In search of the "ground truth" - validation of MRSI and prostate surface segmentation

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In Search of the “Ground Truth”- Validation of MRSI and Prostate Surface Segmentation

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Abstract

Diseases of the prostate gland are common in older men. The symptoms of most prostate disorders are similar and they severely impair the patients' quality of life. The common tests to help doctors identify the suspects are *Digital Rectal Examination (DRE)*, *Transrectal Ultrasound (TRUS)*, *Magnetic Resonance Imaging (MRI)*, and *Magnetic Resonance Spectroscopy Imaging (MRSI)*. The recent developments of *MRSI* extend the diagnostic assessment beyond anatomical information. It provides metabolic information specific to the prostate through the detection of cellular metabolites such as citrate, creatine, and choline. The information obtained from this new technology has the potential to allow an assessment of tumor aggressiveness and its risk for disease progression. As a result, the accuracy of *MRSI* has received considerable research interests.

This project aims to study the accuracy of *Magnetic Resonance Spectroscopy Imaging*, paying attention to the prostate surface and the cancer distribution with respect to it. Reference cancer distribution information is derived from pathological examination of prostatectomy specimens. Reference volume/surface information is derived from FastSCAN¹ (before the application of formalin). For the purpose of validating *MRSI*, two methods are studied to correct the deformation caused by formalin fixation and pathological processing. One is linearly rescaling of the pathological model, in which the local deformations are not considered. The other method, which is believed to be of more robustness and accuracy, is the use of

¹ FastSCAN is a laser scanner made by Polhemus; the details are introduced in Chapter 3.

finite element method to simulate the pathological model deformation. However, both of the two methods do not take the surgical manipulation error into account.

This thesis also highlights several methods that are considered commonly used in medical imaging validation such as the pathological validation and finite element method. The advantages and disadvantages are evaluated as well. Eventually, the project makes use of pathological validation, surface scan validation, and finite element method. The validation metric includes volume calculation, area comparison, Hausdorff distance, 3D surface distances applied to evaluate *MRSI*. ROC-curve (Receiver Operating Characteristic-curve) is derived from the calculation.

Based on the linear rescaling method, the sensitivity, specificity and accuracy of *MRSI* is 60%, 92.3% and 76.4% respectively. Factors that affect the disagreement between the *MRSI* and reference slice have been highlighted and discussed.

Another validation method, which involves using finite element method (FEM) to simulate soft tissue deformation, is also applied to assess the accuracy of *MRSI*. A finite element model of the prostate is made. Through the boundary elements displacing from one model (FE model which is built from pathological model) to another (reference model which is derived from FastSCAN surface), the cancer sites would have displaced according to the surface deformation and elasticity of the gland. This information (cancer position and cancer size) is considered as a gold standard to evaluate *MRSI* accuracy. This part of work is still going on.

Chapter 1

Introduction

1.1 Background

Benign prostatic hyperplasia (BPH) and prostate cancer are two common diseases in older men. Benign prostatic hyperplasia usually leads to urinary symptoms of varying severity in almost 50 percent of men over 60 years old. Prostate cancer remains the most dreadful illness, which has the second highest mortality rate, after lung cancer, among all cancers in men in North America. It is also the sixth most common cancer in Singapore male [1].

The accurate localization of prostate cancer is important as it can affect both surgical and radiation treatment planning. Transrectal Ultrasound (TRUS) is widely used for the guidance of biopsy of the prostate gland. However it is limited by its low sensitivity and specificity in the localization of the tumor. Magnetic Resonance Imaging (MRI) has higher sensitivity for cancer detection but similar to TRUS, it has low specificity. Magnetic Resonance Spectroscopic Imaging (MRSI), which has the additional metabolic information from MRI, may allow more specific diagnosis and localization of prostate cancer. The information obtained from this new technology may allow an extended assessment of tumor aggressiveness and disease progression. As a result, the accuracy of MRSI has received considerable research interests. To validate the accuracy of MRSI, “ground truth” is required. As a matter of fact, research in medical imaging analysis is greatly dependent on

“ground truth” data for the design, training and testing of algorithms for data identification.

In this project, the “ground truths” of prostate surface and cancers are explored. In addition to the exploration of the “ground truths”, the accuracy of MRSI is also validated.

1.1.1 What is Validation?

Validation is the process of examining and reporting properties, effects and/or impacts of a medical technology [2]. Simply speaking, validation means accuracy. A validation method can be thought of as a combination of two components. One component is the definition of corresponding “ground truth”; the other one is the results of an algorithm, of which the component is to be judged. So far, there are no methods that can tell the “ground truth” and this is normally where one tends to run into difficulties. Most validation schemes use standard statistical methods of finding means, standard deviations or root mean square errors. These ways of validation are tedious and thus not routinely performed.

1.1.2 Why is it Important?

A typical radiology examination like MRI or CT may involve reviewing more than a hundred images. The images are not only used for diagnosis but also important aids for treatment planning, surgical rehearsals, education, research, and image-guided intervention. Furthermore, they are useful for studying tumor development and tumor degenerative aspects of diseases and for clinical drug trials. Validation

of medical imaging accuracy allows evaluation of their performance and limitations. At the same time, their intrinsic characteristics can be highlighted. Validation tests can also facilitate the user's task of determining whether a particular medical imaging system meets a set of clinical requirements.

1.1.3 Current Limitations

“Ground truth” is not typically available in any form that can be used readily. For instance, in the case of segmentation of brain tissue from MRI, there is indeed a true boundary of brain tissue for each patient. But nobody is sure of its exact location. Experts can obtain approximations to the true boundaries in the form of manual segmentations, but experiments have shown that there can be up to 15% variations in classifications generated by different experts [3]. The “ground truth” can be tested on synthetic images; however, it is difficult to generate synthetic images that capture the complexities and variabilities of human body. Fiducial markers can be randomly planted into the patient in a known manner and be used as a subsampled “ground truth” to measure the classifications. Nevertheless, it is too invasive to be practical. Another alternative would be to use cadaver brains for marker based validation, but many research groups do not actually do this.

1.1.4 Image Quality

Is an image good or bad? A straightforward definition of image quality is based on the question: How well does an image communicate information required by an observer? This is called **intelligibility** of the image. A more technical definition of

Chapter 1 Introduction

image quality relates to the question: how much does an image deviate from the correct image of the scene? This is called **fidelity** of the images.

Image quality can be measured in terms of diagnostic accuracy, sensitivity, specificity, or ROC-curve (Receiver Operating Characteristic-curve). ROC-curve is a popular statistical method for assessing the overall classification accuracy. Figure 1.1 shows the relationship between sensitivity and specificity. An ROC curve demonstrates several things: it shows the tradeoff between sensitivity and specificity (any increase in sensitivity will be accompanied by a decrease in specificity). The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test; the closer the curve comes to the 45-degree diagonal of the ROC space, the less accurate the test. The area under the curve is a measure of test accuracy. A study of high sensitivity is associated with few patients being told they do not have a tumor where in fact they do have a tumor. A study of high specificity is associated with few patients being told they do have a tumor where in fact they do not have a tumor.

Figure 1.1 ROC-curve

1.2 In Search of the “Ground Truth”

As mentioned before, there is no effective way to get the “ground truth”, but there are dependable ways getting the organ surfaces. From Figures 1.2 and 1.3, before operation, the organ surface can be reconstructed through image stacks, such as MRI, MRSI, TRUS, and Computed Tomography (CT). After operation, the prostate surface (before and after the application of formalin) can be obtained using FastSCAN (refer to Section 3.2.4). The three dimensional surface from pathological slices can also be reconstructed with the details of cancer information. Each way has its own advantages and disadvantages. It is not known for sure which way is nearest to the “ground truth”. Figure 1.2 shows the flow chart of the prostate specimen processing in pathological department (details refer to Appendix A).

Figure 1.2 Flow chart of the prostatic specimen processing

Figure 1.3 "Ground truth" and its manifestations

- E0---error from the expert intervariabilities and intravariabilities;
- E1---error from the ultrasound machine inherent physics, machine calibration and limitation;
- E2---error from MRI machine inherent physics, machine calibration and limitation;
- E3---error from FastSCAN;
- E4---deformation from the surgical manipulation;
- E5---deformation from the procedures of prostate specimen processing.

To reconstruct the prostate surface from the image stacks, the medical images need to be segmented. A lot of algorithms are available now, such as manual segmentation (expert opinion), automatic algorithm (level-set) and semiautomatic algorithm (snakes). Using manual segmentation, there are intra- and inter- observer variabilities (E0), these variabilities can be corrected by many experts with many

times outlining the boundaries [3]; Using the automatic or semiautomatic algorithms, because of the lack of “ground truth”, nobody knows how accurate they are, hence the errors become unpredictable.

The FastSCAN is a new method being used in the “ground truth” study. After the operation, the organ is taken out of the patient’s body; the prostate surface is scanned immediately using FastSCAN (Figures 1.2 and 1.3). Since the FastSCAN accuracy is known (refer to Appendix D, and Section 3.2.4), it is a promising method to obtain the prostate surface and volume information. However, during operation, there are a lot of manual disturbances (E4), which cannot be controlled, and these seriously affect the shape and size of the organs. If the disturbances due to human manipulations of the operation can be predicted, the surface truth of the organs can be found.

After the organ is taken out of the human body, it is dipped into 10% formalin solution for 6 hours. This causes the protein in the cells to denature and become hard and “fixed”. At this time, FastSCAN is used again to get the surface of the gland.

The specimen goes through elaborately overnight cycles, which removes all the water from the specimen and replaces it with paraffin wax. The ‘fixed’ specimen is then trimmed by the microtome and put under the microscope (details refer to Appendix A). Then, pathological slices is reconstructed using software Bubble 3D (refer to Appendix B) at a molecular level. With this 3D reconstruction model, not only the surface is reconstructed, but also the distribution of cancers inside of the organ. However in this step, there are so many disturbing factors (E5), such as the

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effect of formalin, manipulation from microtome sectioning, and paraffin wax. All these factors are not predictable, making the “ground truth” study tough and difficult.

How to get the “ground truth” in an accurate and systematic protocol? In this thesis, the methods and algorithms that used in the validation study are elaborated; the advantage and disadvantage of this method and the errors are analyzed.

1.3 Objectives

In this project, patients with documented prostate cancer who are elected for radical prostatectomy undergo preoperative MRI and MRSI. Reference cancer distribution information is derived from pathological examination of surgical specimens. Reference volume and surface information is derived from FastSCAN (before the application of formalin). Since the prostate specimen shrinks and deforms during the procedures, two possible ways are to be investigated in this project to correct them so that pathological model can be reconstructed three dimensionally nearest to the “ground truth”. A simple linear scaling is the first straightforward solution; the second method is to use finite element model to simulate the deformation, called elastic deformation. The main objectives of the study are:

1. Assess 3D reconstructed model of prostate surface (boundary) from MRSI, the reference surface is obtained from FastSCAN;
2. Validate MRSI prostate internal features, limited to cancers at molecular level, using rescaled prostate pathological slices (2 dimensional) as references;

3. Simulation of "ground truth". Use finite element method to simulate elastic deformation of the prostate, random errors caused by manipulations (such as the formalin effect) and study the accuracy of MRSI by surface (boundary) and cancer distribution.

1.4 Organization of this Thesis

This report is organized as follows:

Chapter 2 introduces the common validation methods used in medical image processing; **Chapter 3** explores the data collection and analysis, including patient selection, acquisition of TRUS, MRI/MRSI, surface scan using FastSCAN, meanwhile, including the two-hole reference system, and explores the 3D model reconstruction; **Chapter 4** outlines a critical device in MRSI validation which is called prostate slicer box; **Chapter 5** states MRSI validation methods and results; **Chapter 6** outlines finite element method to simulate the elastic deformation. **Chapter 7** outlines the future work.

Chapter 2

Validation Methodologies

Validation is needed in medical image processing for the purposes of:

1. Configuring the capability of an image to its function;
2. Interpretation of the image by human or by computer algorithm;
3. Calibration of an image for physical location;
4. Soft tissue deformation and/or movement in medical imaging;
5. Registration of differential image modalities.

This chapter presents a review of the several common methods that appeared in recent literature for medical image validation. They can be classified into eight categories based on the methods used: visual assessment [4, 5, 6], comparisons with manual segmentations [7, 8, 9, 10, 11, 12, 13], testing on synthetic data [14, 15, 16], the use of fiducial markers on patients [17, 18], pathological validation [19, 20], surface scan validation [21], statistical model validation [22, 23, 24, 25], and finite element method [29, 30, 31, 32, 33].

2.1 Visual Assessment

Visual assessment is a method that comparison can be qualitatively assessed by viewing different images (for intra-modality registration), contour overlays (for inter-modality registration), alternate pixel displays, or by comparing anatomical landmarks [4, 5, 6]. These approaches have been applied to rigid registration, and because they involve the inspection of the entire volume domain of the image pairs, they can be extended to non-rigid registration. This approach basically relies on the

human observer to inspect the registration results and reject images that have been registered with insufficient accuracy. The reliability of visual inspection for detecting registration errors is controversial. Observers could detect a translation registration of greater than 2mm in the x and y directions, and greater than 3mm in the z direction. Similarly, the observers could also detect a rotation difference of greater than 4 degrees about any axis at least 80% of the time [4].

Advantages and disadvantages

This is an observer-dependent validation method. The strength of this validation is simple and straightforward. The weaknesses are non-quantitative, subjective and less accurate.

2.2 Comparison with Manual Segmentations

Image segmentation is an essential step for many advanced imaging applications and is a challenging problem. Accurate segmentation is required for volume determination, 3D rendering, radiation therapy, surgical planning, and automated assessment of signal characteristics of potentially malignant tissues. In recent years, many auto or semi-auto algorithms [7, 8, 9, 10, 11, 12, 13, 14], such as level set, snakes, active snake model, geodesic active contours and markov random field have been developed. The common challenge is how to validate these algorithms. It is difficult to quantify in the absence of the “ground truth”. It is thought that a computer algorithm is useful and credible only if it is at least as good as a human expert observer. One way is to compare the algorithms to manual segmentations. To do so, three essential evaluation steps are required [7]:

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1. Acquiring expert opinion, The boundaries of field of interests are manually outlined by experts as references. As manual contouring itself is variable both in inter-observations and intra-observations, a mean contour of those manually outlined contours produced by multiple observers at different time to reduce the variations is necessary.
2. Matching the autohemi-auto segmentations to the manual segmentations.
- 3, The use of quantity metric. Some metric may involve the calculation of the mean distance of surfaces. Similar metric calculation can also be found in overlap measure method, which calculates on binary voxel maps created by intersection of the object surfaces with the voxel grid. The resulting measure is very sensitive to even small differences in overlap, both inside and outside of the object model, and is therefore a strong test for studying segmentation accuracy and consistency.

Figure 2.1 shows the results of overlap measure to calculate the agreement between manual (red color) and automatic segmentation (gray color) of the hippocampus of 21 individuals [7].

Figure 2.1 Result of the comparison between manual segmentation and automatic segmentation

Advantages and disadvantages

The strength of this validation method is that it is less subjective and more reliable compared to visual inspection. It is also the preferred way commonly used by many. Manual segmentation, however, is a laborious, time-consuming, and expensive process. It has been shown that the results are very much dependent on the observer's experience, and consequently, it is variable between observers (inter-observability) and even within an observer when performing the same job at difference time (intra-observability).

The researchers of Harvard Medical School and Brigham and Women's Hospital provided an algorithm known as Expectation-Maximization Algorithm [26, 74] to construct the "ground truth" segmentation from a collection of manual segmentations, and estimate the quality of each segmentation generator. This algorithm can be used as an assessment of the expert's performance.

2.3 Testing on Synthesized Ultrasound Images

Several simulating software tools have been written to simulate ultrasound images. For example, Field I (Jorgen, 1996), Field II (Jorgen 2001), Ultrasim98 (1998), Ultrasim01 (2001). The most commonly used simulating software, named "FIELD", was invented by Jorgen Arendt *et al.* who worked at the Technical University of Denmark. This software was used to simulate an ultrasound image. FIELD was based on the Topholme-Stepanishen method [14, 15, 16]. In this program, various kinds of transducer geometries and excitations can be simulated. A new version of the FIELD program, called FIELD II, was developed for more

flexibility [16]. It was MATLAB based and extended by a number of commands for transducer simulations. These commands were used for defining transducers, setting their properties and calculating fields for these transducers.

The ultrasound simulator was originally intended to allow students to gain experience in ultrasound techniques prior to scanning in the clinical environment. With the transducer, phantom and image processing simulated by a computer with various different parameters can be easily studied. More and more researchers used it as a way of validation. This program was successfully used in a number of universities and yielded accurate results [16]. Figures 2.2 and 2.3 show the images simulated by FIELD II [16].

Figure 2.2 Simulation by FIELD of an artificial kidney [16]

Figure 2.3 Simulation by FIELD of artificial fetus [16]

XiaoDi [27] used FIELD II to evaluate the active contour model. His steps included:

- a) An original image A or phantom A was created by Photoshop;
- b) Phantom A as an input image in FIELD II, a simulated ultrasound image I was created by FIELD II;
- c) Use a boundary detection algorithm (for example, level set or active contour model) to detect boundary of desired object on simulated ultrasound image I;
- d) Compare detected results (boundary) with the known boundary (in step 'a') by a selected evaluating protocol. Figure 2.4 shows the simulation steps [27].

Figure 2.4 The simulation steps.

- (a) Artificial “ground truth” generation, called phantom A;
- (b) Phantom A as an input image to FIELD II and get a simulated image I;
- (c) to (j) Describe the process of boundary detection on simulated image; Three boundaries are detected from inner to outer in sequence [27]

Advantages and disadvantages

Simulating ultrasound is an objective method for evaluating the image-processing algorithm for boundary finding. It is a supplementary method for evaluating image algorithms. However, it takes a long time to create one simulated image (5 to 7 days on a Pentium II 300 MHz computer) and is difficult to create a full 360-degree image. It neither completely captures the ultrasound imaging in the real world nor fully replaces the effect of other algorithms such as expert evaluations. Setting suitable or correct ultrasound properties can be problems for this method.

2.4 Use of Fiducial Markers on Patients or Cadavers

Generating an accurate “ground truth” is critical for reliable validation. However, it is also a difficult problem due to the accuracies required. Extrinsic markers [17, 18] such as bone-implanted markers, stereotactic frames, can be used as gold standards to ascertain validation errors. These fiducial markers also can be used in the cadavers, which can evaluate the accuracy of newly developed devices,

Figure 2.5 illustrates how to use fiducial markers to validate the registration accuracy [17]. The approach was to compare surface-based with marker-based registration results. First, the accuracy of CT fiducial localization was tested by creating a phantom with three fiducial markers, and measuring the central locations with a Coordinate Measuring Machine (CMM) [17]. After CT scanning the phantom at 1mm image intervals, the researchers compared the extracted inter-fiducial distances with the corresponding distances from the CMM, which were known. The average distance error was 0.1 mm, while the maximum distance error was 0.15mm. Thereafter, they measured fiducial locations from intra-operative sensor. Finally, they compared fiducial centroid by intra-operative sensor with CMM-based “ground truth”.

Figure 2.5 Validating registration accuracy [17]

Advantages and the disadvantages

Using fiducial markers is a more reliable and accurate way to validate medical image registration. However, an additional surgery is required, as this method needs to attach markers into patient’s body. This may lead to additional patient trauma at or near the marker attachment sites. It may cause discomfort to the patients. Moreover, this method is labor-intensive. Apart from being invasive, such an approach suffers from errors involved in the localization of fiducial markers. For inter-modality rigid registration, bone-implanted markers have been successfully used to compare different registration methods, but they are not applicable to non-rigid registration of soft, deformable tissues.

2.5 Pathological Validation

There are abundant variations among medical imaging systems. No two scans taken from the same patient correspond absolutely. Variations among manufacturers, techniques used at different institutions, or even the relative age of different medical scanners may yield differences that are difficult to be characterized [19,20].

MRSI is a new development technique that has allowed the *in vivo* examinations of human organs, for example the prostate [20]. With the use of 3D spectroscopic imaging, significantly higher choline levels and significantly lower citrate levels are observed in regions of cancer compared with areas of benign prostatic hypertrophy and normal prostatic tissue. Feasibility and technical developments of prostatic 3D MR spectroscopic imaging have been reported, but the efficacy of 3D MR spectroscopic imaging data in the detection or localization of prostate cancers has not been further evaluated [28].

Juergen Scheidel *et al.* [20] at University of California provided a way that used pathological slices to validate the MRI and MRSI. They tried to assess the effectiveness of combined 3D MRSI and MRI for tumor detection and localization with results according to histopathologic examination as the standard reference. In their project, the prostates were scanned using both MRI and MRSI. After surgical resection, the prostate was coated with India ink and fixed in 10% formaldehyde. The gland was transversely sectioned at 3-4 mm interval in a plane perpendicular to the long axis of the gland. The pathological cross sections were then correlated to the MRI and 3D MRSI findings.

Chapter 2 ValidationMethodologies

Figures 2.6 and 2.7 shown below correspond 3D MRI and MRSI results with histopathologic section (positive and negative results) [20].

Figure 2.6 T3a prostate cancer [20]

- (a) MRI was obtained with an endorectal coil. A tumor (arrows) was seen in the peripheral zone;
- (b) MRSI showed the same section of MRI, the cancer was highlighted by the red color;
- (c) MR spectrum obtained from the abnormal area demonstrated elevated choline and reduced citrate, a consistent pattern with definite cancer;
- (d) Demonstrate a normal spectrum pattern with dominant citrate and no abnormal elevation in choline;
- (e) Fast spin-echo MRI in the same section;
- (f) The pathological slice of the tumor verified the MRSI tumor.

Figure 2.7 Histopathologic stage T2a prostate cancer [20]

- (a) T1 transverse MRI was obtained with an endorectal coil;
- (b) T2 weighted transverse MR image showed a definite cancer;
- (c) The same section, with the information from 3D MRSI overlaid (H indicated voxels with normal [healthy] metabolic spectra);
- (d) Selected MR spectra was obtained from the abnormal imaging, however, the metabolic ratios remained normal;
- (e) Histopathological section from the area of MRI abnormality, no tumor was present in the area, which confirmed that 3D MRSI findings had correctly excluded cancer and that the MRI findings were misleading.

Figure 2.8 showed the results in ROC curves, Az stood for the area under the ROC-curves. The Az values with combined MRI and 3D MRSI for readers were significantly greater than those with MRI alone [20].

Figure 2.9 ROC-curves for Reader 1 (R1) and Reader 2 (R2)

Advantages and disadvantages

Pathological validation evaluated the medical images at a molecular level. However, it had several shortcomings [20]:

- a) It required to remove the organ or gland of interest (for example, prostate);
- b) 2D slice comparison depended on the pathologist's experience as they managed and interpreted views obtained from the microscope;
- c) The size and the shape of the prostate may also change as a result of tissue shrinkage during fixation, possible loss of accuracy;
- d) The angle at which the histopathologic slice was cut often differed from the angle at which imaging was performed (difference of 5° - 20°);
- e) MRI and MRSI were required with 3mm section thickness without gap, but histopathologic slices were 5mm thick, it cannot be fully considered as the correspondence between MRI/MRSI and pathological slices;
- f) The tumors lost the orientation among the pathological slices;
- g) MRSI in large voxels (7 mm^3) [87] reduced the accuracy of the pathological validation.

2.6 Surface Scan Validation

Ahmed H. Eid *et al.* at University of Louisville proposed a way that uses a laser scanner [21] to validate the 3-D stereo reconstruction from a sequence of images. In their experiment, two different 3D reconstruction techniques were examined. The model generated by the scanner was referenced as a “ground truth”. Validation of the reconstructions was made by pair-wise comparisons with the 3D scanning results. This system was not restricted to stereo techniques but it can be used for different techniques of 3-D reconstruction from a sequence of images.

2.6.1 System Set Up

The proposed system consisted of a Cyberware Laser Scanner, and one or more optical cameras, which can be placed on the scanner head. The laser scanner generated a 3D scan of an object by rotating 360-degree. The shaft over which the scanner head was mounted can be controlled in terms of speed and angle of rotation. Therefore, a sequence of referenced images can be acquired by one or more calibrated camera(s), which were mounted on the scanner head. Figure 2.10 demonstrated the scanner system.

Figure 2.10 (a) The system setup (b) The motion mechanism of the system [21]

2.6.2 3-D Reconstruction

Stereo techniques [21] found points in two or more input images that corresponded to the same point in the scene. Knowledge of the camera locations was used to determine the depth of the scene point. This approach had been widely used for shape recovery. A large number of stereo techniques relied on assumptions such as the existence of specific features in the images to produce satisfactory result. For example, featureless and/or textureless scenes were hard to reconstruct in stereo because corresponding points between the different images cannot be accurately found. **Space carving** exploited the fact that points on surfaces are color-consistent. The idea was to carve (remove) some voxels that do not belong to the object until 3D shape agreed with all the input images. Cyberware 3030 was used in the proposed system as the 3-D scanner. The system can digitize thousands of these profiles in a few seconds to capture the shape of the entire object.

2.6.3 Experimental Results

Figure 2.10 showed the experimental results.

Figure 2.11 Upper left: a 2-D image. Upper right: 3D laser scanner. Lower left: space carving. Lower right: stereo techniques [21]

Figure 2.12 Registration of space carving and stereo with the “ground truth”. Left: space carving (white) and “ground truth” (black). Right: stereo techniques (white) and “ground truth” (black)[21]

Figure 2.13 Mis-projection ratio for image generated from the 3D model compared with the original images [21]

Advantages and disadvantages

The use of laser scanner provided a new field to medical imaging validation. It validated 3D models by the ways described in the proceeding paragraphs. However, it also had some shortcomings. Firstly, the accuracy of the laser scanner should be calibrated. Secondly, the reconstruction of the images was a tedious task. Thirdly, laser scan cannot obtain the internal information of an object.

2.7 Statistical Validation

Instead of the validation methods mentioned above, Kelly H. Z., and Simon W. [22,23] of Harvard Medical School and Brigham and Women’s Hospital proposed a way that used certain statistical methods to validate the automatic probabilistic segmentation against the composite latent expert “ground truth”. The idea behind

the statistical models for image validation was to code the variation of the selected parameters, which were used to describe the detected object, in an observed population (the training sets) and characterized this in a compact manner. The parameters were estimated from the available validating image and were used for evaluation of new images. Furthermore, the results from new validations can be incorporated into the model, thus updating a priori information available to the system. They estimated [22] the distribution functions of the tumor and control voxel data parametrically by assuming a mixture of two beta distributions with different shape parameters (α, β), and at the same time built up the parametric modeling. They derived the ROC-curves, dice similarity coefficients, mutual information, and overall possible decision thresholds. Based on each validation metric, an optimal threshold was then computed via maximization. This method was applied to 9 patients, and the results generated using the automatic segmentation algorithm yielded satisfactory accuracy.

Advantages and disadvantages

Statistical validation was a systematic approach to evaluate the accuracy of the automatic segmentation results [22, 23, 24, 25] that generated voxel-wise probabilistic interpretation of the tumor class. The parametric modeling was simple, probabilistic and the procedures were straightforward. But this method also had its shortcomings. It was tedious work to calculate the metric, and the recommended optimal threshold was significantly case and task (metric) dependent.

2.8 Finite Element Method

Finite element method [29, 30, 31, 32, 33] (FEM) is a novel method for validating results of medical image processing. There have been a number of work so far on finite element method simulating soft tissue deformation. It has been mainly used on surgical simulation, non-rigid registration and evaluating relative algorithms. A full description of competing methods is beyond the scope of this report. Instead, an introduction to the different methods and various tissues is discussed.

FEM is based on the simulation of physically plausible, biomechanical tissue deformations. This model can be used effectively in several different applications. For example, FEM for brain modeling has been investigated for image guided surgery procedures [34], for integration into physically based non-grid registration method [35], and for simulation of brain shift in interventional MR imaging [36]. For mammography, FEM has been explored for predicting mechanical deformations during biopsy procedures [37, 38], for improving and testing the reconstruction of elastic properties in elastography [39], and for modality-independent elastography with application to breast imaging [40]. Applying a range of displacements to finite element models of different patient anatomies generates model solutions, which simulate gold standard deformations. From these solutions, deformed images are generated with a range of deformations typical of those likely to occur *in vivo* [41, 42].

Figure 2.14 3-D liver model with 1210 tetrahedra deforms in real time. Left: Tetrahedral mesh. Right: Texture mapped model is deformed [41]

Advantages and disadvantages

Finite element method makes it possible to study the medical images with physical properties. The uses of FE method can provide us of objects deformed from one image model to the next. This assumes that the obtained deformation is taken from an actual physical deformation. On the contrary, it is difficult to implement and it requires complicated and time-consuming computation.

2.9 Conclusion

In this chapter, eight validation techniques that can be used for medical image processing are introduced. They include visual assessment, comparison with expert segmentations, testing on synthetic data, the use of fiducial markers on patients or cadavers, pathological validation, surface scan validation, statistical validation, and finite element method. Every method has its own advantages and disadvantages. Visual assessment is a simple way to compare two images, but it does not

quantitatively evaluate the two images. Consulting expert opinion is a less objective and reliable way, and it is the most commonly used method, nevertheless it is tedious and time-consuming. The use of FIELD II on synthetic data is an objective method, but it cannot truly simulate ultrasound images in the real world. The use of fiducial markers on patients and cadavers is a more reliable and accurate way, however it needs markers to be attached on patients' body and it requires an additional surgery. Pathological validation has the potential to be the most accurate way to evaluate the capabilities of medical images, however, the interpretation of pathological slices under the microscope is heavily dependent on the pathologists' experience. Surface scan validation is a new field to medical image validation, but no internal information is available. According to [22], statistical validation is a systematic approach to validate the accuracy of the automatic segmentation results. It generates voxel-wise probabilistic interpretation of the tumor class. The parametric modeling is simple, probabilistic, and the procedures are straightforward. However it is a tedious task to calculate the metric and the recommended optimal threshold is significantly case and task (metric) dependent. Finite element method is a novel method to validate medical imaging by simulating soft tissue deformation simultaneously considering the tissue properties, but it is difficult to implement and requires complicated and time-consuming computations. In a word, considering the shortcomings of each validation method, a combination of two or three methods may hold good promise to get nearer to "ground truth". This is the reason why a combined validation method (pathological validation, surface scan validation, finite element method) is applied in this thesis.

Chapter 3

Data Collection and Analysis

The procedures of the data collection are tedious and related to several departments in Singapore General Hospital (SGH). Figure 3.1 outlines the work procedures of data collections. Tips is a database developed in CIMIL, NTU; details refer to Section 3.2.5.

Figure 3.1 Data collections in hospital

3.1 Patients

From March 2002 to June 2004, endorectal MRI with spectroscopy were performed on 7 consecutive patients with persistently raising PSA and/or abnormal digital rectal examination (DRE). All the patients were subjected to TRUS before prostatectomy. After the prostate was taken out of the patient's body, FastSCAN was performed before and after the application of formalin to obtain the surface of the prostate specimen. All MRS images were read by a dedicated radiologist who reported the areas of interest as positive or negative separately. All prostate specimens were individually labeled and examined by a single pathologist. Histological findings were correlated with MRSI results.

3.2 Medical Images and Tips

3.2.1 Transrectal Ultrasound

Transrectal Ultrasound (TRUS) is an outpatient procedure that uses sound waves to create a video image of the prostate gland. A small, lubricated probe placed into the rectum releases sound waves (Figure 3.2(a)), which create echoes as they enter the prostate. Prostate tumors often create echoes that differ from normal prostate tissue. The homogeneous medium signal intensity of the peripheral zone serves as an excellent background for the depiction of prostate cancer. Prostate cancer is detected as a hypoechoic area within the peripheral zone of the prostate gland (Figure 3.3). This finding is not specific for carcinoma and also seen in a variety of benign processes [43, 44, 46], e.g., dystrophic dysplastic changes, chronic

prostatitis, and non-specific atrophy. TRUS is capable of tumor detection only if the tumor is localized within the peripheral zone (approximately 70% of cases) [43]; even then, accuracy is reported to be only between 57% and 76%.

Because tumor volume governs patient prognosis and its accurate assessment can influence therapy decisions, volume measurements by TRUS have been attempted. Early results were promising, but a recent study [46] of more than 200 patients demonstrated significant inaccuracies. With TRUS, the results had shown that the lesions up to 1 cm in diameter were overestimated, while lesions larger than 2 cm were underestimated. Until greater accuracy can be guaranteed, TRUS should not be an appropriate modality for tumor volume measurements [46].

The reported accuracy [47] of TRUS in the staging of prostate cancer varies. Some reports have indicated that extension of prostate cancer is detected in as many as 92% of cases; however, large multicenter study found that an accuracy rate was a lower 62%. Identification of invasion of the seminal vesicle was even less accurate on TRUS with sensitivity reported to be 22% and specificity 88%. It is hoped that continuing advances in technology will improve TRUS efficacy. However, a multicenter study showed a continuously poor performance of TRUS, with its ability of detecting extracapsular extension (ECE) matching digital rectal examination. In the evaluation of prostate cancer, however, TRUS remains the most valuable in assisting US-guided biopsy since it can detect some tumors that cannot be felt by DRE. In addition, TRUS is useful to estimate the size of the prostate gland.

Figure 3.2 (a) Transrectal Ultrasound with a probe placed into patient’s rectum (b) Prostate TRUS image

Figure 3.3 Hypoechoic area and hyperechonic area (calcification and prostatic capsule) of the prostate US image

3.2.2 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) (details refer to Appendix C) uses a magnetic field, radio waves and a computer to create detailed image slices (cross sections) of the pelvis and prostate gland. This allows the physician to evaluate different types of normal body tissue, including seminal vesicles, bladder and lymph nodes, as

well as distinguish normal, healthy tissue from diseased tissue. The signal intensity and the detection of prostate cancer depend on the type of imaging sequence used. On T1²-weighted images, the prostate is of homogeneous medium signal intensity. On T2 weighted MR images, prostatic carcinomas are most commonly shown with decreased signal intensity within the high signal intensity normal peripheral zone (Figure 3.5). The detection of prostate cancer on MRI (similar to TRUS) is applicable only to tumors located in the peripheral zone. The normally low or heterogeneous signal intensity of the transition and central zones preclude tumor detection.

While prostate cancer detection rates were reported as high as 92%, the results [48] of large multicenter studies were disappointingly low, with only 60% of lesions greater than 5 mm being detected on MR images. Attempts had also been made to measure tumor volume by MRI.

Although controversial, the value of MRI appeared to be in the staging of prostate cancer [82]. The tumor would lose signal intensity within the peripheral zone. With the endorectal coil, direct visualization of the prostate capsule increased the confident level in the evaluation of prostate cancer. MRI can neither depict nor stage most of prostate cancers within the transition and central zone.

All MR examinations in this project were performed on the 1.5 Tesla whole body GE MR scanners with the use of endorectal coils. Patients were scanned in the supine position using a pelvic phased array with an endorectal coil (details refer to Appendix C). Fast spin-echo T1 weighted images were taken from the aortic bifurcation to the symphysis pubis, with TR/TE = 600-700/6-12 msec, slice

² The explanation of T1 and T2 refers to Appendix C.

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thickness 3.0 mm, interslice gap 0.5mm, image resolution 580x580 pixels, field of view 12x12 cm². T2 weighted fast spin-echo images of the prostate and seminal vesicles were with TR/TE = 4000-6000/90-120 msec, slice thickness 3 mm, interslice gap 0.5 mm, image resolution 580x580 pixels.

Figure 3.4 (a) MRI scanner (b) Prostate T1 weighted MRI image with rectal coil

Figure 3.5 (a) On T1 weighted image, prostate is of homogeneous medium signal intensity (b) On T2 weighted MR image, normal peripheral zone of prostate is of high signal intensity

3.2.3 Magnetic Resonance Spectroscopic Imaging (MRSI)

Recent developments [49, 50, 51] of MR spectroscopic imaging extend the diagnostic assessment beyond anatomic information (refer to Appendix D). MR spectroscopic imaging provides metabolic information specific to the prostate through the detection of the cellular metabolites, such as citrate, creatine, and choline. The information obtained from this new technology may allow an extended assessment of tumor aggressiveness and disease progression.

In the localization of prostate cancer, a combination of MRI and MRSI demonstrated 91% specificity [52], which was the highest value obtained by a non-invasive method. Furthermore, such a combined use significantly improved the evaluation of extracapsular cancer extension and decreased interobserver variabilities.

The spectroscopic imaging volume is selected from the axial T2 weighted images to maximize coverage of the prostate while minimizing inclusion of peri prostate fat. This is accomplished by selecting a rectangular volume encompassing the prostate at the prostatic apex and base. A commercial spectroscopy package GE (General Electric 1.5T LX, PROSE) [49, 50, 51] subsequently determines the position and dimensions of the volume.

Figure 3.6 Prostate MRS image

3.2.4 *FastSCAN (A Handheld Surface Scanning Solution)*

The need for rapid and complete surface acquisition arises not only for validation purpose, but also to aid in the quantification and compensation of interoperation tissue deformation. One method of surface acquisition that shows promise in providing this type of data is through the use of a laser scanner called FastSCAN [78], which is made by Polhemus (the specifications of FastSCAN refer to Appendix E). While any touch will affect the shape of prostate, FastSCAN system offers a non-contact method to accurately capture geometric surfaces. The FastSCAN uses the optical principle of triangulation to obtain a dense point set of surface data. This digitization approach is particularly well suited for “ground truth” study, because it affords a method of rapid surface data acquisition that can be used for the measurement and compensation of tissue deformation (Figure 3.7). To make sure the prostate can be scanned accurately in one go, experiments were implemented in Burn Center of Singapore General Hospital and Machine and Mechanical Lab of Nanyang Technological University. A simple mechanical

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system was set up (Figure 3.8(a)); it included a scanner base and an extended supporting stick, which can hold the prostate so that the FastSCAN can sweep around the prostate surface at one time.

Figure 3.7 FastSCAN instantly acquires three-dimensional surface by gathering measurements made by smoothly sweeping a handheld FastSCAN wand over an object

Figure 3.8 (a) The mechanical system (b) Illustrate the experiment, prostate was being swept by FastSCAN

Figure 3.9 (a) FastSCAN result of the prostate specimen before formalin (b) FastSCAN result of the same prostate specimen after formalin (c) The prostate 2D image

3.2.5 Tips

Tips, an acronym for Testing, Imaging, Pathological and Surgery, is a web-based database system storing data for clinical researchers. The primary objective in developing a web based medical image database is to allow the consolidation of MRI/MRSI, pathological and US images. The sets of raw images (ultrasound, MRI/RIRSI, pathological data) are stored systematically. This facilitates researchers or doctors to search and retrieve information based on preferences or predefined criteria. In addition, the database will also serve to store processed images such as 3D reconstructed models from MR images, pathological images and US images. These models include cancer boundaries and other anatomical areas of interest.

The current version of Tips caters for that purpose. All data including TRUS, MRI, MRSI, FastSCAN data, pathological data collected from clinic are uploaded to Tips. The system shares the information in a consistent and reliable fashion from a central server. The latest version 2.0 was released in April 2004.

Chapter 3 Data Collection and Analysis

The data are stored systematically, therefore it makes automatic data analyzing program possible, Database (Figure 3.10) also allows researchers to develop sophisticated searching function, which is very helpful in enabling the search and location of data quickly when the number of experiment cases grows,

The web-based user interface makes retrieval and access of critical data easier from various locations. The researchers will be able to view the critical non-binary data and data analysis report online, or download large binary files from the database, using a standard web browser, such as Microsoft Internet Explorer. Figure 3.11 shows the Tips user interface.

Figure 3.10 Schematic representation of Tips and its users

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Figure 3.1 1 Tips: a web-based data system for data storing

Tips Technology

Tips is implemented using Java enterprise technology [89]. Two major open source Java packages being used in Tips are STRUTS and Hibernate, both under Apache Jakarta project. These libraries make a rapid development of the application possible.

Tips runs on Apache Tomcat, and uses MySQL as the database server. However, it is portable to any other J2EE application server and other SQL server with minor changes. Tips supports two languages at this moment: English and Chinese.

3.3 The 2-Hole Reference System

To reconstruct 3D pathological model from pathological slices, the foremost concern is to identify the orientation variabilities of these slices, and the positional displacement of one slice to the next. To give a correct reconstruction, a two-hole reference system is proposed (refer to Appendix A), The two holes are made using a surgical needle (of approximately 1 mm in diameter) and a sewing thread. The

needle is inserted into the prostate with the thread, parallel to the posterior surface or along the urethra. A knot is tied to secure the thread in place during sectioning (Figure 3.12). The threads can be viewed by the pathologist under the microscope and marked out in red dots on pathological slices accordingly (Figure 3.13). The two-hole reference provides the criteria for 3 dimensional reconstruction of the prostate. With this method, displacement and orientation integrity is preserved.

Figure 3.12 (a) Simulates the needle with thread going through the prostate, the thread will be kept inside the prostate as a reference for the 3D reconstruction (b) A typical prostate slice with thread reference

Figure 3.13 The reference holes (pointed out by arrows) on the pathological slice are highlighted in red by pathologist

3.4 3D Reconstruction of MRSI and Pathological Models

3D reconstruction techniques involve the building of 3D models from two-dimensional inputs such as x-ray, CT images, MR images, etc. The study carried out on the resulting 3D models helps surgeons in preoperative procedures and to better understand prognosis of disease. This, in turn, helps in the planning of more appropriate and effective treatments. In this project, experts delineate the features of interest in these 2D images manually. The software used in this project for reconstructing 2D images into 3D spatial domain is Bubble 3D (see Appendix B), which is developed on the Java platform [88]. This section describes the methods of reconstruction adopted to generate 3D models of both MRS images and pathological slices.

3.4.1 MRSI Model Reconstruction

1. Image acquisition

The MRI machine used in this project is the 1.5T LX HiSpeed Active-Shield Short-bore Fixed MR System. The stack of prostate images contains T2 16-17 slices, each of which is 580x580 in image pixels, 120x120 mm² in field of view and 3.0 mm in slice thickness; the slice intraspace is 0.5 mm. After obtaining the transverse T2 weighted MR images, a spectroscopic imaging volume is selected to maximally cover the prostate and minimally include the periprostatic fat, surrounding tissues, and rectal air. This will be accomplished by selecting a rectangular volume encompassing the prostate at the prostatic apex and base. A

commercial spectroscopy package GE (General Electric 1.5T LX, PROSE) will subsequently determine the position and dimensions of the volume.

2. Image segmentation

The purpose of segmentation is to find the interface between the fields of interest and the background. The most commonly used segmentation techniques can be classified into two broad categories, namely region segmentation and edge-based segmentation. There are a number of algorithms such as manual segmentation, automatic, semiautomatic algorithms available for the edge-based segmentation. In this project, manual segmentation is used to outline the prostate boundary and the field of interest. One senior radiologist (Dr T.C.H., National Cancer Center, SGH) is individually requested to examine and label the MRSI results.

3.3D model reconstruction and visualization

3D medical image visualization itself is an interdisciplinary field. There are mainly two kinds of visualization, namely volume visualization and surface visualization. The former displays all the data in the field of view, with varying image intensity at every voxel. Different opacity coefficients are set for different tissues, which are classified by image intensity, so that only object of interest can be seen (Figure 3.14(a)). On the contrary, surfaces that are defined in terms of geometric primitives such as polygon meshes or contour lines, is faster to render and more compact in storage. Marching cubes algorithm (Figure 3.14 (b)) and contour connecting are two popular methods to generate the geometric topology of a surface. The former creates a triangle mesh model from volume data with constant density (iso-surface). The contour connecting technique is less complex since it just extracts

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contours in every slice and connects them together. In this project, 3D model reconstruction is created with the help of software Bubble 3D (refer to Appendix B). Bubble 3D use NURBS³ [92] to connect the surface.

Figure 3.15 shows the reconstructed MRSI model build in Bubble 3D with NURBS connecting the slices.

Figure 3.14 (a) Volume visualization from CT data of a foot (b) Surface visualization from CT Data of a human head

Figure 3.15 (a, b) Prostate MRS images with prostate cancer is outlined (c) 3-dimensionally reconstructed prostate MRSI model which is built in Bubble 3D

³Non-uniform Rigid B-spline

3.4.2 Pathological Model Reconstruction

1. Image acquisition and segmentation

Prior to the resection, two through holes (refer to Section 3.3) are made in the isolated prostate specimens. They provide a reference to ensure that the resected prostate specimens are aligned during the reconstruction process. Each prostate is sectioned by a prostate slicer box (refer to Chapter 4) at 3.5 mm intervals in a transverse plane perpendicular to the posterior surface. The slicing interval and angular displacement are made in direct correlation with MRI in the transverse orientation. It is obtained from the apex and extends towards the base. The first slice is labeled with the smallest number starting with slice number, for example A01. The entire surface of the sectioned prostate slices is inked (orientation of the specimen and subsequent sections is made easier by inking the two sides in different colors, for example red for right and blue for left) after fixation in 10% neutralized formalin for 6 hours. The whole mount step-sectioned specimens are then further sliced into thin microtome sections.

Key pathological structures, including tumors and urethra are identified on the microtome slides. The slides are numbered in the order (A01, A02, to A13 in accordance to the protocol practiced by pathologists in the Pathological Department of Singapore General Hospital) from the apex to the base of the prostate. Slides of seminal vesicles and the vas deferens of the gland will be excluded (definitely these structures are unwanted and need to be removed).

Pathological microtome slides are digitized using a Hewlett Packard Precision Scan Pro commercial scanner (refer to Appendix F). Resolution of the resulting images

Chapter 3 Data Collection and Analysis

is standardized at 600 dots per inch (dpi) with a magnification of 1 (100%). The settings should not be changed so as to ensure a constant 1:1 aspect ratio. The reason why images are taken at such high resolutions is to ensure that all anatomical features (cancers, urethra, nodules) are captured and sufficiently clear for valid studies to be carried out. This is despite the fact that in three-dimensional reconstruction the prostate boundary and cancer distribution are the primary characteristics of interest. Figure 3.16 shows the pathological image stack.

Figure 3.16 Pathological image stacks with the fields of interest outlined by the pathologist. A06-Base, A13-Apex (A01 to A05 are seminal vesicles and vas deferens)

2. Reconstruction

Before the pathological slices are reconstructed, the foremost thing is to orientate the slices according to the two reference holes so that all the slices are in alignment, This procedure is done in MATLAB. Figure 3.17 shows the result of slice rotation,

Figure 3.17 The pathological slice rotation according to the 2-hole reference

The methodology of the construction of the 3D pathological model is in a manner closely correlated to the MRSI reconstruction. The surface is formed by the use of NURBS. Figure 3.18 shows the result of the pathological reconstruction.

Figure 3.18 A 3D pathological model reconstruction from pathological slices

Chapter 4

A Novel Device for Sectioning Prostate in Correlation to

MRI⁴

A novel slicing device is invented that enables the orientation of fresh or fixed prostate gross pathological sections to be obtained corresponding to MRI images before they are processed for histological analysis. The correlation of histological preparations and MR images provides insight into biology of disease processes. Based on pre-determined landmarks, the prostate specimen is orientated and sectioned in the device in the same manner as the prostate is scanned by MRI. Seven gelatin phantoms are applied to study the accuracy of the slicer. The result demonstrates that the prostate slicing device has a good accuracy and can potentially allow direct correlation between radiological images and histopathology, it has uses in the evaluation of current and future imaging sequences such as MRSI.

4.1 Background

The cutting of large tissue blocks (for example prostate) for pathological examination is usually performed by hand. There is a high chance of wrong tissue orientation and consecution. Currently, the most systematically cutting prostate method is the sextant-by-sextant method (Figure 4.1) [20], which is used for

⁴ The chapter was published by *The IASTED International Conference on BIOMECHANIC*, August 23-25, 2004, Hawaii, USA.

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evaluating the accuracy of MRI and MRSI. This method is performed by taking three cores equally spaced between the base and apex in the transverse plane of each side of the prostate. To correct these differences in sectioning technique, a tumor site on MR or 3D MR spectroscopy is considered to match the histopathologic site if the tumor is present in the peripheral zone of the same sextant of the prostate (right or left base, right or left middle gland, right or left apex) within a range of one section (craniocaudal distance, $\pm$ 3-4 mm). This method, considering the uses of pathological slices as references, may assess MRI/MRSI accuracy in the molecular level. However, the angle at which the histopathologic sections are cut often differs from the angle at which MR imaging is performed (difference of 5-20 degrees)[20]. Sextant-by-sextant method is too coarse to be applied in the MRSI validation.

To section the brain, a slicing machine was designed by the researchers [53, 54] in Denmark. This device allows small laboratory animal brain specimens to be sliced in any given position. The tissue can be sectioned into slabs with an optional thickness between 0.5 and 20mm [55]. However, this device is only suitable for small laboratory animal brain specimens.

In order to correlate macroscopically obtained prostate tissue slabs with corresponding scanning planes from scanning modalities such as CT, MRI, MRSI, and Positron Emission Tomography (PET), a more accurate tissue sectioning methodology is required. The prostate slicer box is such a device, which is developed in CIMI Lab, Nanyang Technological University. The main function of

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the prostate slicer box is to slice the prostate specimen accurately according to how the organ is scanned using MRI.

Figure 4.1 Sextant-by-sextant method is used in MRI/MRSI validation

4.2 The Prostate Slicer Box

The prostate slicer box is designed for orientated parallel sectioning (for example consecutive sections with the same desired section plane) prostate specimens. The main function of prostate slicer box (Figures 4.2, and 4.3) is to slice the prostate specimen accurately according to how it is scanned using MFU. It allows the prostate to be sectioned uniformly into 3.5 mm segments [45, 56, 57] in controlled correlation to the position of the prostate in MRI scan.

The slicer box consists of five main parts (Figure 4.2), including a cuboid chamber, cutting slits, a handle, which can install a disposable blade, two transparent scales, and a movable stopper. The cuboid chamber is for orientated embedding of the tissue. Cutting slits, which have a fixed distance of 3.5 mm between them, allow the sharp blade passing manually through the slits and simultaneously trimming the tissue block. At the two ends of the chamber, there are scales for the purpose of

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measuring the urethra’s vertical distance from a base datum. The scales enable the pathologist to position the apex and base of the prostate according to the measurement of the vertical dimension of the urethra entry and exit sites. This is represented diagrammatically in Figure 4.4 (a). The trimming blade is sharp to minimize tissue deformation.

Figure 4.2 Prostate slicer box for sectioning the prostate accurately according to orientation to MRI

Figure 4.3 Technical drawing of the prostate slicer box (detail dimensions refer to Appendix H)

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4.3 The Principle of Prostate Slicer Box

The prostate slicer box takes into account the vertical distance between the entry site of the urethra at the base and the exit point of the urethra at the apex surface (Figure 4.4(a)). The vertical displacement is determined from the MR images of which its derivation requires interpretation of anatomical features shown in the captured MR images. The radiologist reports the distance between the upper and lower ends of the prostatic urethra. This distance is used to control prostate specimen x-axis rotation inside the box.

During MRI scanning the prostate, the MRI XY coordinate will form an angle with prostate vertical plane, called angle D (Figure 4.5). The radiologist reports Angle D. The angular displacement, as observed in the sagittal view, is determined y-axis rotation when the prostate specimen inside the box.

The prostate gland is placed in the slicing box and is orientated along the z-axis (Figure 4.4 (b)) using the vas deferens as a reference. Figure 4.6 (a) shows prostate specimen being sliced by the prostate slicer box. Equal thickness tissue slabs with same orientation as the MRI scanning planes are obtained (Figure 4.6 (b)).

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Figure 4.4 (a) Sagittal view of the prostate inside the prostate slicer box (b) Transverse view of the prostate, with positioning of vas deferens to determine orientation inside the prostate slicer box

Figure 4.5 (a) The axial view of X-Y plane inside the MRI field (b) The angular displacement D as observed in the sagittal view is determined by MRI images and reported by radiologist

Figure 4.6 (a) The prostate specimen is being sliced (b) Equal thickness tissue slabs with same orientation as MRI scanning planes are obtained

4.4 Validation

4.4.1 Phantom Preparation

Seven deformable gelatin prostate phantoms (Figure 4.7 (a), Appendix G) are built to study the accuracy of the prostate slicer box. Pieces of rubbers are embedded inside the phantom to simulate the prostate nodules (Figure 4.7 (c, d)). The rubber blocks are cuboid in shape, and the width, length and height are accurately measured before the phantoms are made. A thin plastic tube is inserted into the phantom to simulate the urethra going through the prostate.

The phantoms are scanned in the MRI machine. Transverse T1 weighted sequences are performed in the seven phantoms. The sequences are scanned with a repetition time (TR) of 325 ms; the field of view (FOV) in each slice is 120 mmx120 mm,

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with 3.5 mm slice thickness. The images are with a resolution of 256x256 pixels.

Figure 4. 7 (c) shows the phantom MRI image.

After the MRI machine scans the phantoms, they are trimmed by the prostate slicer box (Figure 4.7 (b)). The phantom slices are scanned into the computer with a HP scanner at a resolution of 600 dots per inch (Figure 4.7 (d)).

4.4.2 Area Calculation

Area calculation is performed on 7 phantoms. The correlation between MRI and phantom slices is performed on a section-by-section basis. First, the boundaries of the prostate and nodule are manually segmented in corresponding image slices. Second, they are registered together using the urethra as the landmark [58]. Third, the disagreement of the areas after registration is visualized by merging them into one image space with respective transparent scales. Finally, this space is partitioned by grids of resolution 1mmx1mm in X, Y directions. Those subspaces are labeled by box numbers, which can clearly tell the nodule position difference. Figure 4.8 illustrates the details of image comparison.

The overlap measure [59] is very sensitive to even small area differences, both inside and outside of the object model, it is therefore a strong test for studying accuracy and consistency of medical images.

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Figure 4.7 Phantom study. (a) A gelatin prostate phantom (b) The phantom is being trimmed in prostate slicer box (c) The MR image of prostate phantom (d) The phantom slice is digitized into the computer using the HP scanner

Figure 4.8 The images are converted to transparency with 1 mmx1 mm grid boxes in X, Y directions

4.4.3 Reslice

For the purpose of evaluating that the prostate slicer box slices the prostate phantom exactly according to how it is scanned using MRI, and the nodule distribution of MR image is same plane with the phantom slice, the phantom is simulated to be resliced and rotated the original slice (+/-) 10-degree along x-axis (Figure 4.9), the area and position of the nodule are calculated and compared with the correspondent MR image (Figure 4.10), the difference will show how accurate of the prostate slicer box. If the original phantom slice corresponds better with the MR image than the rotated slice, one can conclude that the prostate slicer box trims the phantom in the correct plane.

Figure 4.9 Phantom is simulated to be resliced and rotated the original slice 10-degree about axis X

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Figure 4.10 The flow chart of simulated reslicing the prostate phantoms

4.4.4 Statistical Analysis

Phantom data are entered and analyzed using a statistical package [6,11]. Basic 2 x 2 classification tables are used to illustrate the true positive, false positive, true negative, false negative. Positive is established by MRI examination (MRI information as a gold standard). True positive (TP) means both phantom and MRI outlines are in agreement; true negative (TN) means the regions that exclude both phantom and MRI contours; False positive (FP) means the regions include in the phantom area but miss the MRI contours; False negative (FN) means the regions that include in MRI outlines but do not have phantom contours. For the purpose of

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statistical analysis, the MRI imaging results are dichotomized either as positive or negative [76]. With this, the sensitivity and specificity are defined as follows [20]:

$$\text{Sensitivity} = \text{True Positive} / (\text{True Positive} + \text{False Negative}) \quad (4.1)$$

$$\text{Specificity} = \text{True Negative} / (\text{True Negative} + \text{False Positive}) \quad (4.2)$$

$$\text{Positive Predictive Value (PPV)} = \text{True Positive} / (\text{True Positive} + \text{False Positive}) \quad (4.3)$$

$$\text{Negative Predictive Value (NPV)} = \text{True Negative} / (\text{True Negative} + \text{False Negative}) \quad (4.4)$$

$$\text{Accuracy} = (\text{True Positive} + \text{True Negative}) / (\text{the number of pixels}) \quad (4.5)$$

ROC-curve is derived from sensitivity and specificity calculation. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system [77]: 0.90-1 = excellent; 0.80-0.90 = good; 0.70-0.80 = fair; 0.60-0.70 = poor; 0.50-0.60 = fail.

4.5 Validation Results

4.5.1 Phantom results

Table 4.1 summarizes phantom results of the accuracy, specificity and sensitivity based on the nodule intersections on the correspondent MR images and phantom slices. Figure 4.11 is the ROC-curve derived from the sensitivity, specificity calculation.

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Figure 4.11 ROC-curve of the accuracy of prostate slicer box based on phantom study

Table 4.1 The phantom results of the accuracy of prostate slicer box

Sensitivity	87.5%
Specificity	90.2%
Accuracy	89.0%

4.5.2 The Results of Reslice

According to the method explained in 4.4.3, we simulate reslicing the prostate phantoms. Table 4.2 summarizes the results of reslicing the prostate phantom.

Table 4.2 Results of reslicing the prostate phantom

	The number of slices verifies original phantom slice in the correct plane	Absolute area of nodule changes
Rotate the original slice 10 degrees	79.49% (67 / 84)	22.85%
Rotate the original slice -10 degrees	76.92% (64 / 84)	30.83%

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As the results demonstrate in Table 4.2, total 79.49-76.92 % of slices support the prostate slicer box trimming the prostate phantoms in the correct plane; the absolute area difference between the MRI slice and tilted phantom slice is bigger than original slice, and the average area changes are 22.85-30.83 %. These results further demonstrate that the prostate slicer box is fairly accurate.

4.6 Discussions and Conclusions

A main implication from the results of the present study is that the prostate slicer box allows a direct comparison of MR images with corresponding histological sections. The prostate slicer box has a good accuracy and can potentially allow direct correlation between radiological images and histopathologic slices. It has uses in the evaluation of current and future imaging sequences such as magnetic resonance spectroscopy.

Phantom study verified the accuracy of the prostate slicer box is 89.0%. Errors can be attributed to the MRI machine, the expert intervariability and intravariability [3], and the image processing.

Second version of prostate slicer box is being developed in CIMI Lab, NTU. This model has many enhancements over the first version. It allows a significantly higher performance in trimming, particularly for specimen fixation. Because of potential patent filing, discussion on this second version is not included in this thesis.

The precision of the first version of prostate slicer box not only depends on the steady-handedness of the person using it, but also depends on the size, shape and

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consistency of the tissue sectioned. The second version device uses the gelatin to embed the prostate specimen; therefore it totally limits the prostate movement inside the slicer. The gelatin is considered as a buffer as most appropriate in terms of composition, PH value, temperature, oxygenation, and lubricating properties to maintain the variabilities of the tissue being sectioned.

The new version slicer box is designed with multi-blade that can trim the specimen at one time so as to minimize damages and provide samples of uniform and reproducible thickness, eliminating the main source of errors in tissue trimming work.

Chapter 5

MRSI Validation Algorithms and Results

The main requirements concerning validation include: the standardization of image processing methods and data sets, definition of corresponding “ground truth”, and design of validation metric. The standardization of image processing method and data collection has been introduced in Chapters 3 and 4.

Pathological model is rescaled with the rescale factor (RF) to compensate the shrinkage and deformation. RF should be obtained before the evaluation. It can be derived from the Prolate Ellipsoid Equation (Equation 5.1). Thereafter, the FastSCAN surface is defined as surface/volume reference. The linearly rescaled pathological data are defined as “ground truth” of cancer distribution.

In this chapter, the evaluation metric is designed, the verification algorithms are implemented and the results are given. Key issues concerned with the evaluation task are the validation algorithms. Several validation metric, including volume difference, maximum, minimum, and mean surface distance, area calculation, and Hausdorff distance between 2 curves are calculated to demonstrate the agreement and disagreement between MRSI model and reference model.

Two software tools are very important in this validation work. One is MESH [86], which is used to calculate the maximum, minimum, and mean surface distance. The other one is MEDICAL [85], which is used to statistically calculate the ROC-curve.

5.1 Validation Algorithms

5.1.1 Validation Methods

1. Linear rescaling

The first step for validating MRSI involves using the FastSCAN prostate volume as a gold standard, linearly rescaling the reconstructed pathological model according to the volume difference. This is based on a hypothesis that all direction changes due to uniform formalin fixation. For prostatic volume calculation, Prolate Ellipsoid Equation [61] is the most popular method to give volume measurement based on prostatic width, height, and length (Figures 5.1 and 5.2). However, in this project, this equation is applied to derive RF rather than calculate the prostatic volume.

Figure 5.1 Width, height, and length measured in transverse (left) and sagittal sections (right)

Figure 5.2 Prostatic length, width, and height in a 3 dimensional model

The Prolate Ellipsoid Equation:

$$Prostate\ Volume = (height \times length \times width) \times \pi / 6 \quad (5.1)$$

If the prostate pathological model is defined as *volume1*, the volume from FastSCAN is defined as *volume2*, using the FastSCAN volume as a reference, the pathological model is linearly rescaled to correct the shrinkage due to the formalin fixation and pathological deformation. The RF can be derived from Equation 5.1. After calculating the rescale factor, the pathological model is linearly enlarged in the x, y, and z-axes using *RF*.

$$Volume2 / Volume1 = RF^3 \quad (5.2)$$

2. Volume calculation

It is generally accepted that prostate cancer is a progressive disease. Progression of prostate cancer can be defined by the worsening of clinical parameters, such as the prostate volume changes. It is important to calculate prostate volume since it may influence the treatment or operation in patients.

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There are two approaches in prostate volume calculation, the first approach is to calculate it when the prostate is inside the body; the second one is to calculate it after prostatectomy. Before prostatectomy, prostate volume is measured by various methods, such as Transrectal Ultrasound. The most common algorithm used in the volume calculation is Prolate Ellipsoid Equation (Equation 5.1) because it is fast and comparatively accurate [61].

In this thesis, a new volume calculation algorithm is proposed. Since only prostate volume after prostatectomy is of interest and the prostate is of an irregular shape, Delaunay Triangulation is used to divide the prostate into small, non-overlapping tetrahedrons. The sum of all the tetrahedrons is the volume of the prostate. This method requires the coordinates of a cloud of points on the surface to compose the tetrahedrons. Figure 5.3 shows the basic idea of Delaunay Triangulation. The algorithm is implemented in MATLAB.

Figure 5.3 (a) The basic concept of Delaunay Triangulation; (b) Tetrahedrons are divided in the volume

The volume of a tetrahedron is often computed from the coordinates of its vertices than that of its edge-lengths [62]. In this project, however, the tetrahedron volume is calculated using its edge-lengths (refer to Equation 5.3). Edges u, U, v, V, w, W ,

are grouped into pairs (u, U), (v, V), (w, W), according to their opposite positions respectively [62] (Figure 5.4).

Figure 5.4 The pairs of edges of one tetrahedron are determinant of the Equation matrix

$$\begin{aligned}
 Volume &= \frac{1}{288} \begin{bmatrix} 0 & u^2 & v^2 & w^2 & 1 \\ u^2 & 0 & w^2 & v^2 & 1 \\ v^2 & w^2 & 0 & U^2 & 1 \\ w^2 & V^2 & U^2 & 0 & 1 \\ 1 & 1 & 1 & 1 & 0 \end{bmatrix}^{\frac{1}{2}} \\
 &= [(4u^2v^2w^2 - u^2(v^2 + w^2 - U^2)^2 - v^2(w^2 + u^2 - V^2)^2 - w^2(u^2 + v^2 - W^2)^2 \\
 &\quad + (v^2 + w^2 - U^2)(w^2 + u^2 - V^2)(u^2 + v^2 - W^2)) / 12]^{\frac{1}{2}}
 \end{aligned}
 \tag{5.3}$$

3. Software MESH

The surface distances, i.e. maximum surface distance and mean absolute surface distance, are calculated by software called **MESH**, which can be freely downloaded from <http://messh.epfl.ch/>. MESH is an efficient tool that measures distortion between two discrete surfaces (triangular meshes) using Hausdorff distance. Note that in **MESH**, the color value (from dark to bright red) maps the scale of surface distance (from small to large), and the most left bar chart displays the distance distribution on the surface.

Figure 5.5 Software MESH calculates the maximum, minimum, and mean distances between the two model surfaces

5.1.2 Validation Metric

To validate MRSI accuracy, both prostate and cancer volume disagreement and contour disagreement are used in this thesis. The following lists the metric used for evaluating MRSI.

1. Volume difference

As described in Knoll *et al.*'s work [68, 76], the volume difference is one of the metric to measure the disagreement between the MRSI model (AV) and the FastSCAN volume (FV). The calculations for the volume difference (VD) and the absolute volume difference (AVD) are expressed as follows.

$$VD = [(FV \cup AV) - (FV \cap AV)] / 2FV \quad (5.4)$$

$$AVD = |FV - AV| / FV \quad (5.5)$$

2. Maximum surface distance (Hausdorff distance)

The Hausdorff distance metric [90] defines the largest difference between two contours. Given surfaces C and D, each point c on C is calculated the minimum distance to all the points on surface D, $dc(c, D) = \min \{d(c, s), s \in D\}$. This

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minimum distance for each surface point is taken the maximum minimum distance as the "worst-case distance", $hc(C, D) = \max \{dc(c, D), c \in C\}$. The Hausdorff distance metric is not symmetric and $hc(C, D)$ is not equal to $hc(D, C)$, which is accounted for by finally calculating $Hc(C, D) = \max \{hc(C, D), hc(D, C)\}$. The calculation of Hausdorff distance metric is computationally very expensive, as it needs to compare each contour point to all the other ones. A comparison of complex 3D surfaces would require huge number of calculations. However, every method has its limitations, this measure is applied to quantify the agreement and disagreement between the surfaces.

3. Mean absolute surface distance

The mean absolute surface distance [64, 65] can tell how much on average the two surfaces differs. This measure integrates both over- and under-estimation of a contour, and results with intuitive explanation. A similar strategy as Hausdorff metric calculation, named Signed Euclidean Distance, transforms one object and overlays with the second object surface, This calculation is not symmetric, since distances from A to B are not the same as B to A (see the discussion in Hausdorff distance above). Therefore, a common average by combining the two averages is derived. The mean absolute distance does not depend on the object size. As a prerequisite, however, it requires existing surfaces, and therefore it is only suitable for single object comparison. The calculation is not straightforward if a point-to-point correspondence on two surfaces is not available.

4. Area overlap

In [20], Juergen *et al.* use overlap areas defined by two corresponding boundaries to tell the disagreement in details. The overlap areas are defined as follows (Figure 5.6).

True positive (TP) area: the common area is contained by both the pathological contour and the MRSI contour.

False positive (FP) area: the area is enclosed by the MRSI contour but outside the pathological contour.

False negative (FN) area: the area is enclosed by the pathological contour but is missed by the MRSI.

True negative (TN) area: the area is excluded both MRSI and pathological area.

From TP, FP, FN, and TN, sensitivity, specificity, and accuracy can be calculated (refer to 4.4.4). ROC-curve is derived from the calculation.

Figure 5.6 The intersection relationship between pathological slice and MRS image

5. The distance between two curves

The distance-based metric is obtained by calculating the difference in length of the vertices from the reference point (Figure 5.7) [66]. Hausdorff distance, which describes the difference between the two sets of boundaries, is calculated to determine the agreement between pathological slices and MRS images (Figure

5.8). These distances are defined by first choosing a common centroid of the two boundaries from which radial lines are drawn projecting outward. The intersection of these radial lines with the two curves defines the corresponding points. The deficiency of this method is that the boundaries should be simple-shaped because the centroid needs to be determined [67].

Figure 5.7 Local difference, $d_j(\theta_j)$, between pathological slice (solid) and MRSI (dotted) outlined boundaries on slice j

Figure 5.8 Hausdorff Distance between the two curves

5.2 MRSI Validation Results

5.2.1 Rescale Factor

As introduced in 5.1.1 (1), linear rescaling is the first step of the MRSI validation. The FastSCAN volume is regarded as a gold standard; the pathological model volume is linearly rescaled to correct the volume difference caused by the formalin fixation and pathological processing (from Equation 5.2). Table 5.1 summarizes the quantities of RF in this project.

Table 5.1 Summary of the Rescale Factor

	Pathological volume mm ³	Laser scan volume (reference) mm ³	Volume2/volume 1	Rescale factor (RF)
Case1	38156	31421	0.823	0.94
Case2	38156	54283	1.423	1.12
Case3	20137	24530	1.22	1.07
Case4	18885	15507	0.82	0.94
Case5	32353	40830	1.26	1.08
Case6	31233	42554	1.36	1.11
Case7	31707	60560	1.91	1.24
Average				1.1

Observed from Table 5.1, there are 2 cases (case 1 and case 4) of which the pathological model volume is larger than the FastSCAN volume respectively, opposite to the formalin shrinking prostate expectation. The most probable source of this discrepancy is from the pathological model reconstruction, the processing of the

pixel size of the pathological slices. The average RF is 1.1, which demonstrates the pathological models averagely enlarged by 1.1 in x, y, z directions.

In 7 cases, 4 cases have demonstrated that the prostate has shrunk after formalin with average volume change of 6.44%, and 3 cases of the prostate have not shown any sign of the shrinkage.

The problem of having insufficient sample size affects the RF, the errors of the validation work, and the results of calculating formalin’s effect. In this project, a large sample size is needed, but it is limited by the factors beyond author’s control.

5.2.2 Volume Difference

The algorithm mentioned in 5.1.1(2) calculates the proposed FastSCAN volume and MRSI model volume. The same method is applied to the prostate cancer too. The prostate volume differences of 7 patients are quantified as follows:

Table 5.2 Summary of the prostate volume difference between models

Prostate volume	FastSCAN (FV) mm ³	MRSI model (AV) mm ³	AVD %
Case1	31421	25068	20.22
Case2	54283	36565	32.64
Case3	24530	11794	51.92
Case4	15507	15214	1.89
Case5	40830	40230	1.47
Case6	42554	42465	0.21
Case7	60560	51936	14.24
Average	38526	31896	17.5

$$AVD = |FV - AV| / FV$$

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Table 5.2 summarizes the results of the absolute volume difference between MRSI model and FastSCAN model of 7 cases. The same method is used to calculate the prostate cancer volume difference between MRSI model and pathological model (Table 5.3).

It can be seen from Table 5.2, that the average prostate absolute volume difference (AVD) is 17.5%, the average volume similarity between the reference FastSCAN and MRSI model is 82% -83%. According to the standard set up in [76] (a similarity value between 0.7 and 1.0 represents an excellent agreement while a similarity between 0.4 and 0.7 represents a good agreement), there exists an excellent agreement between MRSI and reference FastSCAN volume.

Table 5.3 Summary the cancer volume difference between 2 models

Prostate volume	Pathological model mm ³	MRSI model (AV) mm ³	AVD %
Case1	4372.37	4913.95	12.37
Case2	4913.96	4372.38	12.40
Case3	1420.27	2203.98	55.18
Case4	5822.89	6408.27	10.05
Case5	2412.09	991.5567	55.89
Case6	1443.33	1548.80	6.63
Case7	9082.75	5558.82	38.8
Average	4202	3714	27.3

From Table 5.3, the average cancer volume difference (VD) is 27.3%; the average volume similarity between the reference FastSCAN and MRSI model is 72%-73% that demonstrate a good agreement between the cancer volumes.

5.2.3 Surface Distance (Hausdorff distance & mean distance)

The surface distances, including maximum, mean and minimum distance between the reference FastSCAN surface and the MRSI model, are calculated by the software *MESH* (refer to Section 5.1.1(3)). The summary of prostate surface distances of 7

Table 5.4 Summary of the prostate surface distances between models (FastSCAN surface and MRSI)

	Minimum Distance (mm)	Maximum Distance (mm)	Mean Distance (mm)
Case1	6.02×10^{-5}	8.788	3.23
Case2	6.2×10^{-5}	8.7	3.2
Case3	1.51×10^{-5}	20.56	8.06
Case4	1.93×10^{-3}	23.244	11.04
Case5	3.2414×10^{-4}	10.09	2.90
Case6	8.6076×10^{-6}	3.436	0.84
Case7	2.86×10^{-5}	5.36	1.24
Average	3.5×10^{-4}	11.5	4.4

From Table 5.4, the maximum prostate surface distance between reference FastSCAN model and MRSI model is 11.5 mm, the mean surface distance is 4.4 mm. Comparing to the average prostate size (prostate is a rounded organ with a diameter of about 40 mm) [91], the disagreement between the two models is 4.4 mm / 40 mm = 11%, the average surface similarity of the two models is 89%, which demonstrates there is a consistent result with volume similarity.

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Nevertheless, as demonstrated in Table 5.4, the maximum surface distances of case 3 and case 4 seem a bit large. The disagreement mainly occurs in the two ends of the prostate (see Figure 5.9) where the manual outlines vary a lot because the image quality is worse in the two cases.

Figure 5. 9 Surface distance of case 3, which demonstrates the maximum surface distance (orange color), occurs in the two ends of the prostate

5.2.4 Prostate Cancer Area overlap and ROC Curve

The correlation of cancer between MRSI and pathological slices is performed on a section-by-section basis, The 2 dimensional MRSI slice and correspondence pathological slice are merged together and overlaid by a grid with 1 mm x 1 mm boxes to study the disagreement in detail. Figure 5.10 demonstrates one of the results of the cancer area overlap, and Table 5.5 quantifies the results of Case1. Table 5.6 gives other results of the area overlap. The pixel numbers of cancer intersection are calculated. The true/ false, positive /negative results (refer to 4.4.4) are derived from the cancer area overlap.

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Table 5.5 Area overlap of case 1

	Cancer pixel number (MRI)	Cancer pixel number (path)	Intersection
Slice1	344	366	237
Slice2	437	836	411
Slice3	503	784	305
Slice4	491	1027	376
Slice5	719	668	459
Slice6	573	590	372
Slice7	402	212	183
Slice8	549	361	283
Total	4018	4844	2626

Table 5.6 Summarizes the quantity of intersection of prostate cancer between MRSI and pathological slices

	Cancer pixel number (MRSI)	Cancer pixel number (path)	Intersection
Case1	4018	4844	2626
Case2	1936	2454	1680
Case3	2499	2690	1849
Case4	5026	5848	4229
Case5	954	2434	526
Case6	5405	5029	3371
Case7	4801	6872	3964
Total	24639	30171	18245

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Figure 5.10 The cancer is gridded by the 1 mm x 1 mm boxes; the union and intersection between the MRSI and pathological slices are counted to obtain the true/false, positive/negative value

As defined in 5.1.2 (4),

True positive (TP) area = Intersection = 18245

False positive (FP) area = MRSI-Intersection = 24639-18245 = 6394

False negative (FN) area = Path-Intersection = 30171-18245 = 11926

True negative (TN) area = Total pixel numbers on the slices - MRSI - Path + Intersection = 66×44 (the pixel numbers in width & length) $\times 39$ (the number of slices) - 24639 - 30171 + 18245 = $113256 - 24639 - 30171 + 18245 = 76691$

From TP, FP, FN, sensitivity and specificity, accuracy and ROC curve can be calculated (Refer to 4.4.4).

Sensitivity = True Positive / (True Positive + False Negative) = $18245 /$

$(18245 + 11926) = 60.0\%$

Specificity = True Negative / (True Negative + False Positive) = $76691 /$

$(76691 + 6394) = 92.3\%$

Positive Predictive Value (PPV) = True Positive / (True Positive + False

Positive) = $18245 / (18245 + 6394) = 74.0\%$

Negative Predictive Value (NPV) = True Negative / (True Negative + False Negative) = 766911/(76691 + 11926)= 86.5 %

From the specificity and sensitivity, with the help of software MEDICAL, the ROC- curve is drawn for the assessment of MRSI accuracy. The area under ROC-curve gives the quantity of the results. The results of MRSI validation is shown on Table 5.7, correspondent ROC-curve is drawn from software MEDICAL (Figure 5.11), area under ROC curve is 0.764, which indicates the result is good (refer to 4.4.4).

Table 5.7 The Results of MRSI Validation

Sensitivity	60 %
Specificity	92.3 %
Positive Predictive Value (PPV)	74 %
Negative Predictive Value (NPV)	86.5 %
Accuracy (Area under ROC curve)	76.4%

Figure 5.11 ROC-curve of MRSI validation

5.2.5 The Results of Distance Between Two Curves

Hausdorff distance between the prostate boundaries on the pathological slice and MRS images is calculated in MATLAB. Table 5.8 summarizes the quantities of the results.

Table 5.8 Summary of the Hausdorff distance (mm) between two curves

	Slice1	Slice2	Slice3	Slice4	Slice5	Slice6	Average
Case1	10.6513	10.6247	6.3062	3.9798	5.7636	5.2749	7.1001
Case2	3.5234	3.3426	3.3681	4.41	5.6926	6.7242	4.5102
Case3	12.7887	7.7936	7.09	7.27	5.32	7.07	7.8887
Case4	8.0345	6.0144	7.1821	5.8885	7.6804	-	6.96
Case5	3.0109	1.2849	1.4830	1.7382	2.1561	2.1162	1.9649
Case6	3	2.1755	2.3696	0.9878	1.7832	-	2.0632
Case7	5.2653	2.7822	3.7281	6.8837	6.9517	-	5.1222
Average of average							5.0

The average Hausdorff Distance of the 7 cases is 5.0mm. Considering the actual average prostate rounded shape with diameter 40 mm, the maximum disagreement between the two curves is $5.0\text{mm} / 40\text{ mm} = 12.5\%$. The similarity between two curves is 87%-88%. The results demonstrate an excellent agreement between the pathological slices and MRS images.

5.3 Discussion and Conclusion

In this chapter, absolute volume difference, surface distances, Hausdorff distance between 2 dimensional curves is applied to evaluate the agreement between prostate

surfaces/boundaries. Area overlap method is applied to evaluate the agreement of the cancer distribution between the MRS images and pathological reference slices.

- Absolute volume difference (AVD): from Table 5.2, the average AVD of prostate models is 17.5%, the volume similarity is 82%-83%, which demonstrates an excellent agreement between the MRSI model and reference FastSCAN volume. From Table 5.3, the average AVD of cancer volume difference is 27.3%, the volume similarity is 72%-73%, which demonstrates a good agreement between MRSI cancer and pathological cancer models.
- Surface distance: from Table 5.4, the mean surface distance between the MRSI and FastSCAN surface is 4.4 mm, compare to the average prostate size (rounded shape with 40mm in diameter), the disagreement between the two models is $4.4 \text{ mm} / 40 \text{ mm} = 11 \%$, the average similarity of the two models is 89%, which demonstrate there is an excellent agreement between them.
- Hausdorff distance: from Table 5.8, the average Hausdorff distance between 2 dimensional curves is 5.0 mm, compared to the average prostate size, the maximum disagreement between the two curves is $5.0 \text{ mm} / 40 \text{ mm} = 12.5\%$. The similarity between two curves is 87%- 88%. The results demonstrate an excellent agreement between the pathological slice and MRSI.
- Area overlap: from Table 5.7, the accuracy of cancer area overlap is 76.4%, which demonstrates MRSI has a good accuracy.
- In conclusion, MRSI is an accurate medical image based on the linearly rescaling method. Errors can be attributed to the MRSI machine, the expert intervariability and intravariability, and surgical manipulation error. Errors are

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believed to have come from the processing of the prostate specimen. More cases will be applied to evaluate the accuracy of MRSI.

In 1999, Juergen S. *et al.* in USA also evaluated MRSI accuracy with the uses of pathological slices as a reference [20]. They employed sextant-by-sextant method to slice the prostate, the angle difference between pathological slice and pre-operative medical imaging was 5-20 degrees; the researchers utilized 2 dimensional area overlap method to study the agreement between MRSI and reference pathological slices. Compared to their method, the validation methods in this project are quite advanced. We design a new prostate slicer box to slice the prostate, so that can section the prostate accurately according to pre-operative medical imaging MRSI. The angle difference between MRSI and pathological slices is 10 degrees (refer to chapter 4). Instead of the 2 dimensional area overlap method, we take advantage of volume difference, surface distance, Hausdorff distance to evaluate MRSI accuracy. However, American researchers practiced their methods on more than 500 patients; we only apply our methods on 7 cases because of the reason mentioned earlier. The comparison between the two projects is listed in Table 5.9.

Table 5.9 This project versus project in USA (1999) in determining efficacy of MRSI

		Results of this project	Results from Juergen S. <i>et al.</i> (1999) [20]
Material		Prostate Slicing Box (angle difference less 10°)	Sextant-by-sextant method to slice the specimen (angle difference 5-20°)
		FastSCAN	
		2 -Hole Reference System	
Methods		2 Dimensional Methods	2 Dimensional Methods
		3 Dimensional Methods	
MRSI	Accuracy	76.4%	80.0%
	Specificity	60 %	90%
	Sensitivity	92.3%	95%

Chapter 6

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The main concern of this part of work is to develop a method capable of simulating and characterizing the phenomenon of prostate deformation after prostatectomy so that the pathological model can recover to near the “ground truth” to evaluate MRSI accuracy. Finite element method (FEM) will be applied for numerical simulation of the soft tissue deformation. FEM is a general technique for constructing approximate solutions to boundary value problems. The method involves dividing the domain of interest into a finite number of simple subdomains, the finite elements, and using variational concepts to construct an approximation of the solution over the collection of finite elements. It has been applied for various applications such as surgical simulation and surgical planning [69]. The FE method, in conjunction with an elastic deformation model, is often chosen for its reliable behavior.

6.1 Introduction

6.1.1 Motivation

During the last decade, physically realistic models for surgical planning and image processing have gained increased attention in the medical imaging community. The reason for this is that purely image-based statistical methods do not take into account the physical properties of the objects depicted in the image and often cannot predict any changes in the image. This is especially true when dealing with

medical image data. Different image objects have very different properties and react in a way largely defined by their material characteristics. For example, bone and soft tissue have very different behavior when subjected to equivalent stresses. Therefore, using the model incorporating the object's physical characteristics will improve the accuracy of validation significantly. In preparation for future work, a new finite element based elastic image-matching algorithm is presented. This method is based on the simulation of biomechanical tissue of deformation, which would be used to assess the MRSI accuracy.

6.1.2 Objectives

For the purpose of validating MRSI, there can be two kinds of methods to compensate for the deformation caused by formalin fixation and pathological processing. One is linearly rescaling of the pathological model, using the FastSCAN as a volume/surface reference (refer to Chapters 3, 4 and 5). This method is unfortunately inaccurate since the local deformations are not considered. The other method, which is believed to be more robust and accurate, is the use of finite element method to simulate the pathological model deformation. Same as the linear rescaling method, FastSCAN surface is used as a reference. Through the displacement of boundary elements from one model (FEM model - pathological model) to another one (reference model - FastSCAN surface), the elements of cancer will have some displacement too. This information (cancer position and cancer size) will be considered as a gold standard to evaluate MRSI accuracy. Accordingly, in the future work, the later one will be focused.

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Therefore, the goal of this part of work is to develop methods for simulating the prostate deformation and estimating the “ground truth”. To meet this goal, the following tasks have been identified.

1. Build up prostate finite element model;
2. Determine methods for registration between pathological model and reference FastSCAN surface;
3. Determine methods for approximating “ground truth”;
4. Evaluate these methods on a number of clinical cases to establish their feasibilities.

6.2 Finite Element Modeling of Elastic Membranes and Volumes

6.2.1 General Mathematical Formulation

Assuming a linear elastic continuum without initial stresses or strains, the deformation energy of an elastic body, E , subjected to external applied forces can be expressed as [32,33]:

$$E = \frac{1}{2} \int_{\Omega} \sigma^T \varepsilon d\Omega + \int_{\Omega} F u d\Omega \quad (6.1)$$

Where $\mathbf{u} = \mathbf{u}(\mathbf{x})$ is the displacement vector, $\mathbf{F} = \mathbf{F}(\mathbf{x})$ is the vector representing the forces applied to the elastic body (forces per unit volume, surface forces or forces concentrated at the nodes), Ω is the studied body (where $\mathbf{u}(\mathbf{x}) = (u_x(\mathbf{x}) \ u_y(\mathbf{x}) \ u_z(\mathbf{x}))$)

and $\mathbf{x}=(x, y, z)$ in 3D space), $\boldsymbol{\varepsilon}$ is the strain tensor, which can be written as a vector for notation simplicity.

$$\begin{aligned}
 \boldsymbol{\varepsilon} &= (\varepsilon_x, \varepsilon_y, \varepsilon_z, \gamma_{xy}, \gamma_{yz}, \gamma_{zx})^T \\
 &= \left(\frac{\partial u}{\partial x}, \frac{\partial u}{\partial y}, \frac{\partial u}{\partial z}, \frac{\partial u}{\partial x} + \frac{\partial u}{\partial y}, \frac{\partial u}{\partial y} + \frac{\partial u}{\partial z}, \frac{\partial u}{\partial z} + \frac{\partial u}{\partial x} \right)^T \\
 &= \begin{pmatrix} \frac{\partial}{\partial x} & 0 & 0 \\ 0 & \frac{\partial}{\partial y} & 0 \\ 0 & 0 & \frac{\partial}{\partial z} \\ \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & 0 \\ 0 & \frac{\partial}{\partial z} & \frac{\partial}{\partial y} \\ \frac{\partial}{\partial z} & 0 & \frac{\partial}{\partial x} \end{pmatrix} = \mathbf{L} \mathbf{u} \quad (6.2)
 \end{aligned}$$

And $\boldsymbol{\sigma}$ is the stress tensor, linked to the strain tensor by the constitutive equation of the material. In the case of linear elasticity, with no initial stresses or strains, using a vector notation for $\boldsymbol{\sigma}$ and $\boldsymbol{\varepsilon}$ this constitutive relation is described as

$$\begin{aligned}
 \boldsymbol{\sigma} &= (\sigma_x, \sigma_y, \sigma_z, \tau_{xy}, \tau_{yz}, \tau_{xz})^T \\
 &= \mathbf{D} \boldsymbol{\varepsilon} \quad (6.3)
 \end{aligned}$$

where $\mathbf{D}$ is the elasticity matrix characterizing the properties of the material. The matrix is symmetric due to the symmetry of the stress and strain tensors [32]. For an isotropic material, the properties are the same in every direction. The elasticity matrix of an isotropic material then has the following symmetric form:

$$D = \frac{E(1-\nu)}{(1+\nu)(1-2\nu)} \begin{pmatrix} 1 & \frac{\nu}{(1-\nu)} & \frac{\nu}{(1-\nu)} & 0 & 0 & 0 \\ . & 1 & \frac{\nu}{(1-\nu)} & 0 & 0 & 0 \\ . & . & 1 & 0 & 0 & 0 \\ . & . & . & \frac{1-2\nu}{2(1-\nu)} & 0 & 0 \\ . & . & . & . & \frac{1-2\nu}{2(1-\nu)} & 0 \\ . & . & . & . & . & \frac{1-2\nu}{2(1-\nu)} \end{pmatrix} \quad (6.4)$$

Where Young 's modulus (E) has the same value in any direction: $E = E_x = E_y = E_z$ and Poisson's ratio (ν) too: $\nu = \nu_{xy} = \nu_{xz} = \nu_{yz}$. There are no independent shear moduli, as the material parameters are same at every direction. This reduces the total amount of material parameters to two.

Equation 6.1 is valid either working with a surface or a volume. In this project, the 3D model can be viewed as a model with active surfaces. The boundaries of the objects in the image will be represented as elastic membranes and the surrounding and inner volumes as 3D volumetric elastic bodies.

The continuous displacement field $\mathbf{u}$ within each element is approximated as a function of the displacement at the element 's nodes $\mathbf{u}_i^{el}$ weighted by its shape function $N_i^{el} = N_i^{el}(\mathbf{x})$

$$u = \sum_{i=1}^{N_{nodes}} N_i^{el} u_i^{el} \quad (6.5)$$

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The elements used are tetrahedral (number of nodes per element $N_{node} = 4$, only the vertexes are considered). Hence, the shape function of node I of element el is defined as:

$$N_i^{el} = K(a_i^{el} + b_i^{el}x + c_i^{el}y + d_i^{el}z) \tag{6.6}$$

Where $K = 1/6V^{el}$ for a tetrahedron, the computation of V^{el} and the interpolation coefficients is detailed by Zienkewickz and Taylor in [71].

Figure 6.1 illustrates these concepts on a 2D object. The object is discretized using finite elements (triangles in Figure 6.1 a), forming a mesh. The discretization of the domain allows solving for displacements only at the location of the discretization nodes of the domain. The displacement with each element is linked to the nodal displacements through its associated shape functions. Through such discretization, the integral over the whole domain can be seen as the sum of the integrals over every element. It is possible to evaluate the equilibrium equations separately on every element, and sum up the contribution of every triangle to the vertex to which the triangles are connected thus to build a global equilibrium matrix system.

Figure 6.1 (a) 2D Triangular FE mesh (b) Linear shape function of node i of the triangle element

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For every node i of each element el , the matrix $\mathbf{B}_i^{el} = \mathbf{L}_i \mathbf{N}_i^{el}$ (where $\mathbf{L}_i$ is matrix $\mathbf{L}$ at node i , see Equation 6.2). The function (Equation 6.1) to be minimized on each element el can thus be expressed as

$$E(u_1^{el}, \dots, u_{N_{nodes}}^{el}) = \frac{1}{2} \int_{\Omega} \sum_{i=1}^{N_{Nodes}} \sum_{j=1}^{N_{Nodes}} u_i^{elT} B_i^{elT} D B_j^{el} u_j^{el} d\Omega + \int_{\Omega} \sum_{i=1}^{N_{Nodes}} F N_i^{el} u_i^{el} d\Omega \quad (6.7)$$

Minimizing the total potential energy leads to

$$\frac{\partial E(u_1^{el}, \dots, u_{N_{nodes}}^{el})}{\partial u_i^{el}} = 0 \quad i = 1, \dots, N_{nodes} \quad (6.8)$$

Equation (6.7) becomes:

$$\int_{\Omega} \sum_{j=1}^{N_{Nodes}} B_i^{elT} D B_j^{el} u_j^{el} d\Omega = - \int_{\Omega} F N_i^{el} d\Omega \quad i=1, \dots, N_{nodes} \quad (6.9)$$

This last expression can be written as a matrix system for each finite element:

$$\mathbf{K}^{el} \mathbf{u}^{el} = -\mathbf{F}^{el} \quad (6.10)$$

Matrix $\mathbf{K}^{el}$ and vector $\mathbf{F}^{el}$ are defined as follows:

$$\begin{cases} K_{i,j}^{el} = \int_{\Omega} B_i^{elT} D B_j^{el} d\Omega \\ F_i^{el} = \int_{\Omega} F N_i^{el} d\Omega \end{cases} \quad (6.11)$$

Where every element i, j refers to pairs of nodes of the element el (i and j range from 1-4 for a tetrahedron, 1-3 for a triangle). $\mathbf{K}_{i,j}^{el}$ is a 3 by 3 matrix, and $\mathbf{F}_i^{el}$ is a 3 by 1 vector. The 12 by 12 (9 by 9 for a triangle) matrix $\mathbf{K}^{el}$, and the vector $\mathbf{F}^{el}$ are computed for each element. The coefficients i, j of the local matrix (corresponding to a pair of nodes i, j within the local element) are summed up at the locations $g(i)$, $g(j)$ in the global matrix (where $g(i)$ represents the number of the element's node in the entire mesh). The assembly of the local matrices then leads to a global system:

$$\mathbf{K}\mathbf{u} = -\mathbf{F} \quad (6.12)$$

The solution of Equation 6.12 will provide the deformation field corresponding to the global minimum of the total deformation energy.

Now, the constitutive equation treats model surfaces as elastic membranes and volumes as elastic bodies. Given externally applied forces $\mathbf{F}$ to a discretized body characterized by a rigid matrix $\mathbf{K}$, solving Equation 6.12 obtains the resulting displacements.

The resulting displacements can be used to characterize the deformation of the prostate, which is caused during the pathological processing. And using the shape function, the strain and stress tensor can be derived from the displacement field at every nodal point i , given every tetrahedron element of the FE model where the node belongs to, and using the following relationships:

$$\left\{ \begin{array}{l} \varepsilon_i = L_i N_i u_i \\ \sigma_i = \sum_{el|i \in el} D \varepsilon_i = \sum_{el|i \in el} D L_i N_i^{el} u_i \end{array} \right. \quad (6.13)$$

6.2.2 Mathematical Formulation of Volumetric Elastic Image Matching

The idea is to modify the constitutive equation of volumetric bodies (as presented in 6.2.1) to incorporate an image similarity constraint into the expression of the potential energy of an elastic body, which is subjected to external forces (Equation 6.1). The elastic potential energy then serves as a mechanics-based regularity constraint to the image similarity term.

In the equilibrium equations presented in 6.2.1, (e.g. Equation 6.12) the external forces $\mathbf{F}$ could be computed as a classical optical flow field between the models to be matched. It is a semi-implicit method where the optical flow field would be an initial estimate of the deformation field being regularized by the elastic model. The estimates can then be iteratively refined until equilibrium is reached.

To avoid the separate computation of the forces $\mathbf{F}$, the elastic deformation, and the matching criterion, a deformation field is computed to satisfy both the elasticity constraint and local model similarity constraint between two models to be matched ($I1$ and $I2$). Hence, the total deformation energy to be minimized (Equation 6.1) is expressed as:

$$E = \frac{1}{2} \int_{\Omega} \sigma^T \varepsilon d\Omega + \frac{1}{2} \int_{\Omega} (I_1(x+u) - I_2(x))^2 d\Omega \quad (6.14)$$

Assuming the small deformation field and smooth variation of I_1 , the first order Taylor expansion of $I_1(x+u)$ can be expressed as:

$$I_1(x+u) \cong I_1(x) + (\nabla I_1(x))u \quad (6.15)$$

Using the material's constitutive Equation 6.3 and Equation 6.14, Equation 6.15 becomes

$$E = \frac{1}{2} \int_{\Omega} \varepsilon^T D \varepsilon d\Omega + \frac{1}{2} \int_{\Omega} (I_1 - I_2)^2 - 2(I_1 - I_2) \nabla I_1 u + u^T \nabla I_1^T \nabla I_1 u d\Omega \quad (6.16)$$

As in 6.2.1, the domain is discretized by tetrahedral elements (amount of nodes $N_{nodes}=4$, only the nodes on the vertices are considered), with linear interpolation shape function N^{el}_i linking the continuous displacement to the displacement of the discretization nodes. Similar to that in 6.2.1, for every element el , the matrix $B^{el}_i = L_i N^{el}_i$ is defined. The function to be minimized on each element el can thus be expressed as:

$$E(u_1^{el}, \dots, u_4^{el}) = \frac{1}{2} \int_{\Omega} \sum_{i=1}^4 \sum_{j=1}^4 u_i^{elT} B_i^{elT} D B_j^{el} u_j^{el} d\Omega + \int_{\Omega} \sum_{i=1}^4 (I_1 - I_2)^2 - 2(I_1 - I_2) \nabla I_1 N_i^{el} u_i^{el} d\Omega + \int_{\Omega} \sum_{i=1}^4 \sum_{j=1}^4 u_i^{elT} N_i^{el} \nabla I_1^T \nabla I_1 N_j^{el} u_j^{el} d\Omega \quad (6.17)$$

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Once again, the minimum of this function leads to the following equations,

$$\frac{\partial E(u_1^{el}, \dots, u_4^{el})}{\partial u_i^{el}} = 0 \quad i=1 \text{ to } 4 \quad (6.18)$$

Equation 6.16 then becomes (i=1 to 4)

$$\int_{\Omega} \sum_{j=1}^4 (B_i^{elT} D B_j^{el} + N_i^{el} \nabla I_1^T \nabla I_1 N_j^{el}) u_j^{el} d\Omega = \int_{\Omega} (I_1 - I_2) \nabla I_1 N_i^{el} d\Omega \quad (6.19)$$

Equation 6.19 can be written as a matrix system for each finite element:

$$(K^{el} + G^{el}) u^{el} = F^{el} \quad (6.20)$$

Matrices K^{el} , G^{el} , F^{el} are defined as follows:

$$\begin{cases} K_{i,j}^{el} = \int_{\Omega} B_i^{elT} D B_j^{el} d\Omega \\ G_{i,j}^{el} = \int_{\Omega} N_i^{el} \nabla I_1^T \nabla I_1 N_j^{el} d\Omega \\ F_i^{el} = \int_{\Omega} (I_1 - I_2) \nabla I_1 N_i^{el} d\Omega \end{cases} \quad (6.21)$$

where every element i, j refers to pairs of nodes of the element el , (i and j range from 1 to 4). $K_{i,j}^{el}$ and $G_{i,j}^{el}$ are 3 by 3 matrix, and F_i^{el} is a 3 by 1 vector, the 12 by 12 matrices K^{el} and G^{el} , and F^{el} are computed for each element. Finally, the local matrices and vector of each element can be assembled in a global system:

$$(K + G) u = -F \quad (6.22)$$

where matrix $\mathbf{K}$ is the rigidity matrix. The solution of above equations will provide the deformation field corresponding to the global minimum of the total deformation energy.

6.3 Biomechanical Property of Human Prostate

It has been observed that mechanical properties of soft tissues are due to their structure rather than to the relative amount of their constituent [32]. The structure of soft tissue is clearly responsible for their distinct classification and function. Whatever the approach adopted, in most cases, the mechanical properties of soft tissues can hardly be completely assessed. The constants found in one test only apply to the state of deformation (strain rate, strain range involved). When simple relationships are written, it is generally true only for limited ranges of stresses and strains. Furthermore the mechanical behavior determined on the basic experiments cannot be readily correlated with real condition of the soft tissue where generally the reference state is not completely known. Based on these points, prostatic properties, which will be used in this project, are derived from other's work.

6.3.1 Modeling Linear Material Properties

Most biological tissue displays viscous (velocity dependent) and elastic response. However since only the static displacement is of interest in this project, the great majority of the forces developed can be attributed purely to the elastic response.

The prostate tissue can be considered [32]:

1. Isotropic;

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2. Statistically homogenous;
3. Incompressible;
4. To have linear elastic properties.

With these assumptions, it is possible to define the mechanical behavior of prostate tissue using single elastic modulus E_n , which is a function of strain ϵ_n for tissue type n (on is the stress):

$$E_n = \partial \sigma_n / \partial \epsilon_n = f(\epsilon_n) \quad (6.23)$$

6.3.2 Mechanical Properties of Prostate Tissue

Currently, few studies have been made on determining the mechanical properties of tissue in the prostate. Bharatha *et al.* [81] chose the prostatic biomechanical properties (Young modulus E and Poisson ratio ν) based on their prior experience with brain modeling. Their prostate model is segmented the central gland (CG) and peripheral zone (PZ) as separate structures. A set of values is obtained (CG: $E=30$ kpa and $\nu=0.2$; PZ: $E=3$ kpa and $\nu=0.4$) from which the most anatomically consistent results are produced.

Krouskop T. A. *et al.* [84] studied in their experiments that the prostatic normal tissue was characterized by small variations of the elasticity, and two main tissue types with different elastic moduli composed the prostate.

Jessica C. *et al.* took advantage of Krouskop 's work, they set $E = 60$ kpa and $\nu = 0.495$ in their prostate finite element model. Since Krouskop 's prostate tissue test was logical, precise, reasonable and well accepted by other researchers, the

mechanical properties, Young modulus (E) and Poisson ratio (ν) determined by Krouskop *et al.*'s work are used in this project. They are 60kpa and 0.495 respectively [32, 84]. The relationship between them is listed in Equations 6.24, 6.25:

$$E = \frac{\mu(3\lambda + 2\mu)}{\lambda + \mu} \quad (6.24)$$

$$\nu = \frac{\lambda}{2(\lambda + \mu)} \quad (6.25)$$

Where E is the Young's modulus, ν is the Poisson's ratio; μ and λ are Lames coefficient.

Young's modulus is the elastic modulus for tensile stress, and represents the ratio of stress (force per area) to strain (fractional increase in length) in the direction of the load for a given material. Poisson's ratio is the ratio of the strain perpendicular to the applied load (lateral strain) to the strain in the direction of the applied load (axial strain). Together, these parameters determine the elasticity of the material being modeled.

6.4 General Flowchart of Operation

Figure 6.2 Flow chart of operation

6.5 Methods

6.5.1 Construction of a Finite Element Model of Prostate

1. Pathological data acquisition and segmentation

The patient data are a set of parallel 2D pathological slices of the prostate. All data collection, classification, and segmentation are processed using the same methods as

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those mentioned in Section 3.4.2. The boundaries of prostate and features of interest are manually outlined by the pathologist, After 3D reconstruction (refer to Section 3.4.2), the 3D model is saved as a *.iges (Initial Graphics Exchange Specification) format and as an input to software ANSYS (Figure 6.3) (details of the FEM model built up refer to Appendix I).

Figure 6. 3 A 3D prostate model built by Bubble 3D as an input to ANSYS

2.3D mesh domain creation

FEM software ANSYS, taking the set of prostate contours and segmentation results as an input will generate mesh, Running on an SGI workstation, it creates the 3D computational mesh of the prostate in a few seconds (Figure 6.5), allowing scaling of the volume elements to any size. One type of 3D volume element is used in the model (Figure 6.4). The element is a higher order 3-D, 4-node element, it has a quadratic displacement behavior and is well suited to modeling irregular meshes, This kind of element has 4 nodes. Each node has three degrees of freedom: translations in the nodal x, y, and z directions. The element has plasticity, hyperelasticity, creep, stress stiffening, large deflection, and large strain

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capabilities. It also has mixed formulation capability for simulating deformations of nearly incompressible elastoplastic materials, and fully incompressible hyperelastic materials [72], The elements are assigned linear material properties (refer to 6.3).

Figure 6.4 Element geometry, which is used to build the deformable model

Figure 6.5 Prostate FE model generated in software ANSYS

3. Material properties assignment

Once the 3D mesh is created, each element is assigned material properties according to Section 6.3. Since the biomechanical properties of prostatic cancer and normal prostatic tissue may not have many differences and few research

works have been done on it, both normal and cancer tissue properties are treated as homogeneous in this project.

6.5.2 Model Registration Strategy -- Iterative Closest Point (ICP) Algorithm

Same as the linear rescaling method (Chapters 3, 4 and 5), the prostate surface obtained from FastSCAN is considered as a gold standard. Before comparing the FE model, FastSCAN surface needs to be adjusted to fit that of the FE model. There are 3 critical key points, urethra entry entrance, urethra exit, and model centroid, which can be used to control the rotation and translation of the FastSCAN surface (Figure 6.6). Though three key points can be applied in the rigid registration, there is still not enough information to perform the correlations between the surfaces. The ICP algorithm [70, 73] is a possible solution to solve a key registration problem. For example, given a “model” 3-D shape (or reference surface) and a “data” 3-D shape (or floating surface), one can estimate the optimal translation and rotation that register the two shapes by minimizing the mean square distance between them. This algorithm is useful for multimodel 3-D image registration in medical imaging, for estimating the motion between point sets when the correspondences are not known.

In the ICP algorithm, a data shape P is registered to be in best alignment with a model shape X . Both shapes must be first decomposed into point sets (in this project, all surface information is point clouds). Let N_p , N_x be the number of points

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in the shapes, Then P and X are, respectively, the N_p -tuple $P = (\vec{p}_1, \vec{p}_2, \dots, \vec{p}_{N_p})$ and the N_x -tuple $X = (\vec{x}_1, \vec{x}_2, \dots, \vec{x}_{N_x})$, where $\vec{p}_i, \vec{x}_i$ are 3-D vectors (voxel coordinates $\vec{x}_i = [x_i \ y_i \ z_i]^T$) and $N_x \geq N_p$.

Figure 6.6 Key points (urethra entrance, centroid, urethra exit) used in rigid registration

1. Establishing correspondence

The ICP algorithm registers sets P and X by evaluating for each point $\vec{p}_i$ in P its corresponding point in X , with the minimum distance. This operation is called *evaluation of the distance between a point and a data set* and is denoted by $d(\vec{p}, X)$:

$$d(\vec{p}_i, X) = \min_{j \in \{1, \dots, N_x\}} d(\vec{p}_i, \vec{x}_j) \tag{6.26}$$

where $d(\vec{p}_i, \vec{x}_i)$ is the Euclidean distance of the two points. This process is repeated for all points in P so that, for each point $\vec{p}_i$, the closest point $\vec{x}_i$ in X , $\vec{y}_i$, is found.

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This results in the construction of the set Y of closest points, a process denoted by the closest point operator C :

$$Y = C (P , X) \tag{6.27}$$

Equation (6.27) means Y is an N_p -tuple $(\bar{y}_1, \bar{y}_2, \dots, \bar{y}_{N_p})$ of points of X , such that $\bar{y}_i$ is the point of X closest to $\bar{p}_i$.

2 Implementation

ICP algorithm is applied to find the correspondent points between FE model and FastSCAN surface. This program is written in MATLAB. Figure 6.7 shows the process.

Figure 6.7 ICP algorithm application (a) FE model (red color) is searching for the closest points in FastSCAN surface (green color) (b) Centroid trace in the x, y, and z coordinates (c) Error trace following the iteration of ICP algorithm

6.5.3 Applying the Node Displacement to FastSCAN Surface

The FEM solution requires boundary conditions specified in terms of either applied forces or vector displacements of points on the surface of the object undergoing deformation. Images provide information about the effects of forces but no direct information about the forces themselves [75]. Although the surfaces of the undeformed and deformed object can be identified with the aid of a solid model, the vector displacements can be observed from surfaces in two images.

Boundary conditions are established in the following manner for the prostate. The surface of the prostate pathological model is transferred onto the prostate FastSCAN surface. The FE model for the deformed prostate has the same topology with FastSCAN surface. ICP algorithm (refer to 6.5.2) sets up the correspondence of points between FastSCAN surface and FE model. This correspondence means that the FastSCAN coordinate system (world coordinate) defines a one-to-one geometry-based (F.E. coordinate) between points in the undeformed and deformed prostates. The algorithm examines each node of the tetrahedral mesh that lies on the prostate surface and computes a vector displacement in world coordinates (Figure 6.8). For a linearly elastic system, as assumed for this study, the work is equal to the change in the elastic potential energy given by Equation (6.14).

Figure 6.8 Simulates the displacement vectors

In displacement-based FEM, an equilibrium equation is derived from the goal of minimizing the system potential energy, with respect to the material displacement over the object. Unlike the scalar function in Figure 6.8, material displacement is a 3D vector function over the object. However, the same discretizing method is applied.

Following the displacement of the control points on the prostate boundary, the control points on the cancer boundary will displace too accordingly (Figure 6.9). Both regions within the prostate boundary and cancer boundary will be treated as homogeneous space. The displacement information on cancer boundary will be collected and analyzed to validate MRSI accuracy.

Figure 6.9 The deformable system components

6.6 3D Phantom Study

A phantom is designed to simulate the human prostate tissue, which can withstand large deformation in a controlled manner. The phantom is built using gelatin (refer to Appendix G). A rubber cuboid (12mm*12mm*30mm) is embedded inside the phantom; a plastic tube is used to simulate the urethra.

After MRI scans the phantom, it is swept by the FastSCAN to obtain the surface information. Thereafter, the phantom is trimmed by the prostate slicer box and digitized into the computer. The 3D phantom model is reconstructed and the finite element method is applied to simulate the deformation. Since the rubber embedded

inside the phantom is known, the accuracy of FEM method can be determined. This part of work is still going on.

6.7 Conclusion

A new, mechanics–based deformable model for evaluating the accuracy of MRS images is used in this part of work. The model results from the minimization of a deformable field simultaneously satisfying the constraints of an elastic body and a local image similarity measure. The model provides a physically realistic deformation field and also allows the inspection of the characteristics of inside deformed objects. ICP algorithm is used to find the correspondent points between FE model and FastSCAN surface (reference model). Gelatin phantom is used to study the accuracy of the algorithm of the proposed finite element method. Because of time limitation, the phantom trial results and real case applications are still going on in the next coming year.

There are several advantages using FEM to study the deformation:

1. The first advantage comes from the use of a FE formulation: one can assign different regularization parameters to different parts of the initial image causing some parts of the image to deform rigidly and some others. This is straightforward to do and is within a finite element framework.
2. Posterior use of the initial and deformed FE models of the image can provide us with physical properties of objects deformed from one image model to the next. This assumes that the obtained deformation results from an actual physical deformation.

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3. Finally, a multiresolution can be approached by selectively refining an initial coarse mesh in the regions where more precision is needed without having to build a multiresolution pyramid of the entire input image.

The disadvantages using the FEM to study the deformation:

1. The deformations computed do not satisfy the actual constitutive equations of elasticity as that expressed by the Equation 6.1. Even though one may consider characterizing the stress tensors of a physical deformation that would have yielded the same deformation, such an expression may not be considered as a long-term solution towards physics-based simulation for instance.
2. The expression used as image similarity criterion does not allow for multi-modality image matching.

Chapter 7

Conclusion and Future Work

7.1 Conclusion

With the number of men seeking medical care for prostate disease rising steadily, the need for a fast and accurate prostatic disease detection tool increases accordingly. Magnetic Resonance Spectroscopic Imaging is such a new technology, which is nearly the most accurate medical imaging modality for prostate cancer in non-invasive methods. In this project, the accuracy of MRSI was studied with the combination of several validation methods such as surface scan method, pathological validation, and finite element method.

Two ways are implemented to compensate the errors from formalin fixation and pathological manipulations. One is to linearly rescale the pathological model with the use of FastSCAN volume as reference; the other one is finite element method to simulate the soft tissue deformation with FastSCAN surface as reference. Linear rescaling method is straightforward and comparatively simple, but this method does not consider the local deformations. The finite element method is a way of considering the local deformations with physical tissue properties; however, it needs complex computation.

In this project, the author only finished the work on linear rescaling method to validate MRSI accuracy using 7 cases. The sensitivity, specificity and accuracy of MRSI were found to be 76.4%, 60%, and 92.3% respectively.

Author also outlined the scheme to simulate soft tissue deformation with the use of finite element method, this part of work is still going on.

7.2 Future Work

Future work will focus on using finite element method to simulate elastic deformation of the prostate and study the accuracy of cancer distribution predicted by MRSI. We may consider more knowledge into the registration algorithm to improve the robustness of the correspondent point finding between FE model and FastSCAN surface. Phantom study and a number of clinical cases will be applied to verify the accuracy and feasibility of this method.

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Author's Publications

1. Published

- **Ma Hong Yun**, Phee Soo Jay Louis, Thng Choon Hua, Tan Pauy Hoon, Yuen John, Ng Wan Sing. A novel device for sectioning prostate in correlation to MRI. *The IASTED International Conference on BIOMECHANIC*, August 23-25, 2004, Hawaii, USA.

2. In progress

- **Ma Hongyun**, Ng Wan Sing, Phee Soo Jay Louis, Thng Choon Hua, Tan Pauy Hoon, Herry Ho, Christopher Cheng. Pathological validate MRSI accuracy: apply to human prostate cancer. *Submitted to EURASIP Journal on performance evaluation in imageprocessing.*
- **Ma Hongyun**, Ng Wan Sing, Thng Choon Hua, Tan Pauy Hoon, Herry Ho, Christopher Cheng. Finite element method to validate MRSI accuracy. *Submitted to Computer Assisted Radiology and Surgery, 19th International Congress and Exhibition. June 22-25, 2005, ICC Berlin, Germany.*
- **Ma Hongyun**, Ng Wan Sing, Phee Soo Jay Louis, Thng Choon Hua, Tan Pauy Hoon, Herry Ho, Christopher Cheng. Second version prostate slicer **box** for sectioning human prostate in correlation to MRI.

3. Potential Patent

- Second version prostate slicer **box**

Appendices

Appendix A Routine Pathological Process of Specimen

1. Accessioning

As soon as a specimen arrives in pathological department, the specimen is assigned a pathological number so the pathologists can keep track of it. The number is different with patient's medical record number or hospital identification number. The number begins with the letters PB, followed by the last two number of the year. All of the specimens arrived in a given year are numbered consecutively starting from 1, for example, PB 04- 19163.

2. Fixation

This is a crucial part of the process. In order to make microscopic slides, the tissue must be adequately treated in formalin, a fixative that hardens the tissue and prevents the proteins within the cells from degrading. Fixation allows saving the specimen forever in hospital. The time needed for the adequate fixation depends on the size and fat content of the tissue, but usually it can often be completed in 6 hours.

3. Gross examination

Gross Examination is done after fixation. A physician will examine the specimen, measure its size, describe its colors and texture, and determine if masses are present. The physician should perform the 2-hole reference at this time (Section 3.3). Thereafter, the specimen is trimmed with the use of prostate slicer box (Chapter 4).

4. Processing

The gross tissue slabs are gradually and progressively dehydrated in alcohols overnight on a Tissue Processing Machine. These machines take about **8** hours to properly dehydrate the tissue.

5. Embedding

The processed tissue is then embedded in hot wax to form a tissue block. When the block hardens, it is definitely stable at room temperature.

6. Making H and E slides

A thin (5 micron) section of the tissue is cut from the tissue slab using a microtome (a cutting instrument), and stained with Hematoxylin and Eosin (H and E). The slides are now ready to be examined under the microscope.

7. Reviewing by pathologist

The physician who does the gross examination will review the slides, outline cancers, and make a pathological report.

Appendix B Bubble 3D

Bubble 3D [88] is developed on Java platform for the purpose of reconstructing 2D images into 3D spatial domains. The applications include creating 3D anatomic geometries from MR images, 2D ultrasound images and sectioned prostatic specimens. In addition, Bubble 3D is capable of performing surface-image registration and virtual surgery simulations. The software's ability in carrying out surface registration is a valuable asset to inter-modality studies pertaining to the validation of MRSI to "ground truth" in the detection of prostate carcinoma. Bubble 3D version 2.0 is used extensively in the reconstruction of 3D prostatic volumes for analytic and statistical evaluation. Bubble 3D continues to remain as a powerful tool in 3D reconstruction from 2D image stacks with cross platform capabilities serving medical image analysis and a potential important contributor for surgical and treatment planning. Seven popular 2D image formats (TIFF, FlashPix, JPEG, GIF, BMP, PNG, PNM) and ultrasound 3D image format (Kretz Voluson 530D) are currently supported in Bubble3D.

B.1 Smart Curve Outlining

Bubble 3D offers a sophisticated curve-outlining tool based on non-uniform rational B-spline (NURBS), supporting both interactive open and closed curves outlining. A few mouse clicks can define a smooth NURBS curve to describe boundaries of objects in medical images. An open curve is initialized by 2 points and may be deformed or extended by the new added points. A closed curve is

initialized by 3 points and may be deformed to the desired shape by adding more points. Every user-defined point can be removed or deleted later on. Figures A1, A2 illustrate how the curves are defined.

Figure A1 Open curve outlining

Figure A2 Closed curve outlining

B. 2 Surface Construction

Given a series of parallel 2D curves, a high-quality parametrical surface can be easily constructed by skinning over them with the NURBS interpolation. Figure A3 demonstrates an open surface (baby face) construction and Figure A4 shows how the prostate surface is constructed. The user can fi-eely manipulate the surfaces by adjusting the curves afterwards.

Figure A3 Baby surface: an open surface construction

Figure A4 Prostate surface: a closed surface construction

B. 3 Surface-Image Registration

By using a Genetic Algorithm (GA), a previously constructed NURBS surface can be robustly registered to match the surface within corresponding 3D ultrasound volume data in dozens of seconds, assuming that these two surfaces have similar shape and size. This feature is useful for tracking a surface with known shape during volumetric imaging and for merging sets of 3D volume data of the same organ (taken using different imaging modalities) using the organ surface as a common marker. The registration progress is illustrated in Figure A5.

Figure A5 Register a prostate surface with a 3D ultrasound image

B.4 Needling Simulation

As animation is supported in Bubble 3D, virtual surgery simulation can be achieved by extending the software. Figure A6 illustrates an example of needling simulation on a prostate model using Bubble 3D.

Figure A6 Needling simulation on a prostate model

B.5 Portable Project Data

Except the input images, all of the project data are stored in an Extensible Markup Language (XML) file. XML format is a text-based markup language that is fast becoming the standard for data interchange between different applications and OS platforms. Standard XML parsers written in different languages are available for free. It makes the results of Bubble3D, especially the geometries, much easier to be parsed by other applications. Besides, the constructed surface can be represented as a triangular mesh and output as a STL (StereoLithography) format file for follow-up use.

Appendix C MRI Scanner Specifications

Magnetic resonance imaging (MRI) scan requires the use of a very strong magnetic field. Unlike other devices employed in radiology, MR imaging uses no radiation. The magnet is contained in the housing of the scanner and this creates a magnetic field oriented down the center of the magnet. The patient is placed within the magnetic field by lying on a table, which is placed through the center of the opening of the magnet (Figure A7). The strength of the magnetic field is measured in units called gauss or tesla where 10,000 gauss equals 1 tesla. The earth's magnetic field is approximately 0.6 gauss. The strongest magnetic field permitted in MRI scanning of humans is 1.5 Tesla (1.5T).

The Diagnostic Imaging Department in the National Cancer Center (NCC) at the Singapore General Hospital (SGH) uses the General Electric (GE) Signa 1.5T LX MRI scanner (Figure A7). The software for spectroscopy is PROSE. The software for reconstruction is FUNCTOOL CSI Version 2.1q.

Figure A7 A typical MRI scanner

C.1 Basic Principles of MRI

Three types of magnets (superconducting magnet, resistive magnet, and permanent magnet) are available for uses in MRI. The strongest is a superconducting magnet. This type of electromagnet involves a current flowing in a circular direction in a coil of wire, which creates a magnetic field oriented down the core of the coil. In superconducting magnets, the wire conducts the current without significant resistance because it is cooled to a temperature close to absolute zero by being bathed in a jacket of liquid helium and/or liquid nitrogen. Most MR scanners in use today are superconducting magnets (Figure A8).

Resistive magnets are electromagnets, similar to superconducting magnets, but they are air-cooled therefore have greater resistance to current and create weaker magnetic fields. Permanent magnets are made of solid magnetic material, similar to bar magnets, and create the weakest magnetic fields. However, they can be arranged in a configuration that does not require the patient to be surrounded by the magnet and are used in Open MR scanners.

Figure A8 Actual superconductingMRI magnet with the outer container containing the superconducting wire surrounded by liquid helium

When a patient is placed within an MR scanner, the protons in the patients' tissues, which are primarily protons, contained in water molecules, align themselves along the direction of the magnetic field. A radio frequency electromagnetic pulse is then applied, which deflects the protons off their axis along the magnetic field. As the protons realign themselves with the magnetic field, a signal is produced. This signal is detected by an antenna, and with the help of computer analysis, is converted into an image.

The process by which the protons realign themselves with the magnetic field is referred to as relaxation. The protons undergo 2 types of relaxation. They are T1 or known as longitudinal relaxation and T2 or known as transverse relaxation. Different tissues undergo different rates of relaxation, and these differences create the contrast between different structures, and the contrast between normal and abnormal tissue, seen on MR scans. T1 weighted images emphasize the difference in T1 relaxation times between different tissues. In these images, water-containing structures are dark.

Figure A9 Difference between T1 weighted and T2 weighted MR images of the brain

Since most pathologic processes such as tumors involve edema or water, T1 weighted images do not show good contrast between normal and abnormal tissues as shown in Figure A9. However, they do demonstrate excellent anatomic detail. T2 weighted images emphasize the difference in T2 relaxation times between different tissues. Since water is bright on these images, T2 weighted images provide excellent contrast between normal and abnormal tissues, although the anatomic detail is less than that of T1 weighted images (Figure A9). Proton density images emphasize neither T1 nor T2 relaxation times, and therefore produce contrast based primarily on the amount of protons present in the tissue.

C.2 RF Receiver Coils

The RF receiver coils deserve special mention, as they are relevant to the context of this thesis. These RF receiver coils concerned are the surface coils and the phased array coil configuration.

Surface coils provide advantages in areas where the anatomy of interest is near the surface such as the spine and shoulder. Most surface coils are flat and receive signals more sensitively from the regions close to them; therefore surface coil images appear brighter near the coil plane. This is used to advantage by excluding unwanted tissues while maximizing the signal from target structures. Within its useful region a flat surface coil will exhibit sensitivity 1 to 5 times higher than a cylindrical coil that might cover the region [79]. This increased sensitivity can be used to increase image quality or traded for increased resolution.

Phased array system uses multiple receivers. Each receiver is connected to one of a number of a small volume receiver coils constructed in an array to surround a specific body part. The MR signals from each receiver are combined in a way that adds the MR signal from the patient but allows the random unrelated noise components to be cancelled. The result is the coverage of a large area with the performance of the small coils, and significant noise reduction.

The endorectal coil is an application of the phased array system. The endorectal coil is inserted into the rectum and allows high resolution of the prostate or cervix with extra detail in the surrounding field of view. An example of the endorectal rectal coil used at the diagnostic imaging department of NCC, SGH is shown in Figure A10.

Figure A10 Typical endorectal prostate coil

C.3 The Accuracy of MRI

The accuracy of MRI greatly depends on the type of MRI scanner, the organs to be scanned, and the operator. It should be noted that MR imaging is still subjected to variable results through inter-observer variability. For the human prostate, Claudia *et al*, [80] found MRI to be highly reliable in identifying palpable tumors, with a

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sensitivity of 96%. For nonpalpable tumors, the sensitivity was 58%. However, when nonpalpable tumors were divided between posterior and central gland locations, the sensitivity was seen to be 85% in the peripheral zone but only 15% in the central gland.

Appendix D MRSI information

MR spectroscopic imaging provides metabolic information specific to the prostate through the detection of the cellular metabolites citrate, creatine, and choline. This facilitates lesion characterization, such as the difference of benign and malignant tissue, and also helps in assessing disease progression and treatment response. Using MRSI, the signal from the molecular level is detected, allowing non-invasive assessment of the various metabolites. MRSI is a multi-volume technique that provides spectra from a 2D or 3D grid of adjacent volumes, allowing metabolic information to be obtained from a given voxel or anatomic area. For evaluation of prostate cancer, MRSI requires good spatial resolution (1cm^3 or less), high S/N, efficient water and fat suppression techniques, and short TE for optimum detection of short T2 metabolites.

After obtaining the transverse T2 weighted MR images, a spectroscopic imaging volume is selected to maximally cover the prostate and minimally include the periprostatic fat, surrounding tissues, and rectal air. This will be accomplished by selecting a rectangular volume encompassing the prostate at the prostatic apex and base. A commercial spectroscopy package GE (General Electric 1.5T LX, PROSE) will subsequently determine the position and dimensions of the volume. Because the spectroscopic imaging volume is constrained in size and position, the peripheral zone at the base is sometimes partially excluded. Voxels are considered suitable if they cover 75% peripheral zone. Spectroscopic imaging data are overlaid on the corresponding transverse T2 weighted MR images.

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At MRSI, cancer is characterized by elevated levels of choline or reduced levels of citrate or both (Figure A11). According to the level of citrate, creatine and choline, the voxels are divided into negative, equivocal, or positive separately. For normal prostatic tissue, the ratio of choline and creatine to citrate is 0.22. Voxels in which there is good signal to noise, no partial volume effects, and a ratio of choline and creatine to citrate of more than 0.61 are considered positive. Voxels with a ratio of choline and creatine to citrate of more than 0.48 are considered equivocal.

Figure A11(a) MR spectrum obtained from the abnormal area, demonstrates elevated choline and reduced citrate, a pattern consistent with definite cancer (b) Demonstrates a normal spectrum pattern with citrate dominant and no abnormal elevation in choline.

Appendix E FastSCAN Specifications

Table A1: FastSCAN Specifications [78]

FastSCAN	
Processing Unit	<ul style="list-style-type: none">•Custom electronics video processor•Polhemus FASTRAK® magnetic tracker
Wand	<ul style="list-style-type: none">•450 mm (18 in) in length•2 miniature monochrome cameras•1 laser diode: 670 nm, 1 mW, Class II•Tracker Receiver
Reference System	<ul style="list-style-type: none">•Tracker Transmitter•Tracker Receiver for attachment to movable objects
Resolution	<ul style="list-style-type: none">•Laser line length increases with Wand-Object range, typically 150 mm at 200 mm range (6 in at 8 in)•Resolution along the laser line depends on Wand-Object range, typically 0.5 mm at 200 mm range (0.02 in at 8 in)•Scanning speed is 50 lines/sec, line-to-line resolution depends on scanning speed, typically 1 mm at 50 mm/sec (0.04 in at 2 in/sec).
Range	<ul style="list-style-type: none">•Up to 760 mm (30 in) Wand-Transmitter and Receiver-Transmitter range•75 mm to 680 mm (3 in to 27 in) Wand-Object range
Accuracy	<ul style="list-style-type: none">•With Transmitter as Reference, accuracy depends on Wand - Object range, typically 1 mm at 200 mm range (0.04 in at 8 in)•With Receiver as Reference, accuracy also depends on Receiver-Object range
Environment	<ul style="list-style-type: none">•Operation in the presence of metal objects or electromagnetic fields may interfere with the scanner's tracking and degrade performance. Providing the Transmitter, Wand and Receiver are kept sufficiently far from metal objects or fields they should not pose a problem.•Because scanning relies on the cameras seeing the laser line, some surfaces may not be suitable for laser scanning, e.g. translucent, reflective, and dark or deeply convoluted surfaces.

Appendix F Patient Data Collection Procedures

F.1 Transrectal Ultrasound

The ultrasound data collection system consists of three main parts: Ultrasound machine, oscillator and a computer. The images are collected from Urology Centre, Singapore General Hospital, the procedure is illustrated in Figure A12.

Ultrasound machine - Aloka SSD-1700 for ultrasound imaging.

Oscillator-To hold the Transrectal Ultrasound (TRUS) probe and translate the probe at a constant velocity out of the patient’s rectum for image acquisition.

Computer - To acquire ultrasound images and store them as * JPG format.

Figure A12 The flowchart of US image collection

F.2 MRI / MRSI

MR Images and MR Spectroscopy images are collected from the database located at the Department of Diagnostic Imaging, National Cancer Center, Singapore

General Hospital. The following protocol will outline the derivation of desired images in a systematic manner as well as in a portable 2D format. The images are handled using software e-film version 1.5.1 and can be saved in either JPEG or TIFF format.

Figure A13 shows an e-film interface commonly encountered. Patients’ names and identification numbers have been deliberately left out to ensure that patient’s confidentiality is preserved.

Figure A13 Typical e-film graphic user interface

The procedures are outlined below.

1. Select the patient’s name or ID of interest.
2. Move the mouse over the image and right click. A list of options appears as shown in Figure A13.
3. Select option 4: ‘T1 FSE Prostate’ (Figure A14)

Figure A14 Selecting the appropriate image set

- 4. Next click ‘Edit’ in the menu bar and select all images in series (Figure A15).

Figure A15 Selecting all images in the image set

- 5. The orange indicator at the lower right corner of the image will be shown when all images in the set are chosen (Figure A15).
- 6. Click ‘File’ and select ‘Export’ (Figure A16).

Figure A16 Exporting the selected image set

7. A dialogue box will appear as in Figure A17. Select ‘Yes’ to confirm.

Figure A17 Saving images into portable format

8. Type in a file name and save the images.

The method encountered in the derivation of MR images taken with the endorectal coil and MRS images is similar to the procedure outlined earlier.

F.3 Pathological Data

1 Scanning methodology

The digitalization of step-sectioned microtome slices will be covered in this section. A step-by-step analysis of the procedure will be discussed in detail. Post image processing will be outlined as well. The protocol will seek to establish a consistent methodology and in addressing all known concerns that will cause inaccuracies. A primary area of concern is the maintenance of the 1:1 aspect ratio. The aspect ratio is defined as the width to height ratio of the image or pixel.

2 Equipment requirements

The following apparatus are essential for accuracy and superior image quality. They are a commercial scanner, grid transparency, reflector and masking tape. The grid transparency consists of 5mm x 5mm squares as shown in Figure A18.

Figure A18 Transparency grid consisting of 5mm x 5mm squares

3 Setup

The transparency grid is placed in the scanner and secured by masking tape. This is to prevent accidental displacement of the grid. An arbitrary point is selected and its

location marked and noted. This point shall be the point of reference where the scanning of subsequent slides will be based on.

Figure A19 (a) The standard setup (b) The reflector and the transparent grid (c) Scanning in progress with secured grids

4 Scanning procedures

Pathological microtome slides are digitized using a Hewlett Packard Precision Scan Pro commercial scanner. Resolution of the resulting images is standardized at 600 dots per inch (dpi) at a magnification of 1 (100%). The settings shall not be changed to ensure a constant 1:1 aspect ratio. The sharpen level is fixed at a constant high level. The reason why images are taken at such high resolutions is to ensure that all anatomical features are captured and sufficiently clear for validity studies to be carried out. This is despite the fact that in 3-dimensional reconstruction the boundaries of prostate and cancers are the primary characteristic of interest.

Screen captions have been included to serve as a comprehensive guide to facilitate understanding. The following steps in carrying out the scanning is outlined below:

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1. Create a new folder on the desktop and use the pathological number as file name (Appendix A);
2. To start on clicking the ‘HP precision scan’ shortcut on desktop;
3. Set the resolution to 600 dpi per inch (Do not change these settings throughout the scanning process, this is to ensure that the 1:1 aspect ratio is maintained).
4. Click icon scan and allow time for the scan. Due to the high resolution the scan may take quite some time.
5. After the image has been scanned, click on the menu bar ‘Output type’ and select ‘True Color’.
6. Select the image to be scanned. For convenience, the number of squares to the left selected border is recorded down, similarly to the right, top and bottom. This will make post image processing much simpler and does away with the tedious method of subsequently sizing the images in an image editing software (Figure A20).

Figure A20 Pictorial representation in recording the number of squares from the reference point

7. Next, click 'File' and select 'Save as' to save the selected image into the folder created in step 1.
8. The file name should be in accordance to the slide number usually number A01 to A13.
9. Repeat steps 4 to 8 for each slide in the image set.

5 Post image processing

The scanned images are sized into equal dimensions to facilitate reconstruction using Bubble 3D. The images are processed using Adobe Photoshop version 7.0.

The procedure is outlined as follows:

1. In Adobe Photoshop environment, open the required image stacks to be sized. For example click 'File' and select 'Open'. Move the cursor to the top right hand corner of the image and ensure that the X and Y coordinate is 0.
2. Drag the cursor to enable the whole prostate image is contained within. Record the width and height of the selected box in pixels. This dimension would be applied to other images in the set.
3. Click 'Edit' select 'Cut', click 'File' select 'New' and paste as a new image. Save the new image.
4. Click 'File' select 'new' and enter the dimensions of the image when prompted. Save the blank image. Save the blank image under another corresponding file name.
5. Repeat steps 1 to 4 with another image of the set.

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6. Select the slide that measurements have been made prior to scanning. Drag the cursor such that the width of the box is a reflection of the distance between the two holes. Record the width in pixel.

Appendix G Phantom Making Recipe and Procedures

The phantoms (Chapters 4 and 6) are built up using BAKE KING gelatin produced by Gin Hin Lee Pte. Ltd. The materials used to build up phantom include: plastic clay, Vaseline, superclay, gelatin and hot water. The gel system is composed of two parts: gelatin powder and water. The ratio of the gelatin powder to water determines phantom's elastic properties (a increase in the ratio of gelatin to water produces stiffer gels).

The procedures of making the phantom are listed as follows:

1. Prepare a prostate master mold (Figure A20). Use plastic clay to build up a prostate master mold; the shape and size of the master mold simulate real prostate specimen.
2. Lay some Vaseline on the internal wall of the master mold so that the gelatin phantom is easily taken out from the master mold.
3. Seal the master mold with superclay (Figure 21).
4. Put the rubber and plastic tube into the master mold to simulate the prostate nodule and urethra.
5. Pour the liquid gelatin into the master mold
Liquid gelatin (60g gelatin + 300ml hot water) is beat briskly with a fork, poured into the prostate master mold. The hardness of this proportion is near to human prostate tissue; this has been tested in an undergraduate finial year project.
6. Wait 3 hours until the phantom firms.

7. Take out the prostate gelatin phantom (Figure A22).

Figure A21 Prostate phantom master mold

Figure A22 The gelatin prostate phantom

Appendix H Detail Dimensions of Prostate Slicer Box

The detail dimensions of the prostate slicer box are shows as Figure A23. The unit of the dimensions is millimeter.

Figure A23 Detail dimensions of prostate slicer box

Appendix I FEM Model Build Up

The FEM model is built up in software ANSYS. ANSYS is a commercial software tool. More information is available on <http://www1.ansys.com/ansys/>. To import 3-dimensional model from Bubble3D to ANSYS, unfortunately it requires several steps and involves several software tools (Figure A24). The whole conversion is explained step by step as follows:

Figure A24 Workflow of the transformation from Bubble 3D file into ANSYS

1. **Bubble3D** save the reconstructed 3D model (from MRSI, pathological slices) as *.stl (StereoLithography) format.
2. Convert *.stl format to *.obj (Object Files) format with the use of software **Explore 3D**. This is commercial software, the trial version is available at: <http://www.righthemisphere.com/3dexploration/>.
3. Use **WordPad** to compile the *.obj format, and save it as *.txt format.

4. Open the **MATLAB**, create an *.ibl (Internet-based learning) format file by using a self-written program.

The format of *.ibl file:

```
Open Arclength
Begin section ! 1
  Begin curve ! 1
    1  -2.53  0.59  0
    2  -2.35  0.59  0.35
    .
    .
    10  2.53  0.59  0
  End curve ! 1
Begin section ! 2
  Begin curve ! 2
    1  -2.62  1.18  0
    2  -2.59  1.18  0.12
    .
    .
    12  2.62  1.18  0
  End curve ! 2
Begin section ! 10
  Begin curve ! 10
    1  .....
    2  .....
```

5. Save MATLAB created *.ibl format file.
6. Open software **ProE** - it is commercial software and more information is available at: <http://www.ptc.com/products/proe/wildfire/>. Create continue lines and save it as *.iges (Initial Graphics Exchange Specification) format.
7. Input the *.iges format into **ANSYS**.
8. The detail procedures of create finite element model using ANSYS have been elaborated in Aurelien Lesluye's internship report [83].