Chapter 1

Introduction

Palpation is a qualitative clinical tool that is routinely used in physical examinations for cancer screening in prostate, breast and liver. In this examination, a stiff discrete mass is considered suspicious and requires further evaluation. Although useful, palpation has important drawbacks. It can only evaluate accessible—close to the surface—tissue. Subtle changes, \textit{i.e.} small size tumors in a deep location, may not be detected. Furthermore, this technique is qualitative and subject to interpretation, which means that the evaluation depends on the experience of the physician.

The fact that pathological tissue presents an increased stiffness when compared to surrounding normal tissue [1] was one of the main motivations that prompted research on the field of elasticity imaging. This field can be understood as the
intersection of the study of biomechanical properties, imaging sciences and physics [2]. In the last two decades, research on elasticity imaging has been an international endeavor, the goal being to map the viscoelastic properties of the tissue in an anatomically meaningful manner to provide useful information [2]. As a result, several modalities of elasticity imaging, mostly based on ultrasound but also on magnetic resonance imaging (MRI), have been proposed and applied to a number of clinical applications.

Diagnostic applications, especially those in which palpation was used, have been the main targets for the utilization of elasticity imaging (e.g. prostate cancer, breast cancer). The capability of quantitatively estimating organ stiffness can also be used to evaluate hepatic cirrhosis, renal disease and thyroiditis. Vascular studies have been another area of general interest (e.g. plaque evaluation, wall stiffness in arteries, evaluation of thrombosis in veins). However, clinical applications of elasticity imaging are not limited to diagnosis. Due to the appearance of new thermal ablation therapies such as High Intensity Focused Ultrasound (HIFU) and radiofrequency ablation (RFA), elasticity imaging has been also applied to monitor the lesion creation and the required follow-up studies.

The following section will briefly review the literature on existing elasticity imaging methods. The interested reader is referred to [2,3,4,5] for a comprehensive review on this topic.
1.1 Literature review on elasticity imaging

Several groups have contributed to the field of elasticity imaging. Although the details in the implementation of their approaches vary considerably, all the imaging techniques are required to apply a mechanical force in the tissue, measure the induced local motion, and estimate some elasticity parameter. Table 1.1 classifies the existing approaches according to the imaging modality they are based on, the elasticity information they provide, and the nature of the force applied to the tissue. The two imaging modalities that have been used in elasticity imaging are ultrasound (US) and magnetic resonance imaging (MRI). Since the first techniques were proposed using US, there is more variety in the approaches using this imaging modality. The mechanical force can be applied either externally, via a mechanical actuator in contact with the tissue, or internally, generated by acoustic radiation force directly in the region of interest. The elasticity parameter to be estimated can provide either qualitative or quantitative elasticity information. Qualitative information allows ascertainment of the relative stiffness of the different regions in the image, as opposed to quantitative information which provides a local estimate of the elasticity modulus in the image.
Table 1.1 Summary of elasticity imaging modalities.

<table>
<thead>
<tr>
<th>Modality Name</th>
<th>Based on</th>
<th>Qualitative or Quantitative</th>
<th>Mechanical Force</th>
</tr>
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<tbody>
<tr>
<td>Sonoelastography</td>
<td>US</td>
<td>Qualitative</td>
<td>External</td>
</tr>
<tr>
<td>Crawling Wave Sonoelastography</td>
<td>US</td>
<td>Quantitative</td>
<td>External</td>
</tr>
<tr>
<td>Compression Elastography</td>
<td>US</td>
<td>Qualitative</td>
<td>External</td>
</tr>
<tr>
<td>Acoustic Radiation Force Impulse Imaging</td>
<td>US</td>
<td>Qualitative</td>
<td>Radiation Force</td>
</tr>
<tr>
<td>Shear Wave Elasticity Imaging</td>
<td>US</td>
<td>Quantitative</td>
<td>Radiation Force</td>
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<tr>
<td>Supersonic Shear Imaging</td>
<td>US</td>
<td>Quantitative</td>
<td>Radiation Force</td>
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<tr>
<td>Spatially Modulated Ultrasound Radiation Force Imaging</td>
<td>US</td>
<td>Quantitative</td>
<td>Radiation Force</td>
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<tr>
<td>Vibroacoustography</td>
<td>US</td>
<td>Quantitative</td>
<td>Force</td>
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<tr>
<td>Transient Elastography</td>
<td>US</td>
<td>Quantitative</td>
<td>External</td>
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<tr>
<td>Magnetic Resonance Elastography</td>
<td>MRI</td>
<td>Quantitative</td>
<td>External</td>
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1.1.1 Sonoelastography and crawling wave sonoelastography

Sonoelastography was first introduced by Lerner et al. in 1988 [6]. This elasticity imaging technique estimates the amplitude response of tissues under harmonic mechanical excitation using ultrasonic Doppler techniques. Low amplitude (less than 100 µm) and low frequency (5 – 500Hz) vibration is induced by means of external actuators. Due to a relationship between particle vibrational response and received Doppler spectral variance [7], the amplitude of low frequency shear waves propagating in tissue can be visualized in real-time using sonoelastography. Since tissue stiffness is inversely proportional to the amplitude of internal vibration, a harder abnormal mass or lesion will be depicted as a region with decreased amplitude.
[8]. The simplicity of the approach allows for an implementation which is not only real time but also easy to integrate with current commercial US scanners. The main clinical application for this technique has been prostate cancer detection with promising results \textit{ex vivo} [9,10,11] and \textit{in vivo} [11]. It has also been applied to the measurement of thermally ablated lesions induced by either HIFU or RFA. These lesions can be detected due to the high elasticity contrast with the surrounding tissue. Results from \textit{ex vivo} [12,13] and \textit{in vivo} [14,15,16,17] experiments suggest that sonoelastography can be successfully applied for this task.

In a recent discovery, Wu \textit{et al.} [18,19] used sonoelastography to image slowly moving interference patterns, termed crawling waves, produced by two opposing shear vibration sources with a slight difference in frequency between each other. Wu and his colleagues determined that the apparent velocity of the crawling waves is proportional to the underlying local shear velocity which in turn can be used to estimate the elasticity modulus of the tissue. The estimation of the local shear velocity was performed using local frequency estimators, a technique imported from Magnetic Resonance Elastography (MRE). Other estimation techniques have been proposed by McLaughlin \textit{et al.} [22] and Hoyt \textit{et al.} [23,24] based on arrival times and autocorrelation methods, respectively. Crawling wave sonoelastography has been successfully applied to detect radiofrequency ablated hepatic lesions \textit{in vitro} [24,25], to characterize human skeletal muscle \textit{in vivo} [26,27], and to characterize human prostate tissue \textit{ex vivo}. 
1.1.2 Compression elastography

This technique was first introduced by Ophir et al. [28]. In this modality, tissue is compressed under a (quasi-) static force. The ultrasonic echoes from before and after the compression are compared using cross-correlation techniques to estimate the displacements of the tissue. From the displacements, a strain image is constructed where regions of low strain correspond to stiff masses (lesions or tumors). Due to the simplicity of this technique, a great amount of the research efforts in elasticity imaging were concentrated on this modality, including its implementation in commercial scanners (HI Vision 900, Hitachi Medical Systems, Twinsburg, Ohio, USA; Acuson Antares Premium Edition, Siemens, Malvern, PA, USA). The interested reader is referred to [29] for a comprehensive review of this technique.

This modality has been applied to several clinical applications. De Korte et al. [30] used compression elastography in conjunction with an intravascular ultrasound system to determine the composition and morphology of atherosclerotic lesions concluding that intravascular Elastography can be applied in vivo to identify fibrous and fatty tissue. Kallel et al. [31] compared the Elastographic images of excised normal canine prostates with their corresponding histology. They inferred from the Elastographic images that the peripheral zone has an elevated elasticity modulus. Pallwein et al. [32] recently reviewed the cancer detection performance of compression-elastography-targeted biopsy in human prostates. They found as many
cancers as systematic biopsy with less than half the number of biopsy cores. However, they also commented on the need for computer-assisted techniques to differentiate between benign and malignant tissue. Righetti et al. [33] studied the feasibility of imaging HIFU-induced lesions using compression elastography in *ex vivo* canine livers with positive results. Souchon and colleagues [34] evaluated the capability of this modality to measure HIFU-induced lesions in human prostates *in vivo*. Comparisons with MRI confirmed the potential of compression elastography for monitoring HIFU treatment of the prostate. Varghese et al. measured the area and volume of *in vitro* [34] and *in vivo* [35] RFA lesions using this technique. They found good correlation with gross pathology in both cases. Additionally, they evaluated the utilization of the RFA needle as a compressor and concluded that it was more suitable than the previously used compression plate. In the context of breast cancer diagnosis, studies from Garra et al. [37] and Barr [38,39] indicated that compression elastography has the potential to detect lesions and even help in the distinction of benign versus malignant masses. However, their results still need to be confirmed in a large multi-center trial.

### 1.1.3 Acoustic radiation force - based techniques

Recently, several modalities have investigated the capability of using Acoustic Radiation Force (ARF) [40] to remotely palpate tissue and extract viscoelastic information. Due to the soft tissue’s attenuation, the ultrasound beam transfers part of its momentum to the tissue, pushing it along the direction of the propagating wave.
As seen in Table 1, several groups have used this phenomenon as a mechanism to excite the tissue. We briefly discuss their contributions.

Acoustic Radiation Force Impulse (ARFI) imaging was first introduced by Nightingale et al. [41]. The basic idea of this modality is to create impulses in the tissue using ARFI (pushing beams), and then apply cross-correlation methods to measure the displacements in the tissue (tracking beams). Both, pushing and tracking beams, can be generated by the same imaging transducer. Parametric images showing maximum displacement, the time the tissue takes to reach its peak displacement, and tissue recovery time are used to extract clinical useful information about viscoelastic properties of the tissue. This technique has been applied to breast cancer detection [42], and monitoring of RFA induced lesions ex vivo [43] and in vivo [44].

Shear wave elasticity imaging (SWEI) is a technique in which shear waves, generated by ARF, are imaged and analyzed to extract a quantitative estimate of the elasticity modulus of the tissue. It was first proposed by Sarvazyan et al. [45] and demonstrated in tissue mimicking phantoms [46,47]. Following this idea, Nightingale et al. applied this concept to measure liver fibrosis in vivo [48,49,50].

Another technique proposed by Fatemi and Greenleaf [51] was named Vibroacoustography. Two continuous ultrasound beams with a slight difference in frequency and focused at the same spatial location generate a dynamic radiation
force. As a response, the tissue vibrates sinusoidally in a pattern determined by its viscoelastic properties. Subsequently, the emitted acoustic field is recorded using a hydrophone. The focal point (intersection of the ultrasound beams) is moved to interrogate the tissue in different points in order to form an image. This technique has been applied to image calcifications in human arteries [52], micro-calcifications and small lesions in breast tissue [53], and permanent prostate brachytherapy seeds [54].

Recently, McAleavey and Menon [55] proposed a novel method to estimate shear modulus of the tissue named Spatially Modulated Ultrasound Radiation Force (SMURF). In this technique, ARF is applied in the tissue with a determined spatial variation in intensity. Subsequently, the temporal frequency of the generated shear wave is measured using tracking pushes. The approach was validated through simulations and measurements in phantoms.

1.1.4 Transient elastography

In this technique, proposed by Catheline et al. [56], a low-frequency external vibrator is used to generate shear waves in the tissue which are captured by an ultra-fast ultrasound system (up to 6000 frames/s). The fast imaging of the shear waves makes this technique insensitive to boundary conditions and body motion. Elasticity information is reconstructed by analyzing the shear wave propagation. Transient elastography has been utilized on breast tumor detection [57] and the assessment of in vivo liver fibrosis [58]. It is worth noting that this technique was the foundation for a
start-up company (Echosens, France) which offers a commercial scanner to measure liver stiffness (Fibroscan). Recently, Bercorff et al. [59] proposed to replace the external low frequency vibrator, and use ARF to create a supersonic shear wave. This new technique was named Supersonic Shear Imaging (SSI) and has been used to analyze the viscoelastic properties of breast lesions [60], muscle [61], and liver [62].

1.1.5 Magnetic resonance elastography

Besides the ultrasound-based techniques, MRI has been used to extract viscoelastic information from the tissue in a technique named Magnetic Resonance Elastography (MRE) [63]. In this technique, an external mechanical actuator induces shear wave propagation in the tissue and a phase-contrast MRI protocol is followed to visualize them [64]. In MRE, phase images and subsequently local shear velocity are estimated from the propagation of shear waves. This technique has been used to characterize prostate [65], breast [66], skeletal muscle [67,68], and liver tissue [69].

1.2 Extracting clinical information from elastographic images

In order to extract useful clinical information, all the modalities described above have continuously investigated ways of improving the quality of the images by introducing novel algorithms to process the information, improving the technique’s signal processing, using a quality metric in order to discard poorly acquired images, or building new custom-made equipment. For example, in compression elastography,
Hall and colleagues introduced a quantitative performance descriptor [70] and used it to create high quality elastograms [71] by discarding the low quality frames. Novel approaches to improve the estimation process have been proposed [72-75] in order to obtain more accurate strain estimates. Lindop et al. [76,77] focused on improving the user interface with the sonographers in order to create an easy-to-use and intuitive system. Their modified system was able to select automatically some of the parameters for elastographic imaging and provide real-time feedback on the quality of the elastogram. Hardware developments such as the utilization of a 2D CMUT array [78] or a 4D probe [79] also contributed to improve the images obtained.

Even with all these efforts, the quality of the images still does allow for a high intra- and inter-observer variability [80]. This is aggravated when the images are acquired in vivo. In the particular case when an estimation of the volume or area of a discrete lesion is needed, the images may present a diffuse boundary problem. In these cases, segmentation algorithms can be utilized to improve the accuracy and reduce the variability of the measurements.
1.3 Organization and scope of the thesis

1.3.1 Objectives of the thesis

This thesis focuses on the implementation of image processing tools to acquire information from images acquired with sonoelastography and crawling wave sonoelastography. These algorithms enhance the quality of the images; extract location and size information of discrete lesions; and provide viscoelastic properties of the imaged tissue. The proposed tools are applied to two important clinical applications: Prostate cancer detection and measurement of thermally ablated lesions in liver. The underlying hypothesis is that these algorithms will reduce the variability of the measurements while providing accuracy comparable to a human observer.

1.3.2 Organization: outline

The remainder of this thesis is organized as follows:

Chapter 2 reviews theory used in sonoelastography to detect relative changes in the vibration amplitude of the tissue. Additionally, it presents a study which maps the intensity in sonoelastographic images to actual vibration amplitudes as a function of the imaging parameters used.
Chapter 3 reviews the theory of Crawling Wave Sonoelastography and focuses on the improvement of the quality of the acquired images and their post-processing using a shear velocity estimator.

Chapter 4 applies sonoelastography to the measurement of thermally ablated lesions \textit{in vivo} induced by HIFU and RFA techniques. Within this context, a segmentation algorithm designed to measure lesions in 2D sonoelastography images is introduced. The performance of the algorithm is compared to manual segmentation of the thermal ablated lesions.

Chapter 5 applies sonoelastography to the detection of prostate cancer \textit{ex vivo} and \textit{in vivo}. The segmentation algorithm presented in Chapter 4 is extended to be used in volumetric images. Diagnostic performance of sonoelastography is evaluated for 30 glands \textit{ex vivo} and 10 cases \textit{in vivo}.

Chapter 6 applies crawling wave sonoelastography to the detection of prostate cancer \textit{ex vivo} and to the characterization of viscoelastic properties of cancerous and normal tissue of human prostate. Diagnostic performance of CrW sonoelastography is compared to (pseudo) sonoelastography.

Chapter 7 provides a summary and a conclusion of the present document.