Chapter 6

Prostate cancer detection using crawling wave sonoelastography

6.1 Introduction

Crawling wave (CrW) sonoelastography (see Chapter 3) is a recently developed technique capable of locally estimating the shear wave speed in tissue and, therefore, it can provide a quantitative estimation of the Young’s modulus for a given vibration frequency. By taking several measurements at different vibration frequencies, the viscoelastic properties of the tissue can be inferred. This approach was used by Zhang et al. [25] to measure the viscoelastic properties of veal liver, thermal-treated veal
liver and human prostate \textit{ex vivo}. For all these cases, it was observed that the Young’s modulus slightly increased with frequency. Furthermore, the measurements obtained with CrW sonoelastography were compared with a mechanical measurement method based on the Kelvin-Voight Fractional Derivative model. The experimental results of the two methods were highly congruent.

Recently, Hoyt \textit{et al.} [26, 27] utilized CrW sonoelastography to characterize the viscoelastic properties of human skeletal muscle \textit{in vivo}. This study indicated that there are discernible differences in both shear modulus and viscosity estimates among different relaxed skeletal muscle groups. In addition, the study revealed that voluntarily contracted muscles exhibit considerable increases in both shear modulus and viscosity estimates as compared to the relaxed state.

In this chapter, CrW sonoelastography is applied to \textit{ex vivo} human prostate glands to evaluate its performance in cancer detection. As a second objective, CrW sonoelastography is used to quantify the viscoelastic properties of normal and cancerous prostate tissue.

\section{6.2 Methods}

Fifteen prostatic glands were obtained after radical prostatectomy and embedded in a 10.5\% gelatin mold. Two pistons (Model 2706, Brüel & Kjaer, Naerum, Denmark) were fitted with surface-abraded extensions and located at each side of the mold to
create shear vibration (see Figure 6.1). The ultrasound transducer (M12L, General Electric Healthcare, Milwaukee, WI, USA) was positioned on top of the gelatin mold and equidistant from the vibration sources. Each gland was imaged at three locations: AB1, AB2, and AB3. These locations were chosen to capture images close to the apex (AB1), at middle gland (AB2), and close to the base (AB3) as represented in Figure 6.2. Three movies of crawling wave images, each one with a different vibration frequency (100, 120 and 140 Hz), were acquired at each of the locations. In all cases the frequency offset between the vibration sources was set to 0.25 Hz. The site for the three cross-sections was marked and the corresponding histological slices were obtained. An expert pathologist outlined the cancerous regions in the histological slices. This information was considered as ground truth.

The CrW images were pre-processed following the enhancement methods described in Section 3.4. Subsequently, a two-dimensional shear wave velocity estimator (see Section 3.3.2), with a kernel of 20 by 20, was used to obtain an estimate of the shear velocity of the tissue for each of the vibration frequencies. Figure 6.3 illustrates a flow diagram of the whole procedure. Using the quality metric obtained from slow time filtering, the best two estimations were averaged into a final image representing the shear velocity. This image and its corresponding histological slice were divided into quadrants and compared to evaluate the performance of the CrW technique in cancer detection. To quantify the viscoelastic characteristics of cancerous and normal tissue, the elasticity modulus of true positive and true negative areas were measured.
The semi-automated segmentation algorithm presented in Chapter 4 was modified to identify the boundary of the cancerous tumors in the CrW images. Application of this algorithm is possible, since shear velocity sonoelastograms have similar characteristics to sonoelastographic images. In particular, the lesions in these images also present a lack of boundary definition. The modifications in the algorithm were centered on the pre-processing stage. CrW sonoelastograms were normalized and their intensity values were reversed so that elevated stiffness corresponded to darker regions in the image. Regions with apparent elevated stiffness were selected. An observer initialized the segmentation algorithm to define the boundary of the regions. The remaining area of the prostate was considered as background. A region was marked as cancer on the CrW elasticity image if it had a shear velocity that was greater or equal to 1.25 times that of the background.

In addition, pseudo-sonoelastographic images were reconstructed and compared to histology. These images are created by taking the maximum of the same signal used in slow time filtering, i.e. the highest value that each pixel takes over time.
Figure 6.1. Schematic of the experimental setup. The prostate gland embedded in a gelatin mold (a) is located between shear vibration sources (b). The ultrasound transducer is positioned on top to acquire the crawling wave images (c).

Figure 6.2. The three locations in the prostate gland where crawling wave movies are acquired.
6.3 Results

Representative cases from two *ex vivo* prostate glands, one without cancer and the other with, are presented in Figure 6.4 and 6.5. Figure 6.4 shows CrW images before (a) and after phase multiplication (b). The corresponding shear velocity estimation (c) does not indicate the presence of any stiff region. Histology revealed that this particular cross-section did not have cancer. In Figure 6.5, the corresponding B-mode (a), shear speed (b) and histological (c) images of a cross-section close to the apex (AB1) of a human prostate gland are shown. The shear speed image shows an area with elevated shear speed on the left side of the cross-section which corresponds to a cancerous region in the histological image.
Figure 6.4. CrW image before (a) and after (b) phase multiplication; and its corresponding shear velocity image (c). Histology revealed that this cross-section did not have cancer. The boundary of the prostate gland is shown in pink.

Figure 6.5. Corresponding B-mode (a), shear speed (b) and histological (c) images of a cross-section close to the apex of a human prostate gland. The shear speed image shows a region with elevated shear speed on the left side of the cross-section which corresponds to a cancerous region in the histological image.
Table 6.1 summarizes the performance of CrW sonoelastography and pseudo-sonoelastography for prostate cancer detection in terms of accuracy, sensitivity and specificity. Three cross-sections from each of the fifteen prostate glands were analyzed. Out of the forty-five samples, three were discarded due to poor SNR. These cross-sections were located next to the base of the gland (AB3) and showed a very low quality metric (<0.6). Sixteen of the quadrants were false positives. Six of these quadrants coincide with BPH. Seventeen of the quadrants were false negatives. Three of these were related to elongated tumors with a small size (<4 mm) in the direction of CrW propagation, and two of the quadrants presented an accumulation of small tumors with less than 2 mm diameter each. There were thirty five quadrants considered as true positives and a hundred quadrants considered as true negatives. Overall, CrW sonoelastography outperforms pseudo-sonoelastography. The shear velocity for all included cancerous (true positive) and normal (true negative) tissues was estimated as 4.75±0.97 m/s and 3.26±0.87 m/s, respectively.

Table 6.1. Performance in prostate cancer detection (N=41 cross-sections x 4 quadrants).

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<thead>
<tr>
<th></th>
<th>Accuracy (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrW Sonoelastography</td>
<td>80.4</td>
<td>67.3</td>
<td>86.2</td>
</tr>
<tr>
<td>Pseudo Sonoelastography</td>
<td>67.9</td>
<td>60.8</td>
<td>70.9</td>
</tr>
</tbody>
</table>
In order to understand the viscoelastic effect in the range of frequencies used (100-140Hz), five cross-sections that contained no detectable cancer were analyzed. Results from this quantitative analysis are shown in Table 6.2. The increment in shear velocity with frequency is indicative of a viscoelastic effect.

Table 6.2. Estimated shear wave speeds for normal prostate tissue (N=5 cross-sections with no cancer).

<table>
<thead>
<tr>
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<th>100Hz (m/s)</th>
<th>120Hz (m/s)</th>
<th>140Hz (m/s)</th>
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</thead>
<tbody>
<tr>
<td>Normal Tissue</td>
<td>2.9±0.4</td>
<td>3.1±0.4</td>
<td>3.3±0.5</td>
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6.4 Discussion

This chapter evaluates the performance of Crawling Wave Sonoelastography for prostate cancer detection ex vivo. Additionally, the quantitative nature of CrW Sonoelastography allows estimating the viscoelastic properties of the analyzed glands. Pseudo-sonoelastographic images are reconstructed from CrW movies in order to compare both techniques. Performance of pseudo-sonoelastography in cancer detection is similar to previously reported results [9,11]. In general, CrW sonoelastography outperforms pseudo-sonoelastography; however, a combination of both modalities might provide a better performance in cancer detection. In particular, it was observed that a high elastic contrast could create a region with a very low SNR. Although this condition produced high contrast in pseudo-sonoelastographic images,
it damages the slow time filtering as well as the estimation processes in CrW sonoelastography.

BPH nodules in the prostate glands amounted to one third of all false positives in the CrW analysis. Further study of their viscoelastic properties is required in order to differentiate them from cancer. Artifacts caused by reflections due to the experimental setup (i.e. boundaries of the gelatin phantom) may be another source of false positives. Improvement of the experimental setup may reduce the effect of these artifacts. Small tumors and elongated tumors with a short size in the direction of CrW propagation are an important source of false negatives in this analysis. This is aggravated by the low contrast in elasticity between prostate cancerous and normal tissues [117].

A protocol to analyze the properties of prostate glands ex vivo was developed. A critical part of this process is to mark the cross-section of the gland which is imaged in order to obtain the corresponding histological image (ground truth). Currently, the imaging plane is marked using surgical needles. Even though, the marking is done with extreme care, the imaging and histological planes may not match precisely. Errors in the insertion of the needle as well as deviations when cutting the prostate gland may introduce differences which may be carried into the evaluation of the performance.
An initial analysis of the viscoelastic properties of normal prostate tissue showed that the variation in elasticity is small in the range of frequencies utilized. Therefore, averaging the results of two different frequencies is not only valid but it should improve the final estimation since it is based on two independent results.

In this study, regions were considered as cancer if their shear velocity was greater or equal to 1.25 times that of the surrounding prostate tissue. Therefore, the decision is performed on a case by case (or patient by patient) basis. This criterion follows the rationale presented previously by Zhang et al. [117]. They found that there is an elasticity contrast of 2.6 to 1 between cancerous and normal tissue, but the absolute elasticity values vary from patient to patient. Since there is a square root relationship between the elasticity modulus and the shear velocity of the tissue, a 2.6 contrast in elasticity modulus means a 1.6 contrast in shear velocity values. The threshold of 1.25 is arbitrarily selected to have an increased sensitivity.

Estimated shear velocity values for normal and cancerous tissue are slightly elevated but in the same order of magnitude when compared to previous findings based on mechanical testing using a Kelvin-Voight Fractional Derivative model [117]. However, it is important to note that values from mechanical testing were from samples containing both cancerous and normal tissue. Therefore, it is expected that only cancerous tissue will have higher values. Results indicate that it is possible to differentiate pathological from normal tissue using CrW.
6.5 Summary

In this chapter, Crawling Wave (CrW) Sonoelastography is used to detect cancer in excised human prostates and to provide quantitative estimations of the viscoelastic properties of human cancerous and normal tissues. Results showed good spatial correspondence with histology. Additionally, the estimated shear velocities of cancerous and normal tissue are $4.75 \pm 0.97 \text{ m/s}$ and $3.26 \pm 0.87 \text{ m/s}$, respectively. These results are in agreement with previous reports on the elasticity of cancerous and normal human prostate tissue and suggest that CrW Sonoelastography could be used to improve prostate cancer detection.