Northeast Symposium on Biomedical Optics 2018

Book of Abstracts

Session 1 – Miniaturized optical probes

1. Nano-optic endoscope for high-resolution optical coherence tomography

   Hamid Pahlevani (Harvard, MGH)

Acquisition of high-resolution images from within internal organs using endoscopic optical imaging has numerous clinical applications. However, difficulties associated with optical aberrations and the trade-off between transverse resolution and depth of focus significantly limit the scope of applications. Here, we integrate a metalens, with the ability to modify the phase of incident light at subwavelength level, into the design of an endoscopic optical coherence tomography catheter (termed nano-optic endoscope) to achieve near diffraction-limited imaging at greatly extended depth-of-focus through negating non-chromatic aberrations and chromatic dispersion engineering. We demonstrate endoscopic imaging in resected human lung specimens and in sheep airways in vivo. The combination of the superior resolution and higher imaging depth of focus of the nano-optic endoscope is likely to increase the clinical utility of endoscopic optical imaging.

2. Toward co-localized OCT surveillance of laser therapy using real-time speckle decorrelation

   Raphaël Maltais-Tariant (Polytechnique Montréal)

We present a system aiming for real-time delivery and monitoring of laser therapy using an optical coherence tomography (OCT) system with a double-clad fiber. A double-clad fiber coupler is used to combine both the OCT laser and therapy laser in a single double-clad fiber. The therapy laser is guided through the outer cladding while the single-mode core is used to perform real-time imaging and monitoring of the therapy. On the software side, a normalized second-order correlation function is used to highlight the coagulation of the treated tissues. The algorithm exploits a noise correction strategy to allow monitoring deeper in the sample.

3. Intravascular Photoacoustic Imaging of Lipid-laden Plaque: Technical Development towards Clinical Translation

   Jie Hui (Boston University)

Atherosclerotic coronary artery disease remains the leading cause of morbidity and mortality worldwide. Accurate assessment of atherosclerotic plaque holds great promise for disease prevention and treatment, especially for these with acute coronary syndromes. By converting molecular overtone absorption into acoustic waves via thermo-elastic expansion, intravascular photoacoustic (IVPA) imaging is uniquely capable of mapping lipid deposition within the entire arterial wall with depth resolution. As IVPA is inherently compatible with intravascular ultrasound (IVUS), IVPA/IVUS imaging has been emerging as a hybrid modality for accurate characterization of atherosclerotic plaque. In this talk, I will overview both the fundamentals of IVPA imaging and key technical innovations (including optical excitation source, real-time video-rate IVPA/IVUS imaging system, and functional IVPA/IVUS catheter) developed in Cheng Group towards clinical translation of this technology. Validation results both on human coronary arteries ex vivo and in swine and rabbit models in vivo will also be presented.

Session 2 – Emerging techniques in optical imaging

4. Coherent control of light transmission through turbid media

   Hasan Yilmaz (Yale)

Wavefront shaping techniques have recently been used to enhance total transmission of light through strongly scattering media. Such enhancement of total transmission relies on the selective coupling of incident light into highly transmitting channels. We have studied the properties of such channels, including their spatial structures and angular correlations. Our experimental data and numerical simulation results show that coupling light into high-transmission channels not only enhance the transmitted power and energy density, but also provide a wider field of view for imaging applications.

5. Studying nucleic and plasma membrane mechanics of eukaryotic cells using confocal reflectance interferometric microscopy

   Vijay Raj Singh (MIT)

Mechanical stress on eukaryote nucleus has been implicated in a diverse range of diseases including muscular dystrophy and cancer metastasis. Today, there are very few non-perturbative methods to directly quantify nuclear envelope mechanical properties. Quantitative phase microscopy (QPM) is a powerful tool for measuring cellular biomechanics but its lack of depth discrimination has limited its use to mostly red blood cells. In this talk, development of depth-resolved confocal reflectance QPM is presented as the next generation tool to study membrane biomechanics in complex eukaryotic cells. The system features multiple confocal scanning foci, affording millisecond temporal resolution, with is supplemented by a novel near common-path interferometer enables quantifying nanometer-scale thermally driven nucleic and plasma membrane fluctuations with high sensitivity. Results present the quantification of nucleic membrane fluctuations distinguished from that of plasma membrane in embryonic stem cells and cancer cells. Regulation of nuclear mechanics by external forces generated through the intracellular and extracellular environment is studied.

Session 3 – Neuro-imaging and optical modulation of brain

6. Label-Free Imaging and Genetics-Free Modulation of Brain

   Jonghwan Lee (Brown University)

This talk introduces our three projects: longitudinal optical coherence tomography (OCT) imaging of the rodent cerebral cortex in Alzheimer's disease (AD), label-free imaging of cellular viability in retina and neurospheroids, and minimally-invasive photothermal activation of retinal neurons without optogenetics.

First, we present the result from seven-month longitudinal imaging in AD and normal mice. Data of microvasculature and microcirculation (angiogram, Doppler OCT, capillary RBC flow, etc) were acquired every month along with cognitive function data. About one hundred of the same vessels and their blood flow values could be traced for the period of seven months. The AD mice developed significant hypoperfusion as early as 22 weeks of age, while spatial memory deficits did not manifest until 35 weeks of age. This result provides the longitudinal correlation between the development of vascular abnormalities and AD progression, for the first time to our knowledge.

Second, since the existing methods for measuring cellular viability responses to cancer drugs and environmental toxins involve the addition of exogenous labels, precluding longitudinal studies and resulting in limited diffusion of labeling molecules to the center of 3D tissue spheroids, we demonstrate the use of OCT for cellular viability imaging in 3D spheroids. When we conducted OCT imaging of neurospheroids while manipulating their viability, the OCT intensity and decorrelation signals exhibit correlated changes; interestingly, they show different time courses, suggesting that they may represent different cellular processes.

Finally, we demonstrate cellular-resolution stimulation of neurons in mouse retina explants without optogenetics, using gold nanorods and near-infrared laser. We built and integrated a wide-field fluorescence microscope and a focused, scanning laser stimulation system. Retinas were dissected from GCaMP3 mice, treated with cell-targeted gold nanorods, synapses of which were chemically blocked, and then imaged by the fluorescence microscope. When we illuminated laser pulses on a selected single retinal ganglion cell, simultaneously-recorded calcium images showed that only the illuminated neuron is activated while its neighboring neurons are not.

7. Towards an optical brain functional imaging platform for monitoring stroke recovery

   Morris Vanegas (Northeastern University)

Stroke is the leading cause of serious long-term disability in the US, requiring years of recovery through increasingly complex physical and/or cognitive rehabilitation programs outside the hospital. To ensure fast recovery, these rehabilitation programs must be frequently adjusted to ensure exercises provide the appropriate physical and cognitive load for the stroke survivor. However, side effects of stroke such as aphasia—the inability to communicate through language—make determining a survivor's state of progress through answers to standardized questions difficult. Although the diagnostic superiority of functional magnetic resonance imaging (fMRI) in determining the mental workload of a task has been demonstrated, its use as a tool in this context is hindered by high costs, inaccessibility for frequent use, and inability to move during imaging. Functional near-infrared spectroscopy (fNIRS) in an emerging neuroimaging technique that utilizes low-power near-infrared light to detect brain activation by measuring the associated hemodynamics, similar to fMRI. Although fNIRS has seen an increase in applications due to its low-costs, portability, and potential for long-term monitoring, bulky fiber-based connections, cart-sized optical instruments for high-density probes, and lengthy position and setup times remain major obstacles for translating fNIRS outside research settings. Here, we report on progress towards a wearable flexible-circuit based high density fNIRS system with features tailored towards use in natural environments.

8. Imaging neuronal responses through all cortical layers and subplate of visual cortex in awake mice with optimized three-photon microscopy

   Murat Yildirim (MIT)

Two-photon microscopy has been used to measure neuronal activity mainly in superficial cortical layers, but has severe limitations for imaging deeper layers. Thus, response features of identified neurons in deeper cortical layers have remained unclear. Here, we demonstrate the optical design of a custom-made three-photon microscope to image a vertical column of the cerebral cortex >1 mm in depth in awake mice with low (<20 mW) average laser power. We demonstrated functionality of the microscope by imaging the cross-laminar dendritic structure of layer 5 neurons in GFP-M mice, and functional visual responses of neurons expressing GCaMP6s across all layers of the primary visual cortex (V1) as well as in the subplate in awake mice. These recordings revealed diverse visual selectivity in deep layers: layer 5 neurons were on average more broadly tuned to visual stimuli, whereas mean orientation selectivity of layer 6 neurons was slightly sharper, compared to neurons in other layers. Subplate neurons, located in the white matter below cortical layer 6 and also characterized here for the first time, were less visually responsive, and their orientation selectivity was broader, compared to those of neurons in the cortical layers. These results demonstrate the design and utility of a custom-made three-photon microscope in revealing fundamental differences between neurons in different cortical layers, and between cortical and subplate neurons which have been implicated in the pathogenesis of developmental brain disorders including autism and schizophrenia.

9. The role of Mirror Neuron System in encoding motor complexity

Xinge Li (Boston University)

The mirror neuron system (MNS) responds to motor behaviors both when they are performed and observed. Converging neuroimaging evidence has shown the functional role of the MNS in action understanding. Most studies have focused on the effects of modulations in goals and kinematics of observed actions on MNS activity, but little research has explored the effects of manipulations in motor complexity. To address this, the present study adopted fNIRS to examine the MNS activity of twenty-one healthy adults executing and observing two hand actions that differed in motor complexity. We found motor complexity, represented as the contrast between the simple and complex task conditions, was represented in the MNS regions, i.e., IFG/PMv and IPL/supramarginal gyrus, as well as MOG, motor cortex, TPJ and STS during execution and in motor areas during observation. Our findings suggest that the MNS encodes motor representation of varying motor complexity in a direct and motor-based way.

Poster Session A

10. Two-photon imaging of capillary flow in mouse brain reveals vulnerability of cerebral white-matter to hypoperfusion

Baoqiang Li (Martinos Center, MGH and HMS)

Despite the importance of understanding the regulation of microvascular blood flow in white matter, no data on subcortical capillary blood flow parameters are available. To address this knowledge gap, we employed two-photon microscopy using a far-red fluorophore and photon-counting detection to measure capillary RBC flux in both cerebral gray and white matter in mice. We have found that baseline capillary RBC flux in the white matter was significantly higher than in the adjacent cortical gray matter. Under hypercapnia, RBC flux in the white matter exhibited significantly smaller fractional increase than in the gray matter. Finally, in globally hypoperfused mice, RBC flux in the white matter was reduced significantly in comparison to the controls, while RBC flux in the gray matter was preserved. Our results suggest that white matter blood flow may be less efficiently regulated when challenged by physiological perturbations and more susceptible to hypoperfusion compared to the gray matter.

11. Elucidating breast cancer pathophysiology using integrated dynamic DOT and digital breast tomosynthesis

Bin Deng (Martinos Center, MGH and HMS)

Near-infrared (NIR) diffuse optical tomography (DOT) is emerging as a non-invasive functional imaging method for breast cancer diagnosis and neoadjuvant chemotherapy monitoring. Moreover, dynamic DOT (DDOT) measurements of breast during breath maneuvers, gas inhalation, or mechanical stimulation have shown to offer a novel contrast mechanism that could elucidate tissue pathophysiology. Here, we demonstrated the use of a DDOT apparatus designed for tight integration with commercial digital breast tomosynthesis (DBT) scanners to track hemodynamic changes induced by stepwise mammographic breast compressions. Breast cancer patients presented with either benign or malignant lesions were imaged for 60 seconds under half mammographic force, followed by 60 seconds under full mammographic compression for both breasts. We note a distinctively more pronounced reduction in total hemoglobin concentration in malignant lesions than benign cases across the transition from half to full compression. We conclude that compression-induced changes in breast physiological properties may prove useful in differential diagnosis of breast cancer.

12. Wide-Field Two-Photon Microscopy with Enhanced Axial Resolution and Imaging Depth

Jong Park (MIT)

Wide-field two-photon excitation achieved by focusing beam temporally, so-called temporal focusing, is a technique for performing highly parallelized multiphoton microscopy while still maintaining optical sectioning capability. While the conventional wide-field configuration for temporal focusing suffers from sub-optimal axial resolution, patterning the temporal focusing beam can improve the axial resolution by enhancing the filling of the back aperture of an objective lens. We demonstrate line scanning and multi-spot temporal focusing implemented using a digital micromirror device (DMD) as a pattern generating component. We demonstrate a simple and programmable implementation of the pattern-scanning temporal focusing technique, by employing DMD for enhancing axial resolution. We also propose a method to image deep inside tissue utilizing multiplexed pattern-illuminated temporal focusing followed by computational decoding. By carefully controlling the size of the pattern blocks based on the strength of scattering, the image speed can be increased by optimization of the pattern size dynamically.

13. Plasmonic gold nanorods assisted near-infrared neural stimulation of retinal ganglion cell for retinal prosthetics

Kyungsik Eom (Brown University)

Among the various approach to restore vision, electrical method has been the gold-standard method. However, it suffers limited spatial resolution and requirement of insertion of electrodes. Here, we propose a plasmonic gold-nanorods (GNRs) assisted near-infrared neural stimulation (NINS) to restore vision with high spatial resolution but without insertion of any electronic device. To validate the feasibility of GNRs assisted NINS to restore vision, activities of retinal ganglion cells (RGCs) obtained from the dissected mouse retinas were modulated by GNRs-assisted NINS. We treated antibody-bound GNRs onto the mouse retinas to target retinal ganglion cells, and pulsed infrared light were illuminated onto a single RGC. We found that activities of retinal ganglion cells were modulated by optically stimulating the RGCs. Moreover, by patterning the beam direction, we were able to modulate each RGC.

14. Investigating cellular uptake dynamics of single-walled carbon nanotubes by high-speed confocal Raman microscopy

Maha Yaqoob (MIT)

We have recently demonstrated the first transient cellular uptake imaging of carbon nanotubes with the ability to distinguish multiple pristine carbon nanotube species. Using our custom-built high-speed confocal Raman microscope, we acquired movies of both nanotube-based as well as cell-intrinsic Raman signals. As a follow-up study, we further investigated the cellular uptake dynamics of different species of single-walled carbon nanotubes and quantified their uptake rates. This study provides insight into effective intra-cellular delivery of nanomaterials. Further, this work also demonstrates the possibility of the transient confocal molecular imaging of live cells and tissues using Raman spectroscopy, affording unique photostability and a much greater multiplexing ability than conventional imaging methods.

15. Towards a fiberless, modular, and wearable fNIRS system with built-in 3D self-calibrating orientation sensor network

Morris Vanegas (Northeastern University)

Functional near-infrared spectroscopy (fNIRS) is a non-invasive technique that utilizes non-ionizing near-infrared (NIR) light to determine the hemodynamic changes during brain activations. Although fNIRS has seen an increase in applications due to its low-cost and portability, the bulky fiber-based connections, cart-sized optical instruments for high-density probes, and lengthy position and setup times remain major obstacles for translating fNIRS research outside of research labs or hospitals. For model-based fNIRS data analysis and visualization, acquiring the 3D locations of source/detector fibers typically requires either a structural MRI scan or an expensive 3D tracking system. In this abstract, we report a feasibility study towards a wearable flexible-circuit based high-density fNIRS system where the optode 3D locations can be rapidly self-configured using the on-board orientation sensor network. This system will bring comfort and ultra-portability to fNIRS measurements in natural environments, along with drastically reduced setup time and data robustness monitoring.

16. Single particle Interferometric Imaging sensor for sensitive and rapid label-free bacteria detection

Negin Zaraee (Boston University)

Bacterial contamination and infections have always been a major threat to public health and human life. Specifically, E. coli contamination of water sources is a major problem not only in remote areas with limited water access but also in advanced countries. Here we propose to employ single particle Interferometric Imaging sensor (SP-IRIS) for label-free, rapid, sensitive, low cost and high throughput bacteria detection. The interferometric nature of our detection method will increase the visibility of the bacteria on the substrate. SP-IRIS provides single nanoparticle detection in a common-path wide-field interferometric microscopy setup, where the reflection of illumination from the layered substrate will be the reference light for interferometry. In our proposed method, the E. coli bacteria particles will be captured on the Si-Sio2 chip's surface using corresponding surface probes(antibodies). The captured particle will scatter light upon illumination and the interference of the scattered light with the reference light will result in the final detectable signal. Therefore, we will be able to detect them in a label-free fashion with a low magnification objective and benefiting from a larger field of view and speeding up the process of scanning the sensor surface.

17. Multifactorial Stress Equation: Prediction of Coronary Plaque Rupture

Pallavi Doradla (Wellman Center, MGH and HMS)

Rupture of mechanically unstable plaque is the major cause of acute stroke and myocardial infarction. Plaque rupture occurs when the peak stress in the plaque exceeds the material strength. Finite element modeling (FEM), typically used to calculate the tensile stress, is computationally intensive and impractical as a clinical tool for locating rupture-prone plaques in patients. In this study, we derive a new multifactorial stress equation (MSE) to compute peak stress score (PSS) in necrotic core fibroatheromas (NCFAs) within seconds. Plaque geometries of 61 NCFAs were assessed from the combined OFDI and ultrasound imaging in thirty patients. The tensile stress distribution was calculated for each coronary cross-section and multivariate regression analysis was used to derive the MSE. The MSE-derived PSS showed excellent correlation with the FEM-measured peak stress. This demonstrates that the MSE tool can be used interchangeably to replace FEM. Furthermore, using the MSE tool, we demonstrate that plaque rupture sites were precisely localized in three additional patients. Since MSE can accurately calculate peak stress within seconds, this study may open the powerful opportunity for locating rupture-prone coronary plaques during PCI.

18. Diffuse Correlation Spectroscopy for Cerebral Hemodynamics Monitoring During Mechanical Thrombectomy in Acute Stroke Patients

Parisa Farzam (Martinos Center, MGH and HMS)

A recent breakthrough in the management of ischemic stroke is advancement of mechanical clot removal from large arteries (mechanical thrombectomy) under contrast agent enhanced cerebral angiography. However, a significant portion of patients with complete clot removal suffer from poor outcome and the mechanism behind it is not well understood. It is hypothesized that hyperperfusion is the main cause of poor outcome in patients with complete recanalization. This raises the importance of a noninvasive bedside blood flow monitor to quantitatively measure cerebral blood flow (CBF) during and after thrombectomy. We utilize diffuse correlation spectroscopy (DCS) to continuously monitor CBF during mechanical thrombectomy under angiogram. Our results demonstrate the feasibility of using DCS during thrombectomy procedure. The DCS monitor enables the surgeon to observe the blood flow changes in real-time and alarm the surgeon of the open vessel immediately after the clot removal. In current practice, after each attempt of clot removal the surgeon should inject a contrast agent and take angiogram images to examine the opening of the vessels. Moreover, we aim to correlate the values of optically measured blood flow with the outcome of therapy to better identify the settings that lead to poor outcome towards a personalized treatment plan.

19. Determination of confocal profile and curved focal plane for OCT mapping of the attenuation coefficient

Sabina Stefan (Brown University)

The attenuation coefficient has proven to be a useful tool in numerous biological applications, but accurate calculation is dependent on the characterizing of the confocal effect. This study presents a method to precisely determine the confocal effect and its focal plane within a sample by examining the ratio of two optical coherence tomography (OCT) images. The method can be employed to produce a single-value estimate, or a 2D map of the focal plane accounting for the curvature or tilt within the sample. Furthermore, this method is applicable to data obtained with both high numerical aperture (NA) and low-NA lenses, thereby furthering the applicability of the attenuation coefficient to high-NA OCT data. We test and validate this method using standard samples of Intralipid 20% and 5%, improving the accuracy to 99% from 65% compared to the traditional method and preliminarily show applicability to real biological data of glioblastoma acquired in vivo in a murine model.

20. Investigate optical and molecular biomarkers of cancer treatment response using Spatial Frequency Domain Imaging pre-clinically

Syeda Tabassum (Boston University)

Spatial Frequency Domain Imaging (SFDI) was shown to longitudinally monitor a subcutaneous murine xenograft during chemotherapy. Here, we developed a two-layer Monte-Carlo based look-up-table (LUT) inverse model to mimic subcutaneous tumor physiology, and thus improve accuracy of SFDI results by accounting for the skin layer. The two-layer LUT was validated on custom made two-layer solid phantoms compared to a homogeneous LUT, and sensitivity to imperfect skin layer features was also analyzed. We will also, present results from a large-scale (87 tumors) longitudinal mice study to investigate if SFDI can predict treatment response earlier than tumor volume. Additionally, we will present immunohistochemical (IHC) analysis of several biomarkers (CD31, Glut1, PCNA, Cleaved Caspase-3, Mac1, and Hoechst stain) collected at multiple timepoints during the 4.5-month study. Correlations between IHC and SFDI optical/hemodynamic markers will be presented. This study, in future, will help clinical Diffuse Optical Imaging technologies for monitoring cancer therapies in patients.

21. Scanless volumetric imaging by selective access multi-foci multiphoton microscopy

Yi Xue (MIT)

Simultaneous, high-resolution imaging across a large number of synaptic and dendritic sites is critical for understanding how neurons receive and integrate signals. We demonstrate a new parallelized approach to address such questions, increasing the signal-to-noise ratio by an order of magnitude compared to previous approaches. This selective access multifocal multiphoton microscopy uses a spatial light modulator, to generate multifocal excitation in 3D, and a Gaussian-Laguerre phase plate, to simultaneously detect fluorescence from these spots throughout the volume. We test the performance of this system by simultaneously recording Ca2+ dynamics from cultured neurons at 139 locations distributed throughout a three-dimensional volume. This is the first demonstration of 3D imaging in a “single shot” and permits synchronized monitoring of signal propagation across multiple different dendrites.

22. Depth-resolved mapping of lipids in arterial wall in vivo by intravascular photoacoustic tomography

Yingchun Cao (Boston University)

Vulnerable plaque denotes a plaque that is prone to rupture and causes coronary thrombosis. One of the most important markers of vulnerable plaque is lipid-rich core, however, none of the clinically-available imaging tools can quantitatively measure the dimension of lipid cores, thus providing significant information for atherosclerosis diagnosis. Intravascular photoacoustic (IVPA) tomography has been an emerging tool that can provide lipid-specific detection and morphological information of the arterial wall. Enabled by our recent innovations in IVPA catheter development, which include a collinear catheter design and functional sheath material selection, we successfully implemented in vivo IVPA imaging of pig iliac arteries under clinically relevant conditions. We also developed method for lipid quantification and localization along the entire pullback. Ossabaw swine on atherosclerotic diet show more evident lipid accumulation in iliac artery than that on normal chow diet by IVPA imaging. This indicates a great potential of IVPA imaging in clinical applications.

23. Laser Speckle Micro-rheology for studying the biomechanics of invasion in Breast Carcinoma

Zeinab Hajjarian (Wellman Center, MGH and HMS)

Cancerous breast lesions are often stiffer than normal tissue and tumor extra-cellular matrix (ECM) stiffening, i.e. desmoplasia, is established to trigger neoplastic progression. Nevertheless, the course of ECM micro-mechanical alteration during cancer progression and its role in deciding tumor fate remains poorly understood. This is largely due to absence of imaging tool for micro-mechanical mapping of tissue at cellular scales. We have developed a novel optical technique for imaging the micro-mechanical properties of tumor ECM. In this approach, breast tissue is illuminated by a coherent laser beam and back-scattered rays are collected by a high-speed camera. Spatio-temporal analysis of intensity fluctuations yields the map of viscoelastic modulus, G. Here, we investigated the relationship between tumor stiffness and known markers of disease progression, including size, histopathological grade, and lymph-node status. These studies open new avenues for understanding the link between ECM micromechanical properties and tumor progression towards identifying the mechano-biological mediators of malignancy, as potential therapeutic targets.

Poster Session B

24. Volumetric imaging with multi-Z confocal microscopy

    Amaury Badon (Boston University)

Fast, volumetric imaging over large scales has been a long-standing challenge in biological microscopy. To address this issue, we developed a variant of confocal microscopy that provides simultaneous multiplane imaging over large field of view and at video rate. Our approach combines an axially elongated illumination with a series of reflecting pinholes axially distributed in the imaging plane. Each of these pinholes is associated to a given depth inside the sample and volumetric imaging is achieved without axial scanning. We demonstrate the general applicability of our technique to neuronal imaging of both C. elegans and mouse brains in-vivo.

25. Retinal blood flow quantification from optical coherence tomography speckle intensity fluctuations using neural networks

    Boy Braaf (Wellman Center, MGH and HMS)

A neural network analysis is proposed to extract quantitative flow velocity information from optical coherence tomography (OCT) intensity time series data. The neural network was trained with simulated OCT intensity time series data generated with a one-dimensional transverse flow model. The trained neural network was applied to experimental data obtained with an optical frequency domain imaging system based on a 1050 nm wavelength swept-source for in vivo retinal imaging. Validation of the neural network analysis was performed by cross-sectional imaging of a phantom eye with plastic tubing as an artificial blood vessel perfused with intralipid or swine blood. A linear relation between the set flow speed and detected flow speed was observed. The validation measurement can however be used to calibrate out this effect. In a healthy volunteer the neural network analysis was applied on cross-sectional data of arteries and veins of two central vessels and two higher branch vessels. For the central artery strong pulsatility from the cardiac cycle was measured while for the central vein a constant velocity was observed. Similarly, for the higher branch artery strong pulsatility was observed, while the velocity in the accompanying vein was more constant and only showed a small residual pulsatility effect. The quantitative assessment of blood flow can potentially improve the diagnosis of retinal vascular diseases.

26. Preliminary Investigations of Rupture of Human Tympanic Membrane subjected to High Pressure Loads

    Haimi Tang (Worcester Polytechnic Institute)

To improve the design of hearing protection and Tympanic Membrane (TM) rehabilitation surgeries, it is important to understand the complex TM failure mechanisms under high amplitude excitations. To achieve this goal, we apply High-Speed Digital Image Correlation (HS-DIC) methods for full-field-of-view measurements of cadaveric human TMs subjected to high pressure excitations.
Prior to performing measurements on human TM samples, we validated the measuring capability using orthotropic artificial samples. We managed to successfully perform preliminary HS-DIC measurements of 3D transient shape and displacements on human post-mortem TMs under rapid increase of air pressure until rupture the membrane ruptures. The full-field high spatio-temporal resolution results by HS-DIC methods allow full description of sequential deformation to failure stages during the rupturing process of the TM. This study will help better understand the TM mechanical properties under high strain rates that cause injury and failure.

27. Longitudinal OCT Cortex Imaging for Detection of Early Vascular Changes in Alzheimer's Disease

Jang-Hoon Lee (Brown University)

Alzheimer's disease (AD) diagnosis presently requires manifestation of cognitive symptoms, which occurs after significant disease progression, creating a crucial need for new non-cognitive biomarkers for early diagnosis. Per recent work, cortical vascular abnormalities worsen with AD progression and may present before cognitive symptoms. Due to technical limitations of visualizing blood vessels in vivo, no longitudinal study could be performed until now.
With new optical coherence tomography (OCT) techniques, it is now possible to precisely visualize structure and blood flow in cortical tissue in near-real time, longitudinally in vivo and label-free. 3xTgAD mice and controls underwent longitudinal cortical OCT angiography, Doppler imaging, and memory testing at regular intervals to investigate the correlation between development of vascular abnormalities and Alzheimer's progression. The AD group developed significant hypoperfusion at 18 weeks, with memory deficits not present until 34 weeks, suggesting a new avenue for a low-cost OCT-based prediction and early definitive AD diagnosis.

28. Pseudo-volumetric fluorescence endomicroscopy with a fiber bundle

Jean-Marc Tsang (Boston University)

The development of high resolution, 3D imaging endomicroscopy has recently been gaining interest due to needs in in vivo studies of neuronal dynamics and interactions in deep brain tissue. However, most types of endomicroscopy techniques adopting micro-objectives can hardly perform 3D imaging due to the lack of minimally invasive scanning mechanism. Here, we present a GRIN-lens based fluorescence endomicroscopy capable of obtaining pseudo 3D image of a fluorescent sample without scanning the probe. This technique uses a coherent fiber bundle with a gradient-index (GRIN) lens to achieve an extended depth of focus and two reflecting pinholes for detection. Preliminary results using fluorescent beads showed that a single bead can be detected throughout hundreds of microns depth. We obtain volume information in a single acquisition by determining the intensity ratio of an object in three simultaneously acquired images.

29. Characterizing Coronary Plaque Composition and Stability in Patients with Intravascular Polarimetry

Kenichiro Otsuka (Wellman Center, MGH and HMS)

Polarization-sensitive (PS-) optical frequency domain imaging (OFDI) provides measurements of the polarization properties of tissue together with conventional cross-sectional images of subsurface microstructure. This first-in-human pilot study of intravascular polarimetry consists of 30 patients (acute coronary syndrome; ACS, n = 12 and stable angina pectoris; SAP, n = 18). Polarization features of individual cross-sections were compared with established structural OFDI characteristics. The median birefringence ($p<0.001$) and depolarization ($p<0.001$) showed significant differences among plaque types categorized with conventional OFDI. Stenosis severity was associated with depolarization ($p<0.001$), but not with birefringence. Caps of ACS culprit lesions and ruptured caps exhibited lower birefringence than caps of SAP target lesions ($p<0.001$). This study demonstrates that polarization properties differ between fibrous caps of ACS and SAP lesions, and among different morphological plaque subtypes. Quantitative assessment of plaque structure and composition by intravascular polarimetry may open new avenues for studying plaque progression and detecting high-risk patients.

30. Customizing speckle patterns

Hasan Yilmaz (Yale)

Stroke is the leading cause of serious long-term disability in the US, requiring years of recovery through increasingly complex physical and/or cognitive rehabilitation programs outside the hospital. To ensure fast recovery, these rehabilitation programs must be frequently adjusted to ensure exercises provide the appropriate physical and cognitive load for the stroke survivor. However, side effects of stroke such as aphasia—the inability to communicate through language—make determining a survivor's state of progress through answers to standardized questions difficult. Although the diagnostic superiority of functional magnetic resonance imaging (fMRI) in determining the mental workload of a task has been demonstrated, its use as a tool in this context is hindered by high costs, inaccessibility for frequent use, and inability to move during imaging. Functional near-infrared spectroscopy (fNIRS) in an emerging neuroimaging technique that utilizes low-power near-infrared light to detect brain activation by measuring the associated hemodynamics, similar to fMRI. Although fNIRS has seen an increase in applications due to its low-costs, portability, and potential for long-term monitoring, bulky fiber-based connections, cart-sized optical instruments for high-density probes, and lengthy position and setup times remain major obstacles for translating fNIRS outside research settings. Here, we report on progress towards a wearable flexible-circuit based high density fNIRS system with features tailored towards use in natural environments.

31. Optical Metabolic Investigation of Lobster Hemocyanin Anti-Cancer Effects Using a Home-Built Two-Photon System

Patrick Breeding (University of Maine)

Hemocyanin is the primary respiratory protein found in arthropods, known to play several roles in invertebrate immune systems. Numerous hemocyanins, such as the Keyhole Limpet Hemocyanin (KLH), are currently being evaluated as an anti-cancer therapeutic, shifting cell metabolism to induce apoptosis. Although applications are promising, overharvesting of the Keyhole Limpet for biomedical purposes is leading to species endangerment. The lobster industry stands to offer a suitable replacement, as hemocyanin is the primary protein found in lobsters and is currently discarded as a waste byproduct in lobster processing plants. The goal of this study is to investigate anti-cancer potential of several forms of American Lobster hemocyanin (LH) against lung carcinoma cell lines, using alterations cell viability and redox ratio as metrics for efficacy. Project success will usher the development of a widely accessible biological therapeutic from an otherwise wasted material, yielding a significant value-added product to stimulate sustainable commercial lobstering practices.

32. High-speed shape and transient response measurements of tympanic membrane

Payam Razavi (Worcester Polytechnic Institute)

The human Tympanic Membrane (TM, eardrum) has a unique conical shape, which is believed to play an important role in its function. In other words, knowing the shape and displacements of the eardrum can help better understand the role of the TM in the hearing process. In this poster, we present a new high-speed (>67 kHz) holographic method that can determine both the shape and sound-induced transient displacements of the entire eardrum near-instantaneously (<200 msec). This rapid measurement is immune to disturbances introduced by breathing or heartbeat of live subjects, which makes this system suitable for in-vivo studies. Knowledge of the TM's shape and its displacements helps better define its mechanics and provides a better understanding of the structure and function of TM in the hearing processes, which can also be useful for the diagnosis of middle-ear diseases.

33. Wavelength-encoded microlasers for massively-multiplexed cell tagging

Sheldon J.J. Kwok (Harvard Medical School and MIT)

Understanding the dynamics and interplay of numerous, heterogeneous cell populations in biological systems requires new methods to distinctively label and track many cells. Although optical microscopy using fluorescent probes is ubiquitously used to observe cells, it can distinguish only a handful of individual cells or cell groups at a time because of spectral crosstalk between conventional fluorophores. Here we show a novel class of imaging probes emitting coherent laser light. These probes, made of silica-coated semiconductor microcavities, have tunable emission over a broad range from 1170 to 1580 nm with sub-nm linewidths, enabling massive spectral multiplexing. We demonstrate real-time tracking of thousands of individual cells in a 3D tumor model for several days showing different behavioral phenotypes. Our technology gives access to the previously inaccessible spatiotemporal history of single cells and their interactions in physiological and pathological processes.

34. Visualization of drug distribution of a topical minocycline gel in human facial skin

Sinyoung Jeong (Wellman Center, MGH and HMS)

A topical minocycline gel was developed to treat inflammatory acne vulgaris as a transepidermal drug product. To evaluate the effectiveness of topical minocycline delivery in terms of pharmacokinetics, we propose a visualization and quantification method of the drug within human skin tissue utilizing a phasor approach to time-correlated single photon counting fluorescence lifetime microscopy (TCSPC-FLIM). Using phasor analysis of FLIM, we could differentiate the unique signature of minocycline from endogenous fluorescence of human facial skin. Furthermore, by tracking the signature of minocycline in FLIM images, the distribution of minocycline within the facial skin was successfully visualized and relatively quantified. Based on these results, we believe that the visualization method using a phasor approach to FLIM can play an important role in future pharmacokinetics and pharmacodynamics studies.

35. Toward flexible MMF endoscopy with a proximal calibration method

Szu-Yu Lee (Wellman Center, MGH and HMS)

Current diagnostic tools for pancreatic cysts (PCLs) such as CT, MRI, and endoscopic ultrasound with fine needle aspiration are not sufficiently accurate, which might lead to missed cancer or avoidable resection. As a result, the diagnosis and the management of PCLs is a clinical challenge. Here, we propose an on-site inspection by a multimode fiber (MMF) endoscope providing microscopic features of PCLs. The on-site inspection may serve as a screening tool to distinguish between benign and malignant lesions. MMF endoscopy is an excellent choice to provide the on-site inspection due to its small footprint and ultrahigh resolution. The goal of this project is to address and solve the challenges in exploiting MMF endoscopy to realize the on-site inspection in identified PCLs, which may increase the overall diagnostic accuracy and improve the patient outcomes.

36. Ocular fundus imaging with transmitted light

Timothy Weber (Boston University)

We have developed a method to image the human ocular fundus in transmission using a commercial non-mydriatic fundus camera. The method is based on deeply penetrating near-infrared (NIR) light delivered transcranially near the temple. A portion of this light diffuses through bone and illuminates the posterior eye not from the front, as with conventional methods, but rather mostly from behind. As such, we image light transmitted through the fundus rather than back-reflected off multiple fundus layers. This single-pass measurement geometry simplifies absorption pathlength considerations and provides complementary information to fundus reflectometry. The use of NIR light enables imaging as deep as the choroid.

37. Nonlinear passive earplugs for preventing blast injury of the ear

Soroush Shabahang (Wellman Center, MGH and HMS)

We have developed a reusable passive earplug which transmits low SPL sounds with minimal transmission loss but blocks the high SPL impulses. The earplug design consists of an elastic membrane and a deformation stopper. At low SPL, the membrane freely vibrates transmitting sound with low loss (the ON state). Upon incoming blast, the deformation of the membrane is constrained by the stopper, limiting the transmitted maximum pressure (the OFF state). When the blast is gone, the membrane goes back to its equilibrium position and is turned to the ON state.