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Building an Open-source Simulation Platform of Acoustic Radiation Force-based Breast Elastography

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Abstract

Ultrasound-based elastography including strain elastography (SE), acoustic radiation force Impulse (ARFI) imaging, point shear wave elastography (pSWE) and supersonic shear imaging (SSI) have been used to differentiate breast tumors among other clinical applications. The objective of this study is to extend a previously published virtual simulation platform built for ultrasound quasi-static breast elastography toward acoustic radiation force-based breast elastography. Consequently, the extended virtual breast elastography simulation platform can be used to validate image pixels with known underlying soft tissue properties (*i.e.* “ground truth”) in complex, heterogeneous media, enhancing confidence in elastographic image interpretations.

The proposed virtual breast elastography system inherited four key components from the previously published virtual simulation platform: an ultrasound simulator (Field II), a mesh generator (Tetgen), a finite element solver (FEBio) and a visualization and data processing package (VTK). Using a simple message passing mechanism, functionalities have now been extended to acoustic radiation force-based elastography simulations.

Examples involving three different numerical breast models with increasing complexity – one uniform model, one simple inclusion model and one virtual complex breast model derived from magnetic resonance imaging data, were used to demonstrate capabilities of this extended virtual platform. Overall, simulation results were compared with the published results. In the uniform model, the estimated shear wave speed (SWS) values were within 4% compared to the predetermined SWS values. In the simple inclusion and the complex breast models, SWS values of all hard inclusions in soft backgrounds were slightly underestimated, similar to what has been reported. The elastic contrast values and visual observation show that ARFI images have higher spatial resolution, while SSI images can provide higher inclusion-to-background contrast.

In summary, our initial results were consistent with our expectations and what have been reported in the literature. The proposed (open-source) simulation platform can serve as a single gateway to perform many elastographic simulations in a transparent manner, thereby promoting collaborative developments.

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Keywords

elastography; finite element modeling; shear wave elastography; acoustic radiation force; supersonic shear imaging

Introduction

Breast cancer is the 2nd most common cancer among American women, behind only skin cancers. The American Cancer Society's estimates that in 2016 there are about 246,660 new cases of invasive breast cancer among women in the United States (ACS, 2016). A recent comprehensive report by the American Cancer Society also confirmed that, in general, early detection is the key for decreased mortality (Oeffinger *et al.*, 2015). Annual mammographic screening is often used for early detection of breast cancer, reducing mortality and morbidity, particularly in patients with tumors in fatty breast tissue (Tabar *et al.*, 2011). However, the sensitivity and specificity are not ideal for mammography as described in the literature (Berg *et al.*, 2004). Breast biopsy remains the gold standard for definitive diagnosis of suspicious breast lesions. However, it is painful, exposes the patient to a risk for infection and 75% of the biopsies end up being benign (Huynh *et al.*, 1998). Thus, it is essential to develop reliable, non-invasive, cost effective methods for breast cancer detection and differentiation.

In recent years, acoustic radiation force-based elastography (Palmeri and Nightingale, 2011) has been successfully applied to non-invasive differentiation of breast lesions. In this paper, terminology related to ultrasound elastography follows recommendations by the World Federation of Ultrasound in Medicine and Biology (Shiina *et al.*, 2015). Loosely speaking, acoustic radiation force-based elastography can be divided into two categories: (1) Acoustic Radiation Force Impulse (ARFI) Imaging and (2) Shear Wave Elastography (SWE). In ARFI imaging, acoustic pulses are first used to locally deform the tissue of interest. Then temporal or spatial tissue responses (*e.g.* displacement, time-to-peak [TTP] and maximum displacement) are ultrasonically measured to infer local tissue elasticity. In SWE (*i.e.* point shear wave elastography [pSWE] and supersonic shear imaging [SSI]), acoustic pulses are first used to generate shear wave (SW) propagation. Once the SW is induced, SW wavefronts are ultrasonically tracked to estimate absolute shear wave speed (SWS), which is proportional to the local tissue stiffness.

In a recent meta-analysis (Liu *et al.*, 2016) (33 clinical studies; up to Nov. 2014; 5838 lesions in 5397 patients), data clearly showed that both ARFI imaging and SSI have excellent sensitivity and specificity (85% ~ 90%) in terms of breast lesion characterization. Furthermore, SWE can be useful in upgrading a mass of low suspicion (BI-RADS 3) or downgrading a lesion that will be otherwise classified as BI-RADS 4A (Lee *et al.*, 2014). Because of those successes, acoustic radiation force-based elastography (including ARFI, pSWE, and SSI) is increasingly being employed to characterize breast masses in conjunction with the standard B-mode ultrasound. However, there are still concerns about uncertainties in SWS measurements. Biases among SWS measurements were experimentally investigated (Zhao *et al.*, 2011). In tissue mimicking materials, Zhao *et al.* found that SWS measurements

may be dependent on transducer, depth, and lateral tracking range (Zhao et al., 2011). Another recent inter-laboratory tissue-mimicking phantom study initiated some good discussions regarding how SWS measurements should be interpreted. Particularly, the study concluded that there was a statistically significant difference in the SWS estimation among systems and with depth into the same tissue-mimicking phantom (Hall *et al.*, 2013). The above-referred study was authored by the Quantitative Imaging Biomarker Alliance, a research consortium under the Radiological Society of North America.

Concerns regarding medical imaging modalities such as those mentioned above for SWE are typically addressed through human trials and laboratory tests using tissue-mimicking phantoms. In this study, we are advocating an alternative approach — virtual imaging simulation (Glatard et al., 2013). More specifically, virtual imaging simulation of ultrasound elastography is referred to a process of elastographic system development, which involves computer-aided engineering software (*i.e.* geometry modeling, Finite Element Analysis [FEA], acoustic simulation software) to evaluate elastographic methods without making a physical/hardware prototype (Wang et al., 2015). Such a virtual imaging simulation platform can offer an alternative method to compare the simulated elastographic (e.g. SWS) images with the known but (arbitrarily) complex underlying properties. Such correlation testing between elastographic images and their underlying soft tissue properties could assist us in understanding the measurement uncertainties in elastography. Furthermore, the development of the proposed virtual elastography simulation platform will be open source and therefore, rigorous imaging tests mentioned above can be transparently done.

To our knowledge, building (open-source) virtual imaging simulation platform for acoustic radiation force-based elastography involving in complex (numerical) breast phantoms has not been reported in the peer-reviewed literature, though work has been done for simulations in simple numerical phantoms (Palmeri *et al.*, 2010; Palmeri *et al.*, 2008). Leveraging our early work in simulations of quasi-static SE (Wang *et al.*, 2015), the primary objective of this study is to extend the existing SE simulation platform for acoustic radiation force-based elastography applications. In this feasibility study, we compared our simulation results with published experimental results by others (Palmeri *et al.*, 2008; Deffieux *et al.*, 2011; Zhao *et al.*, 2011). Collectively, the proposed software platform may act like a single gateway (software) platform to enable imaging physicists/scientists to perform a large fraction of all advanced UE simulations (*i.e.* SE, ARFI, pSWE, SSI).

Materials and Methods

As shown in Figure 1, the proposed software platform for acoustic radiation force-based UE involves several key (open-source or free) software packages in multiple steps. FIELD II (Jensen, 1991) is an ultrasound simulator that was used to (1) calculate distributions of acoustic pressure and (2) generate ultrasound echo signals given a weakly scattering medium. Using the acoustic pressures as boundary conditions, FEBio (Maas *et al.*, 2012), an open-source finite element solver for biomechanics, was employed to obtain local tissue deformation. Once a series of pre- and post-deformation ultrasound echo data were obtained, speckle tracking (Jiang and Hall, 2015) was performed to estimate tissue deformation and subsequently assess tissue elasticity, dependent on the modality being simulated. Image

formation procedures in pSWE, ARFI and SSI are well documented in the literature (Bamber *et al.*, 2013).

A. Calculation of Acoustic Radiation Force

Using a high-frequency (5–10MHz) linear array transducer, distributions of acoustic pressure were simulated using FIELD II (Jensen, 1991). An example of FIELD II simulated acoustic pressure field obtained using a 10 MHz linear array transducer was shown in Figure 2. Ultrasound parameters of a 5 MHz and a 10 MHz linear array probes were the same as ones used by Palmeri and Nightingale (Palmeri and Nightingale, 2011) and Zhao *et al.* (Zhao *et al.*, 2011), respectively. Those ultrasound simulation parameters are listed in Table 1. For subsequent FEA simulations to obtain local tissue deformation, the only acoustic pressure within the beam width (full width at half maximum) was used to deform subsequent finite element models, as suggested by Palmeri *et al.* (Palmeri *et al.*, 2008). Normalized acoustic pressures were first projected onto FEA Models and then their amplitudes were scaled to achieve peak displacements of 15 micrometers (Palmeri *et al.*, 2008) in the proximity of the simulated acoustic pushing pulse.

B. Numerical Phantom Generation

Three different numerical breast models of increasing complexity (*i.e.* a simple uniform medium [Model 1], a uniform medium with an (8-mm diameter) spherical inclusion [Model 2] and a complex breast model derived from magnetic resonance imaging data [Model 3]) were used in this study, as shown in Figure 3. Model 1 and Model 2 were built to replicate tissue-mimicking phantoms reported in the literature (Palmeri *et al.*, 2008; Defieux *et al.*, 2011; Zhao *et al.*, 2011). Details of the complex breast model (*i.e.* Model 3) can be found in our previous publication (Wang *et al.*, 2015). To improve numerical accuracy for simulations of SW propagation, all numerical models in this study were meshed by Tetgen (Si and Gartner, 2011) with quadratic tetrahedrons (*i.e.* 10 node tetrahedrons). Of note, the selection of quadratic tetrahedral (finite) elements comes with higher computing expenses but offers improved accuracy as compared to linear tetrahedrons (*i.e.* 4 node tetrahedrons). Mesh sensitivity was tested using two computing grids: 1.1 million and 0.5 million (quadratic) tetrahedrons. The displacement differences are less 10^{-3} micrometers between the aforementioned coarse and fine meshes. Therefore, the coarse mesh was used for subsequent biomedical simulation.

In the coarse mesh, adaptive meshing (Si and Gartner, 2011) was used and the average element size near the inclusion and the pushing beam was on the order of 0.01 mm^3 . Such a fine (mesh) density allowed accurate simulations of mechanical responses induced by the acoustic radiation forces.

C. Biomechanical Simulation

To simulate tissue deformation induced by the acoustic radiation force/pressure (see Figure 1). FEBio (Maas *et al.*, 2012), an open source FEA package, was used to perform biomechanical simulations. Given the small deformation (on the order of 1–15 micrometers) induced by the acoustic radiation forces (Bercoff, 2004; Bamber *et al.*, 2013), all materials used were assumed to be isotropic and linearly elastic as a first approximation. In FEBio, the

Neo-Hookean model (Fung, 1993) closely approximates linearly elastic media under the small deformation. Material properties of Models 1–3 are listed in Table 2. Particularly, material properties of Models 1 and 2 were selected to match published tissue-mimicking phantom experiments (Palmeri *et al.*, 2008; Deffieux *et al.*, 2011; Zhao *et al.*, 2011) for subsequent comparisons, while material properties of Model 3 were chosen to reflect the fact that the elastic contrast between a breast lesion and its background is approximately 8–11 (Krouskop *et al.*, 1998; Wang *et al.*, 2009) at small strains (*e.g.* 1–5%). The mass density of all materials used in this study was set to 1.0 g/cm³. In all models, dimensions of those three models were large enough so that shear wave reflections from exterior edges were avoided, due to the fact that “non-reflective” boundary condition has not been implemented in FEBio. More detailed descriptions related to pSWE, SSI and ARFI are briefly summarized below.

(1) Point Shear Wave Elastography (pSWE)—Acoustic radiation force fields were projected onto Model 1 through cubic spline interpolations in MATLAB (Mathworks Inc., MA, USA), as shown in Figure 4 (red dot region). The acoustic pulse was used to excite the tissue (see the red dots in Figures. 4a–b) for 1 millisecond (Palmeri *et al.*, 2008) while the entire (temporal) length of the dynamic FEA simulation was 8 milliseconds. The normalized acoustic pulse (see Figure 1) was scaled so that the peak displacement at the focal point was around 15 μm (Palmeri and Nightingale, 2011). The time-resolved displacement field between two horizontal red dashed lines (a 1 mm spacing) in Figures 4a was stored and subsequently analyzed to estimate SWS values. In order to obtain a SWS map in two-dimension (2D), this process was repeated for a number of depths (every 1 mm; see Fig. 4(b)).

(2) Supersonic Shear Imaging (SSI)—To approximate plane SW propagation in SSI, impulse acoustic radiation forces whose pulse length was 100 microseconds swept down along the axial depth direction (spaced 1 mm apart) successively (Bercoff, 2004). The time delay between the above-mentioned sequential acoustic pushing was 10 microseconds to ensure the sweeping speed moved faster than the SW propagation speed (Bercoff, 2004). Then, a set of time-resolved displacement fields in the region of interest (ROI) was acquired. FIELD II ultrasound simulations were performed to simulate ultrasound data acquisition with a frame rate of 10 KHz. The sweeping depth ranges were 15 mm (15 locations) and 10 mm (10 locations) for Models 2 and 3, respectively.

(3) Acoustic Radiation Force Impulse (ARFI) imaging—ARFI simulations were performed in conjunction with Models 2 and 3. In the simulated ARFI imaging, acoustic radiation forces with an acoustic pulse length of 100 microseconds were simulated to interrogate multiple spatial locations (spaced 1 mm apart in each direction) sequentially, as shown in Figure 6. Each acoustic excitation was followed by 2 milliseconds of simulated tracking beams to observe the time-resolved tissue responses within the region of excitation (Sharma *et al.*, 2004). This sequence was repeated over ROIs of 20 mm $\times$ 15 mm and 10 mm $\times$ 9 mm for Models 2 and 3, respectively. Time-resolved displacement fields were stored and were used in conjunction with FIELDII for the subsequent ultrasound simulations.

D. Ultrasound Simulations Using FIELD II

All ultrasound simulations were performed by FIELD II (Jensen, 1991). Procedures were the same as described in our previous paper (Wang *et al.*, 2015) and were briefly summarized below. Randomly positioned point scatterers were placed in Models 1–3 to ensure Rayleigh scattering. The scatterer density was 30 scatterers/mm³. Acoustic reflective coefficients were assigned to each and every point scatterer. The corresponding data were chosen based on the literature (Duck, 1990). Perfect matching layers around the boundaries were automatically added by FIELDII to avoid undesirable wave reflections at the boundaries. Acoustic attenuation was not simulated. During FIELD II simulations, around 150 lines were used to cover the entire field of view, resulting in a beam spacing of 0.12 mm for all simulated ultrasound data.

E. Data Analysis

A high-performance computing cluster was used (<http://superior.research.mtu.edu/>). One beam line took approximately 1 minute under MATLAB (Version 2013b, Mathworks Inc. MA, USA; 4 CPUs [Intel Xeon E2560; 2.8GHz] and 16GB of memory).

(1) Speckle Tracking and Displacement Estimation—Once a pair of pre- and post-deformation radio-frequency echo frames were obtained using the above-mentioned FIELD II simulation, a modified block matching algorithm (Jiang and Hall, 2015) was used to obtain axial and lateral displacements within a region of interest (ROI). The tracking kernel size was approximately 1.5mm (lateral) $\times$ 0.6mm (axial). More details of this method can be found in a previous publication (Jiang and Hall, 2015).

(2) Shear Wave Speed (SWS) Estimation—In this study, the time-of-flight (TOF) approach (Palmeri *et al.*, 2008; McLaughlin and Renzi, 2006) was used to estimate SWS in the region of interest (ROI). TOF-based methods employ *a priori* assumptions, including local homogeneity, and a known direction of propagation, such that the arrival time at adjacent positions can be used to determine the shear wave speed (Palmeri and Nightingale, 2011). In this study, the middle point of the shear wave front was identified as a more reliable feature to estimate the shear wave arrival time at fixed lateral positions. The acoustic simulation data were up-sampled to 50 kHz (from 10 kHz) before being processed by the time-of-flight method (Palmeri *et al.*, 2008). To improve reconstruction results of the simulated SSI, a directional filter (Deffieux *et al.*, 2011) was employed to remove off-axis wave interferences among ultrasonically-tracked displacement data, prior to the application of the above-mentioned TOF method.

(3) Evaluation of Elastic Contrast on Elastographic Images—Elastic contrast (EC) (Kallel *et al.*, 2001) was chosen to compare results among different methods (*i.e.* pSWE, SSI, ARFI and SE). The elastic contrast (EC) is defined as follows,

$$EC = \frac{I_t}{I_b} \quad (1)$$

where I denotes the mean values of intensity on the elastogram of interest, and subscripts b and t represent the background and target, respectively. Two different methods for ROI selection were used as shown in Fig 7a–b. In Fig. 7, the middle rectangular or circular ROI within the target (delineated by the contour in orange in Fig. 7a) was used to calculate the mean intensity of the target (I_t), while small squares (Fig. 7a) or the large shaded blue ring (Fig. 7b) were used to calculate the mean intensity of the background (I_b). The area of the target ROI is equal to its counterpart in the background. The “true” elastic contrast between the target and the background of the numerical phantom was calculated based on shear modulus values used in FEA simulations.

(4) Study of Biases in pSWE—In order to show the SWS measurements were dependent on the aperture size, focal depth and lateral tracking ranges, numerical simulations using a 5MHz linear array transducer were performed based on experimental data reported by Zhao *et al.* (Zhao *et al.*, 2011) All ultrasound simulation parameters can be found in Table 1 above. Particularly, the simulated pushing beam was focused on 20 mm and 40 mm depths, respectively; In each focal depth, three different aperture sizes (*i.e.* 32, 64 and 96 active elements) were simulated. All simulations were performed in a numerical phantom as described in Table 2 above. All SWS values were estimated from a lateral tracking range that was slightly away (1–6 mm) from the location of the simulated acoustic excitation.

How the lateral tracking range affects the SWS measurements was also investigated. When the simulated acoustic pushing beam was focused at the depth of 20 mm using three different active aperture sizes, the SWS values were estimated in two lateral tracking ranges: 1–6 mm (hereafter referred as to the near tracking range) and 8 – 13mm (hereafter referred as to the far tracking range) from the focus of the pushing beam.

Results

Preliminary results in this section were used to demonstrate capabilities of the proposed virtual simulation platform. For the sake of clarity, those results were largely divided by simulated imaging modalities.

A. Simulated pSWE

Results from the proposed simulated pSWE obtained from Model 1 were shown in Figures 8 and 9, respectively. In Figure 8, displacement data along different (temporal) phases have been displayed to visualize the SW propagation (see Figures 8b–d). In Figure 8e, the estimated SWS along a lateral (perpendicular to the SW propagation direction) line was 1.31 ± 0.04 m/s. The relative difference between the known SWS (1.26 m/s) and the estimated SWS (1.31 m/s) was approximately 4.0%. The known SWS was estimated by $\sqrt{G/\rho}$ based on its predetermined material properties (see Table 2), where G and ρ are shear modulus and the mass density, respectively.

In Figure 9, two-dimensional (2D) SWS image from Model 1 was generated by repeating the process as illustrated in Figure 4b at different axial depths. The SW front arrival time and the estimated SWS images were shown in Figure 9b–c, respectively. In Figure 9c, the

estimated SWS was 1.32 ± 0.14 m/s, similar to what was reported in the literature 1.3 ± 0.44 m/s (Palmeri *et al.*, 2010). Qualitatively, the displacement time-to-peak (TTP) image (Figure 9b) estimated from simulated time-resolved displacement curves was comparable to the one experimentally obtained (see Figure 6a in the original paper (Palmeri *et al.*, 2008)).

B. Biases in Simulated pSWE

Estimated SWS values using wave data simulated at two different depths are shown in Figure 10. At each depth, three different transmit aperture sizes were simulated. Simulation results clearly exhibited that the SWS measurements may be dependent on the aperture size and focal depth, thereby resulting in biases in SWS measurements. Our simulation results (see Figure 10a) are similar to those experimentally measured (see mean values in Figure 10b) under the same condition. The differences between our simulation results and experimental results (Figure 10a vs. mean values in Figure 10b) were small (around 0.02 m/s or 1.5%). How the estimated SWS values were affected by the lateral tracking ranges are shown in Figure 11. Both the simulation and experimental results showed that the estimated SWS values were higher in the near (lateral) tracking range than those estimated in the far (lateral) tracking range. Again, the differences between our simulation results and experimental results (Figure 11a vs. mean values in Figure 11b) were small (around 0.02 m/s or 1.5%).

C. Simulated SSI

Simulated SSI was performed for Models 2 and 3. Results are summarized in Figures 12–13. “Mach cone-shaped” plane shear waves (Bercoff, 2004) were observed in both models. Our results also confirmed that the angle of the plane shear wave was proportional to the ratio between the SWS and the speed of the moving supersonic source as suggested in the literature (Bercoff, 2004). Visually, the SW propagation both in Models 2 and 3 was progressively distorted by heterogeneities (Figure 12b) and such distortions had been accelerated after the SW wave fronts passed through respective harder inclusion (see Figures 12c and 13c). It is worth noting that the modulus ratio between the background and the inclusion was higher for Model 3 (1:10), as compared to that in Model 2 (1:4). That explains why the (shear) wave interference patterns in Model 3 were clearly noticeable and visually more consistent with the shapes of the inclusion (see Figure 13c).

Figures 12d and 13d show the estimated SWS values as images in Models 2 and 3, respectively. We found that, due to tissue heterogeneities in Models 2 and 3, estimated SWS values from the background were less uniform and the relative variances of estimated SWS from the background increased to 4% (Figure 12d) and 12.5% (Figure 13d) for Models 2 and 3, respectively. Now referring to the inclusion in Model 2, the average estimated SWS was 4.05 m/s and therefore it was underestimated by 9.4% as compared to the known SWS of 4.47 m/s. Similarly, the respective known SWS values were also estimated by $\sqrt{G/\rho}$ based on its predetermined material properties of Models 2 and 3 (see Table 2), where G and ρ are shear modulus and the mass density, respectively. Qualitatively, the inclusion shape in Figure 12d was similar to the shape experimentally obtained (see Figure 12e) in a tissue-mimicking phantom (Deffieux *et al.*, 2011).

In Model 3, the mismatch between the fibro-glandular background and the simulated breast lesion was greater (1:10) and the tissue composition was more complex (Figure 13a). Therefore, the reconstructed shape of the inclusion in Model 3 slightly deviated away from the known size and shape. Notably, there is a slight divot artifact in the reconstructed SWS image as shown in Figure 13d. The same divot was also reported in the literature (Deffieux *et al.*, 2011). Although boundaries of the simulated breast lesion are not well visualized due to the presence of the “divot” artifact, a stiff region in the center of the SWS image well correlated with the simulated breast lesion can be clearly observed. The result shown in Figure 13d is qualitatively similar to what were reported by others (Palmeri *et al.*, 2010).

D. Simulated ARFI Imaging

For visualization purposes, both peak displacement and (displacement) time-to-peak (TTP) images were normalized between 0 and 1. Normalized ARFI peak-displacement and (displacement) TTP images were simulated in Model 2 and Model 3, as shown in Figure 14 and 15. Albeit slight differences, the respective inclusion (lesion) size appeared in the ARFI image was visually the same as what was observed in the respective B-mode image. Clearly, hard inclusions were displaced less than their surroundings. Furthermore, it took less time for hard inclusions to reach their peak displacements (see Figures. 14c and 15c). Estimated ARFI parameters — peak displacement and (displacement) TTP were relatively uniform and their relative variances were approximately 10% (Figure 14 b–c and Figure 15b–c).

E. Elastic Contrast (EC) Evaluation

In Models 2 and 3, elastic contrast (EC) values (Eqn. 1) were estimated for three simulated imaging modalities using Methods A and B (see Figure 7): SSI, ARFI and SE. Results are listed below in Table 3. Overall, SSI shows the largest elastic contrast as compared with the other two qualitative methods — SE and ARFI images.

Discussion and Conclusions

The proposed system leveraged other open-source/freeware packages, namely VTK (Kitware Inc. NY, USA), Tetgen (Si and Gartner, 2011), FEBio (Maas *et al.*, 2012) and Field II (Jensen, 1991). All four software packages have been widely used in biomedical research. Capitalizing on successes of these four existing packages, we demonstrated that a virtual acoustic radiation force-based elastography simulation platform can be implemented. The proposed acoustic radiation force-based elastography simulation platform is an extension of our previous work on a quasi-static SE simulation platform (Wang *et al.*, 2015).

Simulated results by the proposed virtual elastography system in this feasibility study were quantitatively and qualitatively compared to tissue-mimicking and numerical phantom experiments reported in the literature (Palmeri *et al.*, 2010; Bercoff, 2004; Sharma *et al.*, 2004). Overall, we found that our simulated elastographic results were consistent with those published experimental results (Palmeri *et al.*, 2010; Bercoff, 2004; Sharma *et al.*, 2004) as briefly summarized below. In the uniform numerical phantom (**Model 1**), the SWS speed estimated from ultrasound simulations was essentially the same as the SWS speed experimentally measured (1.32 ± 0.14 m/s vs. 1.3 ± 0.44 m/s). However, both our simulated

and experimentally measured SWS values were slightly higher than the theoretical SWS (1.26 m/s as calculated by $\sqrt{G/\rho}$). Visually, the simulated distribution of (displacement) TTP was also comparable to what was experimentally measured (Figure 9b vs. Figure 6a in the original experimental study (Palmeri *et al.*, 2008)). Work by Zhao et al. (Zhao *et al.*, 2011) demonstrated in tissue-mimicking materials that the SWS measurements were dependent on the focal depth, aperture size and lateral tracking range. Using the simulated pSWE, our simulation results in Model 1 (Figures 10 and 11) were able to quantitatively reproduce those experimental results by Zhao *et al.* In the simple inclusion phantom (**Model 2**), shear modulus values within the hard inclusion estimated by the proposed simulated SSI, on average, were approximately 10% lower than what were experimentally reported by Deffieux *et al.* (Deffieux *et al.*, 2011) through visual inspections (see Fig. 10d vs. Fig. 10e), and were 17% lower than the underlying shear modulus value (see Table 2). Palmeri also reported (Palmeri *et al.*, 2010) a similar finding. They found that such an underestimation increased as the stiffness values between inclusion and background further differed. The proposed simulated SSI confirmed their finding. We recognize that more rigorous validations and developments are still needed to ensure soundness of the proposed virtual elastography system.

The outcome of simulated SSI may also be dependent on signal processing techniques used to estimate SWS. One example is shown in Figure 16 in order to exhibit the SWS reconstruction results with and without the directional filter. Figure 16 demonstrated that quantitative differences may be introduced by different data processing strategies. Particularly, in the complex breast model (**Model 3**), when the directional filter (Deffieux *et al.*, 2011) was not applied, the SWS image was quite noisy and the “divot artifact” in the estimated SW images was fairly pronounced (see Figure 16a). After the directional filter had been applied, the SWS image became smoother though the “divot artifact” was slightly visible. The “divot artifact” was largely caused by changes in the SW morphology due to reflections at the stiff-to-soft and soft-to-stiff interface as the shear wave propagates through the boundary (Palmeri *et al.*, 2010). Evidently, SW distortions caused by tissue heterogeneities were clearly observed in our results (Figure 13d).

As reported by Quantitative Imaging Biomarker Alliance (Hall *et al.*, 2013), there were statistically significant differences among tissue-mimicking phantom results when different SWE systems were used. Those quantitative differences could partially be attributed to the fact that different SWE systems could have used different ultrasound system parameters and data/signal processing strategies. Preliminary results (Figures 10 and 11) showed that the proposed virtual elastography system can reproduce some system-dependent SWS measurements. Consequently, the proposed system might be used to further investigate how (ultrasound) system parameters may affect SWS measurements. Since public releasing of those ultrasound system parameters and data/signal processing strategies by vendors is not feasible, performing virtual elastography simulations in heterogeneous, complex but known (viscoelastic) media may enable us to advance understanding of elastographic measurements in complex media, thereby aiding in the interpretation of clinical SSI results. Furthermore, this is an open-source development so that this process can be transparently done. Source

codes of this virtual simulation platform will be made available from Github (<https://github.com/jjiang-mtu/virtual-breast-project>).

In this study, simulated breast tissues including tumors were assumed to be linearly elastic solids as a first approximation. Our preliminary results (see Table 3) suggested that three different modalities (SE, SSI, and ARFI) provided different image contrast values in Models 2 and 3. Particularly, results in Table 3 suggested that SSI offers the highest elastic contrast values as compared to SE and ARFI. This observation is consistent with the tissue - mimicking phantom results reported by Palmeri and Nightingale (Palmeri and Nightingale, 2011) and Peng *et al.* (Peng *et al.*, 2016). In the future, viscoelastic tissue properties will be included in this virtual elastography platform. Once the viscoelasticity is included, the proposed virtual system could also be applied to further investigate elastographic contrast and image resolution in heterogeneous and complex media.

The FIELD II (Jensen, 1991) was adopted because it is one of most widely used ultrasound simulation tool in the medical ultrasound community. Our initial results suggested that the current simulation platform with the FIELD II software performed well in elastic media. Looking forward, since the accurate calculation of the acoustic pressures is one of the key components for successful simulations of acoustic radiation force-based elastography, two potential limitations should be addressed. First, the initial implementation of the Field II (Jensen, 1991) approximates the impulse response by supposing the far field impulse responses sensed by sub-apertures and therefore is limited to the simulation of linear passive scattering from tissue inhomogeneity. Acoustic radiation forces generating detectable tissue deformation may lead to nonlinear acoustic effects (Carstensen *et al.*, 1980). Consequently, the accuracy of acoustic pressure calculation could be affected by using such a linear approximation. K-WAVE (Treeby and Cox, 2010; Treeby et al., 2012), a k-space pseudo-spectral method, has recently been developed to solve the nonlinear acoustic equation and could be used to include nonlinear acoustic effects. Second, frequency-dependent wave dispersion occurring in viscoelastic media may require accurate realizations of transient acoustic pressure fields. An open-access package named FOCUS (McGough, 2004; Kelly and McGough, 2006) demonstrated that it can more accurately solve transient near-field pressure fields as compared to the FIELD II. To address both limitations, other open-access ultrasound simulation packages such as K-WAVE and FOCUS will be investigated in the future.

Tests in ultrasound elastography are often done using human trials and tissue-mimicking phantoms. Human trials often associate with increasingly high costs (Collier, 2009), while developments of realistic tissue-mimicking breast phantoms that can resemble the complexity of human organs and tissue properties remain as a significant challenge (Madsen *et al.*, 2006; Hobson *et al.*, 2008). In this study, we suggest that the proposed virtual ultrasound elastography simulation platform could be used as an alternative. Given more developments and validations, the proposed platform can enable imaging physicists/scientists to perform nearly all ultrasound elastography simulations using a single gateway. This is important because performing advanced ultrasound elastography simulations requires not only interdisciplinary knowledge in acoustic physics, FEA, tissue mechanics, computer-aided design and image/signal analysis, but also a substantial effort to fill gaps among

multiple (commercial or free) software tools. This single gateway software platform could potentially lift this burden away from image physicists/scientists given further developments. Consequently, research efforts can be more steered toward improving our understanding of ultrasound elastography using complex, heterogeneous but known media that emulating *in vivo* breast anatomy. It is our vision that rigorous imaging tests of this kind can be conducted with transparency due to their open-source nature. The proposed system can also be used to accelerate development of new elastographic methods by using the concept of virtual prototyping.

Furthermore, Zhao et al. (Zhao *et al.*, 2011) have also advocated an option to correct system parameter-dependent SWS measurements using computer simulations. The proposed simulation platform seems a good tool for this. A correction table generated through the proposed simulation platform involving realistic anatomy and material properties can be used to compensate for biases due to (ultrasound) system parameter-dependency.

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A List of Abbreviations

ARFI	Acoustic Radiation Force Impulse
EC	Elastic Contrast
FEA	Finite Element Analysis
ROI	Region of Interest
SE	Strain Elastography
SSI	Supersonic Shear Imaging
SW	Shear Wave
pSWE	point Shear Wave Elastography
SWE	Shear Wave Elastography
SWS	Shear Wave Speed
TOF	Time-of-Flight
TTP	Time-to-Peak

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Figure 1.

A graphic illustration of the proposed virtual simulation platform for acoustic radiation force-based UE.

Figure 2.

A plot of an acoustic intensity field produced by FIELD II. Only the center slice is displayed. The focal region (see the white rectangle; approximately $1\text{ mm} \times 1\text{ mm} \times 1\text{ mm}$ cube in 3D) is projected onto the numerical breast models to excite SW propagation or displace adjacent tissues. The color bar represents normalized values from 0 to 1.

Figure 3.

Three numerical breast models of increasing complexity: (a) a uniform medium ($40\text{ mm} \times 40\text{ mm} \times 40\text{ mm}$, approximately 0.5 million finite elements), (b) a uniform medium ($60\text{ mm} \times 60\text{ mm} \times 60\text{ mm}$) with a spherical inclusion (8 mm diameter; approximately 0.5 million finite elements), and (c) a complex breast model ($62\text{ mm} \times 68\text{ mm} \times 41\text{ mm}$). In Model 3, the irregular lesion has a diameter of approximately 5 mm and the final mesh size is 2.0 million quadratic tetrahedrons. The first and second rows are 3D geometries and center slices, respectively.

Figure 4.

A graphic illustration of the simulation setting for simulated pSWE in Model 1. B-mode image simulated using FIELD II is displayed in (a) and (b). In (a), simulated acoustic radiation forces were projected onto the red dot region. The green arrow is the SW propagation direction. The horizontal red dashed lines represent the depth (1 mm) over which shear wave reconstructions were performed for pSWE. Repeating (a) along the axial depth direction, a two-dimensional (2D) SWS image within the white rectangle can be obtained for a large region of interest (ROI) as shown in (b).

Figure 5.

A graphic illustration of the simulated SSI setting for two models: (a) Model 2 and (b) Model 3. Two FIELD II simulated B-mode images were displayed to illustrate compositions of Models 2 and 3, respectively. To generate supersonic sources, acoustic radiation forces were projected onto a series of excitation locations with a pre-determined time delay in a sequence. Red dots in each plot indicate those supersonic sources used to generate the SSI image. The red arrows denote the sweeping (*i.e.* delayed excitation in a sequence) direction of acoustic radiation forces, while green arrows indicate the SW propagation direction. The white rectangle is the region of interest (ROI).

Figure 6.

A graphic illustration of the setting of simulated ARFI imaging for two models overlaid with FIELD II simulated B-mode images: (a) Model 2 and (b) Model 3. Spatially localized acoustic pushes were applied onto respective ROIs sequentially ($20 \text{ mm} \times 15 \text{ mm}$ and $10 \text{ mm} \times 9 \text{ mm}$ for Models 2 and 3, respectively). Each red dot indicates one pushing location used for the simulated ARFI imaging. The number of red dots used was solely for the illustration purpose.

Figure 7.

Illustrations of the process for the calculation of EC using an example strain elastogram. Two ROI selection methods (a)–(b) were used. The rectangles or circles depict respective ROIs in the background and the target. The target was delineated by the manually-segmented contour in orange color in both plots.

Figure 8.

The SWS along lateral direction estimated from Model 1 by using pSWE: (a) a simulated B-model image, simulated displacement images at (b) 1 millisecond, (c) 3 milliseconds and (d) 6 milliseconds after the pushing pulse started, and (e) a plot of estimated SWS. In (e), the blue solid curve represents the estimated SWS, while the red dashed line represents the known SWS for a comparison purpose. The color bar is the acoustic radiation force-induced displacement in micrometer.

Figure 9.

Two-dimensional (2D) SWS image estimated from Model 1 by using simulated pSWE: (a) a simulated B-model image, (b) SW wave front arrival time within the rectangular ROI (10 mm $\times$ 6.5 mm) and (c) estimated SWS within the same ROI (10 mm $\times$ 6.5 mm). Corresponding experimental results (*i.e.* Figures 6a–b in the experimental work (Palmeri *et al.*, 2008)) are available in the literature. The units of color bars in (b) and (c) are millisecond and m/s, respectively. TTP stands for time-to-peak.

Figure 10.

Plots of SWS measured at two focal depths (*i.e.* 20 mm and 40 mm): (a) simulation results by the simulated pSWE and (b) experimental results by Zhao *et al.* At each depth, 3 different (transmit) aperture sizes (32, 64, and 96 elements) were used for the simulated push beam transmission. The experimental results were obtained from the original publication by Zhao *et al.* (Zhao *et al.*, 2011). Error bars in (b) represent one standard deviation.

Figure 11.

Plots of SWS measured at the near and far lateral tracking regions: (a) simulation results by the simulated pSWE and (b) experimental results by Zhao *et al.* The push beam was focused at 20 mm and 3 different (transmit) aperture sizes (32, 64, and 96 elements) were used for the simulated push beam transmission. The experimental results were obtained from the original publication by Zhao et al. (Zhao *et al.*, 2011) Error bars in (b) represent one standard deviation.

Figure 12.

Results of simulated SSI for Model 2: (a) a simulated B-model image, simulated displacement images at (b) 3 milliseconds and (c) 5 milliseconds after the first pushing pulse started, (d) an image of estimated shear modulus (in kPa) and (e) an image of experimentally estimated shear modulus (in kPa) image in a tissue-mimicking phantom (Deffieux *et al.*, 2011). White arrows in (d) and (e) point to the reconstructed inclusion. The color bars in (b) and (c) are in micrometers. (b) and (c) represent the acoustic radiation force-induced displacements at $t = 3$ and 5 milliseconds.

Figure 13.

Results of simulated SSI for Model 3: (a) simulated impedance (left) and B-model (right) images, simulated displacement images at (b) 1 milliseconds and (c) 2.6 milliseconds after the first pushing pulse started, and (d) an image of estimated SWS. White arrows in (d) point to the reconstructed breast lesion using estimated SWS values. The color bars in (b) and (c) are in micrometer; (b) and (c) show the acoustic radiation force-induced displacements. The color bar in (d) represents the SWS in m/s.

Figure 14.

Results of simulated ARFI for Model 2: (a) a simulated B-model image, (b) simulated normalized peak displacement image and (c) simulated normalized (displacement) TTP image. The color bars are unit-less.

Figure 15.

Results of simulated ARFI for Model 3: (a) a simulated B-model image, (b) simulated normalized peak displacement image and (c) simulated normalized (displacement) TTP image. The color bars are unit-less.

Figure 16.

Two simulated SWS images comparing effects (a) without and (b) with the directional filter being applied. Results were based on Model 3 under the same condition by which all images in Figure 13 were obtained. The color bars represent the SWS in m/s.

Table 1

A list of system parameters of a (simulated) linear array ultrasound transducer used for pushing and tracking beams. These parameters were adopted from two published papers (Palmeri *et al.*, 2010; Zhao *et al.*). Both linear array transducers were used for FIELD II simulations.

System Parameters	Values based on (Zhao <i>et al.</i> , 2011)	Values based on (Palmeri <i>et al.</i> , 2010)
Excitation Frequency (MHz)	5	10
Tracking Frequency (MHz)	5	10
Sampling Frequency (MHz)	50	50
Bandwidth (%)	50	50
Element Width (mm)	0.2	0.1
Element Height (mm)	5	5
Spacing Between Elements (mm)	0	0
Number of Active Elements	32, 64, 96	64
Tracking pulse repetition frequency (kHz)	4	10
Lateral beam spacing (mm)	0.1	0.1

Table 2

Mechanical properties of the three numerical breast models. Young's modulus values were extracted from three publications (Palmeri *et al.*, 2008; Deffieux *et al.*, 2011; Zhao *et al.*, 2011) and all materials were assumed to be nearly incompressible.

		Young's modulus (kPa)	Poisson's Ratio
Model 1 (Palmeri <i>et al.</i> , 2008)	Background	4.76	0.499
Model 1 (Palmeri <i>et al.</i> , 2008)	Background	4.61	0.499
Model 2 (Deffieux <i>et al.</i> , 2011)	Background	15	0.499
	Inclusion	60	0.499
Model 3 (Krouskop <i>et al.</i> , 1998; Wang <i>et al.</i> , 2009)	Breast fat	10	0.499
	Cooper's ligament	75	0.499
	Milk duct	10	0.499
	Lesion	150	0.499
	Skin	400	0.499
	Fibro-glandular tissue	15	0.499

Table 3

Tabulated results of elastic contrast (EC) values calculated from three virtual elastography methods. The SSI measurements were converted to elastic shear modulus values using $\sqrt{G/\rho}$, where G and ρ are shear modulus and the mass density, respectively. The underlying elastic contrast values were calculated based on data shown in Table 2.

	Model 2		Model 3	
	Method A	Method B	Method A	Method B
Underlying EC	4	4	10	10
SE	2.32	2.12	1.92	1.72
SSI	3.53	3.23	3.35	3.19
ARFI peak-displacement	2.78	2.67	2.88	2.63
ARFI (displacement) TTP	3.22	3.15	3.20	2.91