Building a virtual simulation platform for quasistatic breast ultrasound elastography using open source software: A preliminary investigation

Yu Wang, Emily Helminen, and Jingfeng Jiang^{a)}

Department of Biomedical Engineering, Michigan Technological University, Houghton, Michigan 49931

(Received 15 December 2014; revised 9 July 2015; accepted for publication 6 August 2015; published 21 August 2015)

Purpose: Quasistatic ultrasound elastography (QUE) is being used to augment *in vivo* characterization of breast lesions. Results from early clinical trials indicated that there was a lack of confidence in image interpretation. Such confidence can only be gained through rigorous imaging tests using complex, heterogeneous but known media. The objective of this study is to build a virtual breast QUE simulation platform in the public domain that can be used not only for innovative QUE research but also for rigorous imaging tests.

Methods: The main thrust of this work is to streamline biomedical ultrasound simulations by leveraging existing open source software packages including Field II (ultrasound simulator), VTK (geometrical visualization and processing), FEBio [finite element (FE) analysis], and Tetgen (mesh generator). However, integration of these open source packages is nontrivial and requires interdisciplinary knowledge. In the first step, a virtual breast model containing complex anatomical geometries was created through a novel combination of image-based landmark structures and randomly distributed (small) structures. Image-based landmark structures were based on data from the NIH Visible Human Project. Subsequently, an unstructured FE-mesh was created by Tetgen. In the second step, randomly positioned point scatterers were placed within the meshed breast model through an octree-based algorithm to make a virtual breast ultrasound phantom. In the third step, an ultrasound simulator (Field II) was used to interrogate the virtual breast phantom to obtain simulated ultrasound echo data. Of note, tissue deformation generated using a FE-simulator (FEBio) was the basis of deforming the original virtual breast phantom in order to obtain the postdeformation breast phantom for subsequent ultrasound simulations. Using the procedures described above, a full cycle of QUE simulations involving complex and highly heterogeneous virtual breast phantoms can be accomplished for the first time.

Results: Representative examples were used to demonstrate capabilities of this virtual simulation platform. In the first set of three ultrasound simulation examples, three heterogeneous volumes of interest were selected from a virtual breast ultrasound phantom to perform sophisticated ultrasound simulations. These resultant B-mode images realistically represented the underlying complex but known media. In the second set of three QUE examples, advanced applications in QUE were simulated. The first QUE example was to show breast tumors with complex shapes and/or compositions. The resultant strain images showed complex patterns that were normally seen in freehand clinical ultrasound data. The second and third QUE examples demonstrated (deformation-dependent) nonlinear strain imaging and time-dependent strain imaging, respectively.

Conclusions: The proposed virtual QUE platform was implemented and successfully tested in this study. Through show-case examples, the proposed work has demonstrated its capabilities of creating sophisticated QUE data in a way that cannot be done through the manufacture of physical tissue-mimicking phantoms and other software. This open software architecture will soon be made available in the public domain and can be readily adapted to meet specific needs of different research groups to drive innovations in QUE. © 2015 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4928707>]

Key words: ultrasound simulation, numerical phantom, elastography, finite element modeling

1. INTRODUCTION

According to the American Cancer Society,¹ breast cancer is the second most common form of cancer (after skin cancer) in American women and the second major cause of death (after lung cancer). It is estimated that one in eight women will get breast cancer in their lifetime. Although breast tumors are often detected by imaging, one clinical dilemma is

that current imaging methods can have low sensitivity and specificity. For instance, mammography, the primary screening modality, on average, has a sensitivity of 67.8% and an accuracy of 70% as described in Berg *et al.*² However, its sensitivity drops from 100% in fatty breasts to about 45% for extremely dense breasts² among younger women. Magnetic resonance imaging (MRI) and ultrasound are often utilized to supplement mammography.² MRI is highly sensitive,^{3,4}

particularly in younger women, for detecting invasive breast cancers but less specific,^{5,6} as compared to mammography. Furthermore, due to time, financial constraints, and patient claustrophobia, one study found that only 57.9% of the patients with an elevated risk of breast cancer agreed to undergo magnetic resonance (MR) imaging after mammography and ultrasound.⁷ Thus, conventional B-mode ultrasound has emerged as a useful and cost-effective modality in the workup of patients with suspected breast masses. Its traditional role has been for differentiating between solid and cystic masses and guiding biopsy procedures. In short, uncertainties in imaging diagnosis have led to a high rate of biopsy procedures being performed, with approximately 75% of the biopsies being benign.⁸ This has become a huge socio-economic burden on the current healthcare system. Annually, it is estimated that about 1.6×10^6 breast biopsies are performed on suspicious masses in the US.

In recent years, ultrasound-based quasistatic elastography^{9–11} (UQE) has been successfully applied to noninvasive differentiation of breast lesions.^{10,12} Under the framework of UQE, echo signals are first acquired before and after breast tissue deformations. Then “relative hardness” information, local strain, is inferred from tissue displacements that are estimated by comparing the pre- and postdeformation echo fields using motion tracking methods.^{11,13,14} UQE has been envisioned as an optional modality to augment standard B-mode imaging, analogous to the use of ultrasound Doppler. However, success of quasistatic elastography is mixed. In a recent meta-analysis¹⁵ of 22 clinical studies (up to February 2011; 4713 lesions in 4266 patients), sensitivity and specificity of quasistatic elastography^{9–11} greatly varied from 40% to 95%, as compared to biopsy results. Sensitivity and specificity are often measures of technical success for diagnosis of malignant breast lesions. Clearly, early results demonstrated that there is a lack of confidence in image details of UQE in the clinical community. Confidence on image interpretations can only be gained by rigorously validating image pixels with underlying soft tissue properties (i.e., “ground truth”) in complex, heterogeneous but known media. Unfortunately, this capability is not yet available for UQE.

Only a few publications for making numerical breast models/phantoms have been documented in the literature. Notably, Azar *et al.*¹⁶ and Samani *et al.*¹⁷ independently proposed MR-based biomechanical models to predict breast tissue deformation. A novel (half-spherically shaped) breast model was created by Bhatti and Sridhar-Keralapura¹⁸ specifically for breast elastography. Using several commercial packages, Bhatti and Sridhar-Keralapura investigated contrast transfer efficiency (CTE)¹⁹ of strain imaging in the study.¹⁸ In a more recent publication, an image-based breast model/phantom was created in conjunction with computer-tomography data, as proposed by Hsu *et al.*²⁰ However, in both studies,^{18,20} breast models/phantoms were not integrated and tested with any ultrasound simulators. Toward this end, this paper aims at developing an open-source virtual simulation platform that can streamline sophisticated simulations for quasistatic ultrasound elastography (QUE). This work would be a

substantial improvement over tests done in simple, uniform, and relatively isotropic media such as tissue-mimicking phantoms.^{21,22}

Performing advanced QUE simulations requires not only interdisciplinary knowledge in acoustic physics, finite element modeling, tissue mechanics, computer-aided design and image/signal analysis, but also substantial effort to fill gaps among multiple (commercial or free) software tools. Collectively, the proposed software platform innovatively fills gaps along the software pipeline and will act like a single gateway (software) platform to enable imaging physicists/scientists to perform advanced QUE simulations. Another key innovative component of the proposed work is its open-source development. Thanks to the advent of open-source development, QUE researchers will no longer work in isolation with limited resources and the interdisciplinary collaboration will be opened up to the entire QUE research community. In addition to collaborative software development, such an open-source platform will allow comparisons and validations of the simulated QUE images with a known but (arbitrarily) complex phantom, and show the correlation between a QUE image and its underlying soft tissue properties. In other words, rigorous imaging tests can be transparently done using simulated complex, heterogeneous but known media.

2. MATERIALS AND METHODS

The use of the proposed virtual ultrasound simulation platform involves multiple components: (1) geometry creation, (2) mesh generation, (3) acoustic simulation, and (4) biomechanical deformation. An illustrative example (Fig. 1) is provided below to demonstrate the specific steps. During the process, the starting point was an image-based geometrical model of breast including different internal components (Sec. 2.A). This geometrical model was based on “average” anatomy and represented by three-dimensional (3D) surface triangles. In order to simulate signals for ultrasound-based QUE applications, both pre- and postdeformed ultrasound echo signals were needed. Therefore, in addition to the undeformed virtual breast model/phantom, a deformed breast model/phantom was also created. A simulated freehand scanning ultrasound transducer was used to deform this virtual breast model/phantom. This deforming process involved in finite element simulations [i.e., finite elements for biomechanics, FEBio (Ref. 23)] and therefore was naturally split into mesh generation (Sec. 2.B) and biomechanical simulations (Sec. 2.C). Both undeformed and deformed virtual breast models/phantoms had to interact with an ultrasound simulator [i.e., Field II (Ref. 24)] to generate simulated ultrasound echo signals.

The proposed virtual simulation platform leveraged existing open-source packages including Field II (Ref. 24) (acoustic simulator), FEBio (Ref. 23) (finite element simulator for biomechanics), VTK (Ref. 25) (data visualization and processing), and Tetgen (mesh generator).²⁶ The nontrivial integration of these open-source packages was described below as a multiple step process.

FIG. 1. A graphic illustration of the workflow of the proposed virtual simulation platform. The geometry of a predeformed breast model (a) is first created based on MR imaging data and, then meshed to tetrahedrons (b). In the following step, randomly positioned point scatterers are placed in the meshed breast model. The density of point scatterer satisfies Rayleigh scattering. Then, predetermined acoustic properties are assigned to each and every point scatterer based on its anatomical affiliation. Once the acoustic properties are assigned, the virtual breast model is converted to a virtual breast ultrasound phantom. Based on displacement data obtained from a biomechanical finite element (FE) simulator (i.e., FEBio), the predeformed virtual breast ultrasound phantom can be warped to create a postdeformed breast ultrasound phantom through interpolations. Finally, using an acoustic simulator to interrogate the pre- and postdeformation breast ultrasound phantoms (c), the pre- and postdeformed radiofrequency (RF) echo fields can be obtained for QUE, respectively.

2.A. Geometry creation

Through image segmentation, landmark geometries such as the skin layer and fibro-glandular layer were created using MRI data from a female cadaver in the Visible Human Project.²⁷ The in-plane resolution of these MRI images was 0.33×0.33 mm with a 0.6 mm slice thickness. All MRI images were imported into a commercially available ScanIP package (Simpleware, Inc., Exeter, United Kingdom)²⁸ to perform intensity-based image segmentation to obtain the skin surface and the fibro-glandular layer [Fig. 2(b)]. Other computer-aided design software (e.g., Solidworks, Dassault Systems, Inc., France) or image segmentation software (e.g., open-source Vascular Modeling Toolkit²⁹) can also be used to create complex geometries.

Small randomly distributed tissue structures such as milk ducts and Cooper's ligaments were added to increase the complexity and realism of the virtual breast model. In the Visible Human Project, MRI data were generated using torso coils and therefore have limited resolution. However, it would be difficult to fully resolve milk ducts and Cooper's ligaments even when breast array coils were used. Similar to the study by Mahr,³⁰ Cooper's ligaments (blue color in Fig. 3) were modeled as clusters of fibers embedded into the subcutaneous fat region toward the skin layer. The breast ducts (green color in Fig. 3) were randomly generated by a collection of bifurcated tubes and mainly confined within the fibro-glandular region. Sizes of milk ducts [diameter 1.9 ± 0.6 mm; see Fig. 2(c)] and Cooper's ligaments (diameter 3–4 mm) were based on ultrasound measurement in the literature.³¹ Furthermore,

FIG. 2. A collection of images related to the virtual breast model: (a) a cross-sectional breast MRI image, courtesy of W. Huang of OHSU, Portland; (b) fibro-glandular tissue geometry segmented from MRI data, and (c) a geometry of milk ducts created using VTK (Ref. 25).

FIG. 3. (a) An illustration of image-based breast phantom creation. Major anatomical regions are derived from 3D MR data, while other lower scale structures (e.g., Cooper's ligament, intraglandular fat, and milk ducts) that are significant to breast mechanics are randomly distributed structures generated by in-house software. Realism can be enhanced through geometrical Boolean operations: for example, (b) tumor invasion (out of the fibro-glandular region) to the subcutaneous fat, (c) tumor growth out of/from breast milk ducts, and (d) tumor disruption of a Cooper's Ligament. In (a), the volume between the skin and fibro-glandular region is mainly occupied by breast fat. Intrafat denotes small adipose compartments within the fibro-glandular region. Of note, for visualization purpose, the number of randomly distributed structures was intentionally reduced.

intraglandular fat [purple color in Fig. 3(a)] is modeled as small adipose compartments (elongated random ellipsoids) within the fibro-glandular region, consistent with observations from B-mode ultrasound data.

Those above-mentioned randomly distributed structures were defined by their boundaries using 3D triangulated surfaces. Boolean operations³² (i.e., `vtkBooleanOperationPolyDataFilter`) were used to alter existing boundaries to accommodate when some boundaries belong to more than one anatomical region. Similar Boolean operations were used when the embedded breast tumor [yellow colored object in Figs. 3(a)–3(d)] may infiltrate out of the fibro-glandular tissue region [Fig. 3(b)], grow out of breast ducts [Fig. 3(c)], and disrupt Cooper's ligaments [Fig. 3(d)].

PYTHON scripts derived from Visualization Toolkit²⁵ (VTK, Kitware, Inc., NY) were used to call a c++ program to create the above-mentioned small structures. Interested readers are referred to Appendix A for algorithmic details.

2.B. Mesh generation

Once a geometric breast model (i.e., multiple 3D complex triangulated surfaces) is obtained, an open-source mesh generator Tetgen²⁶ (version 1.4.2; WIAS, Berlin, Germany) was used to generate high quality tetrahedral meshes as shown in Fig. 1(b). Overall dimensions of the (irregularly shaped) breast model are approximately $62 \times 68 \times 41$ mm, resulting in a volume size of 62600 mm^3 . Tetgen uses constrained Delaunay triangulation to partition any enclosed 3D geometry/space into tetrahedrons. Furthermore, the 3D enclosed breast model/phantom was also automatically divided into six different tissue types as shown in Table V in Appendix B and illustrated in Fig. 3. Two meshes were created. The fine and coarse meshes resulted in approximately 3.5 and 2.2×10^6 finite (computing tetrahedral) elements, respectively.

2.C. Biomechanical simulations

In order to simulate tissue deformation in QUE, an open-source FE package, FEBio (Ref. 23) (University of Utah, UT), was integrated into the proposed virtual simulation platform. Using an in-house PYTHON script, the tetrahedral mesh from Sec. 2.B was imported into the FEBio (Ref. 23) (version 1.8). Mesh sensitivity for FE modeling was performed for the two above-mentioned meshes (i.e., 2.2 and 3.5×10^6 elements). The resultant displacements between those two meshes differed less than 10^{-3} mm for all locations investigated up to 20% of deformation. Therefore, the coarse mesh was used for all subsequent FE simulations. The average element size of the coarse mesh was about 0.03-mm^3 .

FE-simulations were intended to simulate freehand scanning in a clinical setting. As shown in Fig. 1(c), a simulated ultrasound transducer was first put in contact with the skin and then used to push the breast tissue downward in all FE simulations. More specifically, a small contact area on the simulated skin surface (approximately 4×1.5 cm) was selected to compress all breast FE models. As shown in Table I, three bio-mechanical simulations were performed to mimic three different QUE applications, namely, small deformation strain imaging,¹⁰ nonlinear strain imaging,^{33,34} and time-dependent strain imaging.³⁵

In FE simulations, the elasticity of breast tissues was simulated by the Veronda–Westmann (V-W) hyperelastic model.³⁶

TABLE I. Descriptions of FE-simulations related to three QUE applications.

Application	Description of mechanical deformation	Material model
Small-deformation strain imaging	A 2% of (displacement-controlled) compression in a single step	Veronda–Westmann hyper-elastic model (Ref. 36)
Nonlinear strain imaging	A 20% of (displacement-controlled) compression in a multiple step fashion with a 1% increment	Veronda–Westmann hyper-elastic model (Ref. 36)
Time-dependent strain imaging	A uniform pressure resulting in an accumulative 1 N of force; the force was applied from 0 to 1 N in 1 s and held steadily for 14 s	Quasilinear viscoelastic model (Ref. 37) [a mixture of standard linear solid (SLS) model and Veronda–Westmann model]

TABLE II. Parameters of the simulated linear array ultrasound transducer used by Field II.

Parameter	Field II
Sampling frequency (MHz)	100
Center frequency (MHz)	6
Bandwidth (%)	50
Element width (mm)	1.5
Element height (mm)	5
Spacing between elements (mm)	0
Focal depth (mm)	15
Number of active elements	64
Number of scan lines	256

The Veronda–Westmann model can provide an exponential stress–strain curve that is similar to *ex vivo* experimental data of breast tissues by Krouskop *et al.*³⁸ and Wellman *et al.*³⁹ that motivates our choice of the Veronda–Westmann model. More detailed information related to hyperelastic and viscoelastic mechanical parameters used in all three QUE applications can be found in Appendix B.

2.D. Creation of virtual breast ultrasound phantoms

The meshed virtual breast (geometric) model (Sec. 2.B) was converted to a virtual breast ultrasound phantom that could be readily used for subsequent acoustic simulations in Field II (Ref. 24) (Sec. 2.E). Spatial transformations were needed in order to map the coordinates of the virtual breast phantom onto the coordinates of the coordinates of Field II simulator.²⁴ Briefly, during this process, two tasks were completed. First, the dominant FE-compression direction and the (lateral) width direction of the simulated transducer were first set as the axial and lateral directions, respectively, for Field II (Ref. 24) simulations. Second, care was taken to shift the location corresponding to the center of the (simulated) transducer on the virtual breast model to the origin of the acoustic simulation coordinates, as required by Field II.²⁴

After the completion of the above-mentioned spatial transformations, the transformed virtual breast model was first re-sampled to a rectilinear (1-mm × 1-mm × 1-mm) grid. Then, multiple randomly positioned point scatterers were placed in each and every 1-mm × 1-mm × 1-mm grid to ensure the presence of ten point scatterers within a resolution cell. According to an early study by Rao *et al.*,⁴⁰ ten point scatterers

FIG. 4. A schematic illustration of the estimation of the relaxation time T_1 . A compressive force was applied within the first second (i.e., $t_0 = 1$ s). Then, the compression was held until t_1 (i.e., $t_1 = 15$ s). The red curve in the bottom plot is a representative time-resolved strain curve. Given K estimated strains, a relaxation time T_1 can be estimated from this time-resolved strain curve based on Eq. (1). In this study, K is 15, denoting 1 s/strain image.

per resolution cell result in speckle statistics that satisfies Rayleigh scattering. Of note, the ultrasound resolution cell (full width at half maximum) was 0.8 mm^3 , based on parameters listed in Table II. The transformed unstructured mesh of the virtual breast model was used to determine whether or not a point scatterer should belong to a material type to minimize conversion errors. Acoustic attenuation was not considered in our simulations for simplicity.

Acoustic reflective coefficients were assigned to all point scatterers. It is worth noting that each and every point scatterer inherited one of six material types (see Sec. 2.B). The reflective coefficients of six material types required by Field II were empirically chosen to show B-mode contrast, based on acoustic impedance data available in the literature.⁴¹ Once acoustic reflective coefficients were assigned to those randomly positioned point scatterers, the predeformation virtual breast (geometric) model was converted to the predeformation virtual breast ultrasound phantom.

To create a postdeformation virtual breast phantom, FE-simulated displacements were first transformed to the coordinates of the predeformation virtual breast ultrasound phantom. Then, another transformation was needed to simply subtract absolute displacements of the (transducer) contact surface from the already transformed FE-simulated displacements.

FIG. 5. A simulated hypoechoic breast lesion: (a) acoustic reflection coefficient image and (b) a simulated B-mode image by Field II. In (a), 1–5 denote lesion, fibro-glandular tissue, breast fat, Cooper's ligaments, and milk ducts, respectively.

FIG. 6. A simulated milk-duct structure embedded into the fibro-glandular region: (a) acoustic reflection coefficient image and (b) a simulated B-mode image by Field II. In (a), 1–4 denote breast fat, fibro-glandular tissue, milk ducts, and lobe, respectively.

By doing so, all resultant displacements were relative to the (transducer) contact surface. In the last step, acoustic reflective coefficients in the predeformation virtual breast phantom can be interpolated to form the postdeformation virtual breast phantom.

2.E. Acoustic simulation

Once the pre- and the postdeformation virtual breast phantoms become available, Field II (Ref. 24) was used to interrogate virtual breast phantoms to create ultrasound echo data. A linear array ultrasound transducer was simulated and its relevant parameters are listed in Table II. Perfect matching layers around the boundaries were automatically added by Field II to avoid undesirable wave reflections at the boundaries. Acoustic attenuation was not simulated.

2.F. Running simulations

During the acoustic Field II simulation, 256 lines were used to cover the entire field of view (approximately 40 mm). A high performance computing (HPC) cluster was used (<http://superior.research.mtu.edu/>). One beam line took approximately 10 min under MATLAB [Version 2013b, Mathworks, Inc., MA; 4 CPUs (Intel Xeon E2560; 2.8 GHz) and 16 GB of memory]. All other data preparation, analyses, and visualization were done by a high end workstation (Dell Precision R5600, Dell, Inc., Austin, TX with 64GB memory).

2.G. Postsimulation data analysis

2.G.1. Speckle tracking and strain estimation

Once a pair of pre- and postdeformation radiofrequency (RF) echo frames were obtained (Sec. 2.E), a modified block

matching algorithm (MBMA)⁴² was used to obtain axial and lateral displacements within a region of interest (ROI). The tracking kernel size is approximately 1.5 mm (lateral) $\times$ 0.6 mm (axial; approximately 3 wavelength long for 6–7 MHz acoustic wave). More details of this speckle tracking method can be found elsewhere.⁴² Subsequently, we estimated local strains using a least-square method⁴³ using a linear regression window of 1.6 mm. The above-mentioned tracking kernel size and the length of linear regression window were empirically chosen to balance spatial resolution and image quality. They were comparable with what typically used for tracking *in vivo* breast lesions by our group.^{13,42}

2.G.2. Estimation of motion tracking accuracy

Normalized cross correlation (NCC) between a pair of predeformation and motion-compensated postdeformation RF echo fields⁴⁴ was chosen to estimate motion tracking accuracy. Motion-compensation here is referring to a process in which ultrasonically estimated displacements between the pre- and postdeformation ultrasound echo data were applied onto the postdeformation ultrasound data so that the postdeformation ultrasound data were warped back onto the coordinates of the predeformation echo data. In other words, the process of motion-compensation was used to register two RF echo fields with apparent deformation. A higher NCC value between the two registered echo fields implies that the apparent deformation has been more accurately tracked.

2.G.3. Estimation of relaxation time

From a time series of RF echo frames simulated during the simulation of time-dependent strain imaging,³⁵ a series of K

FIG. 7. A simulated Cooper's ligament structure: (a) acoustic reflection coefficient image and (b) a simulated B-mode image by Field II. In (a), 1–4 denote lesion, fibro-glandular tissue, Cooper's ligaments, and breast fat, respectively.

FIG. 8. Results from the Lesion 1 phantom: (a) geometry, (b) reflection coefficient image, (c) B-mode image simulated by Field II where a rectangular box depicts a ROI, (d) FE-simulated axial displacement image within the ROI, (e) ultrasonically estimated axial displacement image, and (f) estimated axial strain image based on (e). The displacement color bars are in millimeters in (d) and (e). In (b), 1–4 denote lesion, fibro-glandular tissue, Cooper's ligaments, and breast fat, respectively.

strain images were first estimated through speckle tracking. Then, one time-resolved strain curve for each and every pixel was obtained as shown in Fig. 4. Each time-resolved strain curve was fitted into a Kevin-Voigt model³⁵ using the Optimization Toolbox in MATLAB (Mathworks, Inc., MA). The formula of strain creep under the Kevin-Voigt model is provided below

$$\varepsilon(t) = \varepsilon_0 + \varepsilon_1 [1 - \exp(-t/T_1)], \quad (1)$$

where ε_0 is the instantaneous elastic strain that occurs immediately after compression, ε_1 is the amplitude of the exponential creep curve. In Eq. (1), the constant T_1 is the relaxation time used in time-dependent strain imaging,³⁵ as illustrated in Fig. 4.

3. RESULTS

Simulation results in this section are used to demonstrate that the proposed virtual simulation platform is capable of performing advanced simulations both for breast ultrasound (Subsection 3.A) and breast QUE (Subsection 3.B).

3.A. Simulated B-mode images of heterogeneous media

Three volumes of interest were selected from the undeformed breast ultrasound phantom (Fig. 1) to perform acoustic simulations. Those three volumes were intended to show: (1) inclusion of a hypoechoic breast lesion, (2) a complex “grape-like” structure of milkducts, and (3) a complex layered structure of Cooper's ligaments embedded in the subcutaneous fat layer. All corresponding reflection coefficients and B-mode images are shown in Figs. 5–7. Only center slices of the simulated reflection coefficient fields are shown.

In Figs. 5(a) and 5(b), a hypoechoic lesion was surrounded by a thin (approximately 0.5 mm thick) hyperechoic layer mimicking lesion encapsulation. In Figs. 6(a) and 6(b), a dark grape-like structure was clearly visible and embedded within the simulated fibro-glandular tissue region. In Figs. 7(a) and 7(b), a complex layered structure mimicking Cooper's ligaments can be seen.

3.B. QUE applications

The first QUE example was to show that breast lesions with complex shapes and compositions can be readily simulated by the proposed platform. In the second QUE example, recent

FIG. 9. Results from the Lesion 2 phantom: (a) geometry, (b) reflection coefficient image, (c) B-mode image simulated by Field II where a white rectangle depicts a ROI, (d) FE-simulated axial displacement image within the ROI, (e) ultrasonically estimated axial displacement image, and (f) estimated axial strain image based on (e). The displacement color bars are in millimeters in (d) and (e). In (a), the arrow points to a cluster of milk ducts. In (b), 1–5 denote lesion, fibro-glandular tissue, cooper's ligaments, breast fat, and milk ducts, respectively.

FIG. 10. Results from the Lesion 3 phantom: (a) geometry, (b) reflection coefficient image, (c) B-mode image simulated by Field II where a rectangular box depicts a ROI, (d) FE-simulated axial displacement image within the ROI, (e) ultrasonically estimated axial displacement image, and (f) estimated axial strain image based on (e). The displacement color bars are in millimeters (d) and (e). In (b), 1–4 denote lesion, fibro-glandular tissue, Cooper’s ligaments, and breast fat, respectively.

advance in nonlinear QUE (Refs. 33, 34, and 45) was simulated using strain imaging, while the viscoelasticity assessment of breast tissues³⁵ was demonstrated in the third QUE example below.

3.B.1. Example 1: Simulations of complex breast lesions via (small) strain imaging

Four virtual breast ultrasound phantoms were created; each contained a simulated breast lesion as shown in Figs. 8(a), 9(a), 10(a), and 11(a), respectively. Hereafter, we will refer them as Lesion 1–4 phantoms, respectively. Detailed hyper-elastic parameters of those four breast phantoms can be found in Table V of Appendix B. The first two breast lesions had relatively simple (nearly spherical) shapes and were designed to simulate benign breast tumors. Particularly, the first breast lesion [Fig. 8(a)] was a simulated solid tumor, whereas the second breast lesion [Fig. 9(a)] originated from a milk duct [see Fig. 9(a)]. This simulated lesion might be similar to an early stage ductal carcinoma *in situ* (DCIS). The last two breast lesions had more complex shape and were designed to mimic breast cancers. The third one was “star”-shaped and contained several protrusions mimicking cancer invasion. In the last one, a simulated necrotic region [see Fig. 11(a)] was contained

within a simulated breast lesion. The Lesion 4 already had a complex shape.

Simulation results of those four virtual breast phantoms are shown in Figs. 8–11. All results were obtained using a 2% compression from the undeformed state. The corresponding acoustic reflective coefficients are displayed in Figs. 8(b)–11(b), respectively, for those four phantoms. Of note, Figs. 8(b)–11(b) illustrate the center slice of those four reflective coefficient fields, respectively. The resultant B-mode images are shown in Figs. 8(c)–11(c), respectively. The FE-simulated axial displacements induced by the 2% compression are shown in Figs. 8(b)–11(b), respectively. The ultrasonically estimated axial displacements are shown in Figs. 8(e)–11(e), respectively. All estimated axial strain images can be seen in Figs. 8(f)–11(f), respectively.

All four simulated breast lesions were clearly visible in respective B-mode and strain images. Their overall sizes and shapes were visually consistent with all phantom designs. Particularly, the (soft) necrotic region in the Lesion 4 phantom was also seen on the corresponding strain and B-mode images. However, the small cluster of (soft) milk ducts was not shown in both the strain and B-mode images.

Estimated NCC values from a range of deformation (0%–6%) for Lesion 1 phantom were compared with clinically

FIG. 11. Results from the Lesion 4 phantom: (a) geometry of a simulated irregularly-shaped cancer, (b) reflection coefficient image, (c) B-mode image simulated by Field II where a rectangular box depicts a ROI, (d) FE-simulated axial displacement image within the ROI, (e) ultrasonically estimated axial displacement image, and (f) estimated axial strain image based on (e). The displacement color bars are in millimeters. In (a), a simulated necrotic zone is inside the simulated cancer. In (b), 1–5 denote lesion, fibro-glandular tissue, Cooper’s ligaments, breast fat, and necrotic zone, respectively. In (a) and (f), arrows point to the simulated necrotic zone.

scanned *in vivo* data and data from a simple tissue-mimicking phantom, as reported by Jiang *et al.*⁴⁴ As shown in Fig. 12, the calculated NCC values from simulated Lesion 1 phantom were lower than NCC values obtained from the tissue-mimicking phantom but were higher than NCC values obtained from clinically scanned *in vivo* data.⁴⁴ Results from other three phantoms were comparable to that of Lesion 1 phantom.

3.B.2. Example 2: Nonlinear QUE via strain imaging

QUE simulations were performed for Lesion 1 and Lesion 3 phantoms up to 20% of deformation QUE (Refs. 33, 34, and 45). Nonlinear stress-strain curves used for the FE-simulations are shown in Fig. 13(a). Detailed hyperelastic parameters associated with those curves can be found in Appendix B (see Table V). B-mode and incremental (~2% frame-averaged) axial strain images at varying preload of the Lesion 1 and Lesion 3 phantoms are shown in Figs. 13(b) and 13(c), respectively. The values appearing above each strain image

FIG. 12. A plot of estimated NCC values between the pre- and motion-compensated postdeformation RF echo fields under a range of deformation (0%–6% frame-averaged compression). Data of the tissue-mimicking phantom and the *in vivo* breast fibroadenoma were replicated from a previous publication (Ref. 44).

indicate the accumulated (preloading) axial strains. In the Lesion 1 phantom, at low preload the simulated breast tumor is stiffer (darker) than the background glandular tissue. At modest (~10%) preload, the simulated tumor loses visibility

FIG. 13. (a) Stress-strain data of all simulated components in two virtual breast phantoms: Lesion 1 and Lesion 3 phantoms. In (a), the right figure is partially enlarged view of left figure (region in light blue rectangle). In (b) and (c) are B-mode (left) and three incremental strain images of those two virtual phantoms, respectively. The white rectangles on B-mode images depict respective ROIs. The small squares showed on strain images in (b) and (c) were used to perform strain contrast analysis. The area of lesion ROI is equal to the area of background ROIs. The incremental strain contrast is the ratio of strain in background ROIs and lesion ROI.

FIG. 14. Images showing the estimated relaxation time T_1 for the Lesion 1 phantom: (a) B-mode image and (b) the estimated T_1 image. In (b), the predetermined T_1 were 4 and 1 s for the Lesion 1 and the background, respectively, while the averaged estimated T_1 constants for Lesion 1 and the background were 3.7 and 2.2 s, respectively. The unit for the color bar in (b) is s.

with the increase of the preload level. In the Lesion 3 phantom, the visibility of the simulated cancer in strain images remains stable as the increase of preloading. Strain contrast values were defined as the ratio between averaged background strain and averaged inclusion strain from equal areas. Calculated contrast values were also shown in Figs. 13(b) and 13(c), and were consistent with the visual perception. During the contrast calculation, a large (square) ROI was placed in the middle of the target (i.e., Lesion 1 or Lesion 3). Four small (square) ROIs were placed in the background near four corners so that influence of strain concentration was minimized. Area of the large ROI was equal to the sum of those four small ROIs. The above-mentioned strain contrast was defined as the average strain ratio between the background and the target.

3.B.3. Example 3: Time-dependent QUE via strain imaging

In this example, a quasilinear viscoelastic model was used to simulate time-dependent tissue behaviors of the Lesion 1 phantom [Fig. 8(a)]. Again, the detailed mechanical parameters can be found in Tables V and VI in Appendix B. Particularly, Lesion 1 was assigned a larger predetermined relaxation time, as compared to its glandular background. Figure 14(b) is the estimated T_1 image. The positive image contrast between the lesion (2.2 s) and background (3.7 s) is clearly visible in Fig. 14(b).

4. DISCUSSION AND CONCLUSIONS

Like many new diagnostic imaging systems, many QUE algorithms perform well and show great promise in phantom experiments but fail to live up to expectations in *in vivo* clinical trials. This is largely because testing done during tissue-mimicking phantom experiments was too simple whereas *in vivo* tissue motion in clinical trials was significantly more challenging. A NCC value between a pair of predeformation and motion-compensated postdeformation RF echo fields⁴⁴ has been used to assess motion tracking accuracy. Estimated NCC values may also be used as a metric indicating the challenging level of motion tracking. Consequently, virtual breast ultrasound phantoms presented in this paper resulted in echo data that have challenged our motion tracking algorithm⁴²

more as compared to a physical tissue-mimicking phantom. However, this is only our first attempt. More features such as sliding and shearing⁴⁶ between tissue interfaces and acoustic attenuation can be further incorporated into the proposed simulation platform to challenge motion tracking algorithms. Further development will enable the proposed virtual platform to be used in early stage virtual clinical trials of QUE systems in a cost-effective manner.

Limitations of QUE reported in the clinical literature⁴⁷ include lack of uniform compression over the entire ROI and imaging artifacts due to motion tracking errors. Both limitations make image interpretation more difficult. In our vision, the proposed virtual platform can be also to generate known but complex QUE data. With the availability of those simulated ground truth training tools for clinicians can be derived to improve their confidence on image interpretation.

The small cluster of milk ducts could not be seen in both B-mode and strain images, largely due to its small size (approximately 2-mm diameter). In Fig. 13, the incremental strain contrast is defined as $\Delta\epsilon_b/\Delta\epsilon_i$, where $\Delta\epsilon_b$ and $\Delta\epsilon_i$ are the incremental strains of the background and the inclusion (Lesion 1 and Lesion 3), respectively. Under the same deformation, the hard inclusion deforms less. For example, at a 5% (accumulative) deformation, the inclusion deforms significantly less than the background: 1.93% vs 4.33% (Lesion 1), 1.55% vs 4.28% (Lesion 3) as shown in Table III. As the load increased to 10% (accumulative) deformation, the inclusion was deformed by 4.12% (on average) in Lesion 1 and 3.15% (on average) in Lesion 3, respectively, while the background was deformed by around 10%. Because the stress-strain curve is nonlinear, the background was stiffened at a faster rate as compared to the stiffness change of the lesion. Consequently, the (overall) incremental strain contrast ($\Delta\epsilon_b/\Delta\epsilon_i$) decreases as the increase of loading. Recall that under the same accumulative deformation (e.g., 15%), Lesion 3 stiffens faster than Lesion 1 (see Tables III and V). That explains why the relative stiffness ratio between the background and the Lesion 3 decreases at a slower rate. Results shown in Table III are consistent with results displayed in Figs. 13(b) and 13(c), where Lesion 3 maintained the incremental strain contrast while the incremental strain contrast decreased more significantly for the Lesion 1 phantom (from 5% to 15% of loading).

TABLE III. Tabulated results of nonlinear QUE. Accumulative strains of the background and lesions were estimated from respective ROIs shown in Figs. 13(b) and 13(c). Strain values in parentheses were accumulative strains from the previous loading step and therefore, respective secant modulus values were calculated from Fig. 13(a) using those strain pairs (i.e., current and previous accumulative strains).

	Accumulative overall compression	5%	10%	15%
Figure 13(b)	Accumulative strain of Lesion 1	1.93% (1.14%)	4.12% (3.25%)	6.79% (5.87%)
	Accumulative strain of background	4.33% (2.84%)	8.71% (7.41%)	13.32% (12.12%)
	Secant modulus ratio (lesion/background)	1.89	1.47	1.30
Figure 13(c)	Accumulative strain of Lesion 3	1.55% (0.91%)	3.15% (2.53%)	3.85% (3.17%)
	Accumulative strain of background	4.28% (3.0%)	8.7% (7.48%)	13.35% (12.14%)
	Secant modulus ratio (lesion/background)	2.1	1.97	1.76

It is also interesting to note that the estimated value of relaxation time constants T_1 deviated from the predetermined values (i.e., 1.0 s vs 2.2 s for the background, 4.0 s vs. 3.7 s for the lesion) as shown in Table IV. This was largely due to the fact that the stress relaxation function $G(t)$ was used to simulate the creep response in FEBio as described in Appendix B. In the stress relaxation function $G(t)$, τ_ε (relaxation time under a constant strain) was used, while a different relaxation time constant τ_σ (relaxation time under a constant stress) was estimated from the time-resolved strain creep [i.e., Eq. (1)]. τ_ε and τ_σ are defined in Appendix B. The ratio between τ_ε and τ_σ should be approximately 2 for the numerical model described in Fig. 14 (Ref. 48) (see Appendix B for a brief explanation). That explains why the estimated (average) relaxation time constant was almost twice than predetermined value for the background. However, the estimated (average) relaxation constant was nearly the same as the predetermined value for the inclusion. We stipulate that the background which occupies the vast majority of the volume stopped its relaxation at 2.2 s, thereby limiting further deformations of the inclusion.

In summary, a virtual ultrasound simulation platform mainly based on open-source software has been initially implemented and tested in this study. Our preliminary results suggest that this virtual ultrasound simulation platform can be used to perform both acoustic and QUE simulations. One significant contribution of this work is the fact that, to our knowledge, advanced QUE simulations of this kind (i.e., real-

istic geometries and tissue composition and properties) have not been reported elsewhere. Particularly, two advanced QUE applications, namely, nonlinear^{33,34} and time-dependent strain imaging,³⁵ were used as show-case examples to demonstrate capabilities of the proposed system. With this significant boost in simulation power, interests in integrating virtual simulations into QUE system design will be stimulated. Another intellectual contribution is that the proposed software innovation enables imaging physicists/scientists to rigorously compare image pixels with underlying soft tissue properties (also known as ground truth) using simulated ultrasound data emulating *in vivo* breast anatomy. Such comparisons are highly desirable and critically important for new applications such as nonlinear^{33,34} and time-dependent³⁵ strain imaging.

ACKNOWLEDGMENTS

This study is funded by a grant from NIH (No. R15-CA179409-01A1) and the start-up funds from Michigan Tech University. Tech support (particularly, Dr. Gowtham) and allocated time from Michigan Tech's HPC facility (Superior HPC) made this study feasible. We also want to thank Professor Timothy Hall from University of Wisconsin-Madison for stimulating discussions that inspired this study. We also want to thank anonymous reviewers for their constructive comments that led to significant improvements of the paper.

APPENDIX A: CREATION OF SMALL RANDOMLY DISTRIBUTED STRUCTURES

A description of creation of randomly distributed structures is provided below for the sake of completeness. These steps were implemented in VTK using standard c++ language. The

TABLE IV. Tabulated comparisons of relaxation constants for the simulated time-dependent QUE. γ is defined in Appendix B.

	τ_ε (s) (pre-determined)	τ_σ (s) (estimated)	$\tau_\sigma/\tau_\varepsilon$
$\gamma = 0.95$			
Background	1	2.2	2.2
Inclusion	4	3.7	0.87

FIG. 15. An example of generating random milk duct and lobe structure using VTK: (a) A milk duct represented by a random tube, (b) a lobe structure represented by a cluster of overlapping spheres, (c) one milk duct connected with a lobe, and (d) several simulated branches of milk ducts and lobes.

detailed procedures related to creating milk ducts including lobes are shown below as a three-step process.

Step 1: Creation of random milk duct

Starting from two random points (i.e., the first line segment of a random curve) within the fibro-glandular region, subsequent points were generated by adding more line segments to continue this random curve. Subsequent directions of this curve were determined by a random vector. This random vector largely followed the direction of the two most recent points on the curve, with a small added fraction (e.g., 20%) of randomness. All points were tested to ensure the curve had been constrained within the fibro-glandular region.

If a predetermined length of the random tube was reached or the random curve had to leave the fibro-glandular region, the process of generating random points would stop. The random curve was the skeleton for the simulated milk duct. The diameter of the tube can spatially vary as specified by the user. Finally, a milk duct structure was linked together smoothly by VTK using `vtkTubeFilter`. An example of the simulated milk duct is given in Fig. 15(a).

Step 2: Creation of simulated lobes

A simulated lobe was represented by a cluster of overlapping random spheres as shown in Fig. 15(b). Typically, a simulated lobe consisted of 3–5 random spheres and occupied 4–9 mm³ in space. Of note, overlapping random spheres were stitched together using Union operations under VTK.

Step 3: Integration of branches

Two random points on the random curve (as described in Step 1) could be selected as the starting point to create bifurcated milk duct structures. Once those two new starting points were selected, the process of generating one new milk duct was the same as that described in Step 1. The new branch of the milk duct was connected to the previous generated milk duct through the same Union operation under VTK. Similarly, all simulated lobes were connected to milk ducts through the same Union operation [see Fig. 15(c)]. Finally, all these branches were linked together to create a tree-like structure to represent milk duct and lobe structure [see Fig. 15(d)].

Creation of the small adipose compartments (elongated random ellipsoids) within the fibro-glandular region was similar to what was described in Step 2 for the generation of simulated breast lobes, except that the small fat compartments were represented as a small cluster of random ellipsoids. Similarly, generating Cooper's ligaments was similar to what was described in Step 1 above.

APPENDIX B: TISSUE MECHANICAL MODELS USED FOR QUE SIMULATIONS

For FE-simulations of QUE, a hyperelasticity model, V-W model,³⁶ was adopted. In the V-W model, the strain energy function is given as follows,

$$W = C_1 \left[e^{(C_2(I_1-3))} - 1 \right] - \frac{C_1 C_2}{2} (I_2 - 3) + U(J), \quad (B1)$$

where C_1 and C_2 are, respectively, the first and second Veronda-Westmann coefficients, I_1 and I_2 are, respectively, the first and second invariant of the right Cauchy–Green tensor. Incompressibility requires the volumetric strain function $U(J) = 0$.

Uniaxial stress–strain curves of glandular tissue, fat, skin, fibroadenoma and invasive ductal carcinoma were fit to the V-W model. Those stress–strain curves were derived based on previously published results.^{38,39,49} To our knowledge, stress–strain curve of Cooper's ligament is not available in the literature. Material properties of the Cooper's ligament were derived from other ligament data in the literature.

In the time-dependent QUE application, viscoelasticity of soft tissues was taken into consideration by a quasilinear viscoelastic material model³⁷ implemented in FEBio.²³ In the quasilinear viscoelastic model, a relaxation function $G(t)$ was used⁵⁰ as follows,

$$G(t) = 1 + \sum_{i=1}^N \gamma_i \exp(-t/\tau_i), \quad (B2)$$

where τ_i represents one of relaxation time values in the Prony series, and γ_i is the viscoelastic coefficient in the Prony series. In this study, N was set to be 1 and Eq. (B2) became a three-element Standard Linear Solid (SLS) model (Fig. 16). The

FIG. 16. An illustration of three-element SLS model. A spring (E_0) and a dashpot (η) are first connected in series (Maxwell body). Then, the Maxwell body is connected with a spring (E_1) in parallel.

TABLE V. Parameters associated with the V-W model.

Tissue type	C_1 (kPa)	C_2
Fat	3	5
Fibro-glandular tissue	4	6.5
Cooper's ligament	25	7
Milk duct	3	2
Skin	300	5
Benign lesion	30	7
Malignant lesion	32	40

stress-strain relationship of the SLS model can be expressed as⁴⁸

$$\sigma + \tau_\varepsilon \dot{\sigma} = E_1(\varepsilon + \tau_\sigma \dot{\varepsilon}), \quad (\text{B3})$$

where the relaxation time constant under a constant strain $\tau_\varepsilon = \eta/E_0$, and the relaxation time constant under a constant stress $\tau_\sigma = \eta/E_1(1 + (E_1/E_0))$. The **creep response curve** of the SLS model can be expressed as⁴⁸

$$\varepsilon(t) = \varepsilon_0 + \varepsilon_0 \frac{E_0}{E_1} (1 - e^{-t/\tau_\sigma}), \quad (\text{B4})$$

where ε_0 is the instantaneous elastic strain that occurs immediately after a compression. The **relaxation function** of the SLS model can be expressed as⁴⁸

$$G(t) = 1 + \frac{E_0}{E_1} e^{-t/\tau_\varepsilon}. \quad (\text{B5})$$

Thus, the quasilinear viscoelastic model was actually a solid mixture of the V-W model³⁶ and the SLS model. When $N = 1$ in Eq. (B2), $\tau_1 = \tau_\varepsilon$ was used for the FE simulation. When Eq. (1) was used to estimate the relaxation constant T_1 , T_1 is actually τ_σ . Therefore, the difference can be analytically expressed as follows,

$$\frac{\tau_\sigma}{\tau_\varepsilon} = \frac{\frac{\eta}{E_1} + \frac{\eta}{E_0}}{\frac{\eta}{E_0}} = 1 + \frac{E_0}{E_1}, \quad (\text{B6})$$

where E_0/E_1 is γ_1 in Eq. (B2) when $N = 1$.

Viscoelastic parameters used in the time-dependent QUE application are shown in Table VI. Relaxation time values (τ_1) were empirically chosen based on findings by Qiu *et al.*³⁵

TABLE VI. Viscoelastic coefficients and relaxation times used in the FEA simulations.

Component	Viscoelastic coefficient	
	(γ_1)	Relaxation time (τ_1) unit: s
Fat	0.95	1
Fibro-glandular tissue	0.95	1.2
Cooper's ligament	0.95	1.5
Milk duct	0.95	1
Skin	0.95	1
Lesion 1	0.95	4

- ^{a)}Author to whom correspondence should be addressed. Electronic mail: jjiang1@mtu.edu; Telephone: (906)-487-1943; Fax: (906)-487-1717.
- ¹ACS, *Breast Cancer Facts & Figures 2011-2012* (American Cancer Society, Atlanta, GA, 2012).
- ²W. A. Berg, L. Gutierrez, M. S. NessAiver, W. B. Carter, M. Bhargavan, R. S. Lewis, and O. B. Ioffe, "Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer," *Radiology* **233**, 830–849 (2004).
- ³M. Kriege, C. T. M. Brekelmans, C. Boetes, P. E. Besnard, H. M. Zonderland, I. M. Obdeijn, R. A. Manolliu, T. Kok, H. Peterse, M. M. A. Tilanus-Linthorst, S. H. Muller, S. Meijer, J. C. Oosterwijk, L. V. A. M. Beex, R. A. E. M. Tollenaar, H. J. de Koning, E. J. T. Rutgers, J. G. M. Klijn, and M. R. I. Screeni, "Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition," *N. Engl. J. Med.* **351**, 427–437 (2004).
- ⁴E. Warner, D. B. Plewes, K. A. Hill, P. A. Causer, J. T. Zubovits, R. A. Jong, M. R. Cutrara, G. DeBoer, M. J. Yaffe, S. J. Messner, W. S. Meschino, C. A. Piron, and S. A. Narod, "Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination," *JAMA, J. Am. Med. Assoc.* **292**, 1317–1325 (2004).
- ⁵C. D. Lehman, C. Gatsonis, C. K. Kuhl, R. E. Hendrick, E. D. Pisano, L. Hanna, S. Peacock, S. F. Smazal, D. D. Maki, T. B. Julian, E. R. DePeri, D. A. Bluemke, M. D. Schnall, T. Julian, W. Poller, K. Schilling, C. Neal, L. Wichterman, P. Seifert, M. O'Loughlin, D. Bluemke, S. Kawamoto, E. DePeri, E. Hendrick, J. Wolfman, S. Smazal, D. Thickman, R. Korn, D. Maki, C. Whitfill, A. Cook, P. Causer, V. Rao, C. Piccoli, E. Ferris, S. Harms, C. Kuhl, N. DeBruhl, N. Hylton, M. Mahoney, E. Pisano, M. Schnall, S. Weinstein, S. Keesara, P. Weatherall, G. DeAngelis, C. Lehman, T. Li, and R. Soulen, "MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer," *N. Engl. J. Med.* **356**, 1295–1303 (2007).
- ⁶S. J. Lord, W. Lei, P. Craft, J. N. Cawson, I. Morris, S. Walleiser, A. Griffiths, S. Parker, and N. Houssami, "A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer," *Eur. J. Cancer* **43**, 1905–1917 (2007).
- ⁷W. A. Berg, J. D. Blume, A. M. Adams, R. A. Jong, R. G. Barr, D. E. Lehrer, E. D. Pisano, W. P. Evans, M. C. Mahoney, L. H. Larsen, G. J. Gabrielli, and E. B. Mendelson, "Reasons women at elevated risk of breast cancer refuse breast MR imaging screening: ACRIN 6666," *Radiology* **254**, 79–87 (2010).
- ⁸P. T. Huynh, A. M. Jarolimek, and S. Daye, "The false-negative mammogram," *Radiographics* **18**, 1137–1154 (1998).
- ⁹J. Ophir, I. Cespedes, H. Ponnekanti, Y. Yazdi, and X. Li, "Elastography: A quantitative method for imaging the elasticity of biological tissues," *Ultrason. Imaging* **13**, 111–134 (1991).
- ¹⁰T. J. Hall, Y. N. Zhu, and C. S. Spalding, "In vivo real-time freehand palpation imaging," *Ultrasound Med. Biol.* **29**, 427–435 (2003).
- ¹¹M. Odonnell, A. R. Skovoroda, B. M. Shapo, and S. Y. Emelianov, "Internal displacement and strain imaging using ultrasonic speckle tracking," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control* **41**, 314–325 (1994).
- ¹²E. S. Burnside, T. J. Hall, A. M. Sommer, G. K. Hesley, G. A. Sisney, W. E. Svensson, J. P. Fine, J. J. Jiang, and N. J. Hangiandreou, "Differentiating benign from malignant solid breast masses with US strain imaging," *Radiology* **245**, 401–410 (2007).
- ¹³J. F. Jiang and T. J. Hall, "A generalized speckle tracking algorithm for ultrasonic strain imaging using dynamic programming," *Ultrasound Med. Biol.* **35**, 1863–1879 (2009).
- ¹⁴Y. N. Zhu and T. J. Hall, "A modified block matching method for real-time freehand strain imaging," *Ultrason. Imaging* **24**, 161–176 (2002).
- ¹⁵X. Gong, Q. H. Xu, Z. L. Xu, P. Xiong, W. L. Yan, and Y. Z. Chen, "Real-time elastography for the differentiation of benign and malignant breast lesions: A meta-analysis," *Breast Cancer Res. Treat.* **130**, 11–18 (2011).
- ¹⁶F. S. Azar, D. N. Metaxas, and M. D. Schnall, "A deformable finite element model of the breast for predicting mechanical deformations under external perturbations," *Acad. Radiol.* **8**, 965–975 (2001).
- ¹⁷A. Samani, J. Bishop, M. J. Yaffe, and D. B. Plewes, "Biomechanical 3-D finite element modeling of the human breast using MRI data," *IEEE Trans. Med. Imaging* **20**, 271–279 (2001).
- ¹⁸S. N. Bhatti and M. Sridhar-Keralapura, "A novel breast software phantom for biomechanical modeling of elastography," *Med. Phys.* **39**, 1748–1768 (2012).

- ¹⁹F. Kallel, C. D. Prihoda, and J. Ophir, "Contrast-transfer efficiency for continuously varying tissue moduli: Simulation and phantom validation," *Ultrasound Med. Biol.* **27**, 1115–1125 (2001).
- ²⁰C. M. Hsu, M. L. Palmeri, W. P. Segars, A. I. Veress, and J. T. Dobbins 3rd, "Generation of a suite of 3D computer-generated breast phantoms from a limited set of human subject data," *Med. Phys.* **40**, 043703 (11pp.) (2013).
- ²¹E. L. Madsen, M. A. Hobson, H. Shi, T. Varghese, and G. R. Frank, "Stability of heterogeneous elastography phantoms made from oil dispersions in aqueous gels," *Ultrasound Med. Biol.* **32**, 261–270 (2006).
- ²²M. A. Hobson, E. L. Madsen, G. R. Frank, J. F. Jiang, H. R. Shi, T. J. Hall, and T. Varghese, "Anthropomorphic phantoms for assessment of strain imaging methods involving saline-infused sonohysterography," *Ultrasound Med. Biol.* **34**, 1622–1637 (2008).
- ²³S. A. Maas, B. J. Ellis, G. A. Ateshian, and J. A. Weiss, "FEBio: Finite elements for biomechanics," *J. Biomech. Eng.* **134**, 011005–011010 (2012).
- ²⁴J. A. Jensen, "A model for the propagation and scattering of ultrasound in tissue," *J. Acoust. Soc. Am.* **89**, 182–190 (1991).
- ²⁵W. Schroeder, K. Martin, and B. Lorensen, *The Visualization Toolkit*, 2nd ed. (Prentice Hall PTR, Upper Saddle River, NJ, 1998).
- ²⁶H. Si and K. Gartner, "3D boundary recovery by constrained Delaunay tetrahedralization," *Int. J. Numer. Methods Eng.* **85**, 1341–1364 (2011).
- ²⁷National_Library_of_Medicine, The Visible Human Project Getting the Data, 2000.
- ²⁸ScanIP, +FE, +NURBS and +CAD Tutorial Guide, Version 5.1 ed., 2001.
- ²⁹M. Piccinelli, A. Veneziani, D. A. Steinman, A. Remuzzi, and L. Antiga, "A framework for geometric analysis of vascular structures: Application to cerebral aneurysms," *IEEE Trans. Med. Imaging* **28**, 1141–1155 (2009).
- ³⁰D. Mahr, "Three-dimensional in-silico breast phantom for multimodality image simulation," Ph.D. dissertation, University of Illinois at Urbana-Champaign, 2009.
- ³¹D. T. Ramsay, J. C. Kent, R. A. Hartmann, and P. E. Hartmann, "Anatomy of the lactating human breast redefined with ultrasound imaging," *J. Anat.* **206**, 525–534 (2005).
- ³²M. J. Aftosmis, M. J. Berger, and J. E. Melton, "Robust and efficient Cartesian mesh generation for component-based geometry," in *35th AIAA Aerospace Sciences Meeting, Reno NV*, 1997.
- ³³S. Goenezen, J. F. Dord, Z. Sink, P. E. Barbone, J. Jiang, T. J. Hall, and A. A. Oberai, "Linear and nonlinear elastic modulus imaging: An application to breast cancer diagnosis," *IEEE Trans. Med. Imaging* **31**, 1628–1637 (2012).
- ³⁴A. A. Oberai, N. H. Gokhale, S. Goenezen, P. E. Barbone, T. J. Hall, A. M. Sommer, and J. Jiang, "Linear and nonlinear elasticity imaging of soft tissue in vivo: Demonstration of feasibility," *Phys. Med. Biol.* **54**, 1191–1207 (2009).
- ³⁵Y. Qiu, M. Sridhar, J. K. Tsou, K. K. Lindfors, and M. F. Insana, "Ultrasonic viscoelasticity imaging of nonpalpable breast tumors: Preliminary results," *Acad. Radiol.* **15**, 1526–1533 (2008).
- ³⁶D. R. Veronda and R. A. Westmann, "Mechanical characterization of skin—Finite deformations," *J. Biomech.* **3**, 111–124 (1970).
- ³⁷Y. C. Fung, *Biomechanics: Mechanical Properties of Living Tissues*, 2nd ed. (Springer-Verlag, New York, NY, 1993).
- ³⁸T. A. Krouskop, T. M. Wheeler, F. Kallel, and T. Hall, "The elastic moduli of breast and prostate tissues under compression," *Ultrasound Imaging* **20**, 260–274 (1998).
- ³⁹P. S. Wellman, E. P. Dalton, D. Krag, K. A. Kern, and R. D. Howe, "Tactile imaging of breast masses: First clinical report," *Arch. Surg.* **136**, 204–208 (2001).
- ⁴⁰N. Rao, S. Mehra, and Z. Hui, "Ultrasound speckle statistics variations with imaging system impulse response," *Presented at the Proceedings of IEEE Ultrasonics Symposium*, 1990.
- ⁴¹F. A. Duck, *Physical Properties of Tissue: A Comprehensive Reference Book* (Academic, San Diego, CA, 1990).
- ⁴²J. Jiang and T. J. Hall, "A fast hybrid algorithm combining regularized motion tracking and predictive search for reducing the occurrence of large displacement errors," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control* **58**, 730–736 (2011).
- ⁴³F. Kallel and J. Ophir, "A least-squares strain estimator for elastography," *Ultrasound Imaging* **19**, 195–208 (1997).
- ⁴⁴J. Jiang, T. J. Hall, and A. M. Sommer, "A novel performance descriptor for ultrasonic strain imaging: A preliminary study," *IEEE Trans. Ultrason., Ferroelectr., Freq. Control* **53**, 1088–1102 (2006).
- ⁴⁵T. J. Hall, A. A. Oberai, P. E. Barbone, A. M. Sommer, N. H. Gokhale, S. Goenezen, and J. Jingfeng, "Elastic nonlinear imaging," *Presented at the Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 2009.
- ⁴⁶R. Zheng, L. H. Le, M. D. Sacchi, D. Ta, and E. Lou, "Spectral ratio method to estimate broadband ultrasound attenuation of cortical bones in vitro using multiple reflections," *Phys. Med. Biol.* **52**, 5855–5869 (2007).
- ⁴⁷W. Wunderlich, E. Stein, and K.-J. Bathe, "Nonlinear finite element analysis in structural mechanics," in *Proceedings of the Europe-U.S. Workshop, Ruhr-Universität Bochum, Germany, 28-31 July, 1980* (Springer, Berlin, New York, NY, 1981).
- ⁴⁸C. R. Ethier and C. A. Simmons, "Introductory biomechanics from cells to organisms," in *Cambridge Texts in Biomedical Engineering* (Cambridge University Press, Cambridge, New York, 2007), p. 1.
- ⁴⁹T. A. Bigelow, "Improved algorithm for estimation of attenuation along propagation path using backscattered echoes from multiple sources," *Ultrasonics* **50**, 496–501 (2010).
- ⁵⁰A. Gerig, J. Zagzebski, and T. Varghese, "Statistics of ultrasonic scatterer size estimation with a reference phantom," *J. Acoust. Soc. Am.* **113**, 3430–3437 (2003).