positive results) [9]. Multi-parametric magnetic resonance imaging (MRI) which includes diffusion weighted imaging (DWI) and Dynamic Contrast Enhanced (DCE) are methods that have the potential to improve detection by enabling a more targeted biopsy and better risk stratification, but its limitations are in terms of a threshold for tumor size and grade. Unclear results from the previously described methods may lead to a prostate biopsy, a procedure in which multiple needle biopsies are taken one at a time from the abnormal or suspicious areas of the gland. The prostatic sample tissues are then analyzed for diagnosis and
grading confirmation.

Due to the anatomical location of the prostate, prostate biopsies are invasive procedures. They are typically performed using guidance and targeting methods such as transrectal ultrasound (TRUS) and, in recent years, a fusion of MRI and ultrasound known as fusion biopsy. Some of the limitations of these techniques are the uncertainty regarding the exact location of the abnormal tissue and clinical complications such as infection and bleeding. Prostate biopsies may also be subject to sampling errors due to motion by the instrument insertion, and consequently quantitative staging the grade of the disease may not be possible.

Many disease processes have been known to cause marked changes in the tissue viscoelastic processes of stiffness and viscosity. For example, hard masses in the thyroid, breast, and prostate, are clinically recognized as suspicious for malignancy. Manual palpation, considered the ‘gold standard’ to detect these hard masses in the body possess limitations when these changes in the mechanical properties of tissues occur in the interior a particular organ or are simply too small to be detected. For prostate cancer, tissue becomes harder than the surrounding normal tissue due to several morphological changes. Palpation becomes subjective to the degree of expertise and judgement of the urologist performing DRE and it is limited to only the posterior region of the prostate close to the rectal wall, besides being a procedure which is uncomfortable for the patient.

Consequently, considering elasticity as biomarker for prostate cancer has the potential to provide quantitative (elasticity) values that could be used to determine ‘threshold’ criteria, to correctly identify pathological from healthy prostate (benign prostatic hyperplasia, BPH) prostatic tissue and in particular clinically ‘significant’ from ‘insignificant’ disease.

Magnetic resonance elastography (MRE) is an innovative and relatively new technique designed to quantitatively assess the mechanical properties of tissues; specifically, the variations
in tissue stiffness, based on MR imaging of the propagation of shear waves. The term ‘elastography’ means ‘elasticity imaging.’ Elastography can be defined as the mapping of the stiffness variations throughout a gland or tissue. For MRE, phase contrast images are obtained by imaging the tissue response after a shear wave is externally introduced. In order to achieve this, the external vibration is synchronized with the modified pulse imaging sequence of the scanner and the motion encoding gradients (MEGs) [33]. Elastography extends the idea of ‘palpating’ regions of the body, previously limited to the physician’s hand by calculating and mapping tissue stiffness of the organ being studied.

The purpose of this study was to integrate MRE information into a Haptic Virtual Reality (HVR) system able to provide a 3D environment with realistic tactile cues that would enhance diagnosis, risk stratification and surgical planning of prostate cancer. A methodology to translate a 3D map of the prostate phantom stiffness to a virtual 3D model with realistic viscoelastic properties will be presented. The algorithm was applied to a commercially-available prostate phantom (CIRS Tissue Simulation & Phantom Technology) and a set of 5 MRE ex-vivo prostates datasets. The proposed HVR prostate simulator will be able to provide realistic viscoelastic properties of the prostate gland and inherent phantom lesions.
II. BACKGROUND

A. Prostate: Clinical Aspects

1. Prostate Anatomy

Found only in men, and placed deep within the pelvis, the prostate is composed of tubuloalveolar glands arranged in lobules surrounded by a stroma (a layer of fibrous cells that has a connective and structural role). A normal prostate dimension may vary according to age, however in younger men it is about the size of a walnut and it is located underneath the urinary bladder, anterior to the rectum. The gland is rich in nerves, smooth muscle, collagen and lymphatics. Within the prostate gland, the ejaculatory ducts join the urethra extending from the urinary bladder. In men, the urethra serves both a urinary and a reproductive function. The prostate gland adds alkaline secretions of a milky consistency to the urethra. The rise in pH enables the sperm to become more mobile. The vas deferens are tubes that carry sperm from the testicles to the seminal vesicles. The seminal vesicles, which are located just behind the prostate gland and are responsible of making most of the fluid for semen, are joined to the prostate via the ejaculatory ducts. They are found on both sides of the prostate along the nerves that control urinary and sexual functions (Fig. 1).
This fibromuscular and glandular organ is made up of four regions or zones according to their function: the peripheral zone (PZ), the transition zone (TZ) and the central zone (CZ). Surrounding the CZ and the TZ, the PZ is the area of the prostate that is closest to the rectum; this area is felt by the urologist performing DRE. It constitutes roughly three quarters of the prostate. It is important to note here that the majority of prostate tumors (approximately 75 %) are found in this zone [29]. The transition zone is the middle area of the prostate, between the peripheral and central zones. It surrounds the urethra close to the intersection of the urethra with the ejaculatory ducts. This zone constitutes 20% of the gland; in men 40 years and older it starts to enlarge, eventually becoming the largest area of the prostate. This is known as benign prostatic hyperplasia. The central zone surrounds the ejaculatory ducts and extends to the transition zone. During DRE, this zone cannot be felt by the urologist since it is located farthest from the rectum. The superior part of the prostate adjacent to the bladder is called the base, and it is composed of smooth cells.
extending to the bladder neck. The lower part of the bladder is called the apex and is composed of striated muscle, which extends to the pelvic diaphragm (Fig. 2).

2. Benign Prostatic Hyperplasia (BPH) and Prostate Cancer

It can be described as an age-related enlargement of the prostate due to an increased number of cells, therefore the name hyperplasia. In an early stage, BPH does not present any signs or symptoms. Nonetheless, as the prostatic tissue keeps growing, it can press on the urethra causing problems passing urine. Some other symptoms may include frequent urination, weak or slow urinary stream, inability to empty bladder completely, among others. Two important point should be noted: first, the prostate naturally gets larger as men age. According to the American Cancer Society: “almost all men by the age of 70 will have some prostate enlargement” [22]. The second point is that BPH does not increase the risk of prostate cancer.
The American Cancer Society’s (ACS) estimates there was about 220,800 new diagnoses of prostate cancer with about 27,540 deaths from this disease for the year 2015. This means that about 1 man in 38 will die of prostate cancer. Prostate cancer can be described as a malignant tumor that starts in the cells of the prostate and has the potential to metastasize or spread to other parts of the body [22]. The prostatic capsule is a series of layers of connective tissue that covers the prostate gland. Within the prostate gland, different types of cells have particular functions: the structural support of the gland is given by the fibrous cells, the liquid portion of the semen is given by the glandular cells and urine flow and ejaculation is controlled by the muscle cells [29]. It is in the glandular cells where almost all prostate cancers develop [22]. The clinical terminology for a cancer that starts to develop in a gland is adenocarcinoma. Generally, adenocarcinomas are commonly found in the peripheral zone and may be felt during DRE. In addition they might be multifocal (can be found in more than one site) and their grade can vary in each site. The grade of a tumor refers to how distinct healthy cells are from cancerous cells, the rate in which the cancerous cells are growing and their likelihood to spread to nearby organs [29].

**B. Current Prostate Cancer (CaP) Diagnosis**

1. **Screening and Early Diagnostic Methods**

With improvements in disease prevention and medical therapies, the American population has continued to age. According to some population estimates and projections (Ortman, et al., 2014) [30] “between 2012 and 2050, the United States will experience considerable growth in its older population. In 2050, the population aged 65 and over is projected to be 83.7 million, almost double its estimated population of 43.1 million in 2012.” The number of aging men afflicted by benign and malignant prostatic disease, has increased and will continue to increase. This epidemiological indicators, have made the prostate a vital and challenging organ to study for
clinicians as well as translational researchers. When testing for prostate cancer, early detection methods that are suggested by an urologist may include: prostate-specific antigen (PSA) test, digital rectal examination (DRE) and multi-parametric imaging.

PSA is a single-chain glycoprotein expressed by prostatic epithelial cells which can help detect prostate cancer at an early stage, when there are no visible symptoms, and can distinguish prostate cancer from benign prostatic hyperplasia. The prostate is responsible for making PSA and although PSA is mostly found in semen, small amounts of this protein could be found in the blood of healthy men. This can be measured with a PSA blood test. An increase in the PSA level does not necessarily mean that a man has prostate cancer.

\[
PSAD = \frac{PSA \ (ng/ml)}{Prostate \ Volume}\ 
\]

(2.1)

PSA density equation: prostate volume is usually acquired via transrectal ultrasound.

A DRE is a physical examination of prostate during which a gloved, lubricated finger is inserted into the rectum. The doctor palpates for abnormalities in the gland, a normal prostate should have a smooth and rubbery consistency. Any lumps (areas that may feel hard to the touch), changes in the size, shape or consistency may be indicators of cancer. DRE can be useful in determining if the cancer is only on other side of the prostate; or if it is on both sides, which may indicate the potential of spreading beyond the prostate to nearby tissues.

PSA and DRE are often done together to find problems with the prostate because using both tests, could provide a better diagnose. As mentioned before, both tests have certain drawbacks and are not 100% accurate. They can sometimes fail to detect prostate cancer when it is present (false negative result) or could suggest that prostate cancer is present when it is not (false positive
mpMRI includes: anatomical imaging (T2-weighted imaging), diffusion weighted imaging, dynamic contrast enhanced imaging and metabolic imaging (magnetic resonance spectroscopic imaging). All the parameters have advantages and disadvantages presented as follows:

- **T2 – weighted imaging (T2WI):** based on this parameter pathological changes within the prostate can be identified as well as cancer margins (the spread of cancer outside the gland). Although T2WI has high sensitivity, the image contrast is not very specific; conditions such as prostatitis, BHP, or post-biopsy hemorrhage can mimic cancer.

- **Diffusion Weighted Imaging (DWI):** can be used to assess prostate cancer presence, spatial extent and aggressiveness. The high cellular density of cancerous tissue restrict water diffusion more than in normal tissues. However, one of the limitations is that not all areas with a low ACD (apparent diffusion coefficient) are aggressive cancers, and not all high grade tumors have restricted diffusion. Therefore, a biopsy may be needed to confirm DWI findings.

- **Dynamic Contrast Enhanced Imaging (DCE):** is performed by injecting a FDA-approved Gadolinium-based contrast agent for the measurement of differences in blood flow between cancer and normal tissue. DCE has excellent sensitivity; it creates a rapid contrast enhancement but low specificity, since conditions such as BPH and inflammation have the same enhancement.

- **Magnetic resonance spectroscopy imaging (MRSI or ¹H MRSI):** measures the concentrations of metabolites (citrate and choline) within tissues and although it has been shown to improve the identification and characterization (location, size and
aggressiveness) it is time-consuming, technically challenging and requires the use of an endorectal coil for high quality images.

2. Clinical interventions related to PCa

At its early stage, prostate cancer may cause no symptoms and PSA or DRE might suggest that cancer is present. In contrast, advanced prostate cancer may present some more visible signs such as hematuria (blood in the urine), impotence (trouble getting an erection) and depending on the aggressiveness, the cancerous cells within the prostate may spread or metastasize to other parts of body, such as the seminal vesicles, the lymph nodes and the bones of the pelvic region. Since other diseases may present similar symptoms, a specific cause should be found. In this case, if any of the early diagnostic methods suggest cancer, a prostate biopsy would be the first clinical intervention step to determine whether the disease is in fact present.

- Prostate Biopsy

When performing a prostate biopsy, urologists frequently rely on transrectal ultrasound (TRUS). A small probe (transducer) is inserted on the rectum of the patient generating ultrasound waves, these waves enter the prostate, propagate and create echoes which are then received by the transducer to create a continuous set of images that are displayed on the video screen in real-time. TRUS is used to look at the prostate when the patient has a high PSA level or has an abnormal DRE result [22]. TRUS therefore can be used to assess the prostate volume (important when assessing a PSA density), characterize noted lesions and more importantly, during a prostate biopsy, it could guide the needles into the right location, which might be suspicious for malignancy.

Through biopsy, a sample of tissue from the area of interest is removed and analyzed under
a microscope. For prostate cancer, a core needle biopsy is the main method to diagnose if cancer is present. With the patient in a lithotomy position (child-bearing position) and using TRUS to visualize the prostate gland, the urologist inserts a thin, hollow needle through the wall of the rectum into the prostate. The procedure is carried out using a spring-loaded biopsy “gun” which inserts and removes the needle in a fraction of a second. When the needle retracts, it removes a small sample of prostatic tissue [22]. Most urologists would take about 12 samples, primarily form the peripheral area of the gland, in the apex, mid-gland and base regions, left and right.

![Biopsy Diagram](image)

**Figure 3:** A) 6-core, B) 10-core and C) 12-core biopsy templates. During biopsy, the urologist aims to obtain samples from the 12 different zones of the prostate to determine if cancer is truly present. Image courtesy Kathleen Tetzlaff.

Prostatic tissue motion caused by the ultrasound probe insertion during a biopsy can make it difficult to accurately obtain evenly dispersed samples throughout a target region. Fusion MRI-Ultrasound biopsy is currently being used to help urologists perform a more targeted biopsy. The taken biopsy samples are analyzed by pathologist to determine if the samples contains cancer cells. If cancer is present, the pathologist would also assign a grade. A biopsy report would include information such as the number of core samples, the percentage of cancer in each of the cores and whether the cancer is on one side (left or right) or both sides (bilateral) of the prostate [9].
Figure 4: End-firing TRUS. The ultrasound probe is inserted to the rectal cavity along with the core biopsy needle “gun.” Prostate tissue samples are taken from the peripheral zone of the prostate and posteriorly are analyzed by a pathologist. Image courtesy of Kathleen Tetzlaff.

- Grading of prostate cancer

The most widely accepted grading system used by pathologists to grade prostate cancers is the Gleason system. This system assigns a grade, using a scale from 1 to 5 based on how much a cancerous tissue compares to healthy prostatic tissue. The highest grade of 5 is given when the cancerous tissue does not present normal healthy characteristics and its cells seem to be spread irregularly throughout the gland. A grade of 1 would be assigned if the cancerous tissue looks like the normal prostate tissue [22].

Because cancers often have areas of different grade, a grade is assigned to the 2 areas that make up the most cancer. The Gleason score (or Gleason sum) is then calculated using these 2 grades. The sum will a number between 2 and 10. Cancers with a Gleason scores of 2 to 4 are considered low-grade and are rarely diagnosed in needle biopsies. Gleason scores of 5 to 7 are considered
intermediate-grade and Gleason scores of 8 to 10 are considered high-grade. Gleason score can be interpreted as the higher the score, the more likely the cancer will grow and spread [22].

- **Staging of prostate cancer**

  Adopted in 1975 by the American Joint Committee for Cancer (AJCC), the tumor, (lymph) node, metastases (TNM) classification is the most commonly utilized clinical staging system for prostate cancer. The system is used to describe the extent to which cancer has spread. “The TNM system for prostate cancer is based on 5 key pieces of information:

  - The extent of the primary tumor (T category)
  - Whether the cancer has spread to the lymph nodes (N category)
  - Absence or presence of distant metastasis (M category)
  - PSA levels at the time of diagnosis
  - The Gleason score, based on the prostate biopsy

  Once the T, N and M categories have been determined, the information is combined with the PSA level and Gleason score in a process called stage grouping. The overall state is expressed in Roman numerals from I (the least advanced) to IV (the most advanced). This process is completed to determine treatment options for the patient and the complete prognosis of the disease in the patient (American Cancer Society, 2015)” [9, 22].

- **Radical Prostatectomy**

  Radical prostatectomy can be referred as the surgical removal of the prostate gland and it is considered the most effective treatment for localized PCa. In the US, this type of surgeries are generally robot-assisted procedures performed using the da Vinci® robot (Intuitive Surgical Inc., Sunnyvale, CA). Before the actual surgery, the surgeon relies on the biopsy report and on the planar mp-MRI images that identify the tumor locations.
With the patient in the lithotomy position, a Foley catheter is inserted through the penis into the bladder. In contrast to the traditional prostate surgery surgical incision, which uses a single large incision, robotic surgery uses small “band-aid” incisions (“ports”) along the abdomen. Through these ports, the arms of the da Vinci® robot are used to place a camera and the instruments. The surgeon removes the prostate, seminal vesicles when indicated, while trying spare muscles and nerves that control urination and sexual functions. The bladder neck and the urethra (with the urinary sphincter muscle) are then reconstructed. Removing the prostate gland virtually guarantees that tumors confined to this organ will be eliminated from the body. However, “in cases where the prostate cancer is of high grade, when the tumor has metastasized outside the gland, or when the tumor is not completely excised, removing the prostate may not ensure that all the cancer is eliminated, putting the patient at risk for recurrence” (Thompson et. al. 2007) [1].

Figure 5: Robotic assisted radical prostatectomy. Image courtesy of Kathleen Tetzlaff.
In this context, performing a radical prostatectomy requires careful surgical planning, with the aim of removing the gland an enough surrounding tissue, while sparing sufficient (healthy) nerves to preserve erectile and urinary function. About 10% to 20% of patients who have their prostate surgically removed have a positive surgical margin after the operation [4]. Improved preoperative planning could reduce the incidence of positive margins and increase the preservation of urinary and sexual functions.

C. Magnetic Resonance Elastography (MRE)

1. Elasticity as a biomarker for CaP

Many disease processes have been known to cause marked changes in tissue mechanical (viscoelastic: stiffness and viscosity) properties. For example hard masses in the thyroid, breast and prostate, are clinically recognized as suspicious for malignancy. Particularly, prostate tumors become harder than surrounding normal prostate tissue due to several morphological changes as a result of disruption to normal tissue homeostasis. For instance, multiple studies have shown the similarity of prostatic tissue response to carcinoma cell invasion to the cellular processes that accompany wound repair, characterized by stromal reaction [6, 7]. Increased collagen deposition in the stroma surrounding the cancer, increment of cellular density and microvascularty and loss of glandular architecture are factors that contribute to the increased stiffness of tissue in prostate cancer [3].

Manual palpation, which is normally performed as part of a regular physical examination relies on this concept. When the physician’s hand applies force to the tissue and causes its deformation, the response to this applied force may indicate stiffness variation in the tissue. Palpation considered the ‘gold standard’ to detect and differentiate soft (healthy) tissue from stiffer (diseased) tissue in the body possess limitations when these changes in the mechanical properties occur within a
particular organ or are simply too small to be detected by palpation. In this context, while prostate DRE relies on this correlation, it is limited to the posterior region of the prostate, near the rectal cavity. Moreover, manual palpation is subjective, since it depends greatly to the experience and knowledge of the physician and does not provide any quantitative results.

The importance of identifying and staging prostate cancer and in particular clinical ‘significant’ CaP, which refers to the high likelihood of the disease to progress and causing mortality from ‘insignificant’ CaP can have a huge impact on how the each patient is treated. For example, patients with low-risk may avoid biopsy and be simply treated with active surveillance, whereas patients with intermediate or high-risk disease may be considered for a more radical treatment and invasive treatment. In the case of CaP, recent advances in biomedical imaging have made possible to extent the idea of palpation by portraying stiffness variations throughout the gland and have reinforced the idea of elasticity as a biomarker for quantifying and assessing tumor grade and lastly, it has provided yet another tool for the study of more than one ‘elasticity’ parameter.

Imaging the induced tissue deformation and finding its correlation to the elastic properties of biological tissues have become the focus of many translational researchers. The potential of tissue elasticity as a good biomarker for prostate cancer is described in (Good et. al, 2013) [5]. The authors provide a systematic review of 33 papers including all studies investigating elasticity’s role in the detection and staging of CaP. The authors conclude that tissue elasticity has a good potential as a biomarker for prostate cancer and highlight the advantage of the ability to use various methods for acquisition. Particularly, a study done by Hoyt et al. [8], “which aimed to improve the current sonoelastographic technique by improving spatial elasticity mapping using crawling waves compared with manual compression/decompression.” This study was particularly important as it
introduced a viscoelastic model Kelvin-Voigt functional derivative (KVFD), as a useful constitutive model for characterizing soft tissue. The KVFD model does not restrict classifying tissues as pure viscous or elastic solid, rather it allows an intermediate combination potentially more applicable to describing biological soft tissues. The review paper concluded by indicating a direct mechanical assessment methods since they provide reproducible objectivity, appealing for use by physicians. The distinctive elastic contrast between normal and cancerous lesions, regardless of the imaging technique used have demonstrated that tissue elasticity is a promising prostate cancer biomarker.

2. MRE: Basic Principles

Compared to other imaging techniques, MRE has the potential to extend the concept of palpation by mapping stiffness variations throughout the prostate gland. In contrast with ultrasound-based elastography, which can only acquire a one-dimension (1D) or 2D wave field, MRE can attain 3D wave field displacement, greatly improving accuracy. Full vector field 3D information which is possible in MRE has two different advantages:

1. True wavelengths can be assessed in 3D space, and not only on projections with overestimated wavelengths as in the case in planar 2D elastography (containing only 1 motion-encoding direction).

2. In tissues, compression waves have much longer wavelength than shear waves. For the case of 3D elastography, the curl can be applied for filtering out the compression wave. The true recovery of the complex shear modulus, can be used to report both elastic and viscous properties of tissues.

MRE can be defined as a non-invasive assessment of variations in tissue stiffness. The term ‘elastography’ means ‘elasticity imaging’. MRE is an innovative and relatively new technique that
uses the principles and applications of magnetic resonance imaging (MRI) and mechanical wave theory to calculate the mechanical stiffness properties of tissues. The resulting elastograms, are a quantitative measure of these properties. MRE consists of three steps:

1. A mechanical vibration or stress is applied in order to deform the tissue or material.
2. Tissue response to the applied stress is encoded into the phase of the nuclear MR signal.
   The motion of the vibration is synchronized with motion encoding gradients (MEGs) and captured with the modified phase contrast MR imaging pulse sequence. The wavelength of the shear waves is shorter in softer tissues and longer in stiffer tissues.
3. The resulting images, containing the temporal and spatial characteristics of the wave field displacement are then processed using an inversion algorithm used to determine tissue’s mechanical stiffness properties.

Figure 6: Diagram of the complete MRE setup, indicating all the major components
III. MOTIVATION

A. Prostate Biopsy and Radical Prostatectomy Limitations

Due to the fact that early prostate cancers usually do not cause any symptoms, early detection of prostate cancer is done with a combination of serum PSA and DRE. PSA screening alone has shown higher detection rate than DRE alone, however, studies have shown that detection rates were highest when the two exams were combined [10]. While a combination of PSA and DRE serve well for screening and could provide an early indicator of asymptomatic CaP, neither of these methods is entirely accurate [9]. The tests can provide abnormal results when a man does not have cancer (false-positive), or normal results can occur even when a man does have cancer (false-negative) [22].

Multiple factors can affect PSA levels: an enlarged prostate, older age, prostatitis, ejaculation, riding a bicycle and certain hormones such as testosterone may increase PSA levels. On the other hand, factors such as: 5-alpha reductase inhibitors (antiandrogen drug), herbal mixtures and aspirin may ‘mask’ a high PSA level. DRE is limited only to the posterior region of the prostate and may be subjected to factors such as the urologist’s experience and training. These limitations can be uncomfortable and can create confusion and anxiety in the patient. Ultimately, the actual diagnosis can only be made with a transrectal ultrasound-guided prostate biopsy.

1. Prostate Biopsy Limitations

Due to the anatomical location of the prostate and the uncertainty of the exact location of the abnormal tissue, prostate biopsies are invasive procedures. Some of the biopsy risks may consist of pain, infection and bleeding. Prostate tissue motion caused by the insertion of the ultrasonic probe into the rectal cavity can make it difficult to accurately target a region during a biopsy, thus reducing confidence in the biopsy. False-negative results can occur even when multiple samples
(greater than 12) are taken, biopsies can still miss a cancer if none of the biopsy needles pass through the cancerous tissue. Patients undergoing 18 or more needle samples experienced increased discomfort and morbidity, far outweighing the benefits [11]. In addition studies have found that 50% of the prostate cancers larger than 1 cm cannot be detected by TRUS [12]. In summary, prostate biopsy is limited to patient risks and discomfort such as prostatitis, acute bleeding, urinary retention, sampling errors and under diagnosis [13].

2. Limitations of mpMRI in the detection of CaP

In recent years, numerous studies worldwide have been done with the purpose of determining the diagnostic accuracy of multiparametric MRI (mpMRI) for prostate cancer detection. A meta-analysis by de Rooij et al. [14], showed a high overall sensitivity and specificity when considering a combination of T2-weighted imaging, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI). The authors imply, there might be a possible role of mpMRI before biopsy in detecting CaP. On the other hand, studies show that there are still limitations on these combined methods. Barral et al. [15] assessed the accuracy of DWI-MRI at 3T with a value of 2000 s/mm² (b-2000 DW-MRI) to detect prostate cancer and found that small tumors with or without a minor Gleason 4 component. Furthermore, when considering the role of MRI before and after prostate biopsy a study by Yoshida et al. [16] found that 3T-MRI could detect cancer cores with a sensitivity of 90.5% in cores with a cancer ratio of 60% and with a sensitivity of 81.8% in those with cancer length of ≥ 5mm. These results indicate that although MRI in combination of other parameters such as DWI or DCE may be suitable for the detection of cancerous lesions with certain characteristics, there are other lesions which may be undetectable, sometimes having the potential to be aggressive. The identification and differentiation of clinically significant CaP becomes then priority for imaging modalities; since over-diagnosis could lead to over-treatment
and underestimating tumor aggressiveness could be fatal for patients.

3. Positive Margins after Radical Prostatectomy

When considering surgical treatment for CaP, especial attention has to be put on surgical planning. The main type of surgery for prostate cancer is known as radical prostatectomy. Some methods used by surgeons as part of surgical planning are whether the tumor can be felt during DRE, Gleason score, any preoperative MRI findings and the percentage of cancer in biopsy samples [4].

Removing the prostate gland, and in some cases, the seminal vesicles and local lymph nodes should be enough to ensure cancer is completely eliminated from the body. The problem arises when CaP is of high grade and the cancer has spread outside the gland. In recent years, when considering radical prostatectomy, urologist as well as patients have put an increased interest in nerve sparing procedures. An adequate development of a correct preoperative plan would be fundamental in reducing the incidence of positive margins after surgery. All the methods have shown to some extent, improvements in the preservation of neurovascular bundles, the nerves that control penile erections and the striated sphincter, which controls urinary functions.

B. Medical Training Simulators (MTS)

1. Overview

In the present day, as part of medical education and preparation, an enormous emphasis is placed upon updating and reforming current training methodologies. This is done to primarily ensure the well-being and safety of the patient at all times, and secondly to provide an added value to the training process. Traditionally, medical training has been based on an apprenticeship model, in which the learning of the novice resident involves the experience of errors while performing a procedure under the guidance and supervision of an expert mentor. Unquestionably, procedural
inexperience on an actual operating room can lead to patient discomfort, complications and in the worst case scenario death.

With the continual advancement of technology, other tools have been developed in order to provide added value to the training; the use of anesthetized animals, cadavers and manikins. Nevertheless, each of these methods possess their limitations: the interaction that occur with the animal’s tissues and anatomy differs from those of living humans, the use cadavers is expensive and a certain procedure can only be performed once and a mistake can render the body useless for future demonstrations and manikins have limitations in their replication of physiology, which could be translated as a limited range of anatomical variability and a constant investment towards its maintenance and repair [17].

Computer simulation is enabling medical training simulators to become more accepted tools in the medical training process. Human sensorial modalities (visual, touch, auditory, taste and smell) have been part of medical practice ever since its establishment as science in early civilizations. Medical training simulators are becoming more accepted tools for providing added value to the training due to factors as described by Coles et at. [17] “virtual models offer the opportunity to simply modify the virtual patient using patient-specific data from one of the many 3D imaging modalities available in the hospital.” Moreover, the addition of two of the sensorial modalities (vision and touch) to the simulation as well as the critical analysis and feedback gathered the system could allow the operator to reach a certain level of proficiency before commencing training with patients.

2. Haptics in MTS

Due to the high fidelity haptics and graphics components, the use simulators are becoming more accepted tools for surgical training. The use simulators have the potential to provide residents
with features such as: (a) deliberate practice in a simulated environment, independent from time, ethical and other restrictions, (b) practice of multiple case-scenarios (common and uncommon) anatomical presentations and (c) a constant analysis of the performance of the operator, with the prospective of providing feedback for additional practice of certain steps of the procedure. In particular, the use of haptic devices in simulation have been beneficial, haptic devices provide a mechanical I/O system, capable of tracking one or more end effectors in physical space and provide ‘force/torque feedback’ between the user and the virtual environment. Commercial force feedback devices can vary in different characteristics, such as the degree of freedom they offer, force/torque they can apply, the shape of the end effector and price. However, all these devices share a similar type of actuation: DC electrical motors, pneumatic or hydraulic actuation. Some of the properties of the devices can have advantages and disadvantages for the type of application they will be used. For example for a simulation of a medical procedure, providing too little or too much feedback will lead to negative training.

![Figure 7: (Left) SensAble Phantom Omni haptic device. (Right) SensAble Phantom Desktop haptic device.](image)

The use of haptics in medical simulations has primarily been to enhance training applications, with a special emphasis put on palpation simulation as the first task in many of the procedures, and needle insertion simulations to virtually recreate procedures such as insertion
points of catheters, application of anesthesia and sampling for biopsy among others.

3. Haptic Elastography Literature review

There has been a wide range of scholarly publications related to the implementation of MRE to multiple organs, including the prostate as well as a wide range of scholarly publications related to the use of volumetric medical data from Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) for the virtual simulation of medical and surgical procedures [28, 32]. In contrast, when an integration between MRE and haptics is considered, the literature was found to be less extensive and not as mature as when considering both topics separately or considering its application for the simulation of prostate cancer.

Palmerius et al. [18] present an algorithm for haptic palpation that utilizes elastography data. The algorithm was implemented with C++ and X3D using a combination of H3DAPI and Volume Haptics Toolkit (VHTK) programming libraries. The clinicians participating on the study declared that *palpating* the elastography data gave them much richer information about the tissue than just the visualization of the same data. Since the implementation was done with visually rendered B-mode ultrasound co-registered with the haptic rendering of hardness from the elastometry data, this system is limited to 2D exploration. Li et al. [19] proposed a unified rendering interface, SenseViewer which allowed users to annotate and label visual, auditory and in particular haptic cues to medical images. This interface, employed MRE for quantitative soft tissue viscoelasticity, making the haptic cues more realistic. In order to add haptic cues to the medical image, and to enable users to touch and feel the virtual organs the users have to design various transparent rendering models by hands and has only been applied to 2D medical images only. Lastly, Selmi et al. [20] presents a virtual reality simulator of a complete learning environment for TRUS image-guided prostate biopsy. Each ‘virtual’ patient database is composed
of clinical information (age, PSA, prostate volume, DRE), an ultrasound image, an MRI image and a prostate mesh. The haptic device in this study, was used to represent the virtual ultrasound probe, providing a constant force to replicate tissue friction. During the simulation, the 2D TRUS image plane is displayed in real time in function of the virtual probe orientation; the needle guide is fixed on the US probe. Although the simulator provides a range of exercises to target different aspects of the surgical gesture; the system did not use any elastography data to achieve a ‘realistic; feel of the prostate, then again, it focused more on the steps of TRUS-guided needle biopsy procedure.

The use of haptics in medical simulation has provided a wide range of advantages as compared to traditional training methods. In addition, better patient outcomes could be achieved by improving the skill and performance of the surgeons by allowing them to practice in a realistic, unconstrained simulated environment [21]. In this aspect, volumetric datasets have become fundamental for the creation realistic models for common and uncommon clinical cases. Each patient represents a unique challenge. A combination of MRE and a Virtual Reality Interface (VRI), may add yet another training method that could be applicable in the surgical planning by providing patient specific information, along with the localization and extent of the tumors.

C. Objective and Hypothesis

The main objective of this thesis, was the development of a haptics-based virtual reality simulation of prostate cancer. In order to achieve this goal, a methodology to translate a 3D map of the prostate tissue stiffness obtained via MRE was designed to recreate a virtual model of the prostate with realistic viscoelastic properties. The methodology was first applied to a commercially-available prostate phantom with multiple artificial tumors for validation, and later applied for the simulation of MRE patient datasets (5). A haptic device was used to provide tactile
feedback to the multi-point contacts between the surgical instrument and virtual anatomical layers and cancerous lesions located in the virtual prostate model.

**Hypothesis:** A combination of visually rendered patient specific 3D models of the prostate, co-registered with haptic rendering of the viscoelastic information from the MRE data would allow clinicians to have a more holistic picture of the patient clinical situation. The addition of haptic cues with values quantified by MRE would add more informational wealth to the 2D images of ultrasound or MRI and could be of more use to urologists in the identification and localization of CaP tumors within the gland for a more accurate biopsy sampling. This same concept, could be expanded for the reduction of positive surgical margins when the tumors are outside the prostate and radical prostatectomy is necessary.
IV. HAPTIC ELASTOGRAPHY EXPERIMENT OF PROSTATE PHANTOM

Note: Some of the information contained in this chapter was accepted as an abstract and presented as a poster with the title: “Haptic simulation of prostate surgical planning based on magnetic resonance elastography” at the Proceedings of the Canadian Urological Association Annual (CUA) Meeting (Vancouver, BC, June 25-28, 2016).

For the simultaneous implementation of graphics and haptic rendering, the creation of efficient 3D models, is essential. This is particularly true when considering medical simulation where not only the models have to be anatomically accurate, for a realistic training simulation, but also efficient to comply with the minimum required graphic and haptic frame rates. Medical imaging modalities such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) provide volumetric datasets were these models could be extracted. Furthermore, given the potential of magnetic resonance elastography for improved differentiation of pathological and healthy tissue, as well as better tumor localization, virtual representations of pathological conditions could also be generated.

For this first study, a prostate phantom was used as a validation tool for the proposed MRE methodology. The specific aims here were the proper identification of the lesions as well as the differentiation between the anatomical structures within the phantom. This chapters begins with the description of the MRE phantom setup, data acquisition and post-processing. It continues with the method of obtaining 3D models based on the MRI images, and concludes with the presentation of the development and implementation of haptic cues added to the phantom volume in accordance to the viscoelastic estimations from the MRE stiffness maps. This last concept will be further expanded in the following chapter.

A. MRE Prostate Phantom Setup, Data Acquisition and Processing

A preliminary magnetic resonance elastography (MRE) experiment was implemented on a commercially-available prostate phantom (CIRS Tissue Simulation & Phantom Technology) to
test the operability of performing MRE experiments on a prostate in an ultra-high field, 9.4 T Agilent horizontal bore preclinical, MRI system (310/ASR, Santa Clara, CA). The phantom is designed with proper materials to provide imaging contrasts under MRI and elastography [23]. It includes an artificial prostate, urethra, seminal vesicles and 3 cancerous lesions (approximately 10mm in diameter) which are stiffer compared to the rest of the immediate surrounding areas. The complete experimental setup is presented on Fig. 8. A piezoceramic actuator attached to a cylindrical rod directing a 400 Hz sound wave to the phantom wall, produced the propagating shear waves needed for MRE imaging. The imaging parameters for the scan, were as follows: modified spin echo pulse sequence, 12.8 x 12.8 cm FOV, 128 x 128 voxel size, 2.0 mm slice thickness, TE/TR 35.0/800 ms, 400 Hz excitation, 8 motion encoding gradients, and 8 Gauss cm\(^{-1}\) gradient strength.

![Figure 8: Picture of the prostate phantom MRE experimental setup: A) Piezoceramic actuator attached to a cylindrical rod. B) MRI cradle and C) Prostate phantom](image)

All three wave displacements components were encoded simultaneously using a novel MRE
pulse sequence, called SampLe Interval Modulation-magnetic resonance elastography SLIM-MRE developed by Klatt et al. [2]. The vibration harmonics of complex wave images are calculated with a sequence of MRE images at different time steps. Only eight phase-difference images are required for the acquisition of all components of the displacement vector. This technique allows the acquisition all three components of a single frequency vibration simultaneously; therefore, it allows the total scan time to be 63% shorter compared to running three separate scans for the x, y and z directions. Another advantage, is that with the complete vector field there is no bias to assumed plane waves and any compression waves can be removed by taking the curl of the vector field, allowing for a shear wave only displacement field. Algebraic Helmholtz inversion of the curled wave field $Q$, were performed to obtain the stiffness images

$$G = -\rho \omega^2 [(\Delta Q)^T \Delta Q]^{-1} (\Delta Q)^T Q \quad (4.1)$$

where $G$ is the complex storage modulus.

The resulting spatially filtered complex wave, for the x, y and z directions is presented on the top row of Fig. 9 (A). Attenuation can be seen as the distance from the mechanical source increases, causing a loss in the signal near the far edge of the prostate phantom. The magnitude image, presented in Fig. 9 (B) bottom left, shows the extent of the prostate as well as the urethra in the center, with the hard lesions just below on either side. As a consequence of magnetic field inhomogeneity, signal loss and boost artifacts are also visible in this image. These correspond to low and high stiffness values respectively in the stiffness map, presented in Fig. 9 (C), bottom right.

To generate the real part of the shear modulus map, the wave image was spatially filtered and directionally filtered prior to full 3D Helmholtz direct inversion. Finally, a median filter stiffness
map was applied. Regions of stiff material in the elastography image correspond quite well with the phantom lesions and urethra. This was found to be consistent with the specification parameters described in the phantom’s datasheet as how each of the components should appear on the MRI and elastography scans: prostate dark appearance with soft, slight contrast with background, urethra brighter and stiffer than prostate and lesions dark and stiffer than any other component. The results of the elastography image point out the feasibility of using MRE on the prostate to identify pathological changes in tissue stiffness.

**Figure 9:** A) 3-dimensional filtered wave image for the slice depicted on the setup schematic. B) MRI magnitude image indicating phantom’s anatomical structures (prostate, urethra and cancerous lesions). C) Real part of the shear modulus map indicating the location of stiffer areas; the urethra and the lesions.

### B. Extraction of 3D models for Haptic Simulation

For the simultaneous implementation of graphics and haptics rendering of multiple objects on a multithread environment, efficient 3D models need to be created. In this context, all the objects must comply with the 60 Hz frame rate used for graphics and the 1000 Hz used for haptic rendering. For haptic applications, polygonal meshes are created from collections of segmented
images from CT or MRI scans (volumetric data). Polygonal meshes can be defined as surfaces in 3D space consisting of multiple triangles. The meshes obtained from segmentation must be carefully decimated; not only to preserve the anatomical topology of the surface, but to maintain an adequate number of polygons for the haptics libraries to perform adequately at the framerate described above. For this project, manual and automated methods were employed using freely available open-source volume processing software tools including: VolView™, ITK-SNAP™, Paraview™. An accurate 3D anatomical model of the prostate phantom was created based on a set of the MRI magnitude images. The process used for obtaining the 3D models is the described in 3 different stages: (1) segmentation, (2) optimization and (3) additional processing. This methodology was developed by Rizzi et al. [24].

1. Segmentation

As a preceding step in the segmentation process, the median of the MRI magnitude data was computed using one of the filters from ParaView™. ParaView is an open-source, multi-platform data analysis and visualization application; which supports a wide variety of visualizations algorithms including advanced modeling techniques such as contouring, polygon reduction and mesh smoothing. Paraview is one of the many Visualization Toolkit (VTK) based applications [24]. The first algorithm used in the segmentation was the Median filter, which substitutes the value at each pixel/voxel, with the mean scalar value of surrounding neighborhood. This procedure allowed the exclusion of any outliers from the MRI scans (rectilinear data), thus removing high-intensity noise from the data and returning a rectilinear output.

The segmentation of the prostate mimicking phantom was done using ITK-SNAP, an open-source software package, developed for the segmentation of 3D anatomical structures; Version 3.2
was used in this work. ITK-SNAP is able to read series of medical images in DICOM format, metafile (.mhd), raw binary, among others. When the image is about to be loaded to the program, an image summary window is displayed by the program containing detailed specifications of the image property (dimensions, voxel spacing) and their values. Once the image has been loaded, the main window contains three different planes: axial, coronal and sagittal. The user can then proceed to enhance the visualization of a specific anatomical part by adjusting the image contrast in the image histogram.

For this project, two types of segmentation were performed: automatic and manual. The automatic portion of the segmentation was done by first defining the region of interest (ROI) and applying a pre-defined threshold function to the input images. The thresholds will highlight the anatomical part under study in white and the rest in blue. As a subsequent step, the user must define the starting values for the algorithm. This is done by placing 3D spheres (“bubbles”) and defining their radii. During each iteration, the ‘noise’ around the highlighted part is eliminated. The number of iterations for the algorithm is based on the user’s criteria and expertise. Manual segmentation was done in order to improve the results of the automatic segmentation. The user is able to erase any segmented voxels that do not correspond and continually regenerate the polygonal mesh. The user is able to label and mark with different colors, different anatomical structures, as presented on Fig. 10. Once the different segmentation are done, they can be stored in the same metaimage (.mhd) file. The final segmentation of the prostate, seminal vesicles, urethra and cancerous lesions was exported as a VTK PolyData file to be further processed.
Figure 10: Segmentation of the different prostate phantom anatomical components, the prostate, urethra and seminal vesicles are indicated with different colors. The segmentation of the phantom lesions are also visible on the last image.

2. Optimization

In this step, the saved 3D volume in uncompressed metimage file format (.mhd) is further processed to construct an optimal volumetric representation of the data, the program used in this step was ParaView™. Fig. 11 describes the virtual reality modeling language (VRML) ‘assembly processes’ used to create the models of the phantom prostate.

![VRML assembly line](image)

Figure 11: Schematic representing the VRML assembly line for the creation of the virtual models.
There are many different filters within ParaView, based on VTK algorithms. The first stage, consisted in using a vtkDataReader filter for reading the data segmented in ITK-SNAP and displaying a volumetric data. The next filter used was vtkContourFilter which extracts the points, curves, or surfaces where a scalar field is equal to a user-defined value. This surface is often called an isosurface [34]. For virtual prostate model 2390 isosurfaces were generated. Next, one of the most critical steps was performed. A vtkDecimateFilter was used with the option of “preserve topology” activated, so as not to lose the anatomical details of the model. The isosurface was drastically decimated using an adaptive edge collage algorithm to reduce the number of polygons to be rendered, as presented in Fig. 12. The degree of decimation is determined by visually inspecting the density of the polygons and subsequently checking the size of the file of the VRML model. After decimation, the size of the file for the virtual prostate went from 39 MB to 884 KB.

![Figure 12: (Left) Higher density of polygons representing the unfiltered “raw” mesh representation of the prostate phantom. (Right) Lower density of polygons, representing the final polygonal mesh after contouring, decimation and smoothing of the model.](image)

### 3. Additional processing

Following decimation, a smoothing filter is applied using the vtkSmoothPolyDataFilter. This filter smooths a polygonal surface by iteratively moving points toward their neighbors. Because
this filter only adjust point positions, the output data is also polygonal. The resulting model contains better-shaped polygons and more evenly distributed points. The number of iterations required for each of the phantom components was determined by observing the smoothness of the model. In this context, small structures such as the urethra and seminal vesicles required less smoothing filtering than larger structures such as the prostate or the gel enclosure. As a subsequent step, a complete scene containing all the different segmentation structures was build. A vtkTransform filter was used to apply transformation to the polygons. The filter allow the user to specify the position, size and orientation of the polygonal data sets. After contouring, decimation and smoothing filtering, the final polygonal mesh of each model was saved in VTK file format to be further converted into a VRML 3D representation to be used in the simulation scene (Fig. 13).

![Figure 13: Complete scene of the virtual phantom prostate model indicating all components. A model of the outside gel enclosure was also generated and its opacity level increased for visualization of inner structures.](image-url)
C. Haptic Simulation of Prostate Phantom MR Elastography

1. Volume Rendering

In contrast to the previous section, which focused on creating medical simulations based on polygonal meshes, this section focuses on the developing of a mathematical model for the computation of force feedback in conformity with the estimations calculated from the volumetric shear modulus map calculated in the MRE experiment.

While our visual system can the tricked into seeing continuous motion by displaying images at (60 Hz), haptic feedback requires a much faster rendering (1000 Hz) for suitable human haptic perception [17]. This leads to a significant amount of computational power even for simple models and have been a limitation when considering including multiple objects in the scene or creating high quality polygonal representations. It has not been until recent years, with the ever-increasing speed and processing power of computers that has been possible to perform real-time visualization of volumetric data.

Modern medical image equipment such as CT and MRI produce vast amounts of data in the form of arrays of slices. Although, they are a complete volumetric representation of the scanned patient anatomy, these datasets can only be observed as a set 2D images, when observed by a radiologist. Therefore, volumetric rendering not only provides a method to graphically display the 2D medical information to a more intuitive 3D representation, but it also provides a method to obtain accurate and detailed anatomical 3D models for haptic rendering and simulation. Moreover, such as the case of MRE, the haptic cues added will be realistic and in agreement with the quantifications from the stiffness coefficients from the elastograms.

2. Implementation of Haptic Rendering

The complete elastography based haptic simulation was developed with a number of
software libraries including Coin3D, 3D Guidance tracker, SIMVoleon and haptics libraries such as OpenHapticsTM which were used to create the haptic cues for the polygonal meshes and the MRE volume data. A haptic device (3DSystems Touch X) was used to interact with the virtual scene containing the models. A Microsoft Visual Studio project was created in order to implement the whole virtual simulation. The developed C++ program, includes and actively interacts with the libraries mentioned above.

![Diagram of volumetric format conversion](image)

**Figure 14:** Procedure flowchart of volumetric format conversion

The experimental dataset used for the simulation was an MRE shear modulus map (G) scan consisting of $256 \times 256 \times 10$ voxels. Each voxel represented a volume of $0.5 \times 0.5 \times 1.25$ mm. From their original DICOM representation to a MetaImage format compatible with the OpenGL (graphics library) used. For this step, the MATLAB Central’s File Exchange was consulted in order to find a function which would perform the conversion from one format to the other. A function called metaImageWrite (IMG, FILENAME) was found. Developed by David Legland, this function takes IMG, a matlab array (the shear modulus G) and writes two metaimage files, one of them being “.mhd” and the other one “.raw.” Both of these files are used when the volume
was loaded in the simulation and both files were included in the folder containing the objects of the scene. Furthermore, one critical step performed was the computation of the real part of the shear modulus (G). Since it is part that contains the stiffness estimations, MATLAB was used to compute and return only the real part of the elements in the complex array of (G).

Another fundamental step performed before the MRE volume could be loaded to the software application was the conversion of the data from ElementType = MET_DOUBLE to eight bit unsigned ElementType = MET_UCHAR. This was done primarily due to minimize the computational expense required for the graphics and haptic rendering. The resulting volume had a scalar range 0 to 255 as compared to the 0 to 7551.73. It is important to note here, that while the original MRE volumetric data was processed, the intrinsic characteristics of each voxel remained the same. In order words, the stiffness coefficient estimations were “scaled down” while preserving their innate characteristics; the highest coefficient of the volumetric data which was previously 7.5kPa now is represented with a scalar value of 255. Fig. 14, presents the complete format conversion flowchart.

![Figure 15: Virtual representation of the MRE prostate phantom volume. The urethra and 2 of the lesions are visible.](image)
Read 3D Polygonal Meshes and MRE Volume

In order to create the simulation, the objects (polygonal meshes) were loaded as Open Inventor nodes. Open Inventor is a high-level 3D graphics engine, written in C++ which is based on OpenGL (Open Graphics Library). The scene graph is organized in a tree structure, where particular parameters and properties of each node are contained within the node. In order to build the scene file, “scene.iv,” Coin3D (coin designer) which is a rapid application development (RAD) was used. The polygonal meshes of the phantom prostate where included in the “scene.iv” file. Similar to the scene file, “cursor.iv” file was created in which a virtual model of a biopsy needle was loaded. It is important to mention here that only the tip of this virtual needle considered when computing the collision detection between the cursor and the object.

In order to read the MRE volume for graphics and haptic rendering, a special function was developed in the program. This function reads the “raw” MetaImage MRE volume and determines all the voxel parameters needed for the computation of the haptic effect. These parameters include, the name of the file, the size, the dimension and the position of each voxel constituting the volume. These parameters are then later saved in a field called voxelData, which is initialized in null every time the program starts. After the program closes, voxelData is deleted from memory. In order to determine if the haptic cursor is inside the volume or not, a Boolean condition was implemented. If the cursor is outside the volume either in the back or the front of the volume, this condition causes to approximate to the next voxel value when the cursor is next to the object. The getVoxel class is a 3 dimensional vector with floating point coordinates and was used to store the value of every voxel of the MRE volume. This value was the estimation coefficient calculated from elastography.

In order to covert the point in the object coordinate system to a voxel, it was necessary to
divide the position of the point in the world (scene) coordinate system by the size of the voxel. In doing this, the 3D array of the volume was converted to a 1D array, allowing the user an easier access to specific voxel informational value within the volume. These voxel values were used in the creation of the custom haptic effect.

**Interaction with the virtual environment**

In order to detect the collision with the virtual objects, the tip of the haptic device was used. The haptics libraries, i.e. SensAble’s Open HapticsHL (haptic library) check for point collision detections between the meshes within the scene and the haptic cursor. The most common collision detection algorithm used is the proxy-based (also known as point-based). This algorithm is based on a spring-damper model. The reaction force is proportional to the penetration depth, shown in Eq. 4.1. The proxy, defined also as the “god-object” is a point which closely follows the position of the haptic device, and it is constrained to the outside of the surfaces of all touchable shapes. The haptic rendering engine constantly updated the position of the proxy. “While the actual position of the haptic device may be inside an object, the proxy will always be outside. When not touching a object, the proxy will always be placed at the device position, but when in contact with and object, the haptic device will penetrate the surface of the shape and the proxy will remain outside of the surface” [35].

\[
\text{Penetration depth} = \text{Haptic device position} - \text{Proxy Position} \quad (4.1)
\]
The forces computed in OpenHaptics can be of two types: collision with objects and haptic effects. This first method was used to generate force feedback for the polygonal meshes of the prostate phantom. Haptic materials properties included in HL are: stiffness, damping (damping), static friction and dynamic friction. These properties can be changed in their Open Inventor files as well as during runtime using a control panel created with Fast Light Toolkit (FLTK). FLTK is a graphical user interface library which is open source and compatible with Open Inventor and OpenGL. The control panel allows the user to choose a particular object within the scene and change its material properties such as stiffness or viscosity. The values for these properties range from 0 to 1. When a collision is detected, the proxy algorithm calculates the forces depending on the object material properties, the proxy position and the haptic device position.

The second method to generate haptic feedback was through the implementation of a haptics effect. Several built-in effects, such as constant, spring, viscous and friction are available through OpenHaptics. A callback function allows the user to access these effects and calculate a force that will be user-programmable and based on a combination of one or more of these effects. The resulting custom effect will be a unique effect that would recreate the desired haptic feedback specified by the user. This method was used in the creation of the viscoelastic/elastography effect.
used to generate haptic feedback perceived by the user when interacting with the virtual environment.

**Development of the Mathematical Model**

When developing a mathematical model to create the haptic cues for the simulation, both stiffness and damping parameters had to be considered. This presented a particular challenge, involving the creation of a custom haptic effect able to simulate not only the (spring like) behavior from the stiffness parameters, but also to provide a damping resistance in proportion to the penetration depth of the haptic cursor within the virtual model. To overcome these limitations a custom haptic effect was developed using OpenHaptics software development kit (SDK), allowing the manual calculation of the feedback force. A spring-mass-damper model developed by Vaughan et al. [26] was particularly considered due to the capability of representing varying stiffness throughout tissue structure. This model presents the concept of a mass connected to a spring combined with a damping element which resists motion; the point mass was attached to the haptic device. Parameters such as the spring constant $k$ representing stiffness, damping viscosity $c$ representing tissue viscous properties and mass $m$, representing the applied force are included in this model.

A variation of this model was implemented in order to compute the force of the custom elastography effect. Since the point mass is attached to the tip of the haptic device, the virtual cursor position had to be determined for every rendering frame, the resulting vector component containing all three directions (x,y,z) was computed. Euler integration of the point mass state is computed to determine the acceleration, velocity and position of the point mass (cursor). The point mass stiffness coefficient used for computation was 0.001 (kg). The kg, unit is a representative unit of this mass as perceived by the haptic device.
The effect starts once the tip of the haptic cursor touches and gets inside the MRE volume. Therefore, when the cursor is outside of the volume, the “apparent” velocity and acceleration of the cursor is zero, and there is no force computed, and no haptic feedback is generated. Once the cursor has touched the volume, the object stiffness force computed is negative since it is representing the elasticity as a way to counteract the applied force in the opposite direction, shown in Eq. 4.2.

\[ F_s = -kx \quad (4.2) \]

where \( F_s \) is the object reaction force, \( k \) is the volume stiffness obtained by MRE and \( x \) is the difference in distance object between the object and the position of the cursor once it enters the object. It is important to note here that \( k \) is the coefficient value of the voxel from the shear modulus map. It was necessary to scale down this coefficient in order to achieve stable force rendering throughout the simulation. The elastography coefficients (0-255) were divided by 512 in order to obtain a maximum stiffness coefficient of 0.5, needed for this stable rendering. In this aspect, the stiffer the tissue (higher \( k \)), more force is required to cause a change in \( x \). The damper represents tissue deformation with time. The effect of the damping was to cause slowing down in the motion of the cursor and therefore cause a viscous effect. The force calculated is opposite and proportional to the velocity of the cursor.

\[ F_d = -cv \quad (4.3) \]

where \( F_d \) is the damping force, \( v \) is the velocity of the point mass (cursor), and \( c \) is the damping viscosity. It is important to note here that for this portion of the project, a critically-damped case was considered. In this case, the system returns to equilibrium as quickly as possible without oscillating. This coefficient was computed as follows,

\[ c^2 = -4 \times m \times k = 0 \quad \text{(critical damping)} \quad (4.4) \]
\[ c = 2 \times \sqrt{m \times k} \quad (4.5) \]

by performing this computation, the damping component added to the calculation of the force generated the viscous feeling felt by the user, while the cursor immediately returned to equilibrium without causing any oscillation of the cursor. This “extra” oscillation was particular felt when an overdamped was considered during the implementation of the model.

The final force sent to the haptic device and felt by the user, is the opposite of the inertiaForce which was calculated by adding the two force components: the springForce \( (F_s) \) and the damperForce \( (F_d) \). The inertia force calculated represents the pulling of the point mass within the object by a spring.

\[ F = F_s + F_d \quad (4.6) \]

where \( F \) is the total reaction force.

The implementation of a spring-mass-damper system allowed for the generation of a viscosity effect of an object with varying stiffness, such as the case of the volumetric MRE scan of the phantom.

D. Discussion

This experiment successfully demonstrated the feasibility of performing MRE experiments on a prostate phantom in an ultra-high magnetic field. Moreover, this study presented the implementation and rendering of haptic force feedback based on two different methods: the collision detection, used for the polygonal meshes of the different anatomical components of the phantom prostate extracted from the MRI scans and the custom haptic effect created to generate haptic feedback from the MRE volumetric dataset.

One of the accomplishments achieved in this study was the simultaneous rendering of the polygonal meshes of the phantom and the MRE in the scene. Although, the MRE volume was
limited by its size, when it was overlaid on the precise scanned location, it clearly matched the segmented models of the urethra and the lesions. This allowed for an experimentation study in which the polygonal meshes force feedback was deactivated. Although both, the polygonal meshes and the volume were graphically rendered, the complete haptic feedback was based on only the haptic effect of the volume. By correctly identifying the lesions on the phantom, this study served as a validation in our methodology and a motivation to expanding our method to MRE data of *ex vivo* prostates. As an additional feature of the simulation, the user was able to move, rotate and translate all the objects within the scene by pressing the button of the haptic stylus. This allowed an intuitive interaction with the virtual environment allowing an intuitive exploration of objects. Another feature of the simulation was the creation of a virtual clipping tool. This tool allows the user to “cut” through a particular plane of the object; by cutting through the plane, the haptic as well as the graphic rendering of that certain portion of the object was not performed, resulting in a partial rendering of the object.

There were a number of considerations presented in the semi-automated process of extracting the models from the MRI scans. For instance, the iterative automatic segmentation of ITK-SNAP required user stoppage when considered necessary. In doing so, the user had to determine the precise amount of iterations to segment the desired areas, while avoiding the crashing of the program. Manual segmentation provided a great tool for correcting over-segmentations created by the automated process. For the model optimization with VTK, one of the considerations was the amount of decimation and smoothing applied to the isosurface obtained from the segmented area. Multiple receptions, varying the degree of decimation and smoothing filtering were performed before determining the appropriate amount for each of the components of the phantom prostate.
One of the major limitations of this study was that the MRE volumetric data consisted of a scanned images consisting of only 20 slices. Although, phantom features such as the urethra and 2 of the lesions were identified and clearly visible, this only represented a partial representation of the complete phantom. In addition, signal loss artifacts due to the magnetic field inhomogeneity was seen in the magnitude image. The closed acrylic enclosure of the phantom container, generated noise and bouncing artifacts. When the wave was introduced through the rectal wall of the phantom, the enclosure caused the propagating wave to bounce continuously causing a visible stiffer area in the lower portion of the phantom which can be clearly seen in the shear stiffness modulus map image. These “stiffer areas,” which in reality should have been softer, where also computed as stiffer areas in the computation of the haptic force.

The created mathematical model provided a great viscoelastic effect to simulate an object with varying stiffness, such as the case of the MRE volume. The major consideration when developing this model was the capability to recreate the viscoelastic behavior of the object. The behavior considered here, was that of a soft tissue, since the object represented was a (phantom) prostate. Soft tissues are viscoelastic, that is, they display a elastic (spring like) and a viscous (damper like behavior). In order to create the haptic cues for the simulation, both stiffness and damping parameters were considered. One of the major challenges encountered in the development of the mathematical model, was the impact of the dampening constant. In the model, this constant relies in the velocity of the haptic cursor and the stiffness coefficient $k$. Small changes in velocity as well as this coefficient caused instability in the rendering of the effect resulting in vibration or “buzzing” of the haptic device, even when the volume was touched lightly.

One of the approaches used to solve this, was the tuning down of the haptic spring stiffness of the effect to a maximum coefficient of 0.5. By performing this operation, the generation of force
feedback from the volume improved significantly but was not completely fixed. Another consideration for this effect was the inability to constantly generate force feedback when the volume was rotated within the scene. These problems motivated the implementation of another volume rendering algorithm, which is further discussed in the next chapter.
V. HAPTIC ELASTOGRAPHY EXPERIMENT OF EX-VIVO PROSTATES

Note: Some of the information contained in this chapter was accepted for publication in abstract form with the title: “Augmented Reality and Haptic Exploration of Excised Prostates using Magnetic Resonance Elastography,” in the Proceedings of the Engineering and Urological Society (EUS) Meeting (San Diego, CA, May 7, 2016).

The concept of translating the quantitative viscoelastic estimations obtained from magnetic resonance elastography, and creating a force feedback from the MRE volumetric dataset is further explored in this chapter. Quantitative elasticity values obtained through the MRE technique offer the potential of determining ‘threshold’ elasticity values, to correctly identify pathological from healthy prostate tissue and in particular clinically ‘significant’ from ‘insignificant’ disease. For this second study, 5 different human prostate specimens obtained from patients who underwent robotic radical prostatectomy were scanned with a modified 9.4 T ultra-high field pre-clinical scanner.

The resulting volumetric data of shear modulus maps, were rendered to create virtual 3D representations of the ex-vivo prostates. Haptic properties of the virtual prostate were computed by: 1) a mass-spring-damper model that provides a variable haptic viscosity effect that is conformity with the estimations from voxel value of the shear modulus map and 2) through a volume haptics rendering algorithm that defines a transfer function providing different stiffness, viscosity, as well as static and dynamic friction to different ranges of the shear modulus. A preliminary pilot study was performed to evaluate the overall simulation. An experienced urologist was requested to analyzed the 3D anatomy of the 5 virtual prostates and determine the location and size of the tumors by visual and haptic feedback.

A. MRE of Ex-Vivo prostates Setup, Data Acquisition and Processing

The MRE processed data used in this section was provided by Steven Kearny, one of the collaborators of this study. This subchapter only intends to summarize the methods involved in
obtaining the patient MRE volumetric data. The complete description of the data acquisition, and processing of the MRE data constituted an experiment on its own and can be found in [27].

This study involved the scanning of 5 ex-vivo prostates specimens. The specimens came from males patients of the University of Illinois at Chicago hospital which underwent radical prostatectomy for the treatment of prostate cancer. The patients were clearly informed about the research and were voluntarily asked to participate. The study involved scanning the prostate specimens after removal from the patient; therefore it did not presented any change in the standard care and posed essentially a zero risk to the patient.

The protocol used for this study was approved by the Institutional Review Board at the University of Illinois at Chicago. All the patient information was anonymized prior to any processing. The MRE scan was conducted immediately following surgical removal of the prostate and was performed within a 2 hour frame window determined by the pathology department. The scan was conducted in an ultra-high field, 9.4 T, preclinical, MRI magnet, consisting of a piezo actuator which is directly connected to a tube containing the specimen inducing a geometrically focused shear wave used for MRE imaging.

The imaging parameters for the scan for each of the prostate specimens is summarized as follows:

<table>
<thead>
<tr>
<th>Scanning Parameters</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOV (mm x mm)</td>
<td>40 x 40</td>
<td>48 x 48</td>
<td>64 x 64</td>
<td>42 x 42</td>
<td>64 x 64</td>
</tr>
<tr>
<td>Resolution (mm)</td>
<td>0.3125</td>
<td>0.5</td>
<td>1</td>
<td>0.3281</td>
<td>0.5</td>
</tr>
<tr>
<td>Slice Thickness (mm)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Number of Slices</td>
<td>20</td>
<td>20</td>
<td>50</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>Number of MEGs</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Gradient Streght (G/m)</td>
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<td>18</td>
<td>15</td>
<td>18</td>
<td>18</td>
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<tr>
<td>Frequency (Hz)</td>
<td>500</td>
<td>500</td>
<td>250</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>25.2</td>
<td>26.1</td>
<td>25.5</td>
<td>27.6</td>
<td>27.6</td>
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<tr>
<td>TR (ms)</td>
<td>750</td>
<td>700</td>
<td>2400</td>
<td>2200</td>
<td>200</td>
</tr>
</tbody>
</table>
Figure 17: Imaging parameters for each of the patient datasets. Adapted from [27]

Figure 18: MRE results of one of the ex-vivo prostates. (Left) Real part of the complex shear wave displacement image. (Center) T2-weighted magnitude image. (Right) Absolute shear stiffness map. Image used with permission of Steve Kearney.

The resulting spatially filtered complex wave image, shows short wavelengths around the bottom and longer wavelengths on the right side. Algebraic Helmholtz inversion was used to generate the absolute shear stiffness map.

B. Haptic Simulation of the Ex-Vivo Prostates

By implementing the methodology described in the previous chapter, a complete simulation of the ex-vivo prostate MRE scans was achieved. The simulation was able to represent a virtual tridimensional model for the 5 different patient datasets. In this aspect, every simulation was patient-specific and provided an opportunity to explore the cancerous lesions contained in the tissue and determine not only their localization but also their extension. The designed methodology used to generate haptic cues for the phantom MRE volume, was also implemented for the MRE patient datasets. This involved the conversion from their original DICOM representation to a MetaImage “.mhd” format compatible with the OpenGL. Next, the voxel values of each of the patient datasets was converted to an eight bit unsigned values. This was done with the purpose of minimizing the computational expense required by for graphics and haptic volume rendering.
Read 3D Ex-vivo MRE Volume

As a preceding step before loading the volume to the program, the MRE volume was optimized for haptic rendering. The “.mhd” file was loaded to ParaView and a median function of 3, 5, and 7 was performed. It was found that median 5 best improved the data while maintaining the graphical topology of the volume. The resulting data was “smoother” compared to the original data, minimizing the any “gaps” in between the voxels. This step was particularly useful in the implementation of the Isosurface haptics rendering algorithm described in the next section. In order to read the MRE volume, the function developed reads the “raw” MetaImage MRE data of the patient prostate and identifies all the voxel parameters needed for the computation of the haptic feedback. These parameters include, the name of the file, the size, the dimension and the position of each voxel constituting the volume. voxelData and getVoxel fields are used to determine whether the haptic cursor is within the volume or not and to store the 3D array of the volume to a 1D array for easier access to the specific voxel informational value within the volume. Once again, only the real part of the shear modulus was used for the simulation.

Volume (Isosurface) Haptics Rendering

In the previous chapter, the implementation of a spring-mass-damper system allowed the generation of a viscosity effect of an object of varying stiffness, such as the case of the volumetric MRE scan of the phantom. However, due to the fact that this model relied in the velocity of the haptic cursor, it was found that continuous changes in the velocity caused discontinuities in the haptic rendering of the effect resulting in vibration or “buzzing” of the haptic device, even when the volume was touched lightly. As an alternative solution, this section describes the implementation of an intermediate representation method. Developed by Rizzi et al. [28] this
algorithm in essence, consists in the detection of collisions between one or more 3D shapes and the proxy point. There is no need to create polygonal meshes since the shapes are defined by a set of voxels from specific transfer functions. Haptic feedback is generated directly from the volumetric data by combining the proxy-based method of OpenHaptics and this algorithm.

One particular characteristic of this algorithm is its ability to simultaneously detect multiple volumetric isosurfaces. “These isosurfaces are defined by individual ranges of voxel intensities. A specific transfer function can be defined for each of the isosurfaces and haptic parameters such as stiffness, viscosity, static friction or dynamic friction can be assigned to corresponding voxels of a certain range of intensities” [28].

Since the MRE volumetric data used in this study is essentially a shear modulus map that displays different estimations coefficients, voxels of different intensities (representing higher or lower stiffness values) can be used to create volumetric isosurfaces. These isosurfaces, or volume layers therefore are composed of a specific voxels of certain ranges of stiffness values. In the case of the MRE volume, since the data was represented as an unsigned 8-bit value, the voxel intensities were between 0 and 255. Three different isosurface layers were created: layer one (Layer_1) was composed of voxels with intensities between 0 and 85, layer two (Layer_2) from 86 to 157 and layer three (Layer_3) from 158 to 255. The resulting simulation is presented in Fig. 18. As it can be seen, the virtual interaction occurred with the one of the *ex-vivo* prostate MRE volumes directly. This means that there was no need to extract any polygonal meshes from the volume. Haptically, red areas (areas of higher stiffness values) were assigned higher haptic stiffness values for haptic rendering as opposed to green and blue areas (areas of lower stiffness values) which were assigned lower haptic stiffness values.
Figure 19: (Left) Transfer function of the MRE volume. (Right) Graphic and haptic rendering of the MRE volume using the isosurface rendering algorithm.

The implementation of this algorithm resulted in a stable haptic rendering and was found as one of the best methods to translate the stiffness coefficients from elastography to a haptic feedback perceived by the user. Compared to the custom haptic effect developed, there was no “buzzing” of haptic device when interacting with the volume. The front and back of the volume could both be felt by the user. When the volume was rotated within the scene, the algorithm was still able to render a haptic effect in conformity with the specific isosurface layers being touched. In terms of the computation of forces, OpenHaptics libraries perform the collision detection of the proxy and the volume, in a similar way as they would do with a polygonal mesh. Overall, the complete simulation of the ex-vivo prostate as well as the cancerous lesions was achieved.

Preliminary Evaluation of the Complete Simulation

A complete simulation with each of the datasets was done and a preliminary pilot study was
conducted by an experienced urology surgeon. The study consisted in analyzing the 3D anatomy of the 5 holographic prostates and determine the location and size of tumors by visual and haptic feedback. The urologist declared that the haptic augmented reality exploration provided an intuitive method to explore the prostate anatomy, and precisely determine the localization of tumors found by the elastography. The urologist involved declared that the addition of haptic cues, enhanced the overall experience by clearly differentiating stiffer areas from softer areas. Although this study was not intended to provide statistically significant data, it served in the assessing of the overall performance of the graphics and haptics rendering as well as its potential to be used for the planning of prostate biopsy.

![Image of haptic and augmented reality interface](image)

**Figure 20:** Haptic and augmented reality interface for exploration of hologram-like prostates using MRE. Force feedback is felt by touching the 3D virtual prostate tissue with the virtual needle mapped to a haptic device stylus (3D Systems touch X).

### C. Discussion

The goal of this project was the development of a methodology to translate the quantitative viscoelastic properties given by the real part of the shear modulus map calculated from the MRE
scans, to a virtual haptic based simulation. Due to the many technical requirements needed for both methodologies, such an integration between haptics and MRE was found to be fairly innovative. Even more so, when considering MRE of the prostate or the haptic simulation of tumors.

This type of integration, allows an intuitive interaction and visualization of the complete elastogram volume as compared to visualizing only one 2D image. The uniqueness of this methodology is the creation of patient-specific simulations which are based on specific MRE scans made from the *ex-vivo* prostate datasets. In this context, the prostate anatomical components as well as any cancerous lesion detected by the MRE will be visible and could be used for the generation of haptic cues. A haptic feedback simulation on a patient specific 3D model would allow a better assessment and staging of prostate cancer; eventually leading to the development of a complete diagnosis based on a non-invasive method. The potential of this integration can be seen in medical simulation, by overcoming the drawbacks such as the ones presented by manikins used for medical training. They are limited in their replication of physiology having only a limited range of anatomical variability.

Virtual models offer the opportunity not only to extent this anatomical variability, but extending it, by the precise localization of tumors. This could have implications in the improvement of planning prostate biopsy or could also serve as a “guided practice” to minimize the side effects of radical prostatectomy. One of the limitations of DRE, in the examination of prostate cancer was that it was only limited to the outside part of the prostate gland. An MRE and haptic integration could extend this idea of manual palpation to the whole gland (in the case of the prostate) not only the external portion.

The previous section described the implementation of an isosurface haptic rendering algorithm. One of its advantages was the ability to interact with the volume directly, without the
need of creating polygonal meshes for each shape. By doing so, necessary steps such as segmentation or optimization could be disregarded. In terms of haptic rendering stability and operability, this algorithm provided a better way to generate haptic cues from the MRE volumetric data. Graphically, it provided an intuitive method of visualizing a full 3D representation of the anatomy of the \textit{ex-vivo} prostates. The creation of 3 isosurface layers, each with unique haptic properties allowed for the haptic computation and rendering of a stiffness varying effect. These isosurface layers are composed of a specific range of voxels of the MRE data. Therefore, the direct interaction with each of these layers, is a direct interaction with the stiffness coefficients and in a sense, a true virtual palpation of the \textit{ex-vivo} prostates was achieved.
VI. CONCLUSION

A haptic simulation of prostate cancer based on magnetic resonance elastography was successfully achieved. The first study presented the implementation and rendering of haptic force feedback based on two different methods: the collision detection, which was used for the extracted polygonal meshes and the custom haptic feedback for the simulation of a prostate phantom MRE volumetric dataset. For the graphic and haptic rendering of the latter, a complete procedure to compute haptic force was described and implemented. A direct interaction with the volume allows the accurate representation of complex anatomical structures for realistic medical simulations.

The second study not only demonstrated the feasibility of the integration of MRE and haptics but also demonstrated the potential to create virtual simulations based on patient-specific models. Another algorithm, which allowed the direct interaction with the MRE volume was implemented. The complete simulation provided an intuitive method of visualizing a full 3D representation of the anatomy of the *ex-vivo* prostates and demonstrated the potential for becoming a tool for the diagnosis and pre-surgical planning of CaP. A preliminary evaluation determined that the simulation provided an intuitive method to extend the idea of manual palpation and exploration to the complete prostate gland, which was furthermore correlated with pathology.

Overall, it was demonstrated that haptic simulation of cancerous tissue of patient-specific models can be created based on MRI and MRE volumetric datasets. The addition of haptic cues added more informational wealth to the MRE images. Some of the contributions of this work are: the development of a methodology to visually and haptically render patient specific 3D models of the prostate, the co-registering of haptic rendering with MRE quantification and the implementation of a software application to help surgeons to identify and localize CaP tumors for diagnosis and planning of biopsy and radical prostatectomy.
APPENDIX

This thesis work involved the scanning of prostate specimens after removal from the patient. This study caused no change in the standard care and essentially posed zero risk to the patient. The protocol for this study was approved by Institutional Review Board (IRB) at the University of Illinois at Chicago Approval # 1066.
April 12th, 2016
Adriana Modica
Managing Editor, CUAJ
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Dorval, QC H9S 5J9

I am writing to request permission to use the following material from your publication (Zumba D, Luciano C, Crivellaro S, Klatt D, Kearny SK, Royston TJ. Haptic simulation of prostate surgical planning based on magnetic resonance elastography. Proceedings of the Canadian Urological Association Annual Meeting, Vancouver, BC, June 25-28, 2016) in my thesis. This material, originally send for your journal as an abstract, will be further expanded and published as a chapter in my Master’s thesis. The material includes the written abstract as well as the images. Unless you request otherwise, I will use the conventional style of the Graduate College of the University of Illinois at Chicago as acknowledgement. This consists of adding this page in the appendix portion of my thesis.

A copy of this letter is included for your records. Thank you for your kind consideration of this request.

Sincerely,

David E. Zumba

The above request is approved.

Approved by: Denise Ymer  Date: 14 April 2016
CUA Manager, Membership and Advertising
April 26th, 2016

Dan Stoianovici, Ph.D
Executive Director, EUS
JHBM, MFL-West, URobotics, D0115
5200 Easter Ave
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A copy of this letter is included for your records. Thank you for your kind consideration of this request.

Sincerely,

David E. Zumba

The above request is approved.

Approved by: Dan Stoianovici
Date: 04/29/16
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22. American Cancer Society [website]

23. CIRS: Tissue Simulation and Phantom Technology
   [Available: <http://www.cirscinc.com/file/Products/053/053%20DS%20061515.pdf>](http://www.cirscinc.com/file/Products/053/053%20DS%20061515.pdf)

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   http://www.cpmc.org/services/surgery/robotic/prostatectomy.html


34. Paraview Reference Guide [website]
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35. Open Haptics Toolkit Programmer’s Guide
VITA

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