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TITLE: Assistive and Autonomous Breast Ultrasound Screening:
Improving PPV and Reducing RSI

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14. ABSTRACT This report describes the fourth year of research activities on technologies that support sonographer-supervised robotic systems for breast ultrasound imaging with qualitative elastography, quantitative elastography, and shear-wave elastography. Major objectives achieved in this period include progress toward stochastic mapping techniques for quantitative compressional elastography and combined quasi-static and shear wave elastography for viscoelastic and nonlinear parameter mapping.					
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1. Introduction

The objective of this research project is to develop technologies that support sonographer-supervised robotic systems for breast ultrasound imaging with quantitative elastography. Elastography provides tissue metrics independent of B-mode image features to deliver improved lesion classification, but current techniques are hampered by sensitivity to variations in probe motion and pressure, resulting in significant operator dependence. By delivering advanced, operator-independent elastography data, the proposed system will address the urgent need to improve the positive predictive value (PPV) of ultrasound to spare women unnecessary biopsies, anxiety, and cost while maintaining quality of care. The main goals in the third and fourth years of the project have been to develop and experimentally verify novel algorithms for robotically assisted breast ultrasound imaging.

2. Keywords

Ultrasound elastography, breast cancer, robotics, human-robot teaming

3. Accomplishments

3.1 What were the major goals of the project

The overall goal of this research is to investigate technologies for improving the positive predictive value (PPV) of ultrasound screening. The specific aims for this research include development and evaluation of a collaborative robotic system for breast ultrasound scanning and elastography (SA1) and perform experiments with robotically assisted elastography in vivo (SA2). Year 1 focused on developing technologies to support human-robot ultrasound scanning systems, while Years 2-4 transitions towards studies and refinement of the collaborative robotic system and ultrasound imaging techniques.

3.2 What was accomplished under these goals

Major objectives achieved in this period include combined quasi-static and shear wave elastography for viscoelastic and nonlinear parameter mapping and progress toward stochastic mapping techniques for quantitative compressional elastography.

Regarding the first topic, we continued to develop methods for measuring the non-linear and viscoelastic properties of tissues enabled by robotically assisted tissue deformation. Our work in the previous report demonstrated the ability to generate images of non-linear modulus parameter (A) using controlled deformations generated by a robotic positioner; these results were published as “Shear Induced Non-linear Elasticity Imaging: Elastography for Compound Deformations” in *IEEE Transactions on Medical Imaging*. Work in this period demonstrated similar results with free-hand scanning and were presented at the 2020 IEEE International Ultrasonics Symposium as “Quantitative nonlinear shear modulus mapping using freehand scanning”.

In this period, we have worked to develop a combined method for estimating viscoelastic and non-linear mechanical properties simultaneously, using controlled deformations. In this approach we model tissue as a hyperelastic material with viscous loss. By measuring the phase speed of multiple frequency components of a broadband shear wave under varying degrees of strain, we can estimate simultaneously the shear viscosity and non-linear parameter.

Simulation of shear wave propagation in nonlinear, viscoelastic media

Simulations were performed using Field II to model the push beam, which acts as the source of the shear wave, and Comsol Multiphysics (v 5.3) to model shear wave propagation in the non-linear and viscolastic medium. A push beam focused at 25 mm with an F/2 aperture size and push frequency of 5 MHz was modeled. The square of the calculated pressure values was treated as proportional to intensity ($I=p^2/\rho c$), and thus radiation force through the relationship $F=2\alpha I/c$. The calculated intensity was scaled to model a body load in COMSOL resulting in a shear wave of comparable amplitude to experiment; a push duration of 200 μ s was modeled. The top surface of the model was displaced to the material to mimic the experimental compound deformations and then use the body force to generate shear wave displacements. A 20 ms delay was allowed between the boundary deformation and push pulse to ensure that the large external boundary deformation does not interfere with the comparatively smaller deformations due to the shear wave propagation.

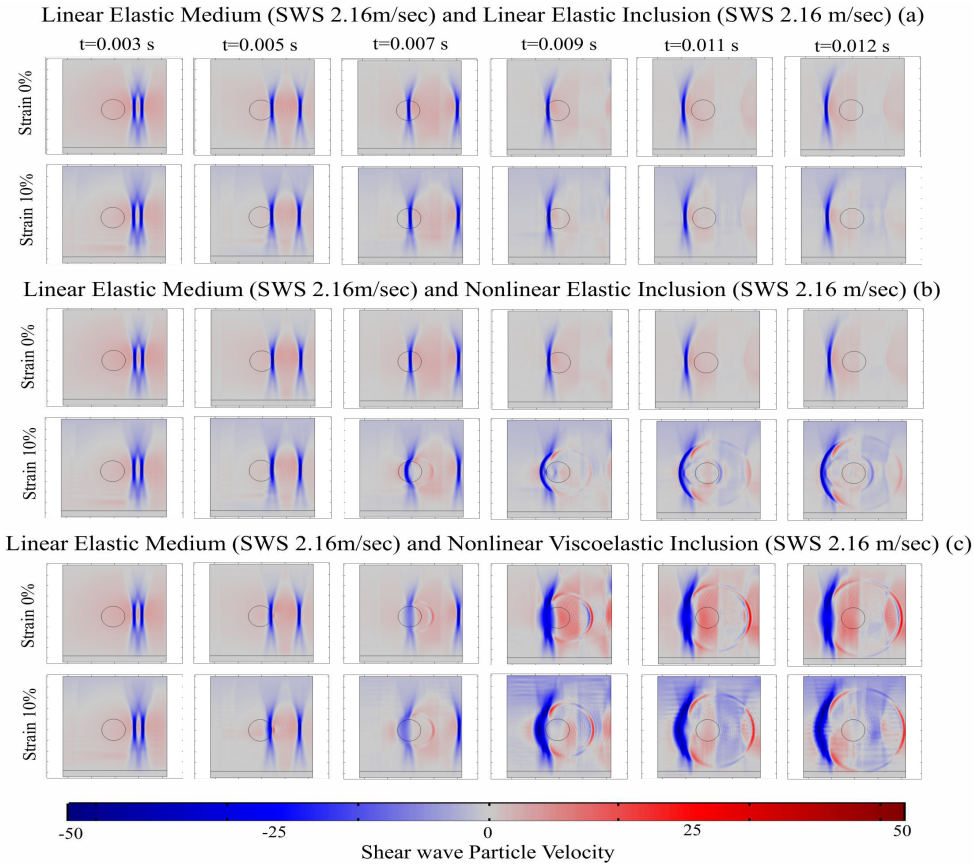


Figure 1. Shear wave propagation in linear elastic and mixed nonlinear/viscoelastic media. The upper two rows depict shear wave propagation in a linear elastic background with a circular “inclusion” with the same properties. Shear wave propagation is undistorted by the inclusion, as the shear wave speed is the same in the background and inclusion, and independent of global strain. In the middle two rows the inclusion is a nonlinear elastic material, with modulus matched to the background at zero strain. In row 3 (zero global strain) the shear wave is undistorted, while in row 4, the shear wave is distorted by the lens action of the inclusion, which, due to the 10% global strain, exhibits higher shear wave speed. In the bottom two rows, the inclusion is both nonlinear and viscoelastic. Under zero static strain the shear wave is broadened by dispersion, while under 10% global strain the increase in group velocity is apparent, in addition to the broadening due to viscoelastic dispersion.

Estimation of viscoelastic and nonlinear properties from shear wave data

In this period of the project, we have developed methods for estimating the viscoelastic and nonlinear parameters, and evaluated these methods in simulated and phantom materials. Stepwise increases in global strain are applied, as a boundary condition in simulation, and by application of a controlled transducer displacement experiment. At each displacement step a shear wave imaging sequence is applied, and local estimates of phase velocity obtained. A local strain estimate is calculated by speckle tracking (as in strain elastography). The combination of shear wave speed and local strain allow estimation of local stress and material non-linearity. The change in phase velocity as a function of frequency allows the viscoelastic parameter to be estimated. Thus, the combination of strain and shear wave imaging with controlled deformation provides the data to recover material nonlinearity and viscoelasticity. In finite element

simulations, the strain and shear wave velocity may be obtained directly from the simulation, while in phantoms ultrasound tracking, described below, was used to obtain these data.

Strain Processing: Axial and lateral displacements were estimated at each of the deformation steps using a 2D cross-correlation-based similarity search algorithm. The displacements were accumulated over all the frames and registered with respect to the initial state of the medium. The axial strain and shear strain were quantified using first derivative least square strain.

SWEI Processing: SW particle velocity data were collected using an ultra-fast plane wave SW elasticity imaging sequence. The push duration was 200 μ s and push frequency was 5 MHz. Eight frames at different steering angles between -5° and 5° were used to improve the frame rate of shear wave tracking. The SW particle displacement versus time at every depth in the region of interest was estimated using 2-D auto-correlation method of Loupas¹. The SW arrival time difference was estimated from cross-correlation of displacement vs time profile. The distance between track elements divided by difference in SW arrival times provides the group shear wave speed (v_s), which is related to the linear shear modulus (μ) by $\mu = \rho \cdot v_s^2$ where ρ is medium density.

Phase Velocity Imaging: We used a local wavenumber imaging method² to create images of phase velocity in soft tissue. This method uses short-space Fourier transform on SW traces to obtain a space-frequency wave-number representation. Spatial maps of SW phase velocity were reconstructed from the wavenumber spectra for a frequency range of 100-800 Hz within the SW broadband excitation. For each frequency of SW excitation, by fitting the phase velocity, shear strain and axial strain to (Eqn.4), the frequency-dependent NLSM map is obtained.

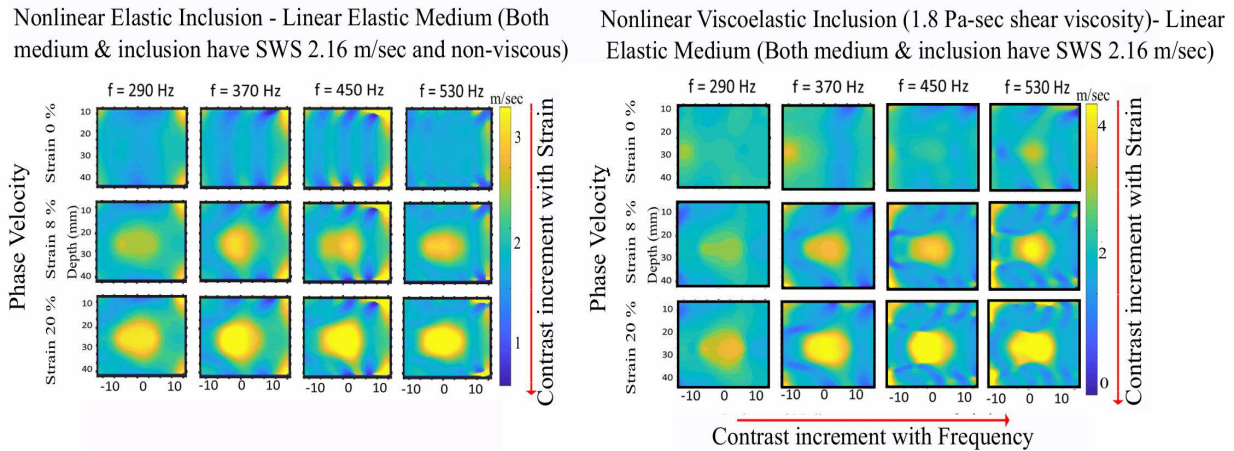


Figure 2. Simulated images of shear wave phase velocity obtained using finite-element modeling of shear wave propagation (as in figure 1) and the reconstruction method described in the text. The left panel demonstrates the results observed with a nonlinear (and non-viscous) inclusion in a linear elastic background. The observed shear wave speed increases in the inclusion, and the increase is independent of shear wave frequency. The right panel demonstrates a viscoelastic *and* nonlinear inclusion, wherein the shear wave speed increases both with frequency and global strain.

¹ T. Loupas, J. Powers, and R. W. Gill, "An axial velocity estimator for ultrasound blood flow imaging based on a full evaluation of the Doppler equation by means of a two-dimensional autocorrelation approach," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 42 no. 4, pp. 672-688, 1995.

² P. Kijanka, and M. W. Urban, "Local phase velocity-based imaging: A new technique used for ultrasound shear wave elastography.," *IEEE transactions on medical imaging*, vol. 38, no. 4, pp. 894-908, 2018

Activities involving robotically assisted compressional elastography this year focused on several topics. First, we continued to develop the mathematics of the stochastic mapping techniques for quantitative compressional elastography. This differs from our previous exploration of qualitative compressional elastography from our paper on “Probabilistic Mapping of Tissue Elasticity for Robot-Assisted Medical Ultrasound” that was presented at the 2019 International Symposium on Robotics Research because we now attempt to resolve the absolute instead of the relative stiffness of the tissue. The approach we have been developing is derived from the more general problem of Simultaneous Localization and Mapping (SLAM) where a robot concurrently tries to develop a map of the environment while trying to localize itself in that environment. We connect this problem to the problem of quantitative compressional elastography by modeling the elastogram and the robot in the state vector that we are trying to estimate from actions and observations taken during a scanning procedure. The robot state vector is represented using joint angles at the pre-compression (zero-strain condition), post-compression (or current state), and joint velocities as shown below.

$$\mathbf{x}_t = [q_{0,1} \quad \dots \quad q_{0,M} \mid q_{t,1} \quad \dots \quad q_{t,M} \mid \dot{q}_{t,1} \quad \dots \quad \dot{q}_{t,M}]^T$$

The elastogram (map) is static (time-independent) and represented by elasticities at every node in the finite element mesh and stored in a vector as follows.

$$\mathbf{m} = [E_1 \quad \dots \quad E_N]^T$$

The developed approach treats these as random variables and estimates the mean and covariance assuming they are distributed normally. This is performed by creating an augmented state vector.

$$\boldsymbol{\mu}_t = [\mathbf{x}_t \quad \mid \quad \mathbf{m}]^T$$

Traditional quasi-static reconstructive elastography seeks to minimize the following objective function, which includes Tikhonov regularization terms (λ , Γ) to enforce a smooth prior. Note that variable z represents measured displacements within the transducer FOV, W is a weighting matrix, and $h(\mathbf{m})$ represents a predictive measurement model of displacements.

$$f(\mathbf{m}) = \frac{1}{2} \|\hat{\mathbf{z}} - h(\mathbf{m})\|_W^2 + \frac{\lambda}{2} \|\mathbf{m} - \mathbf{m}_0\|_\Gamma^2$$

The modified approach estimates not just an optimal solution (or expected μ), but also a covariance matrix (Σ) which captures the covariance between the map and robot state vector variables. This is performed by minimizing the following objective function. Note the time dependence as analysis is performed on a per sample basis acquired over a span of time. In this formulation, $h(\boldsymbol{\mu}_t)$ represents a predictive measurement model for joint angles, internal tissue displacements, and reaction force measurements and is a function of both the robot states and map (elastogram). Additionally, Q_t represents a weighting matrix which captures the

measurement noise characteristics for each sensor and $\bar{\boldsymbol{\mu}}_t$ represents the current belief for the state and map vectors.

$$f(\boldsymbol{\mu}_t) = \frac{1}{2} \|\hat{\mathbf{z}}_t - h(\boldsymbol{\mu}_t)\|_{Q_t^{-1}}^2 + \frac{1}{2} \|\boldsymbol{\mu}_t - \bar{\boldsymbol{\mu}}_t\|_{\Sigma_t^{-1}}^2$$

In this formulation, regularization occurs through the covariance matrix which prevents large steps in areas of the map where there is more uncertainty. However, information from the robot states and nodal elasticities all contribute to every map update, thus the uncertainty in the robot state is accounted for when performing the optimization. To practically carry out this computation, Jacobians for every measurement model are necessary. We derived concise, closed form solutions for each Jacobian which offers a significant computational improvement over numerical estimation.

By modeling the joint states and node stiffnesses as random variables, we have developed an approach that jointly estimates the mean and covariance to recover a model that quantifies the uncertainty of our results. An illustration of this idea is shown in Figure 3. Notice that in this model we attempt to estimate the stiffness of the entire tissue phantom instead of only the windowed region defined by the field of view of the ultrasound transducer. These preliminary results show a higher confidence of estimated stiffnesses in and below the field of view while areas outside of the field of view show a lower confidence.

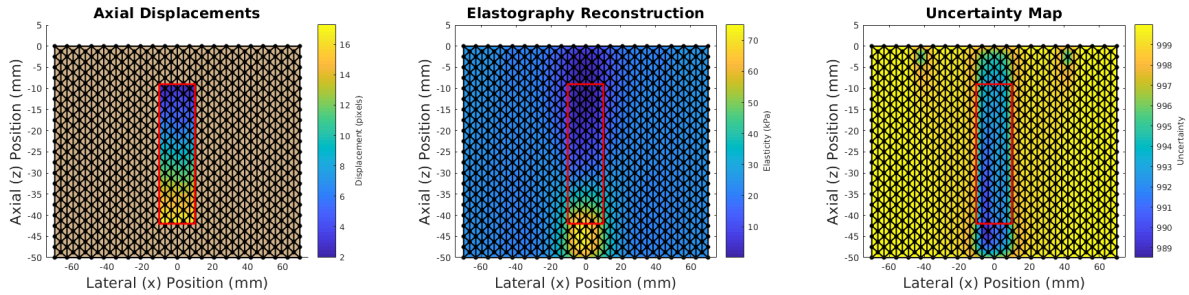


Figure 3. Visualization of robotically assisted compressional elastography collection. Displacements are calculated (left) by data collected within the transducer FOV (red rectangle) which may not encompass the entire phantom. Elastograms (middle) are computed over the entire tissue (as opposed to restricted to the FOV such as in standard reconstructive elastography). Additionally, uncertainty is displayed for the entire tissue (right). Note that the region inside of the FOV exhibits less uncertainty than outside, which indicates the system is more confident about the region it has observed.

One important attribute of the developed approach for stochastic mapping based compressional elastography techniques is robustness against inconsistencies in the observations due to disturbances. One example of this is out-of-plane slip, which would alter the locations of tracked features in a manner inconsistent with our predictive motion model. Since the technique is sensitive to the performance of the displacement estimation, we explored four different approaches to displacement tracking to see if we could improve the consistency of

measurements in an effort to further improve our recovered elastograms. The methods we explored, shown in Figure 4, include 1D time delay estimation (TDE), 2D normalized cross-correlation tracking (NCC), 2D Discrete Cosine Transform (DCT), and 2D Spatial Angular Compounding (SAC). While the 1D TDE and 2D SAC techniques proved to be more computationally efficient, in our experiments they were not shown to be robust to small but unintentional lateral motions by the end-effector induced during deformation of the tissue. We concluded that NCC was faster but exhibited comparable quality measurements to DCT based on an empirical analysis. The other techniques may be revisited when data is collected using the Kuka LBR Med due to the platform's improved accuracy.

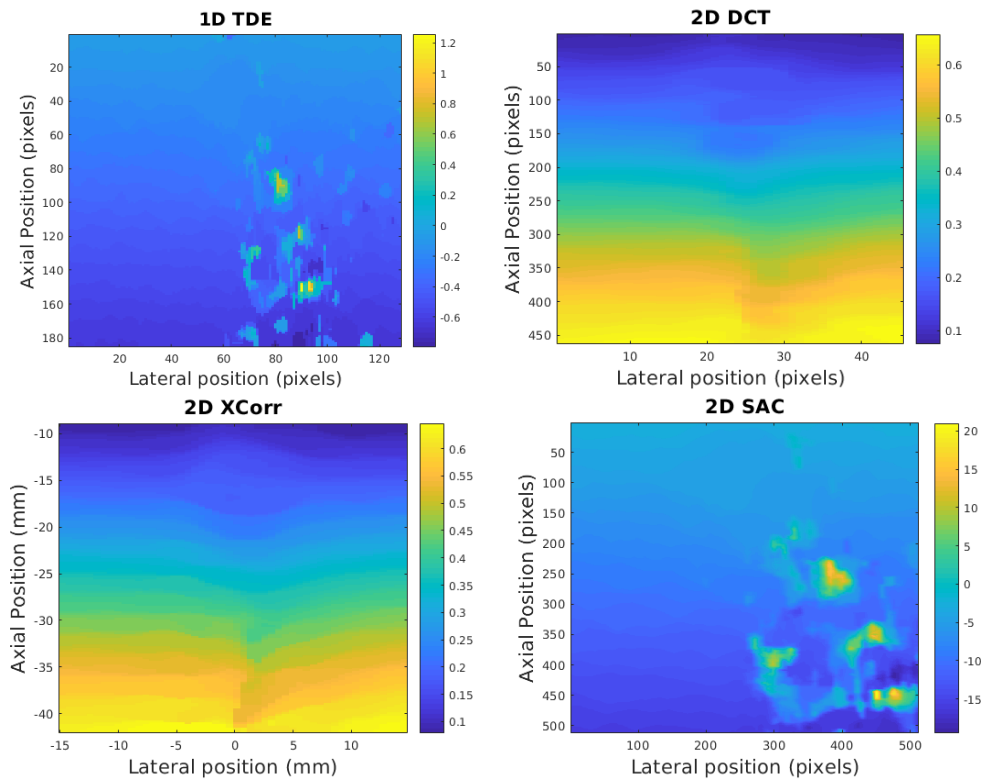


Figure 4 – Four methods of computing axial displacement. While each approach has its own relative merits, the chosen technique was 2D NCC (XCorr – bottom left) due to its robustness and improved computational runtime when compared to the 2D DCT. 1D TDE and 2D SAC were not robust to unintended lateral motions and produced noisy results.

In parallel to the development of the mathematics of the stochastic mapping technique for compressional elastography we also worked on the robotic platforms for acquisition of measurements. One observation from recent measurements with the original 3D-printed apparatus that rigidly mounts the end-effector to the end of the force-torque sense at the end of the manipulator is that the surface strain less even that desired. We redesigned and fielded a new version of the ultrasound transducer mount as shown in Figure 5.

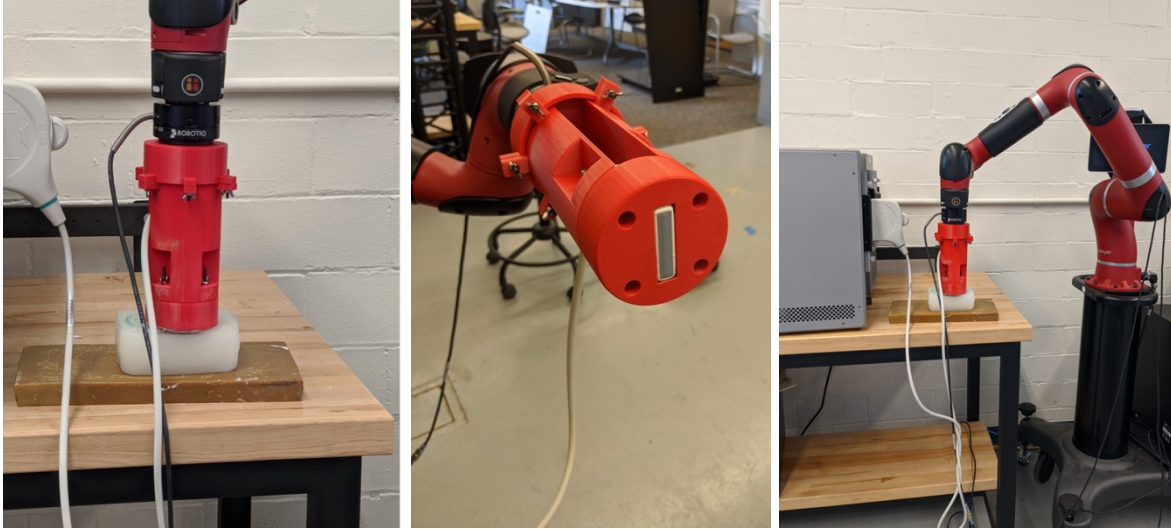


Figure 5 – Modified ultrasound transducer mount. The new design has a flatter base which allows the controller to balance more easily on soft tissue, whereas the previous attachment produced an unintended moment.

The last activity during this year was continued progress in migrating the system to the KUKA LBR Med platform acquired by Howard's Robotics and Artificial Intelligence Laboratory. Although progress in integrating this system was delayed by the university-wide laboratory shutdown in Spring 2020, we have designed, acquired and mounted the KUKA LBR Med on a mobile stand that will permit us to perform experiments in a manner similar to how we currently acquire measurements with the Rethink Robotics Sawyer. During the last three months of the period of performance we expect to finish integration and demonstrate the ability to acquire stiffness measurements of phantoms using robotically assisted compressional elastography and shear-wave scanning on two separate platforms.

3.3 What opportunities for training and professional development has the project provided?

This project has been a part of professional development for two graduate students in PI Howard's Robotics and Artificial Intelligence Laboratory. The research on hybrid force/velocity control for acquiring ultrasound scans under constant force and position setpoints supported the work of Christian Freitas as described in the 2017-2018 annual report in preparation of his master's thesis in Electrical Engineering that he defended in April 2018. The work on stiffness estimation from strain elastography for adaptive hybrid force/velocity control is one of the principal research topics of Michael Napoli's doctoral research. Michael has proposed his PhD Thesis proposal on the topic of quantitative robotically assisted compressional elastography. Both of these individuals have published peer-reviewed research on topics supported by this grant.

This project has also supported one undergraduate and one graduate student in PI McAleavey's ultrasound imaging laboratory. Undergraduate Katelyn Offerdahl (2017-2018) worked to quantify

the performance of shear wave elasticity imaging methods during periods of transducer motion. Her work led to a conference publication in the first year of this project. The work on co-registered shear strain and shear wave speed imaging is the thesis topic of graduate student Soumya Goswami, who continues to be supported by this grant.

3.4 How were the results disseminated to communities of interest?

Results were disseminated to communities of interest through publication of refereed conference papers and research presentations at academic conferences as outlined in Section 6.1.

3.5 What do you plan to do during the next reporting period to accomplish these goals?

During the final period of this project (2/2021-5/2021) we plan to perform measurements of phantom mechanical properties using our platform for research in robotically assisted medical ultrasound. This work will replace our planned activities using human subjects due to the implications of the COVID-19 pandemic. We will also continue technology development as described in the engineering research activities described in RT1-ST4.

4. Impact

4.1 What was the impact on the development of the principal discipline(s) of the project?

Nothing to report for this period beyond the publications and presentations listed below.

4.2 What was the impact on other disciplines?

Nothing to report for this period.

4.3 What was the impact on technology transfer?

There was no technology transfer that occurred under this project during the 2018-2019 period of performance.

4.4 What was the impact on society beyond science and technology?

Nothing to report for this period.

5. Challenges / Problems

5.1 Changes in approach and reasons for change

Due to the impact and continued risks from COVID-19 and the suspension of in-person activities in research laboratories on the University of Rochester campus during part of this reporting

period we have eliminated plans to perform in-vivo or ex-vivo tissue studies involving human subjects. As outlined in our updated and approved statement of work, we will apply the techniques we have been developing to tissue phantoms so that we can safely quantify the performance of the techniques developed for robotically assisted tissue stiffness estimation by maintaining social distance between researchers and eliminating contact with human subjects that would be required by our original IRB protocol. This adjustment of focus will allow us to further our research in probabilistic approaches to stiffness mapping and demonstrate generality of the developed approach on a second robotically assisted ultrasound scanning system.

5.2 Actual or anticipated problems or delays and actions or plans to resolve them

Our plan to scan human subjects was disrupted by the COVID-19 pandemic. We submitted a revised statement of work outlining a plan to replace studies involving human subjects with phantom studies; this revised statement of work was accepted. We plan to complete these phantom experiments in the final months of this project.

5.3 Changes that had a significant impact on expenditures

The no-cost extension and increase in student support costs have impacted the budget with respect to graduate student support.

5.4 Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

A significant change is the (approved) plan to replace studies involving human subjects with phantom studies, due to concerns related to coronavirus.

6. Products

6.1 Publications, conference papers, and presentations

Michael Napoli proposed his PhD thesis on the topic of “Stochastic Mapping for Robotically-Assisted Quantitative Compressional Elastography” in May 2020 and also has a paper in preparation on the topic of stochastic mapping for quantitative compressional elastography. This grant has supported Soumya Goswami in preparing his PhD thesis proposal. Papers published during this year’s period of performance are listed below:

Publications:

- 1) S. Goswami, R. Ahmed, S. Khan, MM. Doyley, SA. McAleavey, “Shear Induced Non-linear Elasticity Imaging: Elastography for Compound Deformations”, *IEEE Transactions on Medical Imaging* 39(11) 3559-3570, 2020
- 2) S. Khan, S. Goswami, F. Feng and S. A. McAleavey, "Characterization and Evaluation of a Hydrogel-PVC Aberrator Phantom," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020, pp. 1-3, doi: 10.1109/IUS46767.2020.9251586.

- 3) S. Goswami, R. Ahmed, M. M. Doyley and S. A. McAleavey, "Quantitative nonlinear shear modulus mapping using freehand scanning," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020, pp. 1-3, doi: 10.1109/IUS46767.2020.9251339.
- 4) S. Goswami, R. Ahmed, M. M. Doyley and S. A. McAleavey, "Local Spectral Nonlinear Elasticity Imaging: Contrast Enhancement in Heterogeneous Elastograms based on Viscoelastic Nonlinear Characterizations," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020, pp. 1-3, doi: 10.1109/IUS46767.2020.9251283.
- 5) F. Feng, S. Goswami, S. Khan and S. A. McAleavey, "Evaluating the Feasibility of Nondiffractive Bessel Beams for Shear Wave Elasticity Imaging: A Simulation Study," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020, pp. 1-4, doi: 10.1109/IUS46767.2020.9251828.
- 6) S. Goswami, R. Ahmed, Fang Fen, Siladitya Khan, M. M. Doyley and S. A. McAleavey, "Imaging the Local Nonlinear Viscoelastic Properties of Soft Tissues: Initial Validation and Expected Benefits," *IEEE Transactions on Medical Imaging* (submitted)

Theses: N/A

Presentations:

- 1) S. Khan, S. Goswami, F. Feng and S. A. McAleavey, "Characterization and Evaluation of a Hydrogel-PVC Aberrator Phantom," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020
- 2) S. Goswami, R. Ahmed, M. M. Doyley and S. A. McAleavey, "Quantitative nonlinear shear modulus mapping using freehand scanning," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020,
- 3) S. Goswami, R. Ahmed, M. M. Doyley and S. A. McAleavey, "Local Spectral Nonlinear Elasticity Imaging: Contrast Enhancement in Heterogeneous Elastograms based on Viscoelastic Nonlinear Characterizations," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020
- 4) F. Feng, S. Goswami, S. Khan and S. A. McAleavey, "Evaluating the Feasibility of Nondiffractive Bessel Beams for Shear Wave Elasticity Imaging: A Simulation Study," *2020 IEEE International Ultrasonics Symposium (IUS)*, Las Vegas, NV, USA, 2020

6.2 Website(s) or other Internet site(s)

There are no websites or internet sites to report.

6.3 Technologies or techniques

There are no technologies or techniques to report.

6.4 Inventions, patent applications, and/or licenses

There are no inventions, patent applications, and/or licenses to report.

6.5 Other products

There are no other products to report.

7 Participants & other collaborating organizations

7.1 What individuals have worked on the project?

Name:	<i>Stephen McAleavey</i>
Project Role:	<i>PI</i>
Researcher Identifier:	<i>eRA Commons User ID: smcaleavey</i>
Nearest month worked	<i>2</i>
Contribution to Project:	<i>Human subjects protocol development and approval, ultrasound shearwave elastography systems development</i>
Other Funding Support:	<i>NIH, NYSTAR</i>

Name:	<i>Thomas Howard</i>
Project Role:	<i>PI</i>
Researcher Identifier:	<i>IEEE PIN: 107736</i>
Nearest month worked	<i>1</i>
Contribution to Project:	<i>Design and development of software robotically assisted breast ultrasound scanning system, design and development of hybrid force/velocity control, simulation and haptic interface software, assisted with development of qualitative and quantitative elastography algorithms.</i>
Other Funding Support:	<i>NSF, ARL, NASA</i>

Name:	<i>Marvin Doyley</i>
Project Role:	<i>Co-PI</i>
Researcher Identifier:	<i>eRA Commons User ID: mmdoyley</i>

Nearest month worked	1
Contribution to Project:	<i>Strain elastography system development lead</i>
Other Funding Support:	<i>NIH</i>

Name:	<i>Michael Napoli</i>
Project Role:	<i>Graduate student</i>
Researcher Identifier:	<i>IEEE PIN: 198132</i>
Nearest month worked	12
Contribution to Project:	<i>Development of controllers and estimators for robotically assisted breast ultrasound scanning system, experiments on hybrid force/velocity controller software capabilities for strain elastography, integration of the elastography software stack with arm control software, interfaces, and sensors, development of new qualitative and quantitative elastography algorithms.</i>
Other Funding Support:	<i>N/A</i>

Name:	<i>Soumya Goswami</i>
Project Role:	<i>Graduate student</i>
Researcher Identifier:	--
Nearest month worked	8
Contribution to Project:	<i>Shear wave and strain elastography sequence development, Phantom validation studies</i>
Other Funding Support:	<i>University of Rochester Department of Electrical Engineering</i>

7.2 Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Since the last reporting period PI Howard has a new sponsored research project with the Army Research Laboratory's Scalable, Adaptive, and Resilient Autonomy program for research on guidance, navigation, and control of unmanned ground vehicles and was awarded a second year on his National Aeronautics and Space Administration Early Career Faculty Award project on grounded language communication for collaborative robots titled "Explainable and Verifiable Models for Human-Robot Teaming".

7.3 What other organizations were involved as partners?

There are no other organizations involved as partners in this research.

8 Special reporting requirements

There are no special reporting requirements. This report reflects the work of PI McAleavey under Award Number W81XWH-17-1-0021 and PI Howard under Award Number W81XWH-17-1-0022. Leadership and organization of research tasks have been marked with the responsible PI and site of the research activities.