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CONTRACTING ORGANIZATION: Georgia Institute of Technology

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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 <i>in-vivo</i> . The developed actuators demonstrated a nearly 500Hz resonance range, while positioning experiments validated the need for active tuning of actuator parameters.					
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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	8
5. Changes/Problems	8
6. Products	9
7. Participants & Other Collaborating Organizations	10
8. Special Reporting Requirements	11
9. Appendices	11

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.

2. KEYWORDS:

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

3. ACCOMPLISHMENTS:

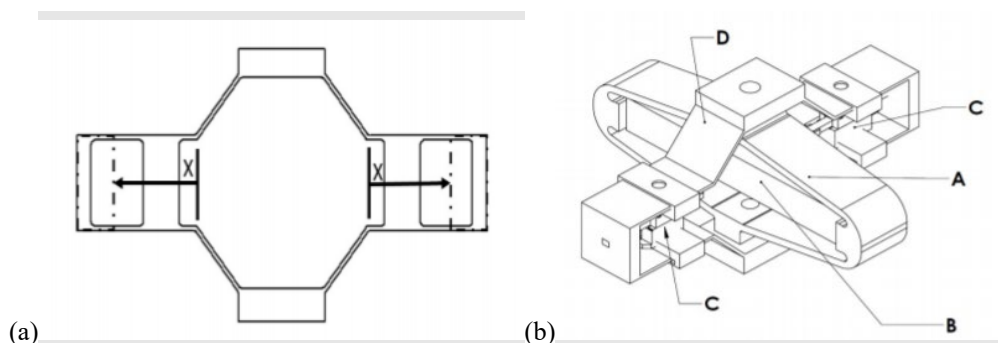
- What were the major goals of the project?

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
<i>Milestone # 1 Complete 3D drawings and FEM analysis results</i>	6	Completed
Subtask 2: Fabrication and MRI compatibility test	4-9	Completed
<i>Milestone # 2 Proof-of-concept prototype and functionality test in the lab</i>	9	Completed
Subtask 3: Implementation and performance testing	6-9	70%
<i>Milestone # 3 Demonstration of multi-source, varying resonant frequency actuation in MRI</i>	12	25%
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	50%
<i>Milestone # 2 Computer algorithms for self-sensing actuation and empirical hysteric parameter estimation</i>	9	50%
Subtask 2: Self-sensing of resonance excitation	6-14	50%
<i>Milestone # 2 Demonstration of resonant detection from self-sensing piezoelectric actuators</i>	14	15%

Subtask 3: Combined with FEM and implement numerical search algorithm	10-18	50%
<i>Milestone #3 Demonstration of self-tuning of resonant frequency for optimal tissue excitation</i>	18	25%
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	25%
<i>Milestone # 1 FEM simulation of the wave fields during multi-source actuation</i>	9-10	50%
<i>Milestone # 2 Ex-vivo validation test of multi-source MRE</i>	9-12	25%
Subtask 2: Submit protocol to IRB/HRPO	4-9	95%
<i>Milestone # 3 IRB/HRPO protocol approval</i>	9	90%
Subtask 3: Install actuators into MRI scanner	9-11	Completed
<i>Milestone #4 Functionality test of the actuators in MRI</i>	11	90%
<i>Milestone #5 MRE data collection with a phantom model</i>	12	90%
<i>Milestone #6 MRE data collection with healthy volunteers</i>	13-24	10%

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

Major progress was made towards the realization of each of the goals of this project. For major task 1, the development of tunable resonance actuators, design, simulation, evaluation, and proof of concept testing has occurred. A design for a mechanical resonator with a tunable resonant frequency is made, with both simulated and experimental validation (please see Fig.1). The resonant frequency is adjusted by sliding the two masses on either side, changing both the inertial and stiffness characteristics of the actuator.



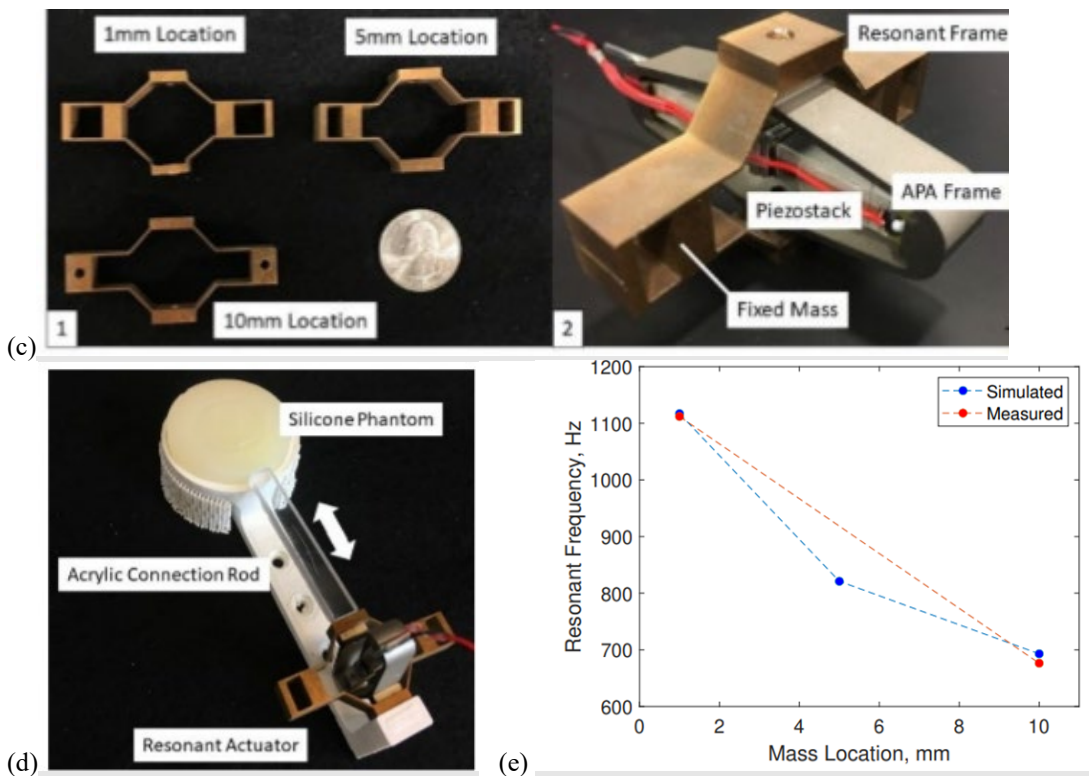


Figure 1 : (a) Tunable resonant actuator frame with sliding side mass. (b) Resonance tuning mechanism having (A) APA150M frame, (B) piezoceramic stack, (C) repositionable mass, and (D) bronze frame. (c) (1) Fabricated bronze resonant frames, (2) APA150M actuator and resonant frame. (d) MRI evaluation stage. (e) Resonant frequency shift results, simulated and experimental

The experimental validation of the designed actuator is shown alongside the simulation results in Figure 1e. Modal analysis was performed to validate the resonant frequency tuning concept (ANSYS 19.1., Ansys, Canonsburg, PA). The first 4 modes of each fabricated frame and APA actuator were compared. To confirm that the piezo actuation does not excite the lowest two modes, a harmonic analysis was completed. The piezoceramic stack shown in Figure 1c was replaced with a set pressure on the contact faces of the APA actuator. This confirmed that the 3rd resonant mode was excited during actuation, providing motion along the desired axis. Resonant frequencies for the three fabricated frames are shown in Figure 1e.

The simulation results were validated through experimental testing of 2 of the frames, the 1mm and 10mm versions, representing the full range of the proposed tunability. The piezoelectric actuator was driven by an amplifier (CA45, Cedrat Technologies), with a swept frequency sinusoidal input. A laser triangulation sensor measured the position of the front face of the actuator with an analog output sampled at 5kHz (optoNCDT ILD2200-20, resolution: 0.3 micron, Micro Epsilon, Germany). For each of the two frames, the driving frequency was swept in a window around the expected resonance over a 1 second period. 1.5 seconds of position measurements were recorded and saved, with the DFT computed in Matlab (fft). The results of the experimental measurements for each frame are shown in Figure 1e. Taking the peak of each spectrum as the resonant frequency, the resonant frequency of the frames is plotted and compared to the prior simulation results. Although there are minor differences in the range of adjustment and the exact resonance values, the experimental results match the simulated ones quite well. These results represent the achievement of the development of a tunable resonance MRE actuator.

Towards major task 2, the development of self sensing methods and algorithms for piezoelectric actuators, progress was made. Particularly, prior work by the PI was investigated, and found to be suitable for use in resonant actuators. Both the theoretical and numerical methods from that work will be adapted and leveraged to complete task 2. Additionally, as part of the self tuning work, a mechanism for active positioning of the resonance drivers was developed.

For major tasks 2 and 3, an active driver positioning robot for image guided MR Elastography is designed. This active positioning robot is essential to developing the automated methods for self tuning and automated dual actuation. Prior MRE actuator This design allowed the displacement wave patterns to be captured from various mechanical vibration loading angles. Furthermore, inside the x-axis carriers, a ring-shaped volume is left empty for contrast agent to be injected. The x-axis carriers are the components in which the spherical ball joints are placed. Design, simulation, evaluation, and proof of concept testing of a single source elastography imaging has occurred prior the design of the multi-source system. This novel MRE actuator positioning system, allowing to capture displacement wave patterns from various mechanical vibration loading angles is shown in Figure 2. The linear positioning of the all the carriers were performed by hydraulic manipulators (syringe-tube-syringe system). As the mechanical vibration source, APA150NM was used initially. But it will be substituted by the tunable actuator structure developed in major task 1.

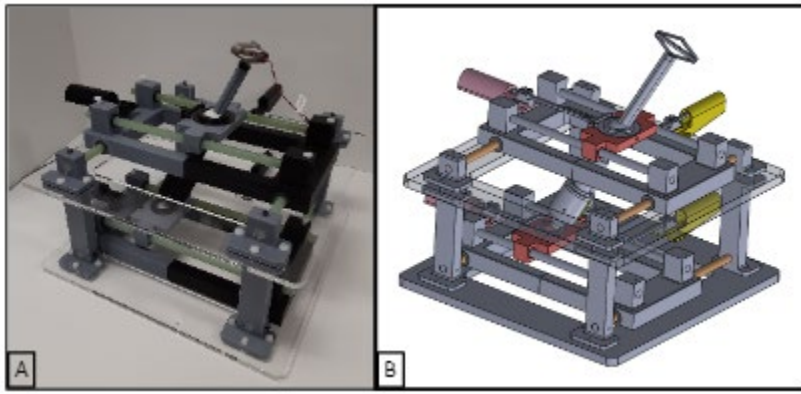


Figure 2: 5 DOF MRE actuator positioning robot. (a) Completed prototype, and (b) CAD model.

During initial prototype testing, an IVD representing phantom made out of Knox-gelatin is used (please see Figure 3 a). Evaluation of the prototype was performed in a 3T MRI scanner. The 5 DOF frame was placed below the structure containing the gelatin phantom, with the spine RF coil placed above it (please see Figure 3b). In addition to the MRE scans performed at 60Hz, structural scans were performed to acquire robot configuration. Figure 3c, shows the clear differences in displacement fields achieved by varying the contact angle of the MRE driver. This result has not been previously demonstrated in MRE, and the applications are numerous.

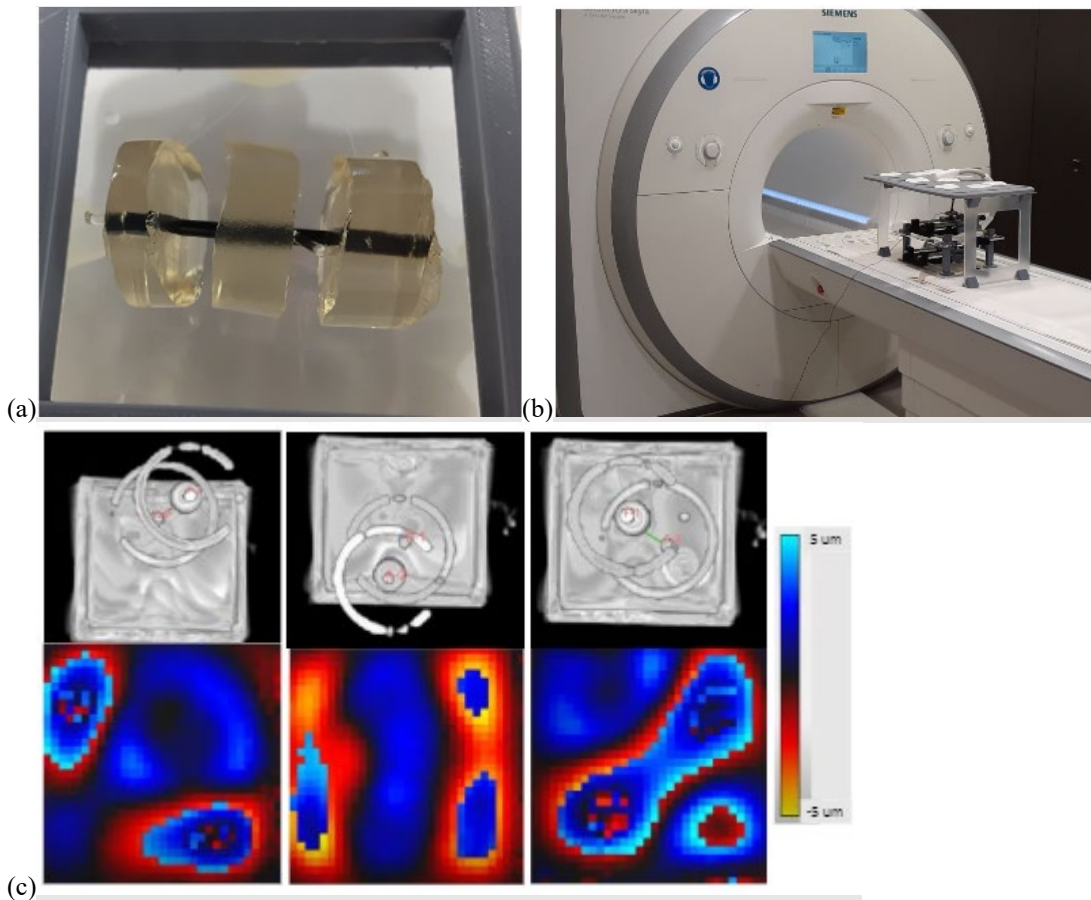


Figure 3: (a) Disc array gelatin phantom. (b) Experimental setup. (c) Displacement fields and associated robot configurations.

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

In the first year of the project, Dr. Ueda and Dr. Kurt have each mentored a graduate student working on the research project. (Waiman Meinhold and Efe Ozkaya respectively). Waiman Meinhold and Efe Ozkaya have 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. A postdoctoral scholar, Aymeric Pionteck, in Dr. Kurt's laboratory also received training in MRE data processing related to this project. Waiman Meinhold and Efe Ozkaya jointly mentored an undergraduate senior design team (Blake Holland, Derek Petti, and Simon Pepa). Through weekly meetings with this team, the graduate students have gained skills and experience in mentoring junior researchers. The graduate students have submitted abstracts to the following conferences, BMEII 2020 – 10th Annual Symposium, and 2021 Summer Biomechanics, Bioengineering and Biotransport

Conference. Moreover, the undergraduate students who were jointly mentored by the graduate students, submitted their work to the undergraduate design competition at 2021 Design of Medical Devices Conference and 2021 Summer Biomechanics, Bioengineering and Biotransport Conference (please see Figure 4). They also presented their work at Stevens Innovation & Expo Conference. In addition, one of the undergraduate students will be continuing on to start a Master's program in the same field.

Although the COVID 19 pandemic limited physical travel during the report period, graduate students held virtual meetings with a variety of collaborators, gaining valuable skills in interdisciplinary scientific collaboration. Finally, a provisional patent followed by a PCT submission is made. During the meetings with the patent office representatives and attorneys, the graduate students gained skills and experience in the development, documentation and protection of intellectual property.

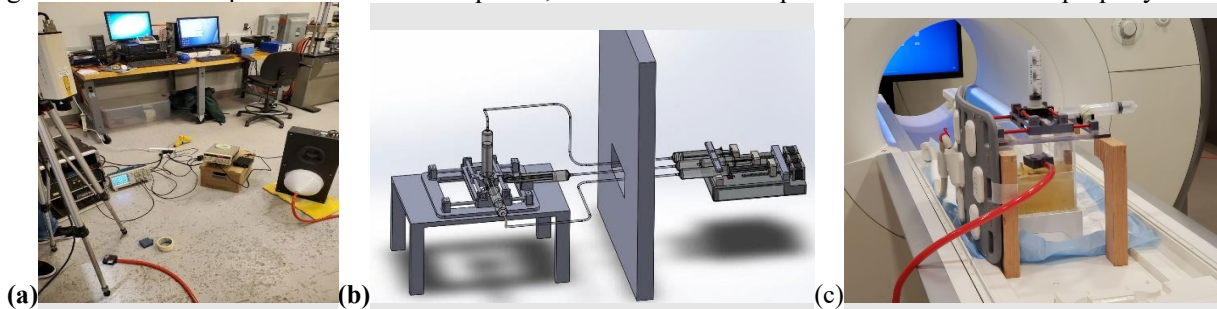


Figure 4. 3 DOF system design made by the undergraduate team. (a) Acoustic actuator testing. (b) CAD model of the movable stage mechanism. (c) Initial prototype of the movable stage mechanism.

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

During the senior design project course, the undergraduate team submitted six progress report and gave six presentations over Zoom to their classmates. Through these presentations, awareness about good posture and the adverse effects of disc degeneration through conditions like herniation was gained.

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

Until the next reporting period, the electronic system design of the hydraulic control unit for the 5 DOF system is aimed to be finalized. Dual piezo-actuator based mechanical vibration system is aimed to be incorporated to the 5 DOF system designed by the graduate students or to the 3 DOF system designed by the undergraduate students. Phantom testing will be performed to acquire the preliminary set of morphological image data, for the performance evaluation of the visual servoing based control.

4. IMPACT:

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

The first repositionable 3D printed MRE actuator system was designed. MRI guided visual servoing is used for semi-automatic position control. Low cost and MR compatible hydraulic manipulators are utilized.

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

In addition to the Pfirrmann score, tissue stiffness can be used as a biomarker to monitor the condition of the IVD. In other words, noninvasive tissue stiffness measurement can be accomplished.

- **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.

- **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**

While performing the initial MRE experiments, the piezoactuator was damaged. The damaged piezoactuator was sent to Cedrat facility in France and repaired. Due to the COVID pandemic, regular access to the scanners at BMEII was limited. As an alternative solution, the MRE experiments were conducted during irregular hours at BMEII, which allowed limited data collection, but impacted research progress negatively, this limitation is not expected to continue beyond summer 2021.

- **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**

The IRB review process has been slowed due to an unanticipated delay in submission of the protocol. Mt. Sinai hospital must be added as an official awardee to the project in order for their IRB to review and approve the human subjects research protocol. This administrative addition has been delayed on both sides due to the COVID 19 pandemic, but is nearly complete. Once the subaward change is completed, we expect to submit and receive approval within weeks.

- **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**
Report only the major publication(s) resulting from the work under this award.
 - **Other publications, conference papers, and presentations.**

W. Meinhold, E. Ozkaya, M. Kurt, A. Hu, J. Ueda "A Parallel Plane Positioning Robot for Image Guided Interventions", BMEII, April 1-2 2020, NYC, New York, USA.

E. Ozkaya*, W. Meinhold*..." Parallel Stage Mechanism for Image-Guided, Targeted MR Elastography", SB3C Conference, Virtual Conference, 2021.

D. Petti, B. Holland, S. Pepa, "Repositionable MR Elastography Actuating Mechanism", Design of Medical Devices Conference, April 12-15, 2021, Virtual.

- **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.

<https://rmam.weebly.com/>

- **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.

International Application PCT/US2021/025131 directed to METHOD AND SYSTEM FOR MRI-GUIDED VISUAL SERVOING.

- **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:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0002-7215-6958
Nearest person month worked:	6 months
Contribution to Project:	Design, testing, conceptualization
Funding Support:	Internal (TA) and NSF
Name:	Efe Ozkaya
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	0000-0003-0583-7507
Nearest person month worked:	6 months
Contribution to Project:	Design, testing, conceptualization
Funding Support:	NSF CMMI 1826270
Name:	Derek Petti
Project Role:	Undergraduate Student
Researcher Identifier (e.g. ORCID ID):	-
Nearest person month worked:	4 months
Contribution to Project:	Design and evaluation
Funding Support:	NA
Name:	Simon Pepa
Project Role:	Undergraduate Student
Researcher Identifier (e.g. ORCID ID):	-
Nearest person month worked:	3months
Contribution to Project:	Design and evaluation
Funding Support:	NA
Name:	Blake Holland
Project Role:	Undergraduate Student
Researcher Identifier (e.g. ORCID ID):	-
Nearest person month worked:	3 months
Contribution to Project:	Design and evaluation
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?**
 - **Organization Name:** Biomedical Engineering and Imaging Institute (BMEII)
 - **Location of Organization:** 1470 Madison Ave, New York, NY 10029
 - **Partner's contribution to the project** providing access to 3Tesla Siemens Scanner and 7Tesla Bruker Scanner
 - **Financial support;** do not exist
 - **In-kind support** computers, MRI sequence protocol design software, MRI coils
 - **Facilities** MRI scanners;
 - **Collaboration** Lazar Fleysher, Paul Kennedy, Kamil Banibaker, Dewey Chu;
 - **Personnel exchanges** Graduate and undergraduate students went to BMEII to perform the MRE experiments; and
 - **Other.**

8. SPECIAL REPORTING REQUIREMENTS

NA

9. APPENDICES: NA