Mini-Symposia Title:

Emerging biophotonic applications based on, or conjoined with OCT technologies.

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Mini-Symposia Speaker Name & Affiliation 6:

Adam P. Wax, Ph.D. Professor of BME and Professor of Physics Dept of Biomedical Engineering, Duke University, Durham, NC

Theme:

- ○ 01. Biomedical Signal Processing
- ◉ 02. Biomedical Imaging and Image Processing
- ○ 03. Micro/Nano-bioengineering; Cellular/Tissue Engineering &
- ○ 04. Computational Systems & Synthetic Biology; Multiscale modeling
- ○ 05. Cardiovascular and Respiratory Systems Engineering
- ○ 06. Neural and Rehabilitation Engineering
- ○ 07. Biomedical Sensors and Wearable Systems
- ○ 08. Biorobotics and Biomechanics
- ○ 09. Therapeutic & Diagnostic Systems and Technologies
- ○ 10. Biomedical & Health Informatics
- ○ 11. Biomedical Engineering Education and Society
- ○ 12. Translational Engineering for Healthcare Innovation and Commercialization

Mini-Symposia Synopsis— Max 2000 Characters

This proposal is centered around Optical Coherence Tomography (OCT) as a versatile imaging technique. Multimodal imaging systems combining OCT with conjoined technologies are being proposed, in order to enhance resolution, penetration depth, speed, and efficacy of decision making in ophthalmology, dermatology, oncology, embryology, etc., revolutionizing research and clinical practice. Our goal is to familiarize fellow EMBS members with new multimodal systems, and provide a platform for discussions. Topics: (1) Novel methods, based on OCT, Optical Projection Tomography, Brillouin Microscopy, and Light Sheet Microscopy, used for structural and functional live imaging of mammalian embryos as a model of human developmental diseases (Overview). (2) Selective retina therapy (SRT), an effective laser treatment method for retinal diseases associated with the retinal pigment epithelium (RPE), is controlled with speckle-variance (sv) OCT by means of proper selection of laser energy and visualizing ophthalmoscopically invisible lesions in the RPE. (3) In-vivo characterization and quantitative imaging of the cornea, based on full-field OCT and optical coherence tomographic microscopy, used to assess corneal transparency, for which to date no clinical tool exists. (4) Retinal birefringence scanning as a fast technique detecting the location of the fovea by analyzing changes in the polarization state of light upon reflection, used to guide OCT in pediatric applications. (5) A novel multimodal imaging system combining photoacoustic microscopy, OCT, and fluorescence microscopy evaluates retinal and choroidal angiogenesis, performing high-resolution in vivo imaging in live rabbit eyes with induced retinal neovascularization (RNV) and retinal vein occlusion and noninvasively visualizing RNV, enhancing imaging with molecular contrast agents. (6) Low cost OCT for point of care use. (PLEASE EXCLUDE JULY 21)

Optics Toolbox for Label-Free Early Embryonic Imaging

Kirill V. Larin, Shang Wang, Irina V. Larina

Abstract— **Optical imaging techniques play an essential role in studying early embryonic development in mouse models. Over the past 15 years, there have been astounding developments in mouse genomics to saturate the genome with mutations and to identify genes with novel roles in development and disease. Thus, mouse is invaluable model to study human developmental diseases. Here, we're developing novel methods, based on Optical Coherence Tomography (OCT), Optical Projection Tomography (OPT), Brillouin Microscopy (BM), and Light Sheet Microscopy (LSM), for structural and functional live imaging of mammalian (mice and rats) embryos. During this presentation I will overview these and other label-free optical methods applied to study normal and pathological embryonic development at different gestation stages.**

I. INTRODUCTION

Optical imaging plays an essential role in uncovering mysteries in the early development of a new life, enabling understanding of organism formation, inspiring strategies for tissue regeneration, and providing insights into better management of congenital defects and embryonic failures.

II. OVERVIEW

Here, we will review the recent progress in the label-free optical imaging of embryonic development. Particularly, we will highlight how the contrast mechanism and imaging capabilities of each technique are advantageous for specific applications in embryonic analysis, with the goal to stimulate new ideas and developments at the interface of photonics and developmental biology. As quantitative biology is becoming prevalent in life science, quantitative assessment achieved from non-labeling optical imaging will be emphasized.

III. DISCUSSION & CONCLUSION

Particularly, we will discuss challenges, solutions, and emerging directions, covering spatial resolution, imaging field of view, imaging speed, integrated optical manipulation and imaging, multi-contrast and multi-modality imaging, and biomechanical imaging for mechanobiology, as shown in Fig 1.

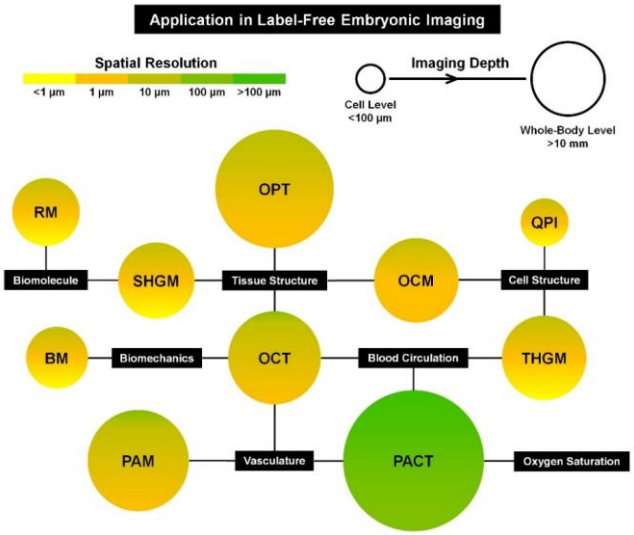

Fig. 1. The characteristics and specific applications of optical techniques for label-free embryonic imaging. Colors represent spatial resolution, and the size represents the imaging depth. BM: Brillouin microscopy; OCM: optical coherence microscopy; OCT: optical coherence tomography; PACT: photoacoustic computed tomography; PAM: photoacoustic microscopy; QPI: quantitative phase imaging; RM: Raman microscopy; SHGM: second harmonic generation microscopy; THGM: third harmonic generation microscopy.

ACKNOWLEDGMENT

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Selective retina therapy monitoring by speckle variance optical coherence tomography for dosimetry control

Soohyun Lee and Jin U. Kang, Johns Hopkins University

***Abstract*— We propose and demonstrate selective retina therapy (SRT) monitoring based on speckle variance optical coherence tomography (svOCT). The svOCT peak values had a reliable correlation with the degree of retinal lesion formation. Laser-induced peak temperature at neural retina and RPE were simulated and correlated with the peak values.**

I. INTRODUCTION

Selective retina therapy (SRT) is an effective laser treatment method for retinal diseases associated with the retinal pigment epithelium (RPE) [1,2]. However, the selection of proper laser energy is challenging because of ophthalmoscopically invisible lesions in the RPE and variational melanin concentration between patients. Here, we applied speckle-variance (sv) OCT to monitoring SRT [3].

II. METHODS

An swept-source OCT imaging system (Axsun Technologies, Inc.) was integrated into a frequency-doubled Nd:YLF laser based SRT system (Lutronic, Korea). The OCT system has center wavelength of 1060 nm, and operates at 100 kHz sweep rate. The wavelength of the pulse laser is 527 nm, and the laser pulse operates at a 100Hz repetition rate and 1.7 μs duration. M-mode OCT images of ex-vivo bovine retina were acquired during irradiation of laser-pulse trains. SvOCT images were calculated by

$$SV_{ij} = \frac{1}{N}\sum_{k=(i-1)\cdot N+1}^{i\cdot N}\left[I_k(j) - \frac{1}{N}\sum_{k=(i-1)\cdot N+1}^{i\cdot N} I_k(j)\right]^2 \quad (1)$$

where i and j are indices of the frame and axial position of the svOCT images, and N is the number of frames used for variance calculation. The svOCT values in photoreceptor and RPE layers were averaged in the axial direction. Microscope images of the treated spots were obtained before and after peeling neural retinal layers off.

III. RESULTS

SvOCT peak values increased with increasing pulse laser energy, and had better correlation with degree of retinal lesion formation than laser energy. The averaged peak value of svOCT was correlated to the temperatures of neural retina and the RPE at melanosome surface. The linear regression of average tissue temperature vs laser energy was calculated for photocoagulated lesions and selectively damaged lesions, respectively and shown below:

$T_M = 124.5+12.4P$, (2) $T_N = 25.5+1.5P$, (3)

where T_M is the temperature in RPE at melanosome surface, T_N is the temperature in neural retina, and P is the averaged peak values of svOCT which is shown in Fig. 1

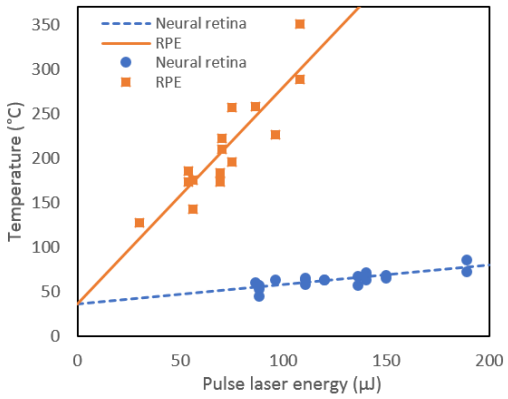

Figure 2. Simulated (lines) and estimated temperature from the svOCT intensity (shapes) at neural retina and RPE.

IV. DISCUSSION & CONCLUSION

It was shown that the SRT could be successfully monitored by svOCT system when integrated into the SRT system. The temperature at neural retina and RPE was estimated by svOCT peak values using temperature simulation results which is consistent with the observed lesion creation. We expect that this svOCT based SRT monitoring approach could be implemented as an automatic dosimetry control.

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Full-field optical coherence tomographic microscopy: an emerging tool for *in-vivo* characterization and quantitative corneal imaging

Kristina Irsch*

***Abstract*— This talk reviews ongoing work towards *in-vivo* characterization and quantitative imaging of the cornea, primarily based on full-field optical coherence tomographic microscopy (FF-OCT of FF-OCM, a high-resolution variant of OCT) and for the purpose of objective corneal transparency assessment, for which to date no clinical tool exists.**

I. INTRODUCTION

Vision as well as retinal imagery is dependent upon the transparency of intervening ocular media, most notably the cornea and crystalline lens (anterior segment), which deteriorates with age. Extreme loss of such transparency, when scattering of light is further increased as a result of infections, pathology, trauma or surgery, also remains a leading cause of blindness worldwide. Despite its significance, current means to assess anterior-segment transparency are extremely limited and usually involve a subjective and qualitatively observation of opacities by means of slit-lamp biomicroscopy

II. METHODS

Several attempts have been made to quantify and/or objectively assess corneal transparency, including via optical coherence tomography (OCT) and confocal microscopy (CM). However, while clinical (time or spectral-domain) OCT systems permit cross-sectional corneal views and the detection of stromal opacities at a higher axial resolution than slit-lamp biomicroscopy, their lateral resolution is limited. CM allows corneal examination at a lateral resolution approaching histological detail but is limited axially.

Full-field optical coherence tomographic microscopy (FF-OCT or FF-OCM [1]), originally developed for 3-D microscopy of *ex-vivo* tissue samples, combines elements of both OCT and CM, thereby achieving both high-resolution cross-sectional and *en-face* views (of about 1 µm). Here we are exploring the application of FF-OCT as an objective tool towards quantifying corneal transparency, addressing an unmet need in ophthalmology

III. RESULTS

A graphical representation of preliminary results on the transparency quantification of *ex-vivo* corneal tissues using objective stromal light-backscattering analysis with FF-OCT are shown in Fig. 1 [2] (collaboration with Prof. Karsten Plamann from the *Laboratoire d'Optique et Biosciences*).

In collaboration with Prof. Claude Boccara's group at the Langevin Institute [3], ongoing work seeks to make FF-OCT suitable for *in-vivo* characterization of the cornea, with the development of a non-contact system that integrates an ultrahigh-speed CMOS camera. To further enhance FF-OCT technology and enable deeper penetration into the corneal tissue, we are also exploring axial motion compensation (collaboration with Prof. Jin Kang, at the Johns Hopkins Whiting School of Engineering [4]) and light manipulation (collaboration with Dr. Alexandre Aubry [5], at the Langevin Institute [6]) techniques.

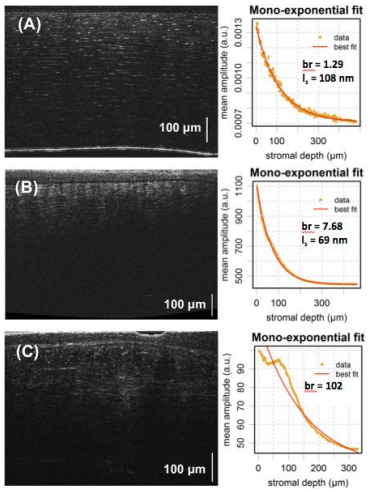

Figure 1. Graphical representation of preliminary results. FF-OCT cross-sections of typical corneal tissues with corresponding stromal-depth (*z*) profiles and transparency analysis [4]. (A) Cornea with intact transparency showing an exponential *z*-profile, confirmed by a Birge ratio (*br*) ≈ 1. (B) Pathological cornea with compromised transparency showing a faster decaying *z*-profile, confirmed by a lower scattering mean-free path (B, l_s=69nm vs. A, l_s=108nm). (C) Pathological cornea with stromal scarring showing a non-exponentional *z*-profile, confirmed by *br*>>1.

IV. DISCUSSION & CONCLUSION

Beyond the characterization of corneal transparency, the presented research will open the door to the characterization of transparencies of other ocular media (most notably the crystalline lens). In addition, the technological FF-OCT enhancements, specifically the implementation of a backscattering matrix approach [5,6], have implications beyond that of ocular media transparency characterization, most notably for imaging through non-transparent ocular media (*e.g.*, retinal imaging through cataract opacities).

ACKNOWLEDGMENT

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Integrating Birefringence Scanning in OCT-centered multimodal Retinal Diagnostic Systems

Boris Gramatikov, Wilmer Eye Institute, Johns Hopkins University

Abstract— **Two retinal scanning systems were combined, one for fixation identification, and the other one for volumetric data acquisition from the fundus. Issues related to the balancing of the polarization-sensitive components in the conjoint system were successfully resolved.**

I. INTRODUCTION

Retinal birefringence scanning (RBS) is a fast technique that detects the location of the fovea by analyzing the changes in the polarization state of light upon reflection from the Henle fibers surrounding the fovea. It can be used for identifying central fixation, or even for eye tracking. When combined with a long working distance optical coherence tomography (LWD OCT) [1], RBS provides valuable information on the validity of the data being acquired. Yet, several issues arise most importantly from the fact that RBS uses information carried by the polarization state of light, while the OCT does not.

II. METHODS

Fig. 1 shows the optical design of the combined system.

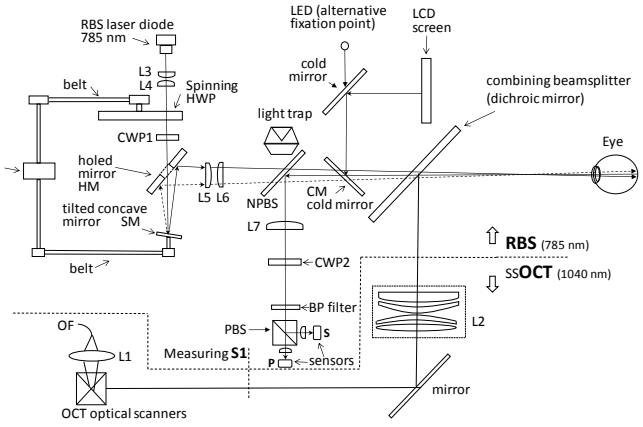

Figure 1. Optical design of the combined system.

Compensating retarders CWP1 and CWP2 were used to balance the polarization changes introduced by mirrors and beamsplitters in the RBS system [2]. A spinning half-wave plate HWP rotates the orientation of the linear polarization, to enable elimination of instrumental noise [3]. The two systems are integrated by means of a combining dichroic mirror. Fig. 2 presents the electronic circuitry of the RBS system.

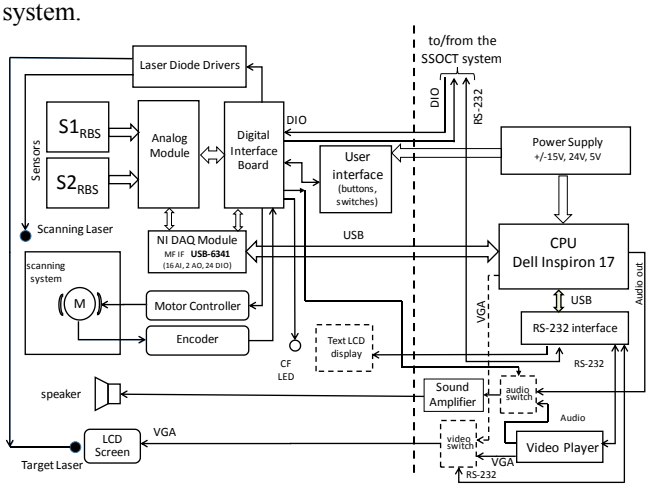

Figure 2. Electronics of the RBS system

IV. RESULTS

The presentation includes illustrations of RBS signals, volumetric OCT images, decision-making rules, ways of attention attraction and improving the human subjects' fixation, discussion on the speed of data acquisition, method of aiming, patient safety, and many other practical issues.

ACKNOWLEDGMENT

The author thanks Drs. David Guyton and Kristina Irsch from the Wilmer Eye Institute for collaborating on this project, and Drs. Cynthia Toth and Joseph Izatt from Ophthalmology/BME departments at Duke University, for their collaboration on a related project involving OCT.

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Multimodal Photoacoustic Microscopy and OCT of the Retina

Yannis M. Paulus, M.D., F.A.C.S., University of Michigan, Ann Arbor, MI, USA

Abstract— **This report describes a novel multimodal imaging system that combines photoacoustic microscopy (PAM), optical coherence tomography (OCT), and fluorescence microscopy (FM) to evaluate retinal and choroidal angiogenesis. High-resolution, *in vivo* imaging was performed in live rabbit eyes with vascular endothelial growth factor (VEGF) induced retinal neovascularization (RNV) and Rose-Bengal induced retinal vein occlusion. This multimodal system can noninvasively visualize RNV in rabbits and can further enhance imaging with molecular contrast agents including gold nanoparticles. This work presents high-resolution visualization of angiogenesis in rabbits using a multimodality system and may represent a major step toward clinical translation of the technology.**

I. INTRODUCTION

Retinal and choroidal neovascularization are major causes of vision loss and blindness around the world, including proliferative diabetic retinopathy and macular degeneration. Early diagnosis can be highly beneficial to the treatment of angiogenesis-related ocular diseases. Many imaging modalities have been adapted to the diagnosis and characterization of ocular neovascularization. Although these modalities can provide valuable information, each has certain limitations. OCT and OCTA provide anatomic information with high resolution but do not exhibit leakage, provide limited visualization of microaneurysms, and have a restricted field of view. Photoacoustic microscopy (PAM) can noninvasively explore the optical absorption properties in biological tissues with high spatial and temporal resolution. A multimodality platform is highly desired to combine the advantages of current imaging technologies.

II. METHODS

A multimodality imaging system with integrated OCT, PAM, and fluorescence microscopy (FM) is developed to evaluate angiogenesis in clinically-relevant animal eyes. High resolution in vivo imaging was performed in live rabbit eyes with several disease models, including vascular endothelial growth factor (VEGF)-induced retinal neovascularization and laser induced retinal vein.[1-3] SD-OCT was adapted from a commercially available OCT system (Ganymede-II-HR, Thorlabs). An OPO laser (NT-242, Ekspla) was used as the illumination source for PAM and FM with a repetition rate of 1 kHz at less than half of the ANSI safety limit. A custom built needle-shaped ultrasound transducer with a central frequency of 27 MHz was used. Forty rabbits, which have an axial length similar to the human eye, were evaluated

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III. RESULTS

High resolution imaging is performed of normal retinal and choroidal microvasculature along with numerous animal models of disease. PAM and OCT of VEGF-induced retinal neovascularization (Fig. 1) demonstrates visualization of retinal neovascularization and normal vasculature in both albino and pigmented rabbits. Imaging characteristics were used to distinguish normal and pathologic microvasculature. Quantification was performed of the neovascularization in the region of interest. Histology and fluorescein angiography were performed. The addition of targeted contrast agents, including gold nanoparticles, allowed for selective molecular targeting of angiogenesis through the Arg-Gly-Asp (RGD) peptide.

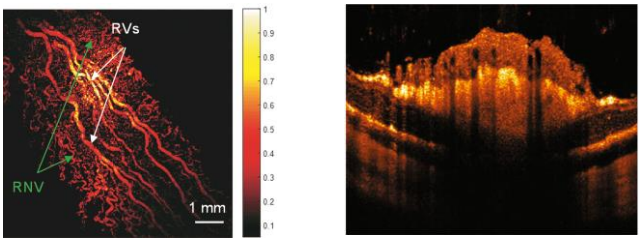

Figure 1. PAM (left) and OCT (right) of retinal neovascularization.

IV. DISCUSSION & CONCLUSION

This report presents an integrated OCT, PAM, and FM evaluation of retinal microvasculature in living large animal eyes. High resolution functional and molecular imaging is achieved to evaluate retinal and choroidal angiogenesis.

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Low cost OCT for point of care use

Adam Wax, PhD, Duke University Biomedical Engineering Dept., Durham, NC 27708

***Abstract*— We have developed a low cost version of OCT for improved access at the point of care. Here we will discuss how we made the advance, clinical validation and extension to other applications outside of ophthalmology.**

I. INTRODUCTION

Optical Coherence Tomography (OCT) is a biomedical optical imaging technique that uses low coherence interferometry to resolve backscattered light by depth. It has become a widely used technique for ophthalmology for its unique ability to non-invasively assess the various layers of the retina. However, the high cost of clinical OCT systems (up to $150,000) has limited access to mostly large eye centers and laboratories. We have chosen to pursue a low-cost OCT system to increase patient access, particularly in low cost settings. To further increase access we have developed a highly portable and robust system, capable of operating at the point of care. This talk will present design and clinical application of low-cost OCT, alongside other advancements that likewise increase utility of this biomedical imaging technology.

II. METHODS

The low-cost OCT uses a low-coherence interferometer set-up, which was entirely incorporated into a handheld scanner, which also housed the light source, reference arm, and sample arm. This greatly reduced the size of the OCT system body (Figure 1). A custom-designed spectrometer was housed inside a 3D-printed system body, along with an integrated mini PC [1]. To allow standalone system operation, a 7-inch TFT touchscreen was incorporated, which offered easy access to controls for data acquisition and display of retinal images. The total cost of parts was $5,037 [2].

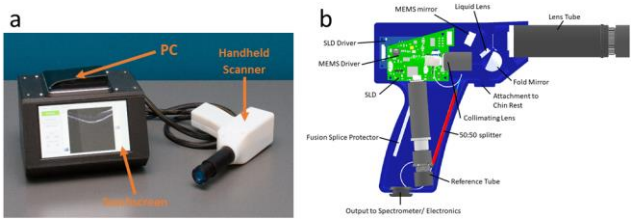

Figure 1: Image of low cost OCT system and schematic of handheld probe

*Research supported by Coulter Foundation, NSF

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III. RESULTS

We compared the low cost device to a Heidelberg Spectralis system. See Table 1:

	Low-Cost OCT	Heidelberg Spectralis
Center Wavelength	830 nm	870 nm
Bandwidth	42 nm	N/A
Number of Pixels per A Scan	512	512
Scanner Output Power	400 - 680 µW	1.2 - 1.3 mW
Imaging Depth	2.7 mm	1.8 mm
Axial Resolution	8.0 µm	7.0 µm
Lateral Resolution	19.6 µm	14 µm
A-Scan Rate	12.5 kHz	40 kHz
Sensitivity	104 dB	N/A
Working Distance	17.5 mm	7-15 mm (estimated)
Scan Range (X and Y)	6.6 mm	9 mm
Weight (with PC)	1.8 kg	
(without PC)		27.6 kg
Volume	250 in^3	3590 in^3
Cost	$ 5,037	> $ 60,000

The system performance was assessed using contrast-to-noise ratio (CNR). The low cost device was found to offer 1.592 vs. 1.687 for the Heidelberg system, a difference of approximately 6%. However, the modest trade off in performance is compensated by a significant reduction in weight, volume and cost [2].

IV. DISCUSSION & CONCLUSION

The low cost OCT has significant impact for improving access to this sight-saving technology. We will further discuss how we are extending this technology to other areas of biomedicine as well.

ACKNOWLEDGMENT

Ge Song, Kengyeh Chu, Sanghoon Kim, Michael Crose, Brian Cox, Evan T. Jelly, from Duke University, J. Niklas Ulrich, from Univ. North Carolina Kittner Eye Center and William Brown, Lumedica Inc. all contributed significantly to this work. Adam Wax is founder and president of Lumedica, Inc. which is commercializing OCT.

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