Chapter 5

Prostate cancer detection using three-dimensional sonoelastography

5.1 Introduction

Prostate cancer is the most prevalent type of cancer in men, and it is second only to lung cancer in cause of death among adult males. In the United States, the number of new cases diagnosed with prostate cancer in 2008 was calculated as 186,320, whereas the number of estimated deaths was 28,660 [107]. Early and accurate detection is a priority in order not only to reduce the mortality rate but also to prevent side effects from local symptoms such as bleeding, urinary tract obstruction and development of metastases.
Current prostate cancer diagnosis relies on a combination of digital rectal examination (DRE), screening based on prostate specific antigen levels (PSA), and biopsy guided by transrectal ultrasound (TRUS) imaging. These methods have shown shortcomings in accuracy and specificity and, therefore, new diagnostic tools are needed. DRE is limited anatomically to the posterior of the gland and may miss cancers in other regions [108]. Also, PSA levels can be increased not only by cancer but other conditions such as hyperplasia and prostatic inflammation [109]. To further complicate prostate cancer detection, TRUS imaging fails to discriminate isoechoic cancers making random biopsies necessary [110]. However, a high number of biopsies per patient yields a low number of cancers detected with this procedure [9].

DRE is based on the premise that pathological processes produce changes in tissue mechanical properties. Under this rationale, imaging the elastic properties of biological tissues has become an area of active research [2,29,3] with some efforts focused on prostate cancer detection [9,111,112,113]. In particular, sonoelastography is a tissue elasticity imaging technique that estimates the amplitude response of tissues under harmonic mechanical excitation using ultrasonic Doppler techniques [6]. Due to a proportional relationship between the vibration amplitude of scatterers and the received Doppler spectral variance [7], the amplitude of low frequency shear waves propagating in tissue can be visualized in real-time using sonoelastography to detect regions of abnormal stiffness [8].
In this chapter, *ex vivo* and *in vivo* results from an on-going study at the University of Rochester are presented. Semi-automatic algorithms to process B-mode US and sonoelastographic images are introduced to determine the size and position of tumors in three dimensions. Results are compared to histological volumes to evaluate the overall performance of sonoelastography.

### 5.2 Methods

The *ex vivo* and *in vivo* studies involving human prostate glands presented in this chapter were approved by the Institutional Review Board of the University of Rochester Medical Center and compliant with the Health Insurance Portability and Accountability Act. In all cases, it was verified that the patient was not treated with radiation or hormonal therapies which alter the gland stiffness and the amount of residual tumor.

#### 5.2.1 Ex vivo experiments

Figure 5.1 illustrates a flow diagram of the methods and procedures used in the *ex vivo* experiments. Thirty human prostate glands were received after radical prostatectomy and embedded in a 10.5% gelatin (300 Bloom Pork Gelatin, Gelatin Innovations Inc., Schiller Park, IL, USA) bowl-shaped mold. Vibration was provided by two parallel rigid metal strips positioned underneath the mold (see Figure 5.2). The strips had a rectangular cross section (90 *mm* in length, 6 *mm* in width and 7 *mm* in height) and
were connected to an external piston (Vibration Test Systems, Aurora, OH, USA). Input signals to the piston were provided by a harmonic waveform generator (Model 3511A Pragmatic Instruments, San Diego, CA, USA) after amplification (Model 2706, Brüel & Kjaer, Naerum, Denmark). The metals strips were vibrated at a combination of low frequencies (105, 140, 175 and 210 Hz) to minimize imaging artifacts resulting from reflections from the boundaries of the mold [10]. Co-registered sonoelastographic and B-mode ultrasound (US) volumes were acquired using a modified Logiq 9 US scanner (General Electric Medical Systems, Milwaukee, WI, USA). Images were obtained at 1-mm spacing in the longitudinal direction (i.e. prostate apex to base) by mounting a M12L linear array probe on a motorized track (Velmex, Bloomfield, NY, USA). The image plane was normal to the long axis of the metal strips.
Radical prostatectomy

US Imaging B-mode and sonoelastographic images

Pathology processing
Fixation, slicing, outlining

Boundary segmentation from B-mode images
Deficit segmentation from sonoelastographic images

Interpolation and 3D reconstruction

Registration

Sonoelastographic tumor
Intersection between sonoelastographic and histology tumors
Histology tumor

Anterior Base
Apex Posterior
Figure 5.1. Flow diagram of the procedures for the \textit{ex vivo} experiment. In the \textit{in vivo} experiment, imaging is performed before the radical prostatectomy.

![Flow diagram of the procedures for the \textit{ex vivo} experiment](image)

Figure 5.2. Ex vivo imaging setup. The ultrasound transducer (a) is placed on top of the gelatin phantom which contains the prostate (b). Vibration was provided by two rigid metal strips positioned underneath the mold (c). The strips were connected to an external piston (d) which was driven by a harmonic waveform generator (e).

![Ex vivo imaging setup](image)

After imaging, the specimen was weighed and measured to determine the maximum length from apex to base, transversely and anteroposteriorly. A landmark device, which consisted of two sets of four $3$-\textit{mm}-diameter mating metal prongs, was inserted longitudinally into the specimen to provide fiducial markers. After fixation, the gland
was measured to assess shrinkage, sliced into 4-mm-thick sections from the apex to the base, and digitally photographed. Tissues were then transferred to cassettes and embedded in paraffin (Paraplast, Sherwood Medical, St. Louis, MO, USA). The tissue was sliced further into 5-μm-thick sections and placed on glass slides. The microscopic whole-mount sections were examined by a pathologist who was blinded to the results from sonoelastography. Areas of carcinoma and benign prostatic hyperplasia (BPH) were outlined with black and blue marking pens, respectively. Subsequently, a histological volume was created by aligning the digital photographs of each histological slide using the holes from the landmark device as a reference. Linear interpolation based on level sets [104] was used to improve the spatial resolution in the long axis (apex to base). The volume was scaled to compensate for shrinkage.

Discrete dynamic contours (DDC) were used to outline the boundary of the prostate gland in each of the B-mode US images resulting in a 3D representation of the surface of the gland [114]. In DDC, four points selected by the user are interpolated to create an initial contour which is decomposed into a set of 40 vertices. The contour is deformed by moving each of these vertices through a series of iterations according to the following kinematic equations:

\[
p_i(t + \Delta t) = p_i(t) + v_i(t)\Delta t
\]  \hspace{1cm} (5.1)

\[
v_i(t + \Delta t) = v_i(t) + a_i(t)\Delta t
\]  \hspace{1cm} (5.2)
\[
a_i(t + \Delta t) = \frac{1}{m_i} f_i(t + \Delta t)
\]  

(5.3)

where \( p_i = (x_i, y_i) \) is the position of the vertex \( i \); \( v_i \) and \( a_i \) are its velocity and acceleration, respectively; \( m_i \) is its mass which is assumed to be 1; and \( t + \Delta t \) represents the time of the next iteration. The initial velocity and acceleration are set to zero.

The force \( f_i \) is composed of three terms:

\[
f_i = w_i^{\text{int}} f_i^{\text{int}} + w_i^{\text{img}} f_i^{\text{img}} + f_i^d
\]

(5.4)

Where \( f_i^{\text{int}}, f_i^{\text{img}} \) and \( f_i^d \) represent the internal, image and damping forces, respectively; and \( w_i^{\text{int}}, w_i^{\text{img}} \) are the respective weights which determine the contribution of the internal and image forces. In our experiments, we used \( w_i^{\text{int}} = 0.4 \) and \( w_i^{\text{img}} = 0.6 \). Image forces are calculated from the intensity values of the image and they move the vertex towards the closest and strongest edge. Internal forces are computed based on neighboring vertices and constrain the vertex to form a smooth contour. The damping force is proportional to the velocity of the vertex and provides stability in the iteration process. The final position of the vertices determines the segmented boundary of the prostate in the B-mode US image. This process is repeated for each of the B-mode scans.
Deficits in the sonoelastographic images (indicative of a stiff or cancerous region) were segmented using the semi-automatic algorithm presented in the last chapter, but extended to the 3D domain. The algorithm was initialized by subjectively selecting the center of the deficit. Subsequently, the algorithm performed a combination of fast marching and level set methods to establish the final segmentation of the lesion. This process was repeated for each deficit found in the sonoelastographic volume. Information from the co-registered images was fused creating a volume showing the deficits found in the prostate gland in 3D.

Registration between the US and pathology volumes was achieved by using the surface of the gland as a marker [115]. The registration process was composed of four steps. First, a rigid registration was used to align the volumes. Then, an affine transformation allowed compensation for shear and scale. Finally, a deformable B–spline registration [102] with a coarse grid was applied followed by another one with a finer grid. The idea of this approach is that rigid and affine transformations bring the registration process close to its global minimum. Only then, non-rigid transformations are used to compensate for deformations in the gland due to mechanical and chemical procedures in the histological processing. This approach was previously evaluated with a fewer number of cases reporting a better performance than rigid or affine registrations alone [120].
To assess the detection performance, 3D sonoelastographic findings were compared in size and position to 3D histology. For deficits to be scored as a true positive, the relative average diameter in sonoelastographic images with respect to histological images had to be between 50% and 150%, and the tumor centers had to be less than 15 mm apart. These criteria were selected to compensate for problems during registration and for the coarse sampling in the histological volume. Only tumors and deficits that were larger than 100 mm$^3$ (2.9 mm in diameter) were considered in the analysis.

5.2.2 In vivo experiments

Eleven patients underwent a TRUS examination the day prior to their scheduled radical prostatectomy. A magnetic tracking device (MiniBird, Ascension Technologies, Burlington, VA, USA) was mounted on the TRUS probe [115]. This device enabled the reconstruction of 3D US B-mode and sonoelastographic volumes of the prostate gland. The external vibration was induced by a specially designed plate using two mechanical actuators (Buttkicker Concert, The Guitammer Company Inc., Westerville, Ohio, USA) each driven by a low frequency harmonic signal. To select the vibration frequency, a sonoelstographic image of the mid-gland was tested starting at 70Hz and increasing the frequency until attenuation did not permit to obtain a good quality of image. The quality was judged in terms of uniformity of the vibration field “filling” the prostate. The highest frequency which allowed a good quality of the image was selected. Deficits in sonoelastographic volumes were identified by achieving a consensus of 3 observers and segmented using the same techniques.
described in Section 5.2.1. After patient surgery, a histological volume was reconstructed and registered to the US images. In order to assess the cancer detection performance, 3D sonoelastographic findings were compared in size and position to 3D histology as in the \textit{ex vivo} experiments.

\section*{5.3 Results}

Sonoelastography found fifty one deficits in the thirty \textit{ex vivo} glands that were examined. Twenty eight of the deficits corresponded to cancerous masses, eleven to BPH nodules, and twelve were unexplained false positives. Seventeen tumors were missed entirely. The average diameter of the detected tumors was $8.0 \pm 2.8 \text{ mm}$ measured in the sonoelastographic images versus $8.5 \pm 3.3 \text{ mm}$ measured in the histological images. The minimum estimated diameter of a detected tumor was $2.51 \text{ mm}$. The undetected tumors measured in average $4.8 \pm 2.1 \text{ mm}$ in diameter.

Figure 5.3 illustrates a representative \textit{ex vivo} case comparing findings from imaging and histology. The sonoelastographic image depicts a tumor in the left posterior part of the gland as verified by histology. Note that the same tumor is not visible in the corresponding US B-mode image. Reconstructed histological and US volumes for the same prostate case are depicted in Figure 5.4. It is observed that the deficit found in the sonoelastographic volume overlaps with the tumor outlined by the pathologist.
Figure 5.3. Corresponding (a) B-mode US image and (b) sonoelastographic image from an *ex vivo* prostate study. Although not visualized in B-mode US, a cancerous mass (red arrows) is depicted in the sonoelastographic image as verified by (c) the histological image (blue outline).
Figure 5.4. Volumes reconstructed from (a) histological images and (b) ultrasound images. The tumor found by the pathologist is depicted in red. The deficit found by sonoelastography is shown in green. The fusion of both volumes is illustrated in (c). The overlap of the tumors from sonoelastography and histology is presented in white.
Representative US B-mode and sonoelastographic images from an *in vivo* prostate scan are shown in Figure 5.5. Inspection of the sonoelastographic image indicates a stiff mass in the anterior zone of the gland, which corresponds to a hypoechoic region in the B-mode image. The corresponding 3D reconstructions for this prostate case along with histology results are depicted in Figure 5.6. From the eleven *in vivo* cases, one was discarded due to poor contact between the gland and transducer. In terms of vibration frequency, two glands were imaged at 70 Hz, one at 80 Hz, two at 90 Hz, two at 100 Hz, two at 110 Hz, and one at 120 Hz.

Sonoelastographic imaging detected twelve tumors. Their average diameter measured $7.4 \pm 4 \ mm$ versus $7.5 \pm 3.5 \ mm$ measured in the histological volume. The smallest detected tumor had an estimated diameter of $3 \ mm$. In addition, twelve other deficits were depicted by sonoelastography. Six of them corresponded to BPH and the rest remained unexplained. Seven tumors were undetected with an average diameter of $3.8 \pm 1.7 \ mm$.

Table 5.1 presents a summary of the performance of sonoelastography for prostate cancer detection in terms of accuracy, sensitivity and specificity. Both, *ex vivo* and *in vivo* experiments, show similar results with accuracy over 70%, and higher specificity than sensitivity.
Figure 5.5. Matched (a) B-mode US and (b) sonoelastographic images from an *in vivo* prostate study. The sonoelastographic image reveals a stiff (cancerous) mass (denoted by arrows) in the middle of the image.
Figure 5.6. Results from an *in vivo* study illustrating (a) 3D reconstruction from the prostate scan and (b) histological image taken from the midgland region. Sonoelastography depicts two stiff cancerous masses (green) that are corroborated by histology (blue outline). Note a small tumor was missed by sonoelastography in the anterior right part of the gland.
Table 5.1. Performance in cancer detection for *ex vivo* and *in vivo* experiments.

<table>
<thead>
<tr>
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<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
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<tbody>
<tr>
<td>30 <em>ex vivo</em> glands</td>
<td>75.0</td>
<td>63.0</td>
<td>78.8</td>
</tr>
<tr>
<td>10 <em>in vivo</em> glands</td>
<td>70.8</td>
<td>63.2</td>
<td>73.9</td>
</tr>
</tbody>
</table>

**5.4 Discussion**

The capability of sonoelastography to find cancer depends on the size and elastic contrast of the tumor in comparison with the normal surrounding tissue [26]. In our experiments, the average diameter was less than 10 mm and the expected elastic contrast was less than 3 [117]. The small size and low contrast represent adverse conditions for the imaging system. On average, the undetected tumors (false negatives) had less than 5 mm and 4 mm in diameter for *ex vivo* and *in vivo* experiments, respectively. The specificity of sonoelastography is lowered by the presence of benign conditions that are stiffer than normal tissue, *e.g.* BPH and calcifications [116]. Although, B-mode imaging may be used to visualize and exclude calcifications, BPH nodules are still responsible for almost half of the false positives. If these false positives are not considered in the analysis of performance, the accuracy and specificity metrics improve up to 80% and 88%, respectively (see Table 5.2).
Table 5.2. Performance in cancer detection for \textit{ex vivo} and \textit{in vivo} experiments without considering false positives caused by BPH nodules.

<table>
<thead>
<tr>
<th></th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 \textit{ex vivo} glands</td>
<td>80.8</td>
<td>63.0</td>
<td>87.7</td>
</tr>
<tr>
<td>10 \textit{in vivo} glands</td>
<td>78.0</td>
<td>63.2</td>
<td>85.0</td>
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On the other hand, the sensitivity of sonoelastography is lowered by the presence of small tumors (<4 mm in diameter). If in the analysis, we only consider malignant masses which are larger than 4 mm in diameter, then the number of false negatives in the \textit{in vivo} experiment is reduced from seven to one and in the \textit{ex vivo} experiments from seventeen to eleven. Table 5.3 shows the performance of sonoelastography when only tumors larger the 4 mm are considered for the analysis.

Table 5.3. Performance in cancer detection for \textit{ex vivo} and \textit{in vivo} experiments considering lesions larger than 4 mm.

<table>
<thead>
<tr>
<th></th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 \textit{ex vivo} glands</td>
<td>81.8</td>
<td>71.8</td>
<td>84.9</td>
</tr>
<tr>
<td>10 \textit{in vivo} glands</td>
<td>83.0</td>
<td>90.9</td>
<td>81.0</td>
</tr>
</tbody>
</table>
Imaging artifacts, called modal patterns, may be another source of false positives in ex vivo experiments. These artifacts appear due to the destructive interference between the shear wave sources and the reflection from boundaries of the gelatin mold. Although chords (multiple-frequency signals) were used to minimize this effect, they are not sufficient to eradicate them. The experimental setup needs to be adjusted so that either modal patterns are further reduced or that their presence can be determined.

In vivo prostate experiments showed high contrast sonoelastographic images. Furthermore, these images are less affected by modal patterns because of the heterogeneous nature of tissue. However, boundary of internal structures, such as the urethra and calcifications caused artifacts (which were not scored as cancer). Technical pitfalls include the change in the overall attenuation of the ultrasound with the angle of rotation of the probe. This effect manifests as aliasing at lateral margins and incomplete penetration at the mid-gland. Coupling of externally induced mechanical vibrations to the prostate tissue is another major obstacle in obtaining high-quality results in vivo. Higher contrast images, and therefore, a better detection rate of lesions, could be obtained by pushing the sonoelastographic experiments to higher frequencies (see Figure 4.2). However, higher attenuation over long distances will diminish the signal at higher frequencies, so better means of applying local vibration at higher frequencies (approaching 200 Hz or higher) need to be developed.
Overall, qualitative sonoelastographic imaging showed an accuracy of over 80% for finding tumors larger than 4 mm in diameter, both in vivo and ex vivo. The majority of these tumors were not visible in conventional B-mode ultrasound. Previous studies found similar improvements from sonoelastography over conventional B-mode US imaging [9]. However, this improvement over B-mode ultrasound is not sufficient to replace biopsy. Therefore, sonoelastography may be a useful tool to guide biopsies.

5.5 Summary

In this chapter, the performance of sonoelastography for prostate cancer detection was evaluated. Ultrasound (US) B-mode and sonoelastographic volumes were acquired from thirty prostate glands ex vivo. Additionally, eleven glands were imaged in vivo using a transrectal US probe. To assess the detection performance, three dimensional (3D) sonoelastographic findings were compared in size and position to 3D histological data. Sonoelastography showed an accuracy of over 80% for finding tumors larger than 4 mm in diameter in both experiments, and slightly underestimated their volumes.

Image segmentation and registration tools were implemented and used to evaluate the performance of sonoelastography. The semi-automated algorithm presented in Chapter 4, was modified and employed for the volume estimation of stiff discrete masses from sonoelastographic images. A Discrete Dynamic Contour algorithm was employed for segmentation of the prostate gland surface from B-mode scans. A registration process,
composed of rigid, affine and b-spline transforms, was utilized to compare the findings of sonoelastography with histology in order to assess the performance in cancer detection.