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CONTRACTING ORGANIZATION: Georgia Institute of Technology

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Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Intervertebral disc degeneration (IDD) is a common condition characterized by the deterioration of the discs separating the spine. Magnetic resonance elastography has shown potential in earlier diagnosis and investigation of DDD, but has been limited by available actuation techniques. This project aims to solve these actuation challenges by developing tunable resonance MRE actuators, establishing control methods for automated tuning and dual actuation, and combining these developments to characterize IVD stiffness in healthy human subjects. The project has been proceeding towards completion of each of the three aims, with development of tunable actuators, theoretical and practical advancements in self tuning capabilities and technology for IVD characterization *in-vivo.* The developed actuators demonstrated a nearly 500Hz resonance range, while positioning experiments validated the need for active tuning of actuator parameters. In support of the tunable resonance system, an active positioning robotic device and control scheme was developed and used to evaluate MRE driver positioning.

15. SUBJECT TERMS: NONE LISTED

16. SECURITY CLASSIFICATION OF: a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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1. INTRODUCTION:

Intervertebral disc degeneration (IDD) is a common condition characterized by the deterioration of the discs separating the spine. The onset of IDD is caused by several factors including genetics, injury, or aging, and is diagnosed using current magnetic resonance procedures. However, these existing MR procedures lack in providing information related to the mechanical state of the discs. With magnetic resonance elastography (MRE), which is a non-invasive in vivo imaging technique based on phase-contrast MRI, the clinical diagnosis of the disc's mechanical condition could now be possible. MRE contains three main steps: 1) Generating shear waves along the imaging target, 2) Using motion encoding gradients to measure the accumulated phase offset among the spins, 3) applying inversion algorithms to acquire elastograms depicting tissue stiffness. MRE allows for the measurement of shear moduli of soft tissues through external excitation, and could therefore be helpful in differentiating pathological changes inside biological tissues. Existing actuator technologies for MRE are not suitable for the high stiffness and small region of interest target that the discs present. Particularly, variable actuation frequency, and the ability to focus excitation to smaller regions of interest are critical features in future characterization of IDD via MRE. This project aims to solve these actuation challenges by developing tunable resonance MRE actuators, establishing control methods for automated tuning and dual actuation, and combining these developments to characterize IVD stiffness in healthy human subjects.

This Y3 annual report will describe the development of a finite element simulation model for the evaluation of actuation strategies in the IVD, continuing actuator characterization, including positioning hysteresis, and human IVD MRE experimental results.

2. KEYWORDS:

Magnetic Resonance Elastography, Intervertebral Disc Degeneration, Tissue Stiffness, Shear Waves

3. ACCOMPLISHMENTS:

- **What were the major goals of the project?**

Specific Aim 1 – Design and fabrication of frequency tunable actuators for MRE applications	**Timeline**	**Status**
Major Task 1	Months	
Subtask 1: Complete design of MRE compatible actuators	1-6	Completed
Milestone # 1 ***Complete 3D drawings and FEM analysis results***	6	Completed
Subtask 2: Fabrication and MRI compatibility test	4-9	Completed
Milestone # 2 Proof-of-concept prototype and functionality test in the lab	9	Completed
Subtask 3: Implementation and performance testing	6-9	Completed
Milestone # 3 Demonstration of multi-source, varying resonant frequency actuation in MRI	12	Completed
Specific Aim 2 – Establishment of automated self-calibration and on-site tuning algorithms for the frequency tunable actuators	**Timeline**	**Site 1**
Major Task 2		
Subtask 1: Formalization of piezoelectric self-sensing theory and hysteresis modeling	3-9	Completed
Milestone # 2 Computer algorithms for self-sensing actuation and empirical hysteric parameter estimation	9	Completed

Subtask 2: Self-sensing of resonance excitation	6-14	Completed
Milestone # 2 Demonstration of resonant detection from self-sensing piezoelectric actuators	14	Completed
Subtask 3: Combined with FEM and implement numerical search algorithm	10-18	Completed
Milestone #3 Demonstration of self-tuning of resonant frequency for optimal tissue excitation	18	Completed
Specific Aim 3 – Characterization of IVD based on stiffness to evaluate the level of disc degeneration	**Timeline**	**Site 1**
Major Task 3		
Subtask 1: Establish theory of multi-source elastography imaging	1-9	Completed
Milestone # 1 FEM simulation of the wave fields during multi-source actuation	9-10	Completed
Milestone # 2 Ex-vivo validation test of multi-source MRE	9-12	Completed
Subtask 2: Submit protocol to IRB/HRPO	4-9	Completed
Milestone # 3 IRB/HRPO protocol approval	9	Completed
Subtask 3: Install actuators into MRI scanner	9-11	Completed
Milestone #4 Functionality test of the actuators in MRI	11	Completed
Milestone #5 MRE data collection with a phantom model	12	Completed
Milestone #6 MRE data collection with healthy volunteers	13-24	Completed

- **What was accomplished under these goals?**

The project has concluded with completion of the three major tasks. For major task 1, the development of tunable resonance actuators, design, simulation, evaluation, and proof of concept testing done in Y1 and Y2 was finished. Resonance of the actuators has been confirmed in laboratory experiments. Finite element analysis of actuator placements relative to the IVD was completed and published. These results demonstrated that multiactuator MRE has valuable potential for the IVD.

Actuator resonance was measured in a benchtop setting using a laser triangulation position sensor. A driver frequency sweep was conducted with position measured throughout, then an FFT was used to plot the amplitude spectrum. The results confirmed those reported in the prior Y1 and Y2 reports. The achieved frequency range was > 500 Hz.

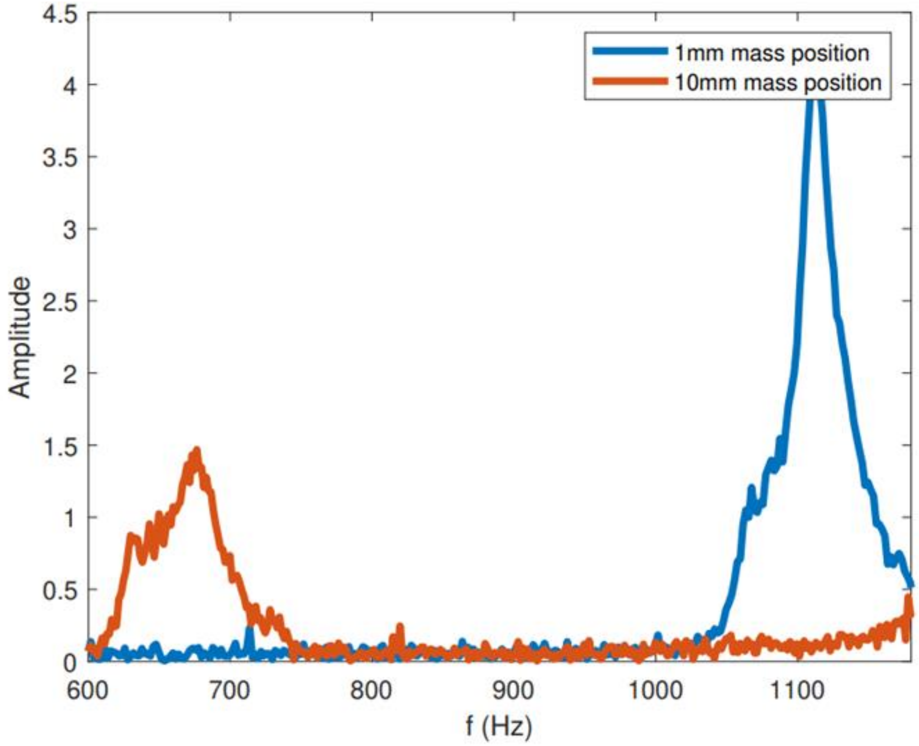

Figure 1: Frequency response of the resonant frame with two different mass locations

Towards the goal of actuator placement and shear wave delivery, an FEM method was developed and applied. The proposed control scheme is shown in Figure 2. The FEM component of the control loop is used to determine optimal driver positioning. Actual driver positioning is done via a 5 DOF stage, accuracy of the controller motion is critical to successful delivery of shear waves.

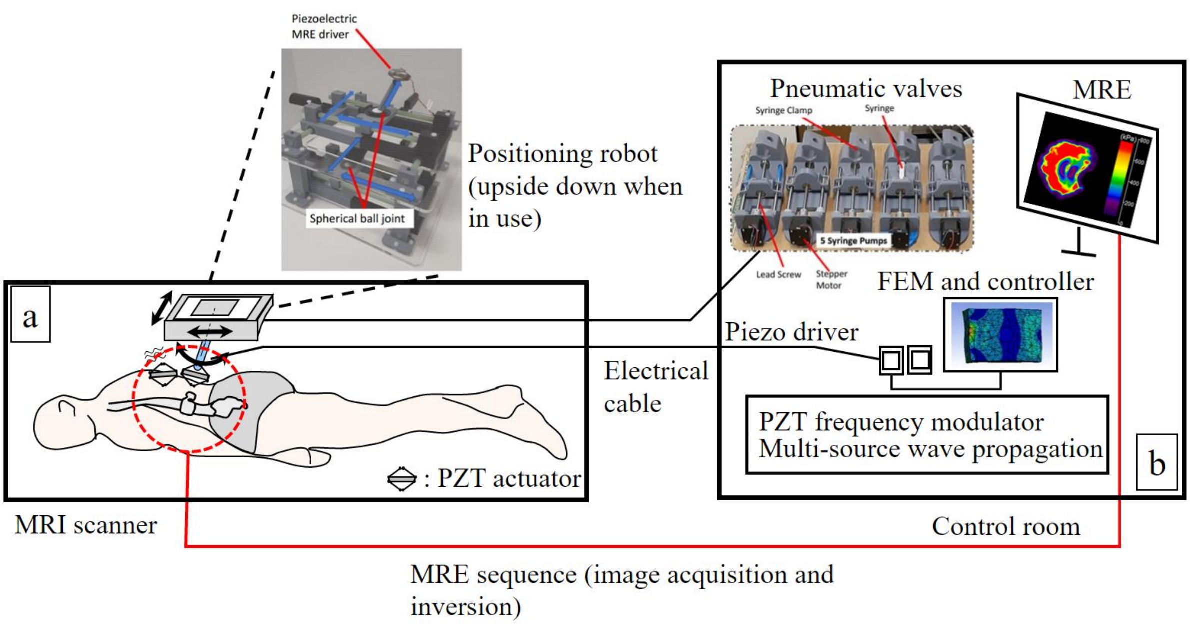

Figure 2: MRE control scheme with FEM, both scanner room (a) and control room (b)

The MRE images resulting from the FEM simulations described under tasks 1, 2&3 are shown below, in Figure 10. It is clear from the results that the locations of the multiactuator system have a significant impact on induced displacements.

Towards major task 2, hysteresis in the piezoelectric stage was characterized. This hysteresis in the stage is critical to accurate automated positioning of the MRE drivers, since the actuators do not have a direct feedback mechanism (encoders). Hysteresis captures the difference between forward and backwards motions per step command, and was found to be generally less than 1 micron per step, but heavily axis and position dependent. The results are shown in Figure 3.

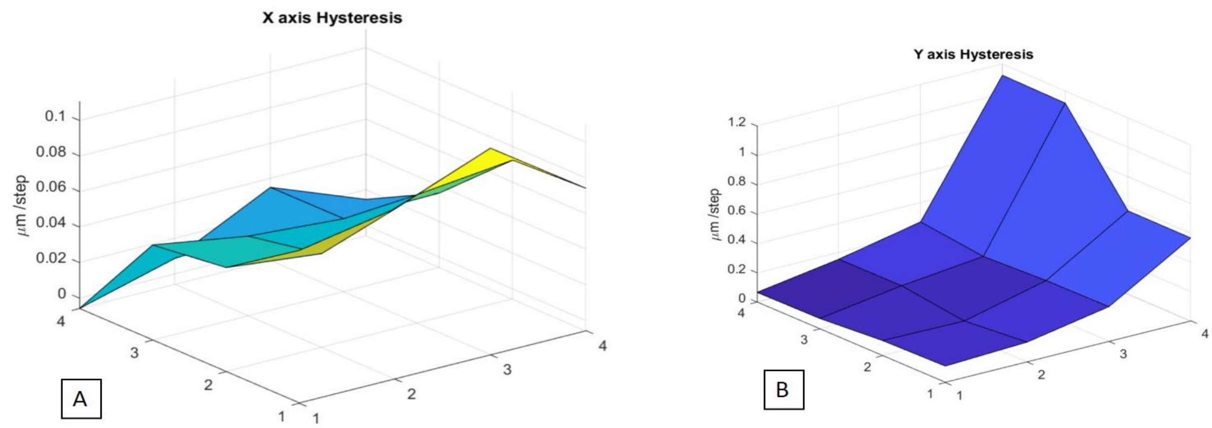

Figure 3 : (a) X axis piezoelectric motor hysteresis (b) Y axis hysteresis

Also towards major task 2, a finite element model was developed along with a numerical optimization method for determining driver locations as shown in Figure 4. Displacements from modeled tissue are inputted into the fitness function of the model. The proposed numerical optimization technique is a genetic algorithm being that it can search the wide search space which expands by three to four variables per actuator simulated. The FEM methods are described in more detail below.

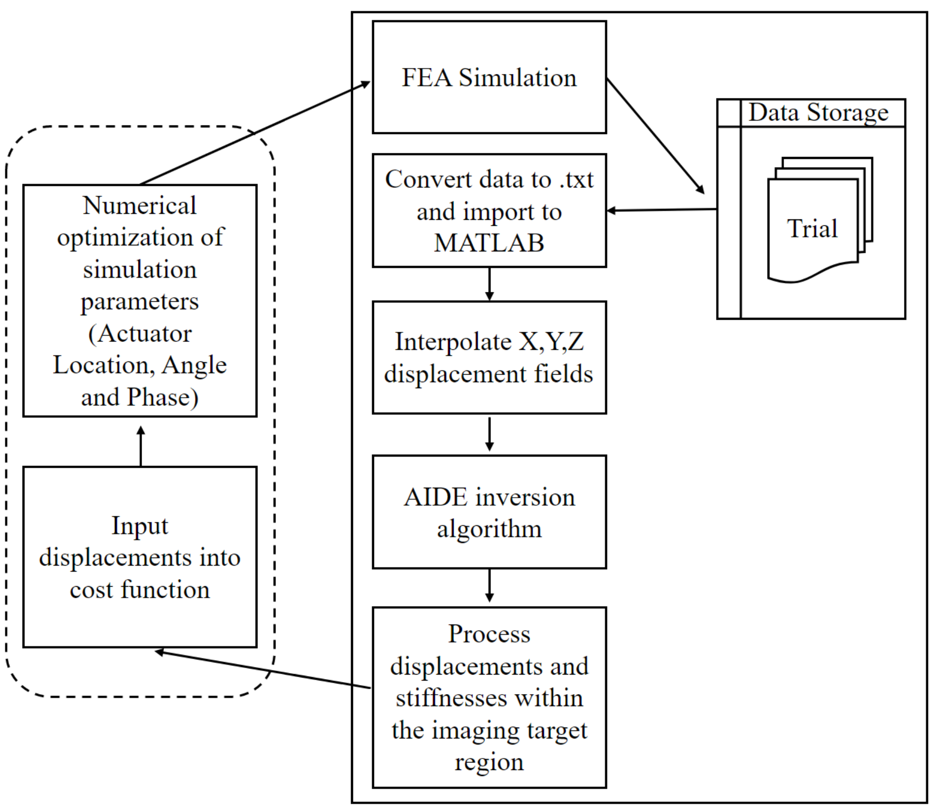

Figure 4: Numerical optimization method.

Towards the completion of major task 3, the simulation and finite element analysis work described in the Y2 report were continued and completed. Optimization of driver positions was demonstrated in a variety of phantoms, as shown below. Figure 5 shows the tissue-like phantoms used in this FEM work. Both homogeneous and heterogenous phantoms models were evaluated.

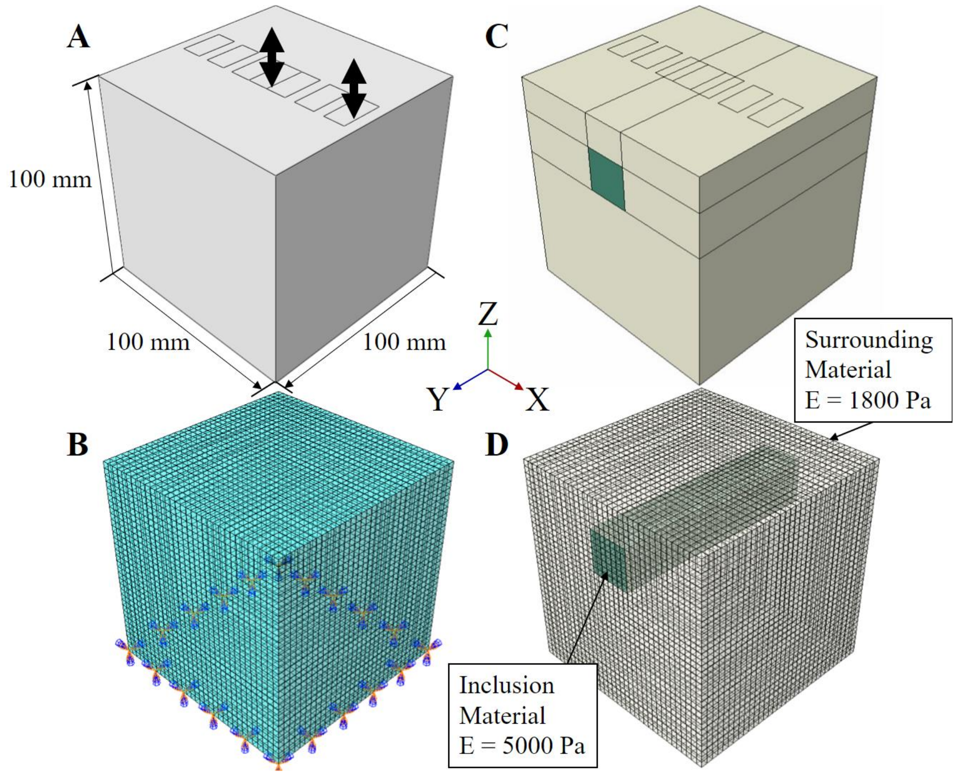

Figure 5: Tissue-like phantom A) Homogeneous model showing the dimensions of the models and the direction of loading. B) Mesh of the models and the constrained bottom xy plane. C) Heterogeneous Model. D) Stiff inclusion in the heterogeneous model and the assigned material properties. Both models use the same constraints, and the same surrounding material properties. Tissue is modeled as a linear elastic and isotropic medium. The rectangular areas in (A) and (C) are used for applying the cyclic 1 Pa load.

Potential load configurations examined are shown in Figure 6. An example multi-actuator configuration is L2R2, where both the L2 surface and the R2 surface are mechanically excited within the simulation.

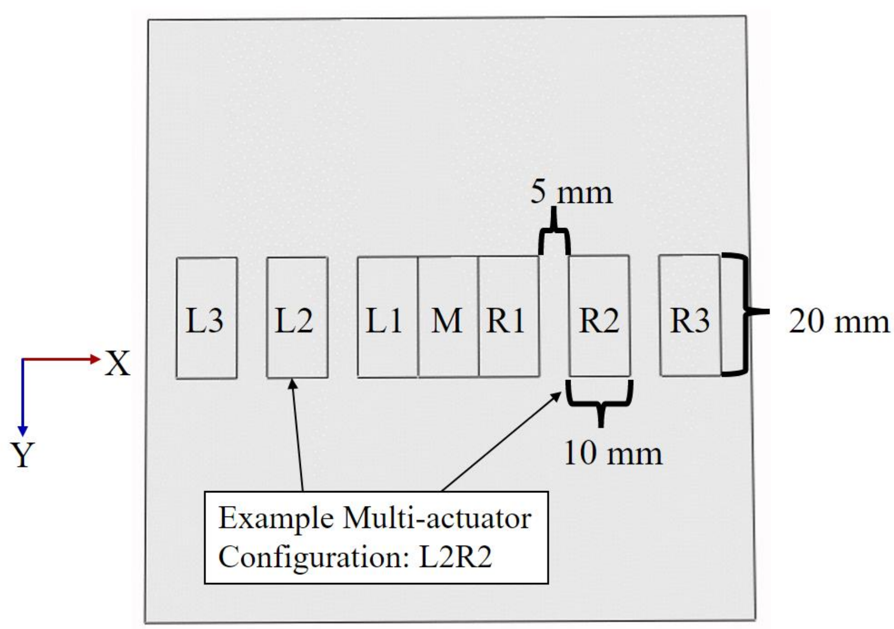

Figure 6: Load configurations

Figures 7 and 8 show the mean displacement amplitudes within the imaging targets for each of the 3 phantom types. The z-component of the displacement field is used for analysis instead of the resultant, since the cyclic load is applied in the z direction. Twenty motion cycles are simulated prior to data collection to limit transient effects. L1, L2, L3, and M are all single actuator configurations. 2L2 is a single actuator configuration but with double the load. L2R1, L2R2, L2R3 are all two actuator configurations. Two actuator configurations each had greater mean displacements than all the single actuator configurations.

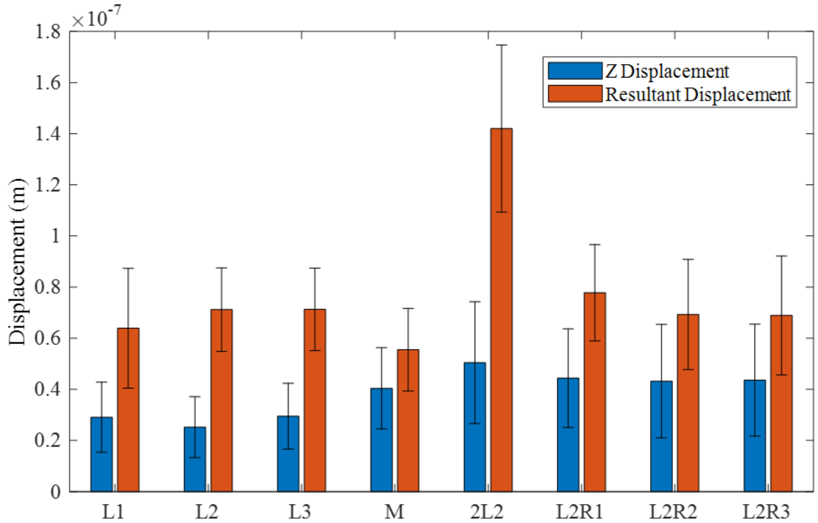

Figure 7: Homogenous phantom results

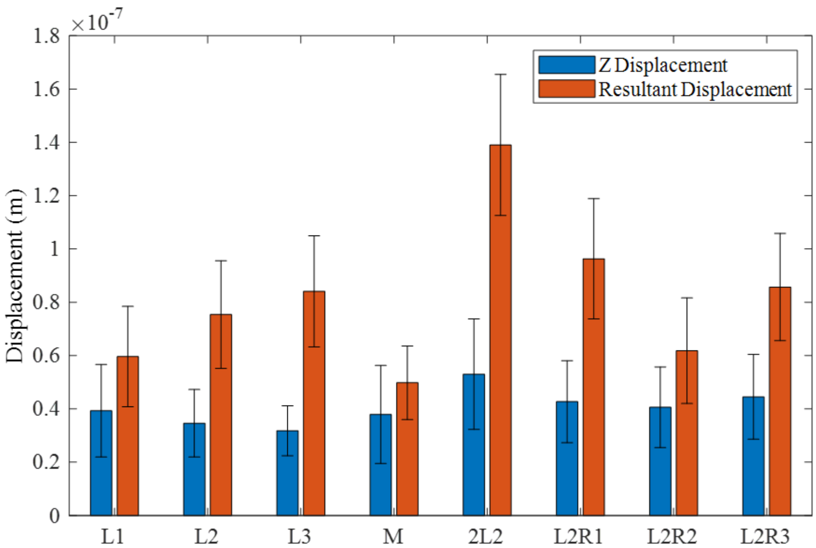

Figure 8: Heterogeneous phantom results

Varied loading angles were also examined in the heterogeneous phantom, with the results shown in Figure 8. The 90-67 loading configuration resulted in the maximum Z axis displacement. Both the resultant displacement and the Z axis displacement varied significantly across the choices of driver angles.

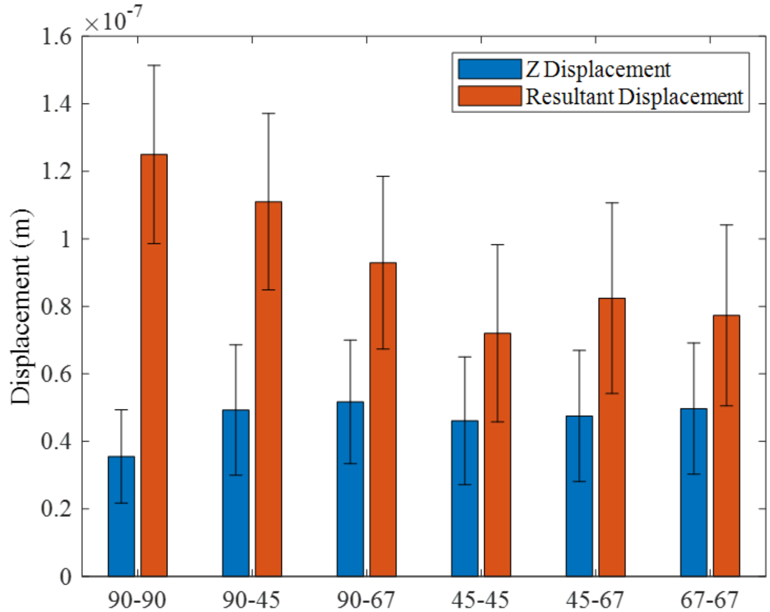

Figure 9: Heterogeneous phantom across varied loading angles

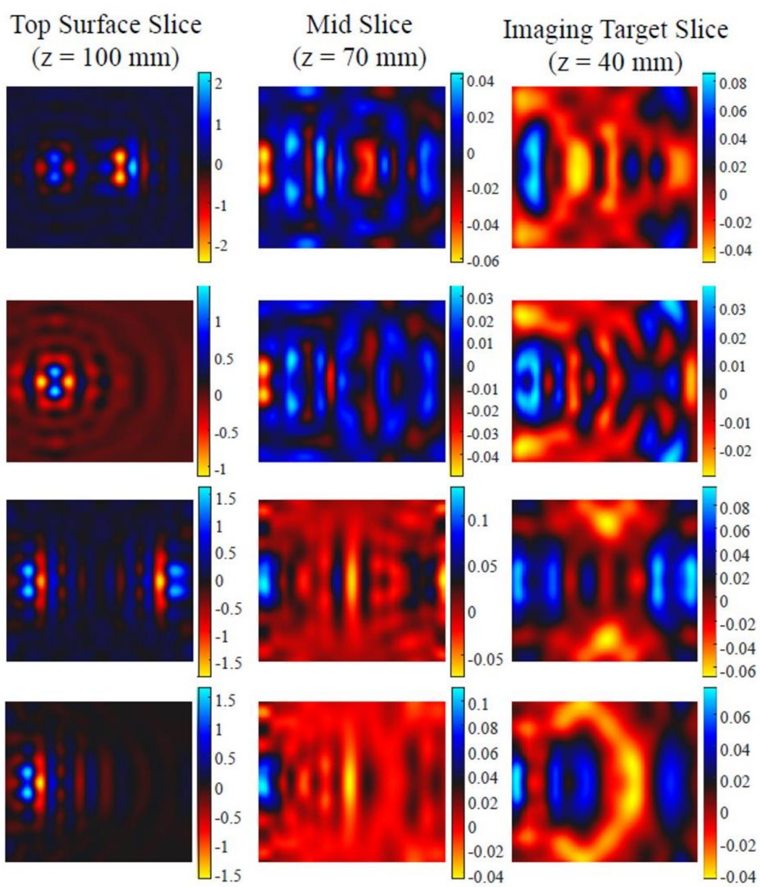

Figure 10: Wave images of the most optimal and least optimal configurations for inducing z displacement within the imaging targets. The units are normalized displacement units (mm/mm). Row 1 used the L2R1 configuration which induced the greatest z displacement amplitude in the homogeneous model and Row 2 used the L2 configuration which induced the lowest z displacement amplitude. Row 3 used the L3R3 configuration with L3 at 90◦and R3 at 67◦, inducing the greatest z displacement amplitude in the heterogeneous model. Row 4 used the L3 configuration and induced the smallest z displacement amplitude in the heterogeneous model.

Challenges with the scanner dimensions precluded the testing of the 5DOF robot with the piezo in human subjects. Instead, a pneumatic driver was substituted, due to the need to place subjects in a supine rather than prone position. The experimental configuration is shown in Figure 11 below. 8 healthy subjects were scanned along with a single subject who had DDD. Actuation frequencies from 50 to 100 Hz were evaluated, to determine the effect of wavelength in the IVD image quality. A representative wave image showing the displacements along each direction is shown in Figure 12. Figure 13 shows a comparison between the MRE image of a subject with DDD and a healthy subject. The mean stiffness values differ by ~30%.

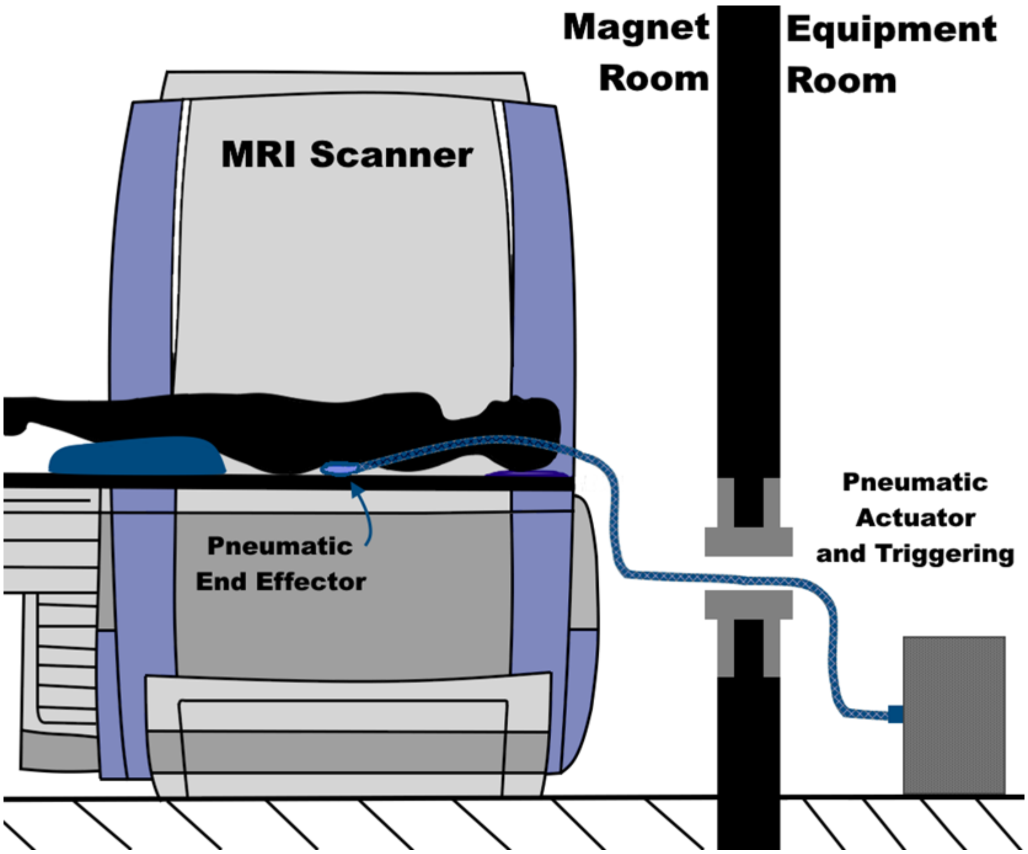

Figure 11. Human experimental setup

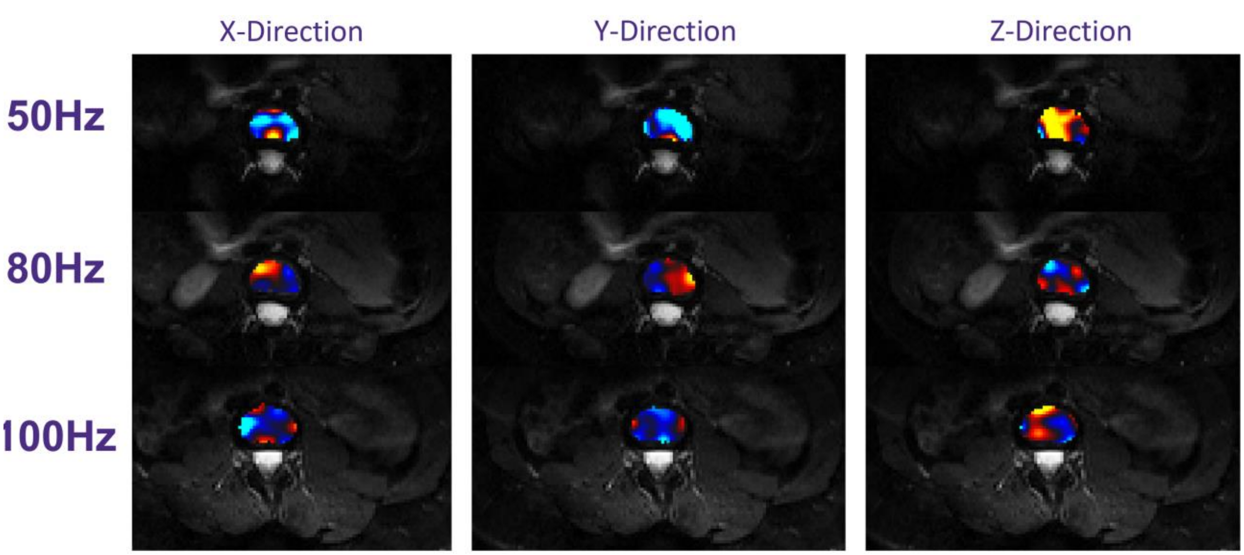

Figure 12. Human subject results at all 3 driving frequencies.

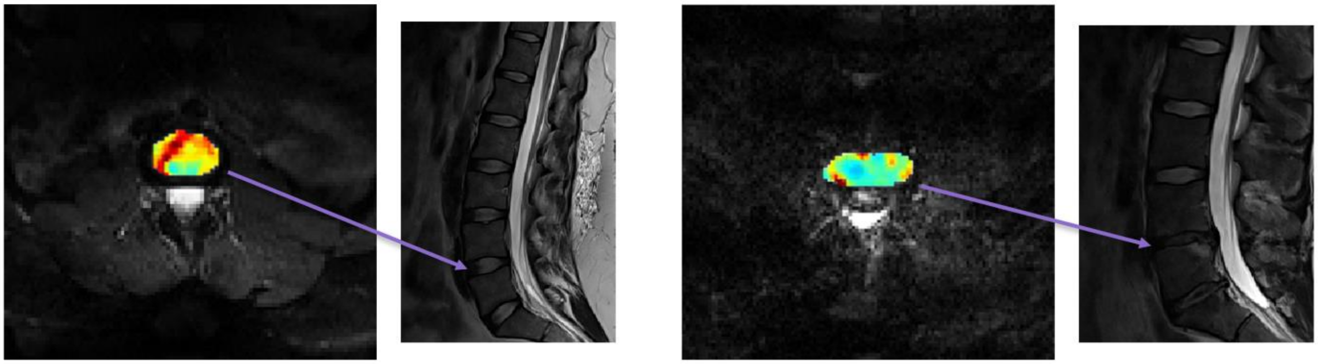

Figure 13. Normal vs. DDD

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

In the third year of the project, Dr. Ueda and Dr. Kurt have each continued to mentor a PhD student working on the research project. (Heriberto Nieves and Emily Triolo respectively) Waiman Meinhold has worked on the project as Postdoc in Dr. Ueda's laboratory . All 3 of the graduate students/Postdocs each had regular meetings with their advisors to discuss research progress and dissemination. The graduate students have also met regularly with each other in order to keep up with their respective progress. The weekly meetings have included a range of interdisciplinary collaborators, MRI imaging experts, and undergraduate mentees. Graduate students held virtual meetings with a variety of collaborators, gaining valuable skills in interdisciplinary scientific collaboration. The nature of the project led to discussions with various potential collaborators, giving the students the opportunity to learn how scientific collaborations can begin. Both of the graduate students met with other MRI facilities to explore experimental logistics for future MRE collaborations.

- **How were the results disseminated to communities of interest?**

A manuscript was submitted and accepted to IEEE American Control Conference 2023. All of the project members discussed the project with prospective future collaborators and other MRE researchers.

- **What do you plan to do during the next reporting period to accomplish the goals?**

NA

4. IMPACT:

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

The results demonstrated the impact of multiactuator driver placement on displacement for MRE. The system development provides a testbed for future MRE actuator evaluation and validation.

- **What was the impact on other disciplines?**

MRE may improve scientific understanding of degenerative disc disease, accurate delivery of shear waves is critical to effective MRE of the IVD.

- **What was the impact on technology transfer?**

The project lead directly to the filing of a joint PCT patent application, Georgia Institute of Technology took the unusual step of filing for the full patent without a commercial partner, indicating their belief in the commercial viability of the IP. This occurred in Y2

- **What was the impact on society beyond science and technology?**

With the proposed MRE actuator system, the researchers aim to make this diagnostic technique became available at every hospital. And since the components are 3D printable, compared to the current FDA approved MRE actuator system, the proposed design will be more affordable. Finally, with the early diagnosis of disc degeneration, it is aimed avoid more serious health conditions such as bulging disc with proper physical therapy and medication.

5. CHANGES/PROBLEMS:

- **Changes in approach and reasons for change**

Nothing to report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

NA

- **Changes that had a significant impact on expenditures**

Nothing to report.

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

NA

- **Significant changes in use or care of human subjects.**

Nothing to report.

- **Significant changes in use or care of vertebrate animals.**

Nothing to report.

- **Significant changes in use of biohazards and/or select agents**

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Heriberto Nieves, Efe Ozkaya, Waiman Meinhold, Jun Ueda Effects of Driver Placement and Phase on Multi-actuator Magnetic Resonance Elastography via Finite Element Analysis, IEEE American Control Conference (ACC), 2023 (accepted)

Report only the major publication(s) resulting from the work under this award.

- **Other publications, conference papers, and presentations.**

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.
- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.
- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.
- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life.

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Jun Ueda
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	0000-0001-7807-6863
Nearest person month worked:	1 Months
Contribution to Project:	Conceptualization, mentoring
Funding Support:	Academic Instruction and NSF
Name:	Mehmet Kurt
Project Role:	Co-PI
Researcher Identifier (e.g. ORCID ID):	0000-0002-5618-0296
Nearest person month worked:	1 Months
Contribution to Project:	Conceptualization, mentoring
Funding Support:	NSF/NIH
Name:	Waiman Meinhold
Project Role:	Postdoctoral Fellow
Researcher Identifier (e.g. ORCID ID):	0000-0002-7215-6958
Nearest person month worked:	12 months
Contribution to Project:	Design, testing, conceptualization
Funding Support:	NSF and this project
Name:	Heriberto Nieves
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0001-8193-3811
Nearest person month worked:	6 months
Contribution to Project:	Computer simulation and evaluation
Funding Support:	NSF GRFP
Name:	Emily Triolo
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-3003-1110
Nearest person month worked:	4.5 months
Contribution to Project:	Computer simulation
Funding Support:	NA

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

Nothing to report.

- **What other organizations were involved as partners?**

8. SPECIAL REPORTING REQUIREMENTS

NA

9. APPENDICES: NA