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TITLE: AI-Assisted 3D Ultrasound for Rapid Diagnosis of Ocular Trauma Injuries

PRINCIPAL INVESTIGATOR: Mahdi Bayat, PhD

CONTRACTING ORGANIZATION: Case Western Reserve University
Cleveland, OH

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14. ABSTRACT

Traumatic injuries to the eye, such as those in the military, require immediate diagnosis to prevent vision loss. These impacts can alter anatomical integrity of the eye causing, for example, retinal detachment. Removal of penetrating intraocular foreign bodies (IOFBs) requires clear visualization for surgical removal. Traumatic injuries coincide with edema and bleeding; thus, limiting the utility of optic based methods such as direct ophthalmoscopy or OCT. Small foreign bodies, may not be well visible in CT imaging, even at highest resolutions. Ultrasound has been used for diagnosis and treatment of ocular injuries. Conventional 2D ultrasound requires skilled users and are subject to large variability. We propose to develop a novel 3D ultrasound system to greatly facilitate diagnosis and treatment of ocular injuries. Our gentle-touch approach via single sweep scanning minimizes the risk of additional injuries. We have created a prototype of the system resulting in anatomically correct volumes of ex vivo eyes. Initial deep learning results show promise in automated analysis of 3D data.

15. SUBJECT TERMS
3D, Ultrasound, Ocular injuries, trauma, retinal detachment, intraocular foreign bodies

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1. Introduction

The overarching goal of this project is to create a 3D ultrasound system for imaging of the eye to remove or minimizes problems associated with current ultrasound imaging of the injured eyes, especially among service members impacted by military trauma. Our approach is to build a prototype 3D ultrasound system and test its various aspects using in vitro, ex vivo and in vivo preclinical models of ocular injuries. Our plan is to test our system on realistic models of trauma, especially those in military including retinal detachment, foreign bodies, variation of optic and vascular integrity. We utilize computer modeling and physical experiments to develop advanced image acquisition, volume reconstruction and enhancement to eventually validate on a rabbit model of ocular injuries. Where applicable, to better understand progress, we included the related major tasks as proposed in our statement of work (SOW).

2. Keywords

3D, ultrasound, ocular injuries, military trauma, retinal detachment, optic nerve sheath diameter, imaging, diagnosis, intraocular foreign bodies, deep learning.

3. Accomplishments

The overall goal of this project is to

- **Develop and optimize a 3D ultrasound system**
- **Experimentally validate on ex vivo and in vivo models of ocular injuries**

To achieve these goals, the following accomplishments are reported based on the statement of work:

- **IACUC obtained**

  We obtained IACUC approval for our animal study from Case Western Reserve University to conduct the research proposed in this project.

  Date accomplished: July 2021.

- **Acuro obtained**

  We obtained ACRU approval for our animal study. We both IACUC and ACURO approval in hand, we are set to start the preclinical studies our project as outlined in the statement of work.

  Date accomplished: November 2021.

Major Task 1:

Developing 3D imaging

We purchased and obtained an ultrahigh frequency wireless portable ultrasound probe from Clarius (Clarius inc, Vancuver, CA) to conduct experiments.

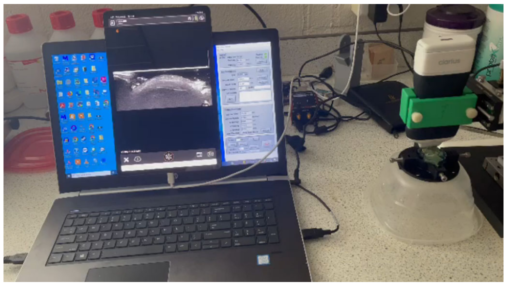


Figure 1: 3D ultrasound prototype during an ex vivo testing

Assembly with stabilizer and initial tests:

We have created the first generation of our 3D ultrasound system using a Clarius ultrahigh frequency probe. The system is currently able to obtain 3D volumetric data using a fully controlled software-hardware integration via tools provided by Clairus as well as our custom-made units. Our 3D system houses the Clarius probe in a custom-made 3D printed holder which can adapt to a variety of connectors for ex vivo and eventually in vivo imaging. Fig. 1 shows our current system in action during an experiment. Fig. 2 shows an example of volume reconstruction using an ex vivo porcine eye. Currently, the motion mechanism is provided using a precise stepper motor instead of using a camera stabilizer. This was mainly due to speed up prototyping using our past experiences with this setup and starting the ex vivo experiments.

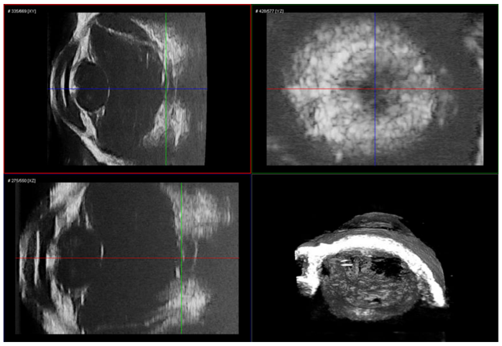


Figure 2: Multiplanar 3D visualization of an ex vivo porcine eye acquired by our prototype

We have created an image processing pipeline that includes automated cropping, morphological operation to reduce image artifacts and tackle uneven illumination and filtering to reduce image noise (Fig. 3). Images were automatically cropped from the cine file to avoid highly reflective gelatin-probe boundary. Morphological operation, i.e., region filling, and top hat filtering were applied to remove cine artifacts and uneven illumination respectively. Finally median filtering was applied to reduce noise.

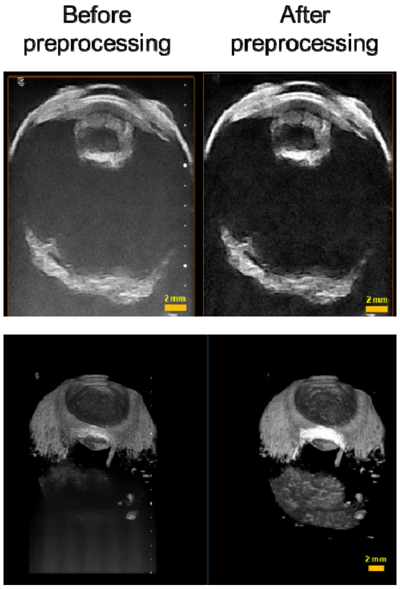


Figure 3: Preprocessing pipeline to denoise and remove image artifacts.

Acquiring ex vivo porcine eyes without incurring any damage has been challenging due to high cost and shipment process. After a few trials, we have been able to procure ex vivo porcine eyes with minimum to no damage via shipping them overnight in submerged saline solution and sufficient padding to prevent any internal damage.

Percentage accomplished: 100%.

Fine tuning and validation on phantoms

We found empirical parameters to create reproducible isovoxel image volumes. We developed ultrasound fine targets using gelatin and suture wires with diameter < 30mu and created 3D volumes which showed consistent results. Examples of wire target image is shown in Fig. 4.

Date Accomplished: April 2022.

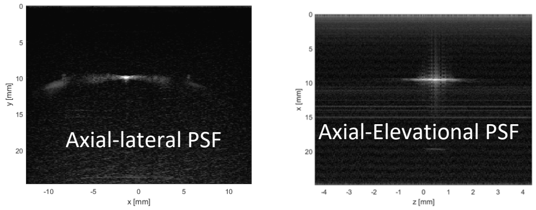


Figure 4: 3D PSF estimated from fine wire target experiment

Major Task 2:

Developing iterative enhancement methods:

PSF estimation: We have conducted precision experiments on custom-made fine target phantoms to fully evaluate imaging characteristics of the developed 3D ultrasound. These included determining 3D point-spread-function (PSF), scanning speed requirement, data acquisition characteristics including number of frames, voxel size etc. Fig. 4 shows volumetric PSF in two perpendicular views to be used in inversion deblurring methods.

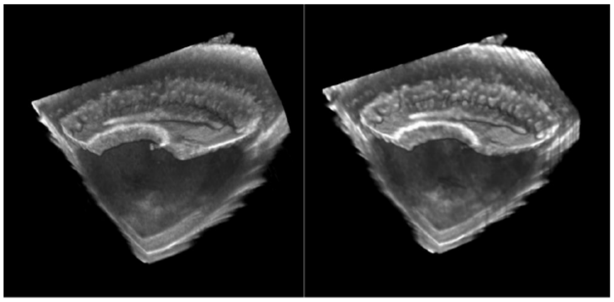
Percentage accomplished: 100%.

Future work: We are currently working on implementing this approach to B-scan images.

Scan conversion and Deconvolution: Since we are using the standard data from the commercial probe, no scan conversion was found to be required. We created a generative adversarial network (GAN) based PSF inversion approach to enhance ultrasound biomicroscopy images (Fig. 5).

Percentage accomplished: 80%.

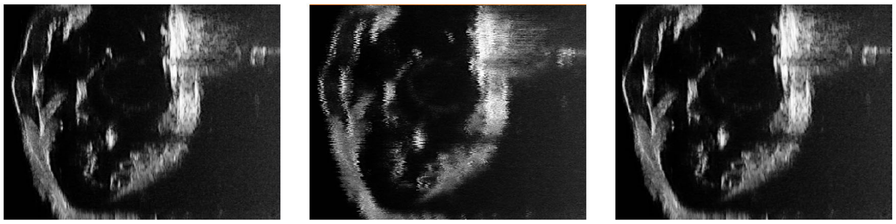
Future works: We are currently working on implementing this approach to B-scan images



Original

Enhanced

Figure 5: 3D volume rendering of ciliary body before and after GAN based deconvolution. After deconvolution, the edges of ciliary body are more visible and easily distinguishable.



Cadaver pig eyes in gelatin phantom with foreign body

Random translation motion introduced within [-5 5] pixels

Motion corrected slice

Figure 6: Demonstration of our motion compensation algorithm performed on data from ex vivo testing. Only a single slice of 3D volume is shown

Motion compensation: Mechanical motion of the probe may create slight jitters due to damped infinitesimal relative probe-tissue relative positions. During in vivo, physiological motions, e.g. respiration, pulsation can create motions that will induce misregistration across adjacent planes in a 3D acquisition. We developed methods based on frame-to-frame similarity to remove such artifacts for enhanced volume acquisition. Fig. 6 demonstrates performance on a porcine model of ocular foreign bodies where artificial motions and added noise were significantly removed by our algorithms.

We have created in vivo motion reduction approach in ultrasound biomicroscopy images. Once we acquire in vivo data for ocular injuries, we will be able to implement and analyze our approach.

Percentage accomplished: 80%.

Future work: Our algorithms work well in in vivo models of biomicroscopy with small motions. We will continue to develop for in vivo and potentially larger motions.

Testing on standard small part and phantoms and ex vivo porcine eyes:

We used our developed 3D US prototype to acquire image volumes from wire phantoms (Fig 4) and ex vivo porcine eyes. Fig 5 shows a typical experimental setting where ex vivo porcine eyes are embedded in tissue mimicking gelatin phantoms and scanned using our 3D system prototype. The model allows more reproducibility and creates the ability to image from multiple angles to verify volume reconstruction performance and rule out orientation-dependent artifacts. This model will also allow better cross modality registration as we plan to perform CT imaging of these ex vivo models of ocular injuries such as IOFBs and retinal detachment.

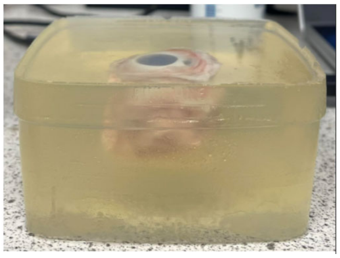


Figure 7: Ex vivo porcine eye case in gelatin for testing

Date accomplished: July 2022.

Major Task 3:

Developing deep learning for automated segmentation and identification:

Ex vivo porcine eye experiments for training GAN: We developed deep learning methods for automatic segmentation of the ciliary processes in the anterior segment. Though these methods are currently applicable to the anterior segment, mainly due to the nature of previously collected dataset, they can be easily extended to whole eye imaging to address problems associated with traumatic injuries as proposed in our grant proposal. Fig. 8 shows our deep learning segmentation of the ciliary body (prediction) as compared to delineation performed by an expert.

Manual segmentation of ex vivo 3D US: To prepare the developed GAN for our tasks (IOFB and RD detection) we continued to perform ex vivo experiments and use manual segmentation as the ground truth.

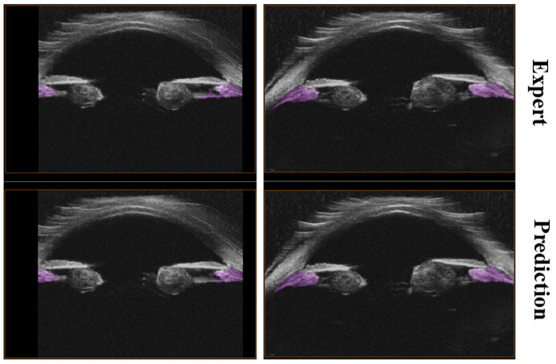


Figure 8: Deep learning segmentation of ocular structure (ciliary body) using our developed methods (prediction) compared to manual segmentation

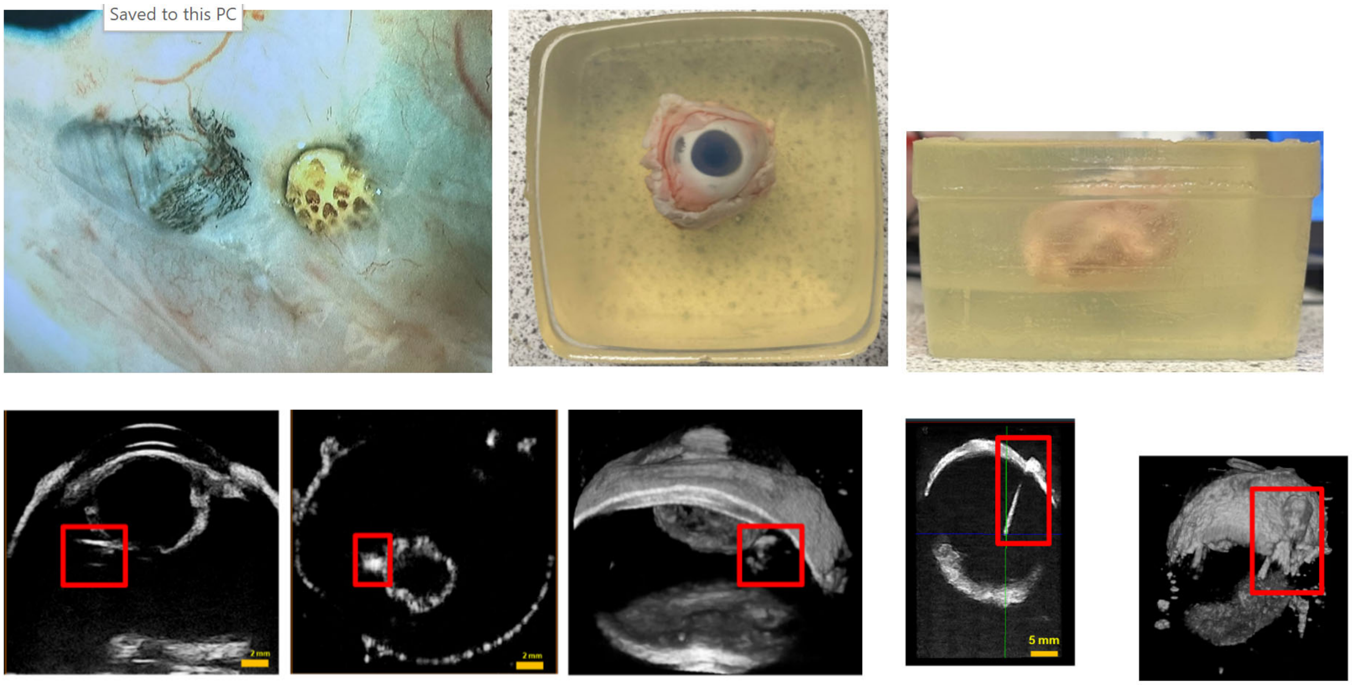


Figure 9: Top panel shows foreign body eye models cast in gelatin phamtom. Bottom panel shows 3D-US images of eyes with plastic and wooden IOFBs.

11 porcine eyes embedded in gelatin phantoms with various types and sizes of IOFBs, including wood, plastic, glass, and metal. An incision was made on each eye on the sclera to insert larger objects, and the incision was closed via suturing. The eyes were imaged using 3D-US.

Deep learning training

Due to delay in acquiring ex vivo samples without damage, we are working on curating manual segmentation of IOFB dataset. Using a weakly labeled dataset, we developed a semi-supervised approach to IOFB segmentation in 3D-ultrasound images. By generating pseudo-labels for the unlabeled data using an initial deep learning model trained on a small, labeled dataset, we leveraged the unlabeled data to improve segmentation performance. The pseudo-labels were refined by keeping only high-confidence predictions on the unlabeled data, and the model was iteratively fine-tuned using both labeled and unlabeled datasets. Our experiments using 11 porcine eyes embedded with various types and sizes of IOFBs demonstrated the effectiveness of our approach. The deep learning segmentation using UNETR achieved a mean Dice score of 0.71±0.04 in cross-validation on the small dataset. Plastic and wooden IOFBs exhibited superior visualization compared to CT; detection of glass and metallic foreign bodies is possible, but precise boundary segmentation is impeded by reverberation. Our work presents a novel and effective method for visualizing and assessing IOFBs using 3D ultrasound images and deep learning segmentation.

Percentage accomplished: 90%.

Future work: We have developed deep learning segmentation methods using a previously acquired dataset by our group. This dataset is limited to the anterior segment. We have already created models for successful induction of IOFBs and RDs in ex vivo eyes. We will continue to build on this model to cover the whole eye and include numerous instances of ocular injuries, IOFBs and RD with manual segmentation for training our deep learning model.

Major Task 4:

Ex vivo validation studies on porcine eyes

Part of the ex vivo validation studies is related to ongoing ex vivo testing. While so far, the focus has been on accomplishing the 3D US system performance, we have initiated parallel validation studies using CT.

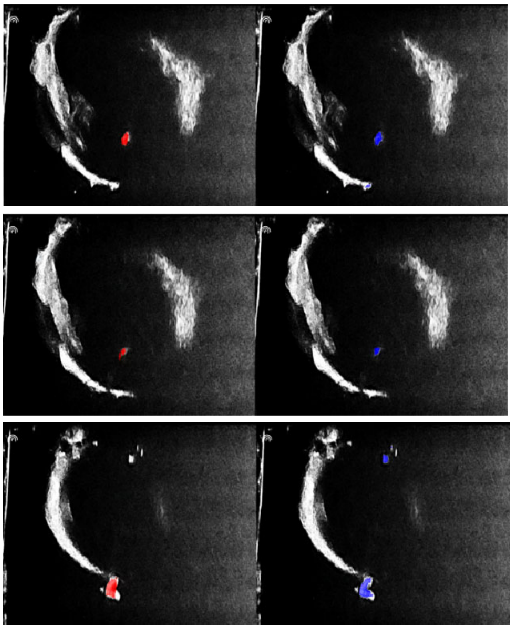


Figure 10: Deep learning segmentation of IOFB. Panels show expert annotation of IOFB (left), prediction from deep learning segmentation (right).

Porcine eyes were scanned with both 3D-US and CT. Experiments show that 3D ophthalmic ultrasound technologies offer superior visualization and assessment of some IOFBs (plastic, Fig. 11) compared to conventional 2D US and CT imaging. The difference in measurements of an IOFB length between US vs CT <2%.

Percentage accomplished: 100%.

Evaluation of images and analyzing data

Accomplished as explained above and shown in Fig. 11.

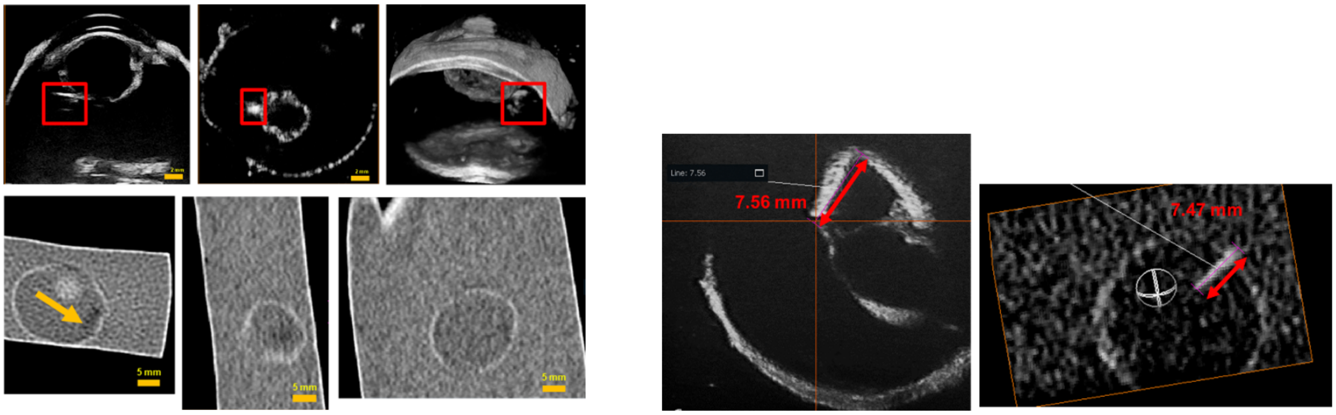


Figure 11: Comparison of 3D-US and CT in visualization of plastic IOFB (left) and length measurements of a wooden IOFB (right).

Major Task 5:

In vivo studies on rabbits

Anticipated date: June 2023

Manual segmentation of in vivo 3D US

Anticipated date: June 2023

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

This project engaged a full time PhD student who is dedicating his PhD work on ultrasound imaging of the eye. He is gaining and developing skills in both system development and artificial intelligence via developing novel deep learning analysis methods.

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

  So far we have presented our works in technical conferences included SPIEو IUS IEEE, Vision Injury Research Forum and have published one manuscript Translational Vision Science & Technology journal

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

  Plans for future works are explained for each milestone above. We have achieved most of our goals in reliability and accuracy of the developed system and we are planning to initiate our in vivo studies to test the utility in more realistic situations. As part of challenges, we anticipate a learning process for inducing relevant injuries similar to those seen in military trauma in rabbit eyes. Our ex vivo studies are meant to equip us with the required skillset to be better prepared for these challenges.

4. Impact

Our goal is to fill a crucial gap in facilitating ocular imaging in vision threatening situations where no other modalities are applicable. Important applications include: identification of IOFBs, surgical planning, and intraoperative guidance, diagnosis of retinal detachment, evaluation of optic nerve as a surrogate of increased intracranial pressure and checking vascular integrity to assess hemorrhage and bleeding. Ultrasound is currently used in treatment of traumatic ocular injuries, especially among service members. However due to 2D planar imaging and requiring manual scanning is risky on injured eyes.

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

Our method will greatly improve volumetric acquisition which in turn allows automated analysis, for example automated detection and segmentation of IOFBS. We anticipate a future portable product that can be easily implemented by non-skilled users in remote and austere environments such as low-level military triage or in emergency department for in ocular injuries in general public.

What was the impact on other disciplines?

The core system development and algorithms developed in this project can be potentially extended to 3D ultrasound imaging of other organs.

What was the impact on technology transfer?

Demonstrating clinical utility in ocular trauma can help us effort in attracting industrial partnership to translate this research into a commercial product for 3D imaging of the eye.

What was the impact on society beyond science and technology?

Nothing to report during this reporting period.

5. Changes/Problems

Changes in approach and reasons for change

The initial idea for creating 3D ultrasound was to use a professional camera gimble with accurate rotation capability to create multi-plane sector scanning. While we are searching for a good hardware for this purpose, we found it helpful to use small size OEM linear motors and performing linear scanning. The acquired volumes are quite satisfactory and will be used as baseline for any other alternative approach including sector scanning. No other problem or changes occurred or seen in our project so far.

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

A delay was related to recruiting a PhD student as explained in this report. No other delays or problems to report.

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

Nothing to report.

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

1- Minhaz, A. T., Cooley, M., Subramaniam, A., Exner, A., Orge, F., Wilson, D., & Bayat, M. (2022, October). End-to-end deep learning for tuning-free non-contrast ultrasound microvessel imaging. In 2022 IEEE International Ultrasonics Symposium (IUS) (pp. 1-3). IEEE.

2- Minhaz, A. T., Wilson, D.L., Orge, F.H. & Bayat, M. (2023, June). Development of Novel 3D Ophthalmic Ultrasound Technologies for Visualization of Intraocular Foreign Bodies. Vision Injury Research Forum (VIRF)

Journal publications.

1- Minhaz, A. T., Sevgi, D. D., Kwak, S., Kim, A., Wu, H., Helms, R. W., ... & Orge, F. H. (2022). Deep Learning Segmentation, Visualization, and Automated 3D Assessment of Ciliary Body in 3D Ultrasound Biomicroscopy Images. Translational Vision Science & Technology, 11(10), 3-3.

2- Ehrenstein, S., Minhaz, A. T., Wilson, D.L., & Bayat, M. (2023, June). Model-based deep learning for tuning-free non-contrast ultrasound imaging of microvasculature. (Submitted)

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name: Mahdi Bayat, PhD

Project Role: PI

Nearest person month worked: 9

Contribution to Project: Dr. Bayat managed and directed this project and supervised graduate students. He also contributed in developing algorithms, collecting data, revising manuscripts and holding regular weekly meetings.

Name: Ahmed Tahseen Minhaz

Project Role: PhD Student

Nearest person month worked: 12

Contribution to Project: Tahseen worked on several aspects of this project. He developed a 3D ultrasound prototype and tested on several phantoms he made. He participated in group meetings and created abstracts and manuscripts. He also developed deep learning methods for segmentation of ocular tissues, image improvement and microvascular imaging.

Name: David Wilson, PhD
Project Role: Co-I
Nearest person month worked: 1
Dr. Wilson participated in group meetings and provided supervision and guidance, especially in developing 3D image analysis algorithms. He also reviewed manuscripts and reports and provided valuable feedback.

Name: Faruk Orge, MD
Project Role: Co-I
Nearest person month worked: 1
Dr. Orge participated in group meetings and provided supervision and guidance, especially in practical and clinical aspects of the project including the development of ex vivo and preclinical models of traumatic ocular injuries. He also reviewed manuscripts and reports and provided valuable feedback.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Mahdi Bayat (PI):
Nothing to Report.

Faruk Orge (Co-I):
Nothing to Report.

David Wilson (Co-I):
New Active
Title: Understanding neural control of the ocular surface
Major Goals: To bring new tools and models to study molecular, cellular, and functional interactions across systems responsible for neural control of the ocular surface and examine how they change under different inflammatory and pain conditions
Status of Support: awarded
Project Number: U01 EY034693
Name of PD/PI: Jenkins M (PI), Golczak M, Taylor P, Wilson D, Saab C, Dupps W, Sayegh R (Co-I’s)
Source of Support: NEI
Primary Place of Performance: Case Western Reserve University

Project/Proposal Start and End Date: 12/01/2022 – 11/30/2027
Total Award Amount (including Indirect Costs):
Overlap: none

Title: Broad Bandwidth Transducers for High Resolution Information Rich IVUS
Major Goals: We will develop a new intravascular ultrasound system that has several distinct advantages as compared to current systems. This new system will enable cardiologists to better understand, diagnose, and treat coronary artery disease.
Status of Support: awarded
Project Number: R61HL156154-01A1
Name of PD/PI: Fleischman, Aaron
Source of Support: NHLBI
Primary Place of Performance: Cleveland Clinic Foundation
Project/Proposal Start and End Date: 6/10/22 – 4/30/2025
Total Award Amount (including Indirect Costs):
Overlap: none

Title: AQP4 and glymphatic function in post-stroke recovery
Major Goals: 1) To develop a novel MRI method for in vivo quantification of the glymphatic function. 2) To investigate the role of AQP4 and the glymphatic system in post-stroke recovery.
Status of Support: Active
Project Number: R01 NS124206
Name of PD/PI: Yu, Xin (Contact PI) & Flask, Chris
Source of Support: NIH/NINDS
Primary Place of Performance: Case Western Reserve University
Project/Proposal Start and End Date: 7/1/2022-6/31/2027
Total Award Amount (including Indirect Costs):
Overlap: none

Title: Optical Tools to Assess the Role of Cardiac Function in the Development of Congenital Heart
Major Goals: Our proposal centers on creating optical imaging to investigate mechanical stresses experienced by cells lining the beating, early-stage heart tube and how these cells and adjacent tissues respond in gene expression in each area of the heart during normal, diseased, and rescued conditions.
Status of Support: awarded
Project Number: 5R01HL126747
Name of PD/PI: Jenkins M
Source of Support: NHLBI

Primary Place of Performance: Case Western Reserve University
Project/Proposal Start and End Date: 3/16/2022-2/1/2025
Total Award Amount (including Indirect Costs):
Overlap: none

Title: Pericoronary fat: MACE risk from non-contrast CT and the role of iodine perfusion in contrast CT (R01 HL167199-01)
Goal: Using CT exams, we will analyze fat around the coronary arteries (pericoronary fat), a tissue that has been implicated in biological studies of atherosclerosis. Using cardiac CT perfusion studies, we will analyze the effect of iodine perfusion on the characteristics of pericoronary fat and identify potential iodine confounds in the commonly applied coronary CTA exam. We will create an image processing and deep learning approach for analyzing pericoraony fat in non-contrast CT images, a significant undertaking as arteries are barely visible in non-contrast CT. We will then compare pericoronary fat signatures in non-contrast CT to those in the commonly applied CTA exams. Finally, we will compare predictions for major adverse events from pericoronary fat assessed from non-contrast CT images to that obtained with coronary CTA. A potential output of our work will be to create a new analysis method for non-contrast CT images predictive of cardiovascular health.
mPI: Wilson
NIH NHLBI
Primary Place of Performance: Case Western Reserve University
Project/Proposal Start and End Date: 02/15/2023 – 01/31/2027
Requested funding:
Status: ACTIVE
Overlap: none

Closed Grants

Title: Cancer Imaging and Therapy Analysis Platform (CITAP).
R44 CA213601 (mPI: Gargesha, BioInVision, and Wilson) 09/20/16 - 08/31/20. annual sub-contract to lab. We will develop cryo-imaging and software for analysis of cancer.

Title: Interdisciplinary Biomedical Imaging Training Program.
NIH T32EB007509. PI: Wilson. 9/1/2007-8/31/2022. This training grant supports predoctoral trainees in Biomedical Engineering and Physics in imaging.

Title: Image-guided EMT inhibition for treating metastatic breast cancer.

(NIH R01CA194518) PI: Lu, co-I: Wilson. 7/1/2015-6/30/2020. This project will be focused on developing new Image-guided therapeutic strategy by targeting proteins in key biological events associated with metastasis to treat life-threatening metastatic breast cancer. Dr. Wilson's role is image analysis.

Title: Three-dimensional ultrasound imaging for ophthalmology.

Case-Coulter Translational Research Partnership. 9/1/2018-8/31/2019. mPIs: Wilson and Orge.

What other organizations were involved as partners?

Nothing to report.

8. Special Reporting Requirements

See attachment.

9. Appendices

None.