Abstract—This article describes a novel system for quantitative and volumetric measurement of tissue elasticity in the prostate using simultaneous multi-frequency tissue excitation. Elasticity is computed by using a local frequency estimator to measure the three-dimensional local wavelengths of steady-state shear waves within the prostate gland. The shear wave is created using a mechanical voice coil shaker which transmits simultaneous multi-frequency vibrations transperineally. Radio frequency data is streamed directly from a BK Medical 8848 transrectal ultrasound transducer to an external computer where tissue displacement due to the excitation is measured using a speckle tracking algorithm. Bandpass sampling is used that eliminates the need for an ultra-fast frame rate to track the tissue motion and allows for accurate reconstruction at a sampling frequency that is below the Nyquist rate. A roll motor with computer control is used to rotate the transducer and obtain 3D data. Two commercially available phantoms were used to validate both the accuracy of the elasticity measurements as well as the functional feasibility of using the system for in vivo prostate imaging. The phantom measurements were compared with 3D Magnetic Resonance Elastography (MRE), where a high correlation of 96% was achieved. In addition, the system has been used in two separate clinical studies as a method for cancer identification. Qualitative and quantitative results of 11 patients from these clinical studies are presented here. Furthermore, an AUC of 0.87±0.12 was achieved for malignant vs. benign classification using a binary support vector machine classifier trained with data from the latest clinical study with leave one patient out cross-validation.

Index Terms—Ultrasound, prostate cancer, absolute vibro-elastography, shear wave elastography.

I. INTRODUCTION

In the field of medical imaging, elastography has been introduced as a modality that can be used to measure and display the mechanical properties of tissue [1]. The additional information provided by elastography compared to conventional imaging can be used to help diagnose and guide treatment of a number of different diseases that include fibrosis in liver and kidney [2], [3], [4], dysfunction in the placenta during fetal development [5], neurological diseases in the brain [6], [7], and cancer in multiple organs such as prostate [8], [9], [10], breast [11], [12], and thyroid [13], [14], [15]. In the field of ultrasound elastography [16], [17], several different methods have been proposed, with the trend moving from relative, quasi-static techniques [18], [19] to absolute, quantitative techniques, commonly referred to as shear wave elastography (SWE) [20], which are known to reduce user dependence and improve repeatability [21]. In SWE, tissue stiffness is quantified on the basis of the speed of shear wave propagation in the tissue, with a higher speed corresponding to stiffer tissue. The most...
common way to induce shear waves in tissue is by using acoustic radiation force (ARF) that sends a high-power focused beam to the tissue utilizing the ultrasound’s transducer [22]. However, the main drawback of ARF methods is that there is a limit imposed on the amplitude of the acoustic impulse, which restricts the maximum signal-to-noise ratio that can be achieved. This limitation arises from the fact that acoustic impulses can lead to transducer face and tissue heating which can damage both the device and the tissue [23]. As a result, strict FDA guidelines control the amplitude and duration of pulses that can be used. The issue is especially restrictive if continuous or repeated full-volume imaging is required, such as, as needed in guided interventions.

To overcome these limitations, harmonic or vibro-elastography (VE) has been developed that uses an external vibrational source to induce shear waves within the tissue. In this method, the ultrasound can operate independently in its normal imaging mode—allowing continuous imaging. Some of the recent advances in VE include: reverberant shear wave elastography [24], probe oscillation shear wave elastography [25], crawling wave sono-elastography [26], and time-harmonic elastography [27]. Our group has previously also developed a new kind of quantitative elasticity measurement technique called Shear Wave Absolute Vibro-Elastography (S-WAVE) which uses steady-state multi-frequency external excitation and measures the displacement field of shear waves over a volume [28], [29]. The elastic modulus is computed either by solving an inverse finite element method (FEM) [30] problem or by measuring the wavelength of a three-dimensional steady-state shear wave field [31]. The benefit of multi-frequency elastography has been demonstrated in Magnetic Resonance Elastography (MRE) [32] as well as in other shear wave speed imaging methods [33]. S-WAVE has been implemented using different hardware and different imaging settings for specific organs such as in vivo liver [34], ex vivo placenta [35], [36], and breast [37], [38].

In 2022, for males, it is estimated that prostate cancer (PCa) will be the most common form of cancer diagnosed in Canada [39] and in the United States [40]. Regular B-mode ultrasound has a very poor sensitivity and specificity of 0.40 and 0.50 for PCa detection [41]. Multiple studies have shown improvement in PCa detection using SWE. A meta-analysis [42] of 8 such studies [9], [21], [43], [44], [45], [46], [47], [48] demonstrated a pooled sensitivity and specificity of 0.83 (95% CI, 0.66–0.92) and 0.85 (95% CI, 0.78–0.90), respectively. The most commonly used ultrasound system for prostate elastography is SuperSonic Imagine’s Aixplorer system (SuperSonic Imagine, Aix-en-Provence, France). In fact, the Aixplorer system was used in 7 of the studies from the meta-analysis in [42] except for [46] where a Siemens’ Virtual Touch Tissue Quantification (VTTQ) system (Siemens Healthineers, Erlangen, Germany) was used instead. The Aixplorer system uses an end-firing 2D transrectal transducer and the Siemens machine uses a 2D convex transducer, therefore, with this system, the prostate had to be imaged from the abdomen or the perineum of the patients. Both are 2D systems and use ARF-based tissue excitation and therefore have the same set of limitations as mentioned earlier for ARF-based SWE. 3D SWE for prostate has also been recently published [49] which also uses ARF-based excitation. Its volumetric sweep for 100 planes takes 14 min to complete.

In this article, we propose and characterize a new S-WAVE system for the prostate that can perform 3D volumetric and continuous imaging at the same depth as conventional ultrasound without causing tissue or transducer face heating, as opposed to ARF-based methods. With a fast volume acquisition time of just 2 min for 100 planes, the elasticity volume measured with this system can be registered to real-time ultrasound images and can be used for real-time guidance during biopsy procedures without bearing significant additional operating room time. Some initial findings with this setup have previously been summarized in [50], and are expanded here with further details of the system, the methods used, the characterization of the system, and updated clinical findings. The following are our novel contributions:

1. First prostate 3D quantitative elastography system with simultaneous multi-frequency tissue excitation and fast volume acquisition rate.
2. First use of, external, non-invasive transperineal excitation to induce shear waves to the prostate that have been reported to produce repeatable and consistent results with MRE [51].
3. First use of a bandpass sampling technique [52] for prostate imaging to allow tracking of high-frequency tissue motion with an ultrasound frame rate that is well below the Nyquist rate. This removes the need for either a programmable transducer crystal firing sequence to increase the frame rate [53] or an expensive parallel receive ultrasound system. With this approach, the ultrasound machine can operate in conventional B-mode, without a pulse sequence modification, while the radio frequency (RF) data is streamed to an external computer.
4. Motorized volumetric acquisition with a commonly used 2D transducer without changing the volume boundary conditions; the only current 3D commercially available transducer for prostate imaging is an end-firing wobbler that substantially deforms the prostate, making it difficult to correlate histology results with imaging.
5. Validation with commercial quality assurance tissue-mimicking prostate and elastography phantoms—comparing measurements to a 3D MRE system [54].
6. Analysis of elasticity measurements with whole-gland sampling biopsies acquired during a clinical study and development of a classifier for cancer detection using pathology from biopsy cores. This complements an earlier study reported in [55] that compared histology results from excised prostates following prostatectomy procedures with S-WAVE images taken with this system.

The contributions of this article can be utilized in any generic system developed for multi-frequency 3D prostate SWE, which can be stand-alone and independent of the ultrasound machine or transducer used.

The following sections of the article are organized as follows. Section II covers the details of the hardware required for the whole system and the signal processing pipeline for
S-WAVE. Section III and IV cover the details and results from the system characterization with phantoms and the clinical studies. Lastly, Section V discusses the results, limitations, and future improvements and Section VI concludes the article.

II. METHODS

A. Hardware Setup

This section describes the implementation of S-WAVE hardware for prostate imaging. The main hardware, seen in Fig. 1a consists of the ultrasound machine with a transrectal ultrasound (TRUS) transducer to acquire raw RF data, a TRUS robot to roll the transducer & obtain a 3D volume, a transperineal shaker to provide mechanical excitation, and a cart with a computer & control boxes for computation of elasticity, generation of excitation frequency, and TRUS robot control. Each component of the system is described next.

1) Ultrasound Machine: A BK Pro Focus ultrasound machine (BK Medical, Herlev, Denmark) is used with a BK 8848 4-12 MHz endocavity biplane transducer that is set to operate at 9 MHz: this is the default setting for prostate imaging for this transducer. From the ultrasound, echo data in the form of in-phase/quadrature (IQ) modulated data is streamed to the external computer with a DALSA Xcelera-CL PX4 full frame grabber card (Teledyne DALSA, Waterloo, ON, Canada). On the external computer side, RF lines are reconstructed from the IQ data by reversing the modulation process.

2) TRUS Robot: To obtain 3D data, a separate control system called the TRUS robot is used to rotate the transducer along its long axis– capturing 2D planes (sagittal planes) of RF data using its linear array. The BK 8848 transducer is attached to a conventional brachytherapy TRUS stabilizer (Micro-Touch TM, CIVCO Medical Solutions, Kalona, IA, USA) and stepper (EXII Stepper, CIVCO Medical Solutions, Kalona, IA, USA). This stepper comes with an encoder to read the “roll” angle of the transducer, which is useful for monitoring needle insertion during transperineal biopsy and brachytherapy intervention.

We designed a specific computer-controlled “roll” motor, with an encoder, that fits in the place of the stepper’s encoder– allowing our software to accurately control the angle of the transducer’s rotation. This modification does not alter any of the features of the stepper (such as fine control of the transducer’s translation in the z-axis) and therefore the operator can use it similarly to an unmodified stepper. Fig. 1a shows the TRUS robot along with the attached roll motor and its control box that provides power to the motor.

3) Transperineal Shaker: Multi-frequency excitation is applied transperineally using a shaker made with a linear hollow core voice coil (HVCM-051-025-013-01, Moticon, Van Nuys, CA, USA). A dome-shaped rod is connected to this shaker which makes contact with the perineum of the patient and generates forces in the inferior-superior direction. This rod is made from solid-core stainless steel of 5 mm diameter and is bent in a shape that allows the shaker to be positioned away from the moving TRUS robot. The shaker is mounted on the patient’s table by using a CIVCO Assist T M flexible arm (CIVCO Medical Solutions, Kalona, IA, USA). The flexible arm is maneuvered in order to provide good contact with the perineum; once that is achieved, the arm is locked into position using its handlebars. A control box was made in-house and uses an Agilent U2761A function generator (Agilent Technologies, Santa Clara, CA, USA), controlled by the external computer, to output the desired excitation frequencies. Fig. 1a displays the shaker together with the CIVCO arm, rod, and control box. The excitation signal, s(t), is the sum of the multiple individual sinusoids:

\[
s(t) = \sum_{n=1}^{N} a_n \sin(\omega_n t)
\]

where N is the number of frequency components, each having amplitude a_n and frequency \omega_n. The higher \omega_n, the higher the attenuation of the signal with depth. To compensate for this, higher a_n is set for higher \omega_n. The weights should be adjusted according to the combination of excitation frequencies chosen which can be done directly from the computer during image acquisition.

B. Signal Processing Pipeline for S-WAVE

1) Bandpass Sampling: There are two viable methods for sampling tissue motion at high frequencies—one that uses Doppler/Angiography-like sequences to acquire tissue motion in small sectors [53] and one that uses bandpass sampling [52]. The bandpass sampling method does not require users to program the ultrasound machine sequencer, and therefore works with any generic ultrasound machine that can unload RF lines to an external link, even when the machine is in clinical mode. The native frame rate of focused B-mode acquisition, due to speed-of-sound limitations, is on the order of 20-60 Hz for typically sized images. At this low frame rate, it is not possible to sample tissue motion at higher frequencies, at 70 Hz and above, which is required to produce small enough shear wavelengths to fit within the region of interest and give a good resolution of prostate elastography images. Bandpass sampling allows for the reconstruction of phasors of motion with frequencies higher than the Nyquist frequency. This is possible as the excitation frequencies and the sampling frequency (f_s) are known. Due to having a low f_s, the reconstructed phasor will be aliased and appear with a lower frequency. If f_s satisfies (2), the reconstructed signal will resemble the original spectrum in the measurable baseband.

\[
\frac{2f_c + B}{m + 1} \leq f_s \leq \frac{2f_c - B}{m}
\]

where f_c is the center frequency of the signal, B is the bandwidth, and m is the integer number of spectral half-shifts (f_s/2) needed to map the original spectrum in the baseband [52]. For multiple excitation frequencies, B of 10 Hz around every frequency component is a good choice to avoid overlap in the baseband.

2) Image Acquisition Settings: The volume acquisition consists of a programmed scan of the TRUS covering a rotation from −45° to 45° with increments of 0.9°, acquiring 100 discrete imaging planes each with M = 20 time-series sagittal frames of RF data. The depth and width of the
imaging for each plane are set to 55.2 mm and 60 mm, respectively, which are the preset values for prostate imaging on this ultrasound machine. Each RF frame contains 216 scan lines that are sampled at 50 MHz. RF frames are captured using the maximum achievable sampling rate at this depth and width, which is $f_s = 43.06$ Hz for this ultrasound machine. Following the bandpass sampling method, shear wave excitation frequencies are therefore selected so that they are not multiples of $f_s = 43.06$ Hz or $f_s/2 = 21.53$ Hz and such that they do not overlap in the baseband.

3) Tissue Motion Estimation: The tissue displacement is measured in the axial direction as a function of time following...
a speckle tracking algorithm [56]. In this algorithm, the scan lines are first divided into multiple overlapping windows with window size of 1 mm and spatial overlap of 84%. Displacements between these time-series windows are calculated by finding the maximum normalized cross-correlation (NCC) using cosine-fitting for sub-sample displacement resolution. This generates time-series displacement images for each imaging plane in the volume.

4) **Phasor Fitting:** Assuming a linear tissue response, the displacement in each voxel \( d(t_i) \) is the sum of complex phasors \( U_{1:N} \) with excitation frequencies \( \omega_{1:N} \).

\[
d(t_i) = \sum_{n=1}^{N} \text{Re} \left[ A_n e^{j \omega_n t_i} \right]
\]

where \( A_n \) and \( \theta_n \) are the amplitude and phase of phasor \( U_n \) \( t_i \) is known from the ultrasound’s scan sequence delay table and \( \omega_{n} \) is the known excitation frequency.

To recover the best fit for \( U_n \), only its \( A_n \) and \( \theta_n \) need to be calculated. By representing (3) in its trigonometric form and taking the real part, the unknown and known parameters of \( U_n \) can be expressed in the matrix form of \( x \) and \( A \) of size \((2N+1,1)\) and \((M,2N+1)\), respectively (since there are \( M = 20 \) frames, \( i = 1 : M \)). Similarly, \( d(t_i) \) is represented as a column vector \( b \) of size \( M \).

\[
d(t_i) = \sum_{n=1}^{N} \left[ A_n \cos \theta_n \cos \omega_n t_i - A_n \sin \theta_n \sin \omega_n t_i \right]
\]

\[
v_i = \frac{\sum_{i}^{N} \left[ A_0 a_2(t_i) \right] \sin \omega_n t_i}{\sum_{i}^{N} \left[ A_0 a_2(t_i) \right]}
\]

\[
\hat{x} \approx (A^T A)^{-1} A^T b
\]

From \( \hat{x} \), the amplitude and phase, and therefore the phasor, are found at each excitation frequency for every voxel. Thus 2D phasor images of each plane are obtained. These images contain a 2D projection of the steady-state shear waves, as can be seen in Fig. 2.

The goodness of the phasor fit or in other words, the quality factor (QF) can be estimated based on the ratio of the energy of the fitted signal and the energy of the fitted signal plus the difference in energy of the fitted and original signal as expressed in (8). The closer this value is to 1, the better the fit.

\[
\text{QF} = \frac{||A\hat{x}||^2}{||A\hat{x}||^2 + ||A\hat{x} - b||^2}
\]

5) **Phase Lag Compensation:** As the 3D data is collected in chunks and not simultaneously, there is time delay present between each line and each plane of the acquired data. The displacement data must be shifted in time to represent an equivalent simultaneous measurement. The time delay between lines can be calculated by \( T_1 = \frac{1}{\pm \times 10^6} \), where 216 is the total number of lines in each plane. The plane-wise time delay, \( T_p \), of each plane is recorded with respect to the data capture start time. Following [53], the phasors at each line \( l \) and each plane \( p \) are compensated by multiplying a complex exponential with the appropriate amount of time delay:

\[
U_{(n,l,p)}^{\text{synced}} = U_{(n,l,p)} e^{-j \omega_n ((-1) \times T_1 + T_p(p))}
\]

The frame grabber card saves time stamps of every received frame with a precision of 0.1 ms. From these timestamps, precise \( T_p \) can be calculated for each plane.

6) **3D Scan Conversion, Filtering, and Masking:** The set of synchronized 2D displacement phasor images is then scan-converted based on transducer-specific parameters to get 3D phasor volumes for each excitation frequency. The NCC calculated during tissue motion estimation from Section II-B.3 can be used as an indicator of the quality of displacements. Displacement voxels estimated based on high NCC means high confidence in the tracked motion at that voxel. Phasor voxels with NCC lower than 92% are masked out to improve the overall quality of the phasors. A Butterworth bandpass filter of 3\( rd \) order is then applied to these 3D phasor volumes in the frequency domain, which reduces motion artifacts and noise in the phasors. The cutoff frequencies for this bandpass filter are set to remove frequency components that correspond to the elasticity measurement outside 1-60 kPa. This range was chosen based on the expected elasticity range of in vivo prostate tissue (healthy and cancerous) [57].

7) **Elasticity Estimation:** It can be shown that dynamic and external excitation at a given temporal frequency \( \omega_n \) produces steady-state “compression” and “shear” waves within a given material [58]. The spatial frequencies, or wavenumbers (angular), of the compression wave, \( k_{cn} \), and the shear wave, \( k_{sn} \), are functions of the Lamé parameters of the material which describe its viscoelastic properties. We approximate \( k_{sn} \) using lognormal quadrature filters as Local Frequency Estimators (LFE) [31], [59]. The LFE algorithm involves the use of 6 directional filters in the 3 orthogonal axes (\( \pm X, \pm Y, \pm Z \)). These are implemented in the \( k \)-space with a \( \cos^2 \) dependence in the half-space and zero in the other half-space [60]. After filtering, the \( k_{sn} \), at each voxel for each \( \omega_n \) is estimated from the filtered phasor volumes. The corresponding Young’s modulus at frequency \( \omega_n \) is computed as \( E_n = 3 \rho (\omega_n / k_{sn})^2 \), with \( \rho = 1000 \text{ kg/m}^3 \) (as the density of the soft tissue can be estimated to be similar to that of water). Because the excitation frequencies are very close to each other, we ignore the frequency dependency and compute the average elasticity at a given voxel as:

\[
E = 3 \rho \frac{1}{N} \sum_{n=1}^{N} (\frac{\omega_n}{k_{sn}})^2
\]

Averaging the elasticity estimated from different \( \omega_n \) values reduce artifacts that can arise during displacement estimation,
as the wave pattern and hence the low shear wave amplitudes will not be at the same physical location.

The system can complete the 3D sweep in \( \approx 2 \) min and therefore has a volume rate of \( \approx 0.5/\text{min} \). This is for a 3D volume with 100 planes taken at 0.9\( ^\circ \) increments. The acquisition time can be further reduced if a smaller field of view, larger angular increments, or a combination of both are used. The first part of the data processing which includes tissue motion tracking, phasor fitting, and phasor lag compensation occurs simultaneously with the data acquisition– where every plane is processed as soon as the data is available before proceeding to the next plane. This is possible since our S-WAVE software is implemented to run on a CUDA-enabled GPU, allowing parallel processing. All results presented in this work were processed with an NVIDIA GTX Titan X GPU. After the last plane has been collected, the only steps left are 3D scan conversion, filtering, and elasticity estimation which takes \( \approx 30 \) sec more. One thing to note is that if only 2D reconstruction is used, results can be updated with a refresh rate of \( \approx 2 \) Hz as the system does not need to wait until the last plane is collected.

Each step of the full signal processing pipeline is illustrated in Fig. 2.

### III. Validation Setup

#### A. Validation on Phantoms

Two commercially available CIRS phantoms (Computerized Imaging Reference Systems, Norfolk, VA, USA) were used to characterize the system. A multi-frequency excitation signal with 69 Hz, 75 Hz and 80 Hz components was used to generate the shear waves. These frequencies were chosen based on the findings of a clinical study and will be explained in Section III-B.1. With the sampling rate, \( f_s = 43.06 \) Hz, the excitation frequencies are measured as 17.1 Hz \((69 - 2f_s)\), 11.1 Hz \((75 - 2f_s)\) and 6.1 Hz \((80 - 2f_s)\) in the baseband and are therefore far enough apart for accurate frequency reconstruction. The amplitude of each frequency is weighted as 0.29 : 0.34 : 0.37 (lowest to highest). Higher frequencies attenuate faster and therefore are weighted more. Our S-WAVE software can show 2D phasor reconstructions in-real-time (see Fig. 1a) and based on this, the intensity of the excitation signal is adjusted until the shear waves can be seen propagating through the imaging medium.

**1) Prostate Phantom:** A CIRS 053L model prostate phantom was used which contains a simulated rectum for transrectal transducers. This phantom is enclosed in a hard plastic shell with an exposed side that represents the perineum. The phantom contains a prostate gland (\( \approx 53 \text{ cm}^3 \)) with urethra, seminal vesicles, and three lesions which are each \( \approx 1 \) cm in diameter. This phantom was used to mimic how a patient will be scanned and therefore demonstrates the feasibility of the system’s use in a clinical setting. This is shown in Fig. 1a. The manufacturer quotes that the lesions are stiffer than the gland, but they do not provide any quantitative stiffness measurements for either the prostate or the lesions. To validate the measurements, a Philips Ingenia Elition 3.0T X MRI (Philips Healthcare, Best, The Netherlands) was used to perform 3D MRE [54] using the same excitation frequencies and the same reconstruction technique. 3D regions of interest (ROI) for the lesions and prostate gland were then drawn from the anatomic volumes in either of the imaging modalities, and the elasticity values within these ROIs were compared. To test if the S-WAVE measurements between the lesions and the prostate had a statistically significant difference, an unpaired \( t \)-test was conducted. More details of the dimensions of this phantom and how it was scanned with our system are provided in Fig. 1b.

**2) Elasticity Quality Assurance Phantom:** Next, a CIRS 049 model elasticity quality assurance phantom was used, which contains a homogeneous background with four 2 cm spherical inclusions. Each of these inclusions had a different stiffness value, with two being stiffer and the other two being softer than the background material. The transducer had to be operated upside down to scan this phantom which does not contain a simulated rectum. Also, as the linear array of the transducer can only cover half of the phantom’s length, only two inclusions could be scanned at a time. Therefore, separate scans were acquired to image all four lesions. More details of the dimensions of this phantom and how it was scanned with our system are provided in Fig. 1c.

Even though the manufacturer provides the estimated elasticity range for the background and the inclusions of this phantom (see Table II), these reported values cannot be compared directly as it is well known that the measured value of elasticity has a dependence on the excitation frequency and the measurement technique used [61], [62], [63]. This is also written on the manufacturer’s datasheet as a disclaimer. Therefore, for a more accurate validation, we compare the measurements with 3D MRE using the same set of excitation frequencies and the same reconstruction method similar to Section III-A.1. Using MRE, this entire phantom could be imaged in a single scan. 3D ROIs were drawn for the background and four individual inclusions, which were then used to compare elasticity measurements between modalities. An ANOVA test was carried out on the S-WAVE measurements of 4 inclusions and the background (comprising 5 groups in total) to determine whether there were any significant differences between them. Subsequently, a post-hoc analysis was performed using unpaired \( t \)-tests to evaluate the significant differences between each pair of groups. In total, 10 tests \((5!/2!(5 - 2)!))\) were conducted for the 5 groups using a Bonferroni corrected \( p \)-value of 0.005.

Altogether, to assess if there was any significant difference between the S-WAVE and MRE measurements for the different regions of the two phantoms, a paired two-tailed \( t \)-test was conducted.

#### B. Patient Data Collection

This section describes the data collection procedure for the two clinical studies conducted using this proposed system.

**1) Prostatectomy Study:** In this institutionally approved study, signed consent was obtained from 10 patients with clinically organ-confined PCa undergoing robot-assisted radical prostatectomy at Vancouver General Hospital (Vancouver,
Fig. 3. CIRS 053L: Comparison of reconstructed phasors and elasticity map results using MRE and S-WAVE with the same multi-frequency excitation and the same reconstruction technique. Two different planes are shown, which cover all three lesions present within the phantom. The average and standard deviation of the prostate gland (PG) and the lesions (L1-L3) in these planes are shown for both MRE and S-WAVE. Positive identification of all three lesions can be seen for both imaging modalities.

Fig. 4. CIRS 049: Comparison of reconstructed phasors and elasticity map results using MRE and S-WAVE with the same multi-frequency excitation and the same reconstruction technique. All four inclusions can be seen from a single plane in the MRE, while two scans had to be acquired for S-WAVE since the transducer can only scan half of the phantom (6 cm) at a time. The average and standard deviation of the background (BG) and the inclusions (I1-I4) for these planes are shown for both MRE and S-WAVE. Positive identification of all four inclusions compared to the background can be seen for both imaging modalities.
As this was the first clinical trial with this system, no prior information of its ideal excitation frequency range for in vivo prostate tissue was known. High-frequency excitation has the benefit of more robust \( k_s \) estimation but with the drawback of poorer penetration depth. To determine the ideal excitation frequency range, we captured several S-WAVE volumes from each patient with excitation frequencies ranging from 75 Hz to 180 Hz before the prostatectomy procedure. To reduce the time required to collect these data in the operating room, we chose a frequency step of 2.5 Hz (rounded to the nearest integer as required by our function generator). Data was then collected at successive excitation frequencies until shear waves were no longer visible—indicating the frequency limit after which shear waves are not reaching the prostate. Immediately following the prostatectomy, the excised prostate was sent to pathology, where whole-mount histopathology slides were obtained by evenly slicing the gland. A pathologist at Vancouver General Hospital then examined slices of excised prostate glands and outlined any cancerous regions, assigning a Gleason score (GS) for each region. In order to compare the elastography results to histopathology slices, which are transverse slices, the elastography volume must first be interpolated into a Cartesian grid from the stack of sagittal slices. A slice-to-surface, particle-filter-based registration technique [64] is then used to match the histopathology slices to the corresponding transverse planes in the elastography volume. This registration method reports a Dice coefficient of 90.1±5.8% between segmentations of the prostate from the ultrasound images and the histopathology slices. The annotations of these registered whole-mount histopathology images can then be used as the ground truth to evaluate the cancer detection capability of our prostate S-WAVE system. A data analysis approach to the multi-parametric nature of the images collected with this system has been presented earlier in [55]. In that prior work, features extracted from the absolute, real, and imaginary values of the phasor images as well as the quantitative elasticity values were all used to train a random forest classifier to identify cancer which achieved an area under the curve (AUC) of 0.82±0.01 for detecting PCa in the peripheral zone and an AUC of 0.79±0.01 in the overall gland.

2) Focal Therapy Study: The main purpose of this study was to investigate the feasibility of focal therapy in low-dose-rate prostate brachytherapy (LDR-PB) for early-stage PCa patients. A total of 17 patients consented to the study and were recruited in an institutionally approved pilot study at BC Cancer (Vancouver, BC, Canada). In this pilot study, the patients first underwent multi-parametric Magnetic Resonance Imaging (mpMRI). After the mpMRI, 2 patients withdrew and 1 patient was not eligible to continue the study.

The remaining 14 patients received whole-gland transperineal template mapping biopsy (TTMB) to determine the presence and location of tumours within the gland. Based on prostate size and following a needle template (see Fig. 7a), 20-50 transperineal biopsy samples were obtained for each patient. The average number of extracted cores was 1/cm² of prostate tissue. This was done to ensure adequate coverage (directed by mpMRI to ensure that suspicious areas are sampled) while avoiding unnecessary trauma to the prostate. During the biopsy procedure, each core was deposited in a separate labelled container with a clinically assigned core number and sent to pathology for hemotoxylin and eosin (H&E) staining and cancer identification. An expert pathologist from BC Cancer then reported the presence, pathology, and location of cancer within the cores. More details of this study and its initial clinical outcome are available in [65].

Observations from the Prostatectomy study (Section III-B.1) showed that consistent wave penetration was possible for all frequencies lower than 90 Hz. With the frequency range now known, a multi-frequency signal was selected such that components were evenly spaced in the baseband which allows for accurate bandpass reconstruction. This signal comprised of 69 Hz, 75 Hz and 80 Hz (which correspond to baseband frequencies of 17.1 Hz \((69 - 2f_s)\), 11.1 Hz \((75 - 2f_s)\) and 6.1 Hz \((80 - 2f_s)\) respectively). Similar to the phantom validation, for every case, the overall intensity of the excitation signal was adjusted based on real-time 2D phasors from the external computer. Using an automatic transperineal biopsy registration technique [66], the pathology results for the biopsy cores were mapped to the ultrasound domain. This technique takes needle bending into account and therefore provides a better estimation of the core’s location within the gland. This method retains the same expected positioning error of 5 mm as TTMB. The extraction length for the cores is set to 22 mm on the biopsy gun, but the actual extracted core length varied due to tissue breaking and shrinkage. These changes are also considered in this registration technique, and more details about the method can be found in [66].

S-WAVE with registered core data was available from 10 patients who received TTMB in this study. Out of these 10 patients, data from 3 patients had to be discarded, 1 due to corrupted data and the other 2 due to having significant respiratory movement resulting from deep snoring of the patients—where the prostate was moving in and out of the imaging window during the 3D sweep.

For these 7 patients (FT-P01 to FT-P07), using the location of the registered cores, 5 mm margins are drawn to account for any registration error. Using these margins, for each core type, a total of 20 features are extracted which include the mean \((\mu)\), standard deviation \((\sigma)\), maximum, minimum, and median values of elasticity taken from the individual frequency and averaged elasticity maps. The list of these 20 features is shown in Table I. A binary support vector machine (SVM)
classifier was then trained with these features to identify between benign or malignant with leave one patient out cross-validation (LOOCV). The SVM classifier was implemented with MATLAB R2021a (The MathWorks Inc., Natick, MA, USA) and its parameters were tuned automatically for each cross-validation using MATLAB’s built-in hyperparameter optimization function.

IV. RESULTS

A. Phantom Results

For the CIRS 053L phantom, the elasticity estimates of the three lesions and the prostate gland with our S-WAVE system and 3D MRE are presented in Fig. 3. Two matching planes are shown, among which all three lesions are visible. The projected steady-state shear waves for each of the excitation frequencies can be seen from the fitted displacement phasors. The last column shows the average elasticity map based on the three excitation frequencies. The apex of the prostate phantom is located on the left side of the sagittal images shown in the figure. The vertical axis represents the axial line of the ultrasound image and runs from the transducer (at the bottom of the image) upward. The seminal vesicles can be seen on the right side of the B-mode and T2-weighted (T2W) images. From the figure, it can be seen that neither the phasors nor the elasticity estimate for the S-WAVE technique is present outside the gland. This is because the background of this phantom is anechoic, and therefore motion estimation fails for this region. MRI, however, can image the background and therefore elasticity can be estimated beyond the prostate gland with MRE. In this figure, qualitatively, the lesions can clearly be seen to have higher stiffness than the prostate gland. Table II shows the average and standard deviation of the measured elasticity for each 3D ROIs of this phantom measured using both S-WAVE and MRE. The unpaired $t$-test between the S-WAVE measurements of the lesions and the prostate gland resulted in $p < 0.05$, indicating a statistically significant difference between the measurements.

Similarly, results for the CIRS 049 phantom are presented in Fig. 4. Displacement phasors at each excitation frequency are also shown in this figure, with the average elasticity map in the last column. The average and standard deviation of the elasticity measured within the annotated 3D ROIs for the background and the four different inclusions of this phantom are given in Table II for measurements taken with both S-WAVE and MRE. Qualitatively, the inclusions, moving from the stiffest to the softest, can be clearly seen from the left to right side of the figure for both imaging modalities. The ANOVA test for the S-WAVE measurements of the 5 different groups/regions resulted in a $p$-value of less than 0.05, indicating a statistically significant difference between at least two groups. Subsequently, the following post-hoc analysis revealed a $p$-value of less than 0.005 for all 10 tests, meaning that the measurements for all groups were significantly different from one another.

Using measurements of the phantoms taken with S-WAVE and MRE from Table II, with a total 7 points of measurements (prostate gland (PG), background (BG), lesions (L1-L3), inclusions (I1-I4)), correlation and regression analyses were conducted. A high cross-correlation of 96% was measured using the two methods with these 7 measurements. The best linear fit line can be seen in red in Fig. 5– where the gradient of this line is 1.0002. The quality of this linear fit can be measured with the coefficient of determination ($R^2$) which is measured to be 0.89. The closer $R^2$ is to 1, the better the data fit this line. Bland-Altman (B&A) plot analysis was also conducted to analyze the level of agreement between the methods and determine the presence of any bias. This is also presented in Fig. 5, where the blue line shows the presence of statistically significant bias.
Fig. 6. Prostatectomy study: Results from 4 patients are shown here. The distance (in mm) of these planes from the base of the prostate is indicated in the figure. The corresponding histopathology images are found based on a particle-filter registration technique. The segmentation of the prostate and the cancerous regions from the histopathology images are registered to the ultrasound images and are shown in white dashed contours and red contours, respectively. Quantitative measurements of the benign and malignant regions are also listed in the figure.

of a small bias of 0.15. The level of agreement is shown with the red dashed lines. Doing the paired two-tailed t-test resulted in no statistically significant difference in the measurements between the S-WAVE and MRE \( p > 0.05 \).

B. Patient Results

An extended analysis of the S-WAVE data from the Prostatectomy study was published in our prior work [55]. For demonstration, some of the cases (PS-P01 to PS-P04) are illustrated in Fig. 6, showing elasticity maps with their corresponding histopathology. The figure shows the segmentation of the prostate gland (white dashed) and the malignant region (red) on the B-mode and elasticity maps after the registration step. For each interpolated transverse plane, the corresponding histopathology image is shown in this figure. The quantitative average and standard deviation of elasticity for the healthy gland and the cancerous regions are also reported in this figure. A good correlation can be observed with the cancerous regions being stiffer in general than the rest of the prostate gland. The full analysis of the Prostatectomy study can be found in [55].

For the Focal therapy study, comparisons of S-WAVE images with registered whole-gland biopsy results for all 7 patients are illustrated in Fig. 7a. Biopsy cross-sections are registered with the interpolated transverse slices of the B-mode using the automatic biopsy core registration technique and superimposed on the images. The biopsy cores are colour-coded, where green, blue, and red circles indicate samples that are benign, positive (contains malignant tissue but in a different plane), and malignant (contains malignant tissue in the current plane), respectively. Orange cross marks identify grid locations of the needle template used to guide needles during the biopsy. Due to the possibility of needle bending, cores are not always centred in the template grid locations and can be seen to drift for some cases in Fig. 7a.
Fig. 7. Focal therapy study: a) Results from all 7 patients. The registered needle guide and the biopsy cores are superimposed onto the B-mode and elasticity maps. For each case, two transverse planes are shown which cover all of the 22 positive cores in this cohort. The distance (in mm) of these planes from the base of the prostate is indicated in the figure. For the cores, green, blue, and red circles indicate samples that were determined to be benign, positive (malignant tissue present somewhere in the core), and malignant (malignant tissue present in the current plane of the core), respectively. Orange cross marks are grid locations from the needle guide. The average and standard deviation of elasticity of the benign and malignant cores for each patient is tabulated here. The malignant cores are numbered and annotated for each patient based on the clinical core number assigned during the biopsy. b) The boxplot distribution of the benign, positive, and malignant parts of positive cores for each patient. The green asterisks indicate the mean values while the slope of the green lines connecting the mean values can be used to visualize the difference between the means.

On average, there were $3.1 \pm 1.3$ positive cores and $26.0 \pm 9.6$ benign cores per patient. Two transverse planes are shown from each patient in Fig. 7a, such that all 22 positive cores from all the patients can be seen. Some of the cores were outside the imaging field of view and were discarded for the rest of the calculations. The average and standard deviation of elasticity of the benign and malignant parts of the cores for each patient are tabulated in the same figure. For the benign cores, the average is reported along with the total number of cores. For the malignant cores, results are shown individually and are numbered based on the clinical core number assigned during the TTMB. These clinical core numbers are also annotated on the images for each patient. The majority of the malignant cores can be seen to be stiffer than the average.
benign core. This difference is very small, however, and this is expected primarily because the patients from this study only had early-stage cancer [67]. In this cohort, 70% of the malignant cores had a GS of just 3+3 while the remaining 30% had a GS of 3+4, as labelled in the table from Fig. 7a. A detailed distribution of the elasticity values between the benign, positive, and malignant parts of the positive cores are visualized with boxplots for all patients in Fig. 7b. The green asterisks represent the mean values and the slope of the green visualized with boxplots for all patients in Fig. 7b. The green asterisks represent the mean values and the slope of the green

With all 20 features, the SVM classifier could distinguish between cancer vs non-cancer with an overall average AUC of 0.87±0.12 from the LOOCV. The best operating points (thresholds) for each cross-validation were calculated by finding the minimum distance from the upper left corner of the training receiver operating characteristic curve (ROC) where the true positive rate is 1 and the false positive rate is 0. For each cross-validation fold, the ROCs from the training and test data are shown in Fig. 8 with their corresponding operating point, threshold, and AUC. Using these thresholds, the average sensitivity, specificity, and accuracy of this classifier were calculated to be 0.80±0.20, 0.84±0.10, and 0.83±0.10, respectively. The detailed results of each cross-validation are tabulated in Table III.

V. DISCUSSION

Similar to most other work in the field of ultrasound elastography [22], [24], [25], [34], [68], we have relied on 1D tissue displacement tracking in the axial direction only. Although 2D/3D motion tracking may be helpful, in some of our studies we found that the additional noise and large inter-sample distance in the lateral direction do not add to elasticity reconstruction quality. The reason for this is still unclear, and it is likely dependent on the type of pulse sequence used. This is still a topic of research for us. Nevertheless, 1D axial displacement tracking has shown to produce similar results to MRE which is a modality that can estimate motion with the same level of accuracy in all three directions [34].

We can estimate the goodness of the phasor fit (QF) for each voxel based on the equation in (8). From the phantom study, the average QF was 0.98 for the CIRS 053L phantom and 0.94 for the CIRS 049 phantom. For the patients, the average QF was 0.94 with a patient-wise standard deviation of 0.04. This indicates that the quality of the phasors estimated from the tracked motion was very high using this system.

Fig. 8. Receiver operating characteristic curves for training and test data for each fold of LOOCV with the SVM classifier. The optimum points are indicated on the curves with dots. The corresponding AUC and threshold (T) for each fold are also given in the legend.

**TABLE III**

RESULTS FROM THE SVM LOOCV FOR THE FOCAL THERAPY STUDY

| LOOCV    | AUC  | Sensitivity | Specificity | Accuracy |
|----------|------|-------------|-------------|----------|
| FT-P01   | 0.85 | 0.50        | 1.00        | 0.95     |
| FT-P02   | 0.98 | 1.00        | 0.76        | 0.77     |
| FT-P03   | 0.86 | 0.67        | 0.88        | 0.86     |
| FT-P04   | 0.96 | 1.00        | 0.88        | 0.88     |
| FT-P05   | 0.91 | 1.00        | 0.80        | 0.83     |
| FT-P06   | 0.95 | 0.80        | 0.90        | 0.88     |
| FT-P07   | 0.60 | 0.60        | 0.67        | 0.65     |
| **Average** | **0.87±0.12** | **0.80±0.20** | **0.84±0.10** | **0.83±0.10** |

This is still a topic of research for us. Nevertheless, 1D axial displacement tracking has shown to produce similar results to MRE which is a modality that can estimate motion with the same level of accuracy in all three directions [34].

The phantom study results demonstrate a statistically significant difference between the measurements of the different elements (background, prostate gland, lesions, inclusions) of the phantoms using our proposed S-WAVE system. Furthermore, no statistically significant difference was found between measurements of S-WAVE and MRE, indicating that the system can estimate elasticity as well as MRE. When compared to the range of values reported by the manufacturer, the results suggest that both our system and MRE underestimated the elasticity measurement of two of the stiffest inclusions (I1 and I2) in the CIRS 049 phantom. This is expected, as both techniques used an excitation signal with low excitation frequencies. Based on the equation for computing elasticity (10), for a given excitation frequency $\omega_n$, $E_n \propto \frac{1}{k_n^2} \equiv E_n \propto \lambda_n^2$, where $\lambda_n$ is the wavelength of the shear wave. Therefore, the stiffer the material, the longer the wavelength is for a constant $\omega_n$. A longer wavelength means fewer wavefronts occur within the scanning area, and therefore less accurate phasor fitting can be performed. This is more pronounced for the inclusions that have a scanning diameter of just 2 cm. To improve the estimates of these small, stiff lesions, $\omega_n$ must be increased which in turn will produce lower $\lambda_n$. Indeed, in [34], for the same CIRS 049 phantom and using the same 3D MRE with LFE reconstruction but with an excitation signal of 210-250 Hz, a closer estimate of the stiffer inclusions
could be made compared to the manufacturer provided range. Although it is possible to use higher excitation frequencies with this system, shear waves at excitation frequencies over 90 Hz are attenuated and do not travel all the way through the prostate and therefore is difficult to use for prostate imaging, based on the findings from Section III-B.1.

For the results shown from the Prostatectomy study in Fig. 6, one of the main limitations is that the registration technique used to transfer the annotations from the histopathology images to ultrasound images is based on an affine transformation, which does not consider regional deformations separately and therefore larger deformations of the in vivo prostate, particularly around the rectum, are not well aligned using this registration technique. This is evident for all 4 cases shown in this figure and can be seen to a large extent for PS-P01 and PS-P02. Furthermore, errors can be introduced as the registration is based on the segmentation of the prostate in the ultrasound volume and histopathology slices, and not based on image intensity or features. For the plane that is 23.3 mm away from the base for PS-P02, it can be seen that the registered contour has an offset from the rectum wall. If the contour was stretched more downward and deformed around the rectum wall, the malignant contour would better line up with the stiff region that can be seen from the anatomical left of the elasticity map.

Similarly, for the Focal therapy cases, the registration of TTMB cores is even more challenging. There is no way to know the exact location of the cores based on the information taken during the traditional TTMB workflow. The location relative to the needle guide can only be estimated with an expected error of 5 mm. This error increases further when needle bending occurs. Furthermore, errors can be introduced from breakage and shrinkage of the core tissue. By taking a 5 mm dilated margin around the core, we attempted to reduce the error that might come from the registration step, but this means that additional variations are added to the measurements. For instance, FT-P07 had the worst result in the LOOCV training and this is evident when we look at the elasticity maps for FT-P07 from Fig. 7a, where the cluster of positive cores on the anatomical left of the patient (Mal core 10, 16, and 20) seems to be aligned slightly more to the left side of the stiff region in the prostate. Interestingly, the Mal 22 core, which is on the right side of the patient, is also slightly off to the left of a stiff region. This might be due to a registration error. This is also why the boxplot distribution of the positive and malignant parts of the cores shows no difference from the benign cores for this patient as shown in Fig. 7b.

As there were very few positive cores for each patient (2-5 cores) in the Focal therapy study, the calculated sensitivity changes significantly based on the selected operating point from the ROC curve and therefore the standard deviation for sensitivity is quite high, as seen in Table III. Even though very promising results are achieved, the number of cases was limited and we believe that a larger sample will allow for a more generalized classifier to be trained with a more complex set of features. We are currently using this system in a new clinical study (OPTiMAL) at BC Cancer (Vancouver, BC, Canada) investigating the use LDR-PB boost to reduce cancer relapse for unfavourable risk patients. With the additional cases, future work includes an extended analysis of the Focal therapy study and OPTiMAL data to further quantify the correlation between elasticity as measured by this system and cancerous tissue. In OPTiMAL, a commercially available software is being used to more accurately map the path of the needle and the location of the core during TTMB. This means that the location of the cores within the S-WAVE volumes can be more reliably located. Nevertheless, the challenges of tissue shrinking and tissue breakage would still exist.

Overall, even though our system did produce elasticity maps with areas of higher stiffness corresponding to most malignant regions (as demonstrated in this article with the 11 patients in both studies), multiple stiff regions were also estimated that did not correspond to malignancy. These could be due to a number of different biological phenomena, such as calcification, benign prostatic hyperplasia, and edema. Therefore, classifiers with a more intricate set of features perform better compared to threshold-based cancer identification from the stiffness maps.

We had a data failure rate of 30% in the Focal therapy cohort– where data from 2 patients had to be eliminated due to significant movement in the prostate resulting from respiratory motion. Although the proposed system is an order of magnitude faster than other 3D prostate SWE systems, both ultrasound [49] and MRE [69], the 2 min acquisition time is still a problem if there is movement in the prostate while the data is being collected. We observed that if local anesthesia with sedation was used, patients would fall into a deeper sleep and snore vigorously– causing a significant movement in the prostate. Instead, if spinal epidural or general anesthesia was used, where respiratory motion can be controlled, the prostate motion was less prominent. If the respiratory motion is controlled and can be predicted, it can be removed during the motion tracking algorithm. Another option would be to use prostate stabilization needles to hold the prostate in place however that would be an invasive procedure.

It is also important to note that the transducer and the shaker rod must be carefully adjusted when the system is configured. If the transducer pushes up on the rectum too much or if the shaker rod pushes too hard on the perineum of the patient, the prostate can deform and compress– resulting in incorrect elasticity estimates. The best way to ensure that this does not happen is to use the fine control knob of the TRUS stabilizer and adjust the y-axis of the transducer. Using an endocavity balloon with the transducer also allows compressing the rectum uniformly in all directions, providing better coupling, and therefore removing the need of pushing up hard against the rectum.

VI. Conclusion

This article has outlined a new ultrasound elastography platform that can be used to measure and display the 3D absolute value of the stiffness of tissue. A specific implementation of the system that can be used for prostate imaging to help identify cancerous tissue has been described in
detail. Elasticity is computed by averaging the values obtained from several frequencies that can be applied simultaneously. The system has been validated using two commercial CIRS phantoms and two clinical patient studies to perform elastic modulus measurements of the prostate. The results of the phantom validation show strong agreement with the MRE measurements, including a correlation of 96% and no statistically significant difference between the two modalities. For the two clinical studies, the visual correlation between stiffness elasticity values (as measured by our system) and cancerous regions (identified in pathology) has been demonstrated. An analysis of S-WAVE data from patients in the Focal therapy study has been carried out in which an SVM classifier trained with leave one patient out cross-validation resulted in an average AUC of 0.87±0.12 for cancer detection with the leave one patient out cross-validation. The study has been carried out in which an SVM classifier trained with leave one patient out cross-validation resulted in an average AUC of 0.87±0.12 for cancer detection with leave one patient out cross-validation. The results of the study have been carried out in which an SVM classifier trained with leave one patient out cross-validation resulted in an average AUC of 0.87±0.12 for cancer detection with leave one patient out cross-validation.

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