SPIE/NIH WORKSHOP
BIOPHOTONICS FROM BENCH TO BEDSIDE

INTERNATIONAL YEAR OF LIGHT 2015

2015

SPIE/NIH WORKSHOP
BIOPHOTONICS FROM BENCH TO BEDSIDE.

Technical Program

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24–25 September 2015

Masur Auditorium
National Institutes of Health
Bethesda, Maryland, United States

Organized by

NIH National Institutes of Health
Turning Discovery into Health
NINDS, NICHD, NIBIB, NHLBI

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Welcome

As we embark on a new era in optical imaging techniques that move from bench to bedside at an extremely rapid rate, we welcome you to the SPIE/NIH Workshop: Biophotonics from Bench to Bedside 2015. Quantification of intrinsic chromophores, scattering properties, and targeted probes provide valuable functional information for diagnosing disease and monitoring therapies. With these advances, optical methods have become critical tools for translational research and studying the fundamental molecular origins of disease processes - from photonic studies of nanoscale interactions to ultrahigh-resolution microscopy. This workshop at the National Institutes of Health will be devoted to all aspects of bringing optical imaging technology from the desktop, where quantitative theories are devised; to the bench, where the instrumentation is designed and tested; and finally, to the bedside, where performance is validated in a demanding clinical setting.

The United Nations has deemed 2015 the International Year of Light and Light-Based Technologies. Advancements in both biophotonics and translational science have broad significance, and UNESCO has proposed continued research in photonics and lasers as a scientific cornerstone. Conveying this message through presentations, posters, and panel discussions, we hope workshop participants will take away a thorough view of the field of biophotonics currently and new ideas regarding its future direction.

You should be proud to be at the forefront of efforts to discover and develop the latest light-based technologies and tools. We look forward to meeting you during the workshop.

WORKSHOP CHAIRS

Amir Gandjbakhche
National Institutes of Health (USA)

Bruce Tromberg
Beckman Laser Institute and Medical Ctr., Univ. of California, Irvine (USA)

Israel Gannot
Johns Hopkins Univ. (USA) and Tel Aviv Univ. (Israel)

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PHOTON IS OUR BUSINESS

MODULATED IMAGING
SEE BEYOND

Massachusetts General Hospital · Harvard Medical School
Wellman Center for Photomedicine

KEYNOTE AND INVITED SPEAKERS

Sam Achilefu
Washington Univ.
School of Medicine

Robert Alfano
Keynote Speaker
The City College of
New York

Adela Ben-Yakar
Univ. of Texas at Austin

David Boas
Keynote Speaker
Massachusetts
General Hospital,
Harvard Univ.

Zhongping Chen
Beckman Laser Institute
and Medical Clinic

Vicky Demas
Google

Krista Donaldson
D-Rev

Sergio Fantini
Tufts Univ.

Jim Fujimoto
Keynote Speaker
Massachusetts Institute
of Technology

Israel Gannot
Hopkins Univ. and
Tel Aviv Univ.

Irene Georgakoudi
Tufts Univ.

Tayyaba Hasan
Wellman Ctr. for
Photomedicine

Ik-Kyung Jang
Massachusetts General
Hospital

Jim Olson
Fred Hutchinson Cancer
Research Ctr.

George Patterson
National Institute of
Child Health and Human
Development

Guillermo Tearney
Wellman Center for
Photomedicine, Massachusetts
General Hospital, Harvard
Medical School (USA)

Brian Pogue
Thayer School of
Engineering at
Dartmouth

Nimmi Ramanujam
Duke Univ.

Melissa Skala
Vanderbilt Univ.

Peter So
Massachusetts Institute
of Technology

Bruce Tromberg
Beckman Laser Institute
and Medical Clinic

Lihong Wang
Keynote Speaker
Washington Univ.
in St. Louis

Chris Xu
Cornell Univ.

WORKSHOP TECHNICAL COORDINATORS

Fatima Chowdhry
National Institutes of
Health

Jana Kainerstorfer
Carnegie Mellon Univ.

Contents

SPECIAL EVENTS

PANEL DISCUSSION

Translational Research

Thursday 24 September 2015
4:00 to 5:00 pm

PANELISTS:

Gabriela Apiou
Harvard Medical School, Wellman Ctr. for Photomedicine, Massachusetts General Hospital (USA)

Gabriela Apiou, PhD, is an Assistant Professor of Dermatology, Harvard Medical School. She received her PhD degree summa cum laude in Biomedical Engineering from Ecole Nationale Supérieure des Arts et Métiers (ENSAM) Angers, France in 1998 and her Habilitation à Diriger des Recherches (HDR) diploma in Health and Life Sciences from University Paris Est Créteil, France in 2010. Since 1995, she has worked for global leaders in the biomedical engineering and pharmaceutical industry. Her professional experience is centered on the application of physics and engineering principles to resolve clinical problems that involve biotechnology and medical gases with a specific focus on inhaled therapeutics and delivery devices. Since 2011, she has been working for Massachusetts General Hospital (MGH) as the Director of the Translational Research Core for Wellman Center for Photomedicine and since February 2015 as the Director of Translational Research Training and Development for the MGH Research Institute. In this position, she has a leadership role in training the faculty, facilitating and accelerating transition of technological and medical research to clinical practice. She is driven by the desire to advance patient care through the development and promotion of interdisciplinary and collaborative work into an international and innovation driven environment.

Conor Evans
Wellman Ctr. for Photomedicine, Massachusetts General Hospital, Harvard Medical School (USA)

Dr. Conor L. Evans received his degrees from Brown University (BS in Physical Chemistry) and Harvard University (PhD in Chemistry). The Evans lab's research is focused on the development and clinical translation of optical microscopy and spectroscopy tools, with specific interests in ultrasensitive detection of molecular markers, label-free imaging of tissues, and the imaging and quantification of tissue oxygenation.

Georg Schuele
Abbott Medical Optics (USA)

Georg Schuele received a PhD in physics from University Lübeck followed by a postdoctoral position at Stanford University. His work is focused on transitioning initial concepts to a medical device. He currently is the Director of Research Laser Cataract Systems and Senior Associate Research Fellow at Abbott Medical Optics.

Eva Lankenau
Opto Medical Technologies (Germany)

Since 1994 she has worked on the R&D of OCT. After her PhD in Physics she worked on different OCT prototypes. These developments led to the idea of developing a universal OCT-Camera. She established a new company in 2010, the OptoMedical Technologies GmbH, which she manages.

Peter König
Univ. of Lübeck (Germany)

Dr. König received his MD from the University of Giessen (Germany). He is professor of anatomy at the University of Lübeck and a member of the German Center for Lung Research (DZL). His lab focuses on using microscopic techniques to get insight into dynamic immunological processes and structural changes in airway diseases in animal models and humans.

Guillermo Tearney
Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School (USA)

Guillermo Tearney MD, PhD is Professor of Pathology at Harvard Medical School, an Affiliated Faculty member of the Harvard-MIT Division of Health Sciences and Technology (HST), and the Associate Director of the Wellman Center for Photomedicine at the Massachusetts General Hospital. He received his MD magna cum laude from Harvard Medical School and received his PhD in Electrical Engineering and Computer Science from the Massachusetts Institute of Technology. Dr. Tearney's research is focused on developing and validating non-invasive, high-resolution optical imaging diagnostic methods, such as optical coherence tomography.

The NIH Bench-to-Bedside Pioneer Award

Thursday 24 September 2015
5:00 to 5:30 pm

The 2015 Workshop Lifetime Achievement Award will be presented to Katarina Svanberg, Lund Univ. Hospital (Sweden), for her contributions in the fields of photodynamic therapy and spectroscopic imaging methods.

Welcome Reception/Poster Session I

Thursday 24 September 2015
5:30 to 7:00 pm
Location: FAES Terrace

Registered participants are invited to browse the posters, network with colleagues, and enjoy light refreshments. Authors of poster papers will be present to answer questions about their work. Please wear your conference badge.

POSTER AUTHORS: Please put up your poster during the morning or afternoon coffee break and plan to stand by your poster during the poster session to interact with attendees. Posters must be removed from the boards following the session. Posters that remain on the boards will be discarded.

Lunch Break and Poster Session II

Friday 25 September 2015
11:00 am to 12:30 pm
Location: FAES Terrace

Registered participants are invited to browse the posters and network with colleagues during the lunch break. Authors of poster papers will be present to answer questions about their work. Please wear your conference badge.

POSTER AUTHORS: Please put up your poster during the morning coffee break and plan to stand by your poster during the poster session to interact with attendees. Posters must be removed from the boards following the session. Posters that remain on the boards will be discarded.

PANEL DISCUSSION

Funding and the Future

Friday 25 September 2015
4:00 to 5:00 pm

PANELISTS:

Houston Baker
NCI, National Institutes of Health

Richard Conroy
NIBIB, National Institutes of Health

Behrouz Shabestari
NIBIB, National Institutes of Health

DAILY CONFERENCE SESSION SCHEDULE

THURSDAY 24 September	FRIDAY 25 September
TECHNICAL CONFERENCE: SPIE/NIH BIOPHOTONICS FROM BENCH TO BEDSIDE	
SESSION 1: **Introduction,** 8:15 to 9:30 am	**Session 5:** **Cancer: Metabolomics to Genomic**s, 8:00 to 9:20 am
COFFEE BREAK, 9:45 to 10:15 am	COFFEE BREAK, 9:20 to 9:45 am
SESSION 2: **Brain,** 10:15 to 11:45 am	**SESSION 6:** **Image Guided Therapy/Surgery**, 9:45 to 11:00 am
LUNCH BREAK, 11:45 am to 12:45 pm	LUNCH BREAK/POSTER SESSION II, 11:00 am to 12:30 pm
SESSION 3: **A Multidisciplinary Approach to Global Health Innovation**, 12:45 to 2:00 pm	**SESSION 7:** **Advanced Optical Microscopy**, 1:00 to 2:00 pm
COFFEE BREAK, 2:00 to 2:20 pm	COFFEE BREAK, 2:15 to 2:45 pm
SESSION 4: **Optical Coherence Tomography**, 2:20 to 3:40 pm	**SESSION 8:** **Keynotes by SPIE Britton Chance Biomedical Optics Award Recipients**, 2:45 to 4:00 pm
COFFEE BREAK, 3:40 to 4:00 pm	
PANEL DISCUSSION: **Translational Research**, 4:00 to 5:00 pm	**PANEL DISCUSSION: Funding and the Future,** 4:00 to 5:00 pm
PIONEER AWARD: NIH Bench-to-Bedside Pioneer Award, 5:00 to 5:30 pm	
Welcome Reception/Poster Session I, 5:30 to 7:00 pm	

Registration Desk Hours

Room: Masur Auditorium Foyer

Thursday. . . . . .7:00 am to 4:30 pm

Friday . . . . . .7:30 am to 4:30 pm

Clinical Center (Building 10) Food Service

Attendees will need to make their own arrangements for lunch during the workshop. The Clinical Center (Building 10) offers two cafeterias, located on level B1 and the 2nd floor, as well as two coffee shops outside the Masur Auditorium.

Coffee Breaks

Location: FAES Terrace

Coffee will be served during the morning and afternoon breaks.

Internet Access

Guest wireless service is available at the NIH Clinical Center. This service provides access to the Internet and social media only. Please note that the network is not secure or encrypted, and it does not allow access to any NIH internal systems, services, or resources. To access the guest wireless service, simply follow these steps:

1. Select the NIH-Guest-Network in "available wireless networks" from a laptop or mobile device, then click the "connect" button.
2. Once you launch a web browser (such as Internet Explorer, Mozilla Firefox, Safari), you will be redirected to a page displaying the network Terms and Conditions.
3. After reading the Terms and Conditions, click "Accept" and you will have immediate access to the Internet.

Smoke-Free Campus

NIH is a smoke-free campus. Smoking is prohibited in all areas.

CONFERENCE NIH200

Thursday–Friday 24–25 September 2015

SPIE/NIH Biophotonics from Bench to Bedside

Conference Chairs: **Amir H. Gandjbakhche,** National Institutes of Health (USA); **Bruce J. Tromberg,** Beckman Laser Institute and Medical Clinic (USA); **Israel Gannot,** Johns Hopkins Univ. (USA), Tel Aviv Univ. [Israel)

THURSDAY 24 SEPTEMBER

REGISTRATION AND COFFEE
LOCATION: MASUR AUDITORIUM . . . . . 7:30 AM TO 8:15 AM

SESSION 1
LOCATION: MASUR AUDITORIUM . . . . . THU 8:15 AM TO 9:30 AM

Introduction

Session Chairs: **Amir Gandjbakhche,** National Institutes of Health (USA); **Bruce J. Tromberg,** Beckman Laser Institute and Medical Clinic (USA)

8:15 am: **Welcome and Introduction**, Amir Gandjbakhche, National Institutes of Health (USA) . . . . . [NIH200-1]

8:25 am: **Welcome and Introduction**, Bruce J. Tromberg, Beckman Laser Institute and Medical Clinic (USA) . . . . . [NIH200-2]

8:35 am: **Welcome and Introduction**, Richard D. Leapman, National Institutes of Health (USA) . . . . . [NIH200-3]

8:45 am: **Life Sciences at Google** *(Invited Paper)*, Vicky Demas, Google . . . . . [NIH200-4]

Coffee Break . . . . . Thu 9:45 am to 10:15 am

SESSION 2
LOCATION: MASUR AUDITORIUM . . . . THU 10:15 AM TO 11:45 AM

Brain

Session Chair: **Joseph P. Culver,** Washington Univ. School of Medicine in St. Louis (USA)

10:15 am: **Functional Near Infrared Spectroscopy – History, Advances, Applications** *(Keynote Presentation)*, David A. Boas, Athinoula A. Martinos Ctr. for Biomedical Imaging (USA) . . . . . [NIH200-6]

10:55 am: **Quantitative analysis of cerebral hemodynamic oscillations for the study and assessment of the cerebral microcirculation** *(Invited Paper)*, Sergio Fantini, Tufts Univ. (USA) . . . . . [NIH200-7]

11:20 am: **Tumor Paint molecular imaging for surgical guidance in adult and pediatric brain tumors** *(Invited Paper)*, James M. Olson, Fred Hutchinson Cancer Research Ctr. (USA) . . . . . [NIH200-8]

Lunch Break . . . . . Thu 11:45 am to 12:45 pm

SESSION 3
LOCATION: MASUR AUDITORIUM . . . . THU 12:45 PM TO 2:00 PM

A Multidisciplinary Approach to Global Health Innovation

Session Chair: **Nirmala Ramanujam,** Duke Univ. (USA)

12:45 pm: **Photodynamic Therapy: does it have a role in Low to Middle Income Countries?** *(Invited Paper)*, Tayyaba Hasan, Wellman Ctr. for Photomedicine (USA) . . . . . [NIH200-9]

1:10 pm: **A see and treat paradigm for cervical cancer** *(Invited Paper)*, Nirmala Ramanujam, Duke Univ. (USA) . . . . . [NIH200-11]

1:35 pm: **Commercializing and scaling global health products for impact via the market** *(Invited Paper)*, Krista Donaldson, D-Rev (USA) . . . . . [NIH200-10]

Coffee Break . . . . . Thu 2:00 pm to 2:20 pm

SESSION 4
LOCATION: MASUR AUDITORIUM . . . . . THU 2:20 PM TO 3:40 PM

Optical Coherence Tomography

Session Chair: **James G. Fujimoto,** Massachusetts Institute of Technology (USA)

2:20 pm: **Optical coherence tomography: development and applications** *(Keynote Presentation)*, James G. Fujimoto, Massachusetts Institute of Technology (USA) . . . . . [NIH200-12]

2:40 pm: **In vivo vascular biology studies using intravascular OCT: the Massachusetts General Hospital OCT Registry** *(Invited Paper)*, Ik-Kyung Jang M.D., Massachusetts General Hospital (USA) . . . . . [NIH200-13]

3:00 pm: **Long range optical coherence tomography of upper airway: imaging and diagnosis of pediatric obstructive sleep abnea and neonatal subglottic stenosis** *(Invited Paper)*, Zhongping Chen, Beckman Laser Institute and Medical Clinic (USA) . . . . . [NIH200-15]

3:20 pm: **To be announced** *(Invited Paper)*, Guillermo J. Tearney M.D., Wellman Ctr. for Photomedicine (USA) . . . . . [NIH200-14]

Coffee Break . . . . . Thu 3:40 pm to 4:00 pm

PANEL DISCUSSION
LOCATION: MASUR AUDITORIUM . . . . THU 4:00 TO 5:00 PM

Translational Research

PANELISTS:

Gabriela Apiou, Wellman Ctr. for Photomedicine, Massachusetts General Hospital, Harvard Medical School (USA)

Conor Evans, Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School (USA)

Georg Schuele, Abbott Medical Optics (USA)

Eva Lankenau, Opto Medical Technologies (Germany)

Peter König, Univ. of Lübeck (Germany)

Guillermo Tearney, Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School (USA)

CONFERENCE NIH200

PIONEER AWARD
LOCATION: MASUR AUDITORIUM . .THU 5:00 PM TO 5:30 PM

NIH Bench-to-Bedside Pioneer Award

Session Chair: **Bruce J. Tromberg,**
Beckman Laser Institute and Medical Clinic (USA)

Award presentation to

Katarina Svanberg, Lund Univ. (Sweden)

WELCOME RECEPTION/POSTER SESSION I
LOCATION: MASUR AUDITORIUM .....THU 5:30 PM TO 7:00 PM

Registered participants are invited to browse the posters, network with colleagues, and enjoy light refreshments. Authors of poster papers will be present to answer questions about their work. Please wear your conference badge.

POSTER AUTHORS: Please put up your poster during the morning or afternoon coffee break and plan to stand by your poster during the poster session to interact with attendees. Posters must be removed from the boards following the session. Posters that remain on the boards will be discarded.

Probing pediatric disease with diffuse optical spectroscopies, David R Busch, The Children's Hospital of Philadelphia (USA); Tiffany Ko, Univ. of Pennsylvania (USA); Jennifer M Lynch, Maryam Y. Naim, Daniel J. Licht, The Children's Hospital of Philadelphia (USA) . . . . . [NIH200-28]

Post-operative regional cerebral hemodynamics in neonates with critical congenital heart disease, Tiffany S Ko, Univ. of Pennsylvania (USA) . . . . . [NIH200-29]

High-resolution myocardial imaging using spectral domain optical coherence tomography (SD-OCT) system with low noise supercontinuum light source, Xinwen Yao, Columbia Univ. (USA); Charles C Marboe, Columbia Univ. Medical Center (USA); Christine P Hendon, Columbia Univ. (USA) . . . . . [NIH200-30]

Towards the automatic classification of endomyocardial tissues for intracardiac OCT, Yu Gan, Columbia Univ. (USA); David Tsay, Columbia Univ. Medical Center (USA); Syed B Amir, Columbia Univ. (USA); Charles C Marboe, Columbia Univ. Medical Center (USA); Christine P Hendon, Columbia Univ. (USA) . . . . . [NIH200-31]

Hyperspectral oximetry of an image-derived, 3D-printed vascular network phantom, Pejhman Ghassemi, U.S. Food and Drug Administration (USA); Jianting Wang, US Food and Drug Administration (USA); Anthony Melchiorri, Univ. of Maryland (USA); Jessica Ramella-Roman, Florida International Univ. (USA); Scott Mathews, Catholic Univ. of America (USA); James Coburn, U.S. Food and Drug Administration (USA) and US Food and Drug Administration (USA); Brian Sorg, National Institutes of Health (USA); Yu Chen, Univ. of Maryland (USA); Joshua Pfefer, U.S. Food and Drug Administration (USA). . . . . [NIH200-32]

Sub-diffuse structured light imaging provides wide-field assessment of tissue microstructure biomarkers, Stephen C Kanick, David McClatchy, Brian W Pogue, Thayer School of Engineering at Dartmouth (USA) . . . . . [NIH200-33]

In vivo evaluation of the effect of device/tissue variables in NIRS-based intracranial hematoma detection: Towards standardized cerebral tissue phantoms, Jianting Wang, Stanley Huang, Matthew R Myers, Cristin Welle, Joshua T Pfefer, U.S. Food and Drug Administration (USA) . . . . . [NIH200-34]

Applications of the Foldscope in eyecare, Carl J Bassi, Edward Jarka, Univ. of Missouri-St. Louis (USA); Manu Prakash, Stanford Univ. (USA) . . . . . [NIH200-35]

Safety and efficacy of Regadenoson in myocardial perfusion imaging(MPI) stress tests: a review, Ambereen Ahmed M.D., A&M Assorted Therapy, LLC (USA) . . . . . [NIH200-36]

Pre-treatment protoporphyrin IX concentration in actinic keratosis lesions predicts response to aminolevulinic-acid based photodynamic therapy, Stephen C Kanick, Scott C Davis, Yan Zhao, Thayer School of Engineering at Dartmouth (USA); Tayyaba Hasan, Wellman Ctr. for Photomedicine (USA); Edward V Maytin, Cleveland Clinic (USA); Brian W Pogue, Thayer School of Engineering at Dartmouth (USA); Michael S Chapman, Dartmouth Hitchcock Medical Ctr. (USA) . . . . . [NIH200-37]

Real-time depth control for handheld microsurgery tools based on CP-SSOCT distal sensor, Gyeong Woo Cheon, Yong Huang, Phillip Lee, Johns Hopkins Univ. (USA); Peter L. Gehlbach, Johns Hopkins School of Medicine (USA); Jin U. Kang, Johns Hopkins Univ. (USA) . . . . [NIH200-38]

Core biopsy guidance with encoder-based OCT imaging, Nicusor V Iftimia, Physical Sciences Inc. (USA); Sharjeel Sabir, MD Anderson Cancer Center (USA); Jesung Park, Physical Sciences Inc. (USA) . . . . [NIH200-39]

Non-invasive and minimally invasive strategies for optical detection of cancer and anatomic structures, Patrick J Treado, Shona D Stewart, Heather Kirschner, Aaron Smith, Jeffrey Horn, ChemImage Corp. (USA); Bergein F. Overholt, Gastrointestinal Associates, P.C. (USA); Chris Post, ChemImage Corp. (USA); Jeffrey Cohen, ChemImage Corp (USA) . . . . . [NIH200-40]

Toward clinical endoscopy for upper airway elastography: pressure-dependent porcine trachea deformation via swept-source anatomical OCT, Amy L Oldenburg, Ruofei Bu, Hillel Price, Sorin Mitran, Carlton Zdanski, The Univ. of North Carolina at Chapel Hill (USA) . . . . [NIH200-41]

Measurement of the deep brain hemodynamics in transmittance mode by time-resolved spectroscopy, Hiroaki Suzuki, Etsuko Ohmae, Toshihiko Suzuki, Daisuke Yamashita, Kenji Yoshimoto, Shu Homma, Yukio Ueda, Yutaka Yamashita, Hamamatsu Photonics K.K. (Japan). . . . . [NIH200-42]

Real-time monitoring of airway mucus hydration via diffusion of gold nanorods using polarization-sensitive OCT, Richard L Blackmon, Patrick R Sears, Lawrence E. Ostrowski, David B. Hill, The Univ. of North Carolina at Chapel Hill (USA); Brian S Chapman, Joseph B. Tracy, North Carolina State Univ. (USA); Silvia M. Kreda, Amy L. Oldenburg, The Univ. of North Carolina at Chapel Hill (USA). . . . . [NIH200-43]

Photoacoustic imaging with alexandrite lasers, Marc Klosner, Gary Chan, Chunbai Wu, Donald F. Heller, Light Age, Inc. (USA) . . . . . [NIH200-44]

Brain-computer-interface (BCI) and communication in the completely locked-in state, Ujwal Chaudhary, Bin Xia, Univ. of Tübingen (Germany); Lenardo G Cohen, National Institutes of Health (USA); Niels Birbaumer, Univ. of Tübingen (Germany). . . . . [NIH200-45]

Fiber-optic techniques towards multiregional, functional brain imaging and perturbation in freely moving animals, Jaepyeong Cha, Johns Hopkins Univ. (USA); Yung-Tian A Gau, Johns Hopkins Univ (USA); Gyeong Woo Cheon, Dwight E Bergles, Jin U Kang, Johns Hopkins Univ. (USA) . . . . . [NIH200-46]

Basal cell carcinoma diagnosis and ablation therapy guidance with combined reflectance confocal microscopy/optical coherence tomography imaging, Nicusor V Iftimia, Physical Sciences Inc. (USA); Milind Rajadhyaksha, Memmorial Sloan Kattering Cancer Ctr. (USA) . . . . . [NIH200-47]

Noninvasive diagnosis of middle ear pathologies using phase-sensitive optical coherence tomography, Nicusor V Iftimia, Jesung Park, Physical Sciences Inc. (USA). . . . . [NIH200-48]

Optical diagnosis of acute urinary tract infection: a novel approach, Babak Shadgan M.D., Univ. of British Columbia (Canada). . . . [NIH200-49]

Diffuse optical monitors of the neonatal brain during extra corporeal membrane oxygenation therapy, David R Busch, Ann L McCarthy, Madeline E. Winters, John J. Newland, Jennifer M. Lynch, Genevieve Du Pont-Thibodeau, The Children's Hospital of Philadelphia (USA); Constantine Mavroudis, Hospital of the Univ. of Pennsylvania (USA); Peter J. Schwab, Univ. of Pennsylvania (USA); Erin M Buckley, Georgia Institute of Technology (USA); Arjun G. Yodh, Univ. of Pennsylvania (USA); Maryam Naim, Daniel J. Licht, The Children's Hospital of Philadelphia (USA) . . . . . [NIH200-50]

Imaging brain function in children with autism spectrum disorder with diffuse optical tomography, Adam T Eggebrecht, Bradley L Schlaggar, John N Constantino, Joseph P Culver, Washington Univ. School of Medicine in St Louis (USA) . . . . . [NIH200-51]

Non-invasive functional neuroimaging in the mouse using structured illumination diffuse optical tomography, Matthew D Reisman, Adam Q Bauer, Washington Univ. in St. Louis (USA); Zachary Markow, Grant Baxter, Washington Univ in St Louis (USA); Joseph P Culver, Washington Univ. in St. Louis (USA) . . . . . [NIH200-52]

Mapping large-scale functional connections with ChR2-evoked hemodynamic signals, Adam Q Bauer, Grant Baxter, Andrew Kraft, Michael Bruchas, Jin-Moo Lee, Joseph Culver, Washington Univ. School of Medicine in St Louis (USA) . . . . . [NIH200-53]

Mapping brain function at the bedside during acute stroke recovery using high-density DOT, Karla M Bergonzi, Adam T Eggebrecht, Andrew K Fishell, Jin-Moo Lee, Joseph P Culver, Washington Univ. in St. Louis (USA) . . . . . [NIH200-54]

Towards the prediction of preterm birth using full Mueller matrix imaging of cervical collagen, Susan Stoff, Nola Holness, Jessica C Ramella-Roman, Florida International Univ. (USA) . . . . . [NIH200-56]

Novel calibration-free framework for continuous spectroscopic monitoring of blood analytes: pain-free glucose detection, Nicolas Spegazzini, Jeon Woong Kang, Rishikesh Pandey, Massachusetts Institute of Technology (USA); Ishan Barman, Johns Hopkins Univ. (USA); Ramachandra R Dasari, Peter T C So, Massachusetts Institute of Technology (USA) . . . . . [NIH200-58]

High-resolution retinal imaging: closer to the clinic, Mircea Mujat, Ankit Patel, Nicusor Iftimia, R. Daniel Ferguson, Physical Sciences Inc. (USA) . . . . . [NIH200-59]

Imaging birefringent tissues using polarization-sensitive optical coherence tomography and Stokes imaging polarimeter, Yuqiang Bai, Joseph Chue-Sang, Jessica C. Ramella-Roman, Florida International Univ. (USA) . . . . . [NIH200-61]

Depth discrimination in coherent hemodynamics spectroscopy, Angelo Sassaroli, Jana M Kainerstorfer, Tufts Univ. (USA); Xuan Zang, Tufts Univ (USA); Sergio Fantini, Tufts Univ. (USA) . . . . . [NIH200-62]

Oscillations of oxyhemoglobin and deoxyhemoglobin concentrations feature a different phase relationship in the healthy breast and brain, Kristen Tgavalekos, Jana M Kainerstorfer, Angelo Sassaroli, Sergio Fantini, Tufts Univ. (USA) . . . . . [NIH200-63]

Integrated RFA/OCT catheter for real-time guidance of cardiac radio-frequency ablation therapy, Xiaoyong Fu, Yves Wang, Michael Jenkins, Rakesh Souza, Christopher Snyder, Case Western Reserve Univ. (USA); Mauricio Arruda, Univ. Hospitals Case Medical Center (USA); Andrew Rollins, Case Western Reserve Univ. (USA) . . . . . [NIH200-64]

Development of quantitative biomarkers for wet AMD from OCT imagery, John M Irvine, Steven Duncan, Draper Lab. (USA); David Floyd, Nathan Lowry, David O'Dowd, Draper Lab (USA); Richard J Wood, Draper Lab. (USA) . . . . . [NIH200-65]

Monitoring acute cerebral blood flow dynamics during cardiac arrest and resuscitation with laser speckle imaging, Christian Crouzet, Robert H Wilson, Beckman Laser Institute and Medical Clinic (USA) and University of California, Irvine (USA); Maryam H Farahabadi M.D., Department of Neurology (USA) and School of Medicine (USA) and University of California, Irvine (USA); Afsheen Bazrafkan, Univ. of California, Irvine (USA); Bruce J Tromberg, Beckman Laser Institute and Medical Clinic (USA) and University of California, Irvine (USA); Yama Akbari M.D., Univ. of California, Irvine (USA); Bernard Choi, Beckman Laser Institute and Medical Clinic (USA) and University of California, Irvine (USA) . . . . . [NIH200-66]

A compact instrument for the monitoring of microcirculation, Noah J Kolodziejski, Christopher J Stapels, Radiation Monitoring Devices Inc. (USA); Daniel McAdams, Daniel E Fernandez, Matthew Podolsky, Radiation Monitoring Devices Inc (USA); Dana Farkas, Northeastern Univ. (USA); Purushottam Dokhale, James Christian, Radiation Monitoring Devices Inc. (USA). . . . . [NIH200-67]

Noncontact FLIR measurement of sweatpore reactivity corresponds with PTSD symptoms, Jide Familoni, U.S. Army Night Vision & Electronic Sensors Directorate (USA); Kristin Gregor, VA Boston Healthcare System, National Center for PTSD, Women's Health Sciences Division (USA); Bobby Lowery Jr., EOIR Technologies (USA); Michael Suvak, Suffolk Univ. (USA); Ann Rasmusson, Boston Univ. (USA) . . . . . [NIH200-68]

Can the blood-brain barrier disruption be assessed by monitoring of the indocyanine green washout?, Adam Liebert, Daniel Milej, IBBE PAS (Poland); Wojciech Weigl, Uppsala Univ. Hospital (Sweden); Anna Gerega, Michal Kacprzak, Piotr Sawosz, Beata Toczylowska, Roman Maniewski, IBBE PAS (Poland) . . . . . [NIH200-69]

Imaging and reconstruction of the neonatal nasal cavity with an optical coherence tomography probe, Albert W Aparicio, Beckman Laser Institute and Medical Clinic (USA) and Howard University College of Medicine (USA) and Howard Hughes Medical Institute (USA); Andrew E Heidari, Erica Su, Cyrus T Manuel, Jessica C Chuang, Zhongping Chen, Brian J Wong, Beckman Laser Institute and Medical Clinic (USA) and University of California, Irvine (USA) . . . . . [NIH200-70]

Living cells metabolic imaging in tissue by dynamic full field OCT (D-FFOCT), Claude Boccara, Institut Langevin (France); Clement Apelian, Langevin/LLTECH (France); Fabrice Harms, LLTech SAS (France). . . . . [NIH200-71]

Coherent hemodynamics spectroscopy: a new tool to measure cerebral autoregulation, Jana M Kainerstorfer, Carnegie Mellon Univ. (USA); Angelo Sassaroli, Kristen Tgavalekos, Sergio Fantini, Tufts Univ. (USA) . . . . . [NIH200-72]

Solid hemoglobin-polymer composites: stable, realistic phantoms for spectroscopy and imaging, Hyounguk Jang, Univ. of Maryland, College Park (USA); T. Joshua Pfefer, U.S. Food and Drug Administration (USA); Yu Chen, Univ. of Maryland, College Park (USA) . . . . . [NIH200-119]

In search for biomarkers of brain development in early childhood: pilot study using functional near infrared spectroscopy, Afrouz Azari-Anderson, National Institutes of Health (USA) . . [NIH200-120]

In search of functional biomarkers in human prefrontal cortex for individuals with traumatic brain injury (TBI) using functional near-infrared spectroscopy: a machine learning approach, Nader Shahni Karamzadeh, National Institutes of Health (USA) . . . . . [NIH200-121]

Modulation of low frequency hemodynamic oscillations in the TBI population, Victor Chernomordik, National Institutes of Health (USA) . . . . . [NIH200-123]

CONFERENCE NIH200

FRIDAY 25 SEPTEMBER

SESSION 5
LOCATION: MASUR AUDITORIUM . . . . . FRI 8:00 AM TO 9:20 AM

Cancer: Metabolomics to Genomics

Session Chair: **Brian W. Pogue,**
Thayer School of Engineering at Dartmouth (USA)

8:00 am: **Mitochondrial organization of 3D tissues as a diagnostic cancer biomarker** *(Invited Paper)*, Irene Georgakoudi, Tufts Univ. (USA) . . . . . [NIH200-16]

8:20 am: **Optical imaging of cellular metabolic heterogeneity in cancer** *(Invited Paper)*, Melissa C. Skala, Vanderbilt Univ. (USA) . . . . . [NIH200-17]

8:40 am: **Predicting pre-surgical neoadjuvant chemotherapy response in breast cancer using Diffuse Optical Spectroscopic Imaging (DOSI): results from the ACRIN 6691 study** *(Invited Paper)*, Bruce J. Tromberg, Beckman Laser Institute and Medical Clinic (USA); Zheng Zhang, Brown Univ. (USA) and The ACRIN 6691 Study Group (USA) . . . . . [NIH200-18]

9:00 am: **Breaking tissue depth barriers in cancer photodynamic therapy** *(Invited Paper)*, Samuel Achilefu, Washington Univ. School of Medicine in St. Louis (USA). . . . . [NIH200-19]

Coffee Break . . . . . .Fri 9:20 am to 9:45 am

SESSION 6
LOCATION: MASUR AUDITORIUM . . . . .FRI 9:45 AM TO 11:00 AM

Image Guided Therapy/Surgery

Session Chair: **Jana M. Kainerstorfer,**
Carnegie Mellon Univ. (USA)

9:45 am: **Towards clinical femtosecond laser surgery guided with multiphoton microscopy** *(Invited Paper)*, Adela Ben-Yakar, The Univ. of Texas at Austin (USA) . . . . . [NIH200-20]

10:10 am: **Thermal imaging as a tool for real time feedback for cancer treatment and monitoring** *(Invited Paper)*, Israel Gannot, Johns Hopkins Univ. (USA) and Tel Aviv Univ. (Israel). . . . . [NIH200-21]

10:35 am: **Targeted fluorescent surgical tracers in vivo: Affibody-IRDye development for human neurosurgery** *(Invited Paper)*, Brian W. Pogue, Thayer School of Engineering at Dartmouth (USA). . . . [NIH200-22]

LUNCH BREAK/POSTER SESSION II
LOCATION: MASUR AUDITORIUM . . . . FRI 11:00 AM TO 12:30 PM

Registered participants are invited to browse the posters and network with colleagues during the lunch break. Authors of poster papers will be present to answer questions about their work. Please wear your conference badge.

POSTER AUTHORS: Please put up your poster during the morning coffee break and plan to stand by your poster during the poster session to interact with attendees. Posters must be removed from the boards following the session. Posters that remain on the boards will be discarded.

Differentiating malignant versus benign breast lesions based on static and dynamic optical contrast during breast compression, Bhawana Singh, Massachusetts General Hospital (USA) and Harvard Medical School (USA); Bernhard Zimmerman, Massachusetts General Hospital (USA) and Massachusetts Institute of Technology (USA); Bin Deng, Qianqian Fang, David Boas, Massachusetts General Hospital (USA) and Harvard Medical School (USA); Jayne Cormier, Richard Moore, Daniel Kopans, Mansi Saksena, Massachusetts General Hospital (USA); Stefan Carp, Massachusetts General Hospital (USA) and Harvard Medical School (USA) . . . . . [NIH200-73]

Mimicking H&E stained histology on digitally acquired images via dual modality confocal strip mosaicing microscopy: towards a rapid real time bedside diagnosis of skin tumors, Manu Jain, Sanjee Abeytunge, Gary Peterson, Melissa Murray, Kishwer Nehal, Chin-Shan Jason Chen, Milind Rajadhyaksha, Memorial Sloan-Kettering Cancer Ctr. (USA) . . . . . [NIH200-74]

Pulse thermography for search of breast tissue occlusions, Marija Strojnik, Gonzalo Paez, Ctr. de Investigaciones en Óptica AC (Mexico). . . . . [NIH200-75]

Research of extending whole slide microscopy capability by using a Darkfield Internal Reflection Illumination (DIRI) for brain and microfluidics applications, Yoshihiro Kawano, Olympus Corp. (Japan) and Department of Biomedical Engineering, Graduate School of Biomedical Engineering, Tohoku Univ (Japan); Takuji Ishikawa, Tohoku Univ. (Japan) . . . . . [NIH200-77]

A portable near-infrared spectral tomography system for in vivo monitoring of breast tumor response to neoadjuvant chemotherapy, Yan Zhao, Brian Pogue, Keith paulsen, Shudong Jiang, Thayer School of Engineering at Dartmouth (USA) . . . . . [NIH200-78]

Ongoing clinical experience using quantitative protoporphyrin IX guided intracranial tumor resection, Jonathan D Olson, Stephen C Kanick, Kolbein K Kolste, Jaime J Bravo, Thayer School of Engineering at Dartmouth (USA); David W Roberts, Keith D Paulsen, Dartmouth Hitchcock Medical Center (USA) . . . . . [NIH200-79]

Detection of dermal epidermal junction and its morphology, Kivanc Kose, Memorial Sloan Kettering Cancer Ctr/ (USA); Christi Alessi-Fox, Caliber Imaging & Diagnostics, Inc. (USA); Jennifer G. Dy, Dana H. Brooks, Northeastern Univ. (USA); Milind Rajadhyaksha, Memorial Sloan Kettering Cancer Ctr. (USA) . . . . . [NIH200-80]

Confocal microscopy imaging to guide laser ablation of basal cell carcinomas, Heidy Sierra, Chih-Shan Jason Chen, Memorial Sloan Kettering Cancer Ctr. (USA); Nehal Kishwer, Anthony Rossi, Memorial Sloan-Kettering Cancer Ctr (USA); Milind Rajadhyaksha, Memorial Sloan Kettering Cancer Ctr. (USA) . . . . . [NIH200-81]

Cerenkov radiation dose imaging during human breast and skin radiotherapy, Brian W Pogue, Jacqueline Andreozzi, Rongxiao Zhang, David Gladstone, Thayer School of Engineering at Dartmouth (USA); Lesley A Jarvis, Geisel School of Medicine (USA) . . . . . [NIH200-82]

Bioeffects of low intensity laser light interactions with cells and photodynamic drugs, Darayash B Tata, Moin Hassan, Ilko Ilev, U.S. Food and Drug Administration (USA) . . . . . [NIH200-83]

Development pathway for Affibody-fluorescence guided neurosurgery for EGFR-positive tumors, Brian W Pogue, Keith D Paulsen, Thayer School of Engineering at Dartmouth (USA); Joachim Feldwisch, Affibody AB (Sweden); Dan Draney, LI-COR Biosciences (USA); Theresa Strong, University of Alabama Birmingham (USA) . . . [NIH200-84]

A generalizable videomosaicing method for creating panoramic reflectance confocal microscopy images, Kivanc Kose, Memorial Sloan-Kettering Cancer Ctr. (USA); Mengran Gou, Jennifer G. Dy, Octavia Camps, Dana H. Brooks, Northeastern Univ. (USA); Milind Rajadhyaksha, Memorial Sloan Kettering Cancer Ctr. (USA) . . . . . [NIH200-85]

Mucin 1 antibody-conjugated dye-doped mesoporous silica nanoparticles for breast cancer detection in vivo, Juan Vivero-Escoto, Univ. of North Carolina at Charlotte (USA) and The Center for Biomedical Engineering and Science (USA); Laura Moore Jeffords, Univ of North Carolina at Charlotte (USA); Didier Dreau, Univ. of North Carolina at Charlotte (USA) and The Center for Biomedical Engineering and Science (USA); Merlis Alvarez-Berrios, Univ of North Carolina at Charlotte (USA); Pinku Mukherjee, Univ of North Carolina at Charlotte (USA) and The Center for Biomedical Engineering and Science (USA) . . . . . [NIH200-86]

YC-27 urea compound for detection of prostate cancer using photoacoustic imaging, Bhargava Chinni, Shalini Singh, Kent Nastiuk, Univ. of Rochester (USA); Hans Schmitthenner, Navalgund Rao, Rochester Institute of Technology (USA); John Krolewski, Vikram Dogra, Univ. of Rochester (USA) . . . . . [NIH200-87]

Feasibility of intraoperative imaging with reflectance confocal microscopy to potentially guide Mohs surgery, Eileen S Flores, Miguel Cordova, Kivanc Kose, William Phillips, Anthony Rossi, Kishwer Nehal, Milind Rajadhyaksha, Memorial Sloan-Kettering Cancer Ctr. (USA) . . . . . [NIH200-88]

Two-photon fluorescence lifetime endomicroscopy for metabolic imaging, Wenxuan Liang, Guanghan Meng, Johns Hopkins Univ. (USA); Ming-Jun Li, Corning Incorporated (USA); Xingde Li, Johns Hopkins Univ. (USA) . . . . . [NIH200-89]

Angle-resolved low coherence interferometry for the detection of cervical dysplasia in vivo, Derek Ho, Tyler K Drake, Steven C Gebhart, Duke Univ. (USA); Anna-Barbara Moscicki, Karen K Smith-McCune, Teresa M Darragh, Loris Y Hwang, Univ. of California San Francisco (USA); Adam Wax, Duke Univ. (USA) . . . . . [NIH200-90]

Influence of cell penetrating peptide branching on cellular uptake of quantum dots, Joyce Breger, James Delehanty, Kimihiro Susumu, George Anderson, Eunkeu Oh, U.S. Naval Research Lab. (USA); Markus Muttenhaler, Philip Dawson, The Scripps Research Institute (USA); Igor Medintz, U.S. Naval Research Lab. (USA) . . . . . [NIH200-91]

Dynamic light scattering for detection of alpha crystallin lens protein as a new biomarker for cataract and aging, Manuel B Datiles III, National Institutes of Health (USA); Rafat R Ansari, NASA-Glenn Research Ctr. (USA); Jing Tian, Johns Hopkins Univ. School of Medicine (USA); Frederick L. Ferris III, National Institutes of Health (USA); Walter J. Stark M.D., Johns Hopkins Univ. School of Medicine (USA) . . . . . [NIH200-92]

In vivo mesoscopic voltage-sensitive dye imaging of brain activation, Qinggong Tang, Univ. of Maryland, College Park (USA); Vassiliy Tsytsarev, Univ. of Maryland, School of Medicine (USA); Aaron Frank, Yalun Wu, Chao-wei Chen, Univ. of Maryland, College Park (USA); Reha S Erzurumlu, Univ. of Maryland, School of Medicine (USA); Yu Chen, Univ. of Maryland, College Park (USA) . . . . . [NIH200-93]

Two photon and confocal imaging of postnatal development of the blood-brain barrier in rat motor cortex and auditory brainstem, Lingyan Shi, The City College of New York (USA) and Biomedical Engineering Department in City College of New York (USA); Quetanya Brown, Chang Daphne, Tsui Grace, Bingmei Fu, The City College of New York (USA); Adrian Rodriguez-Contreras, The City College of New York (USA) and The Graduate Center, The City University of New York (USA) . . . . . [NIH200-94]

Mobile-phone based microscopy for imaging and sizing of single DNA molecules, Qingshan Wei, Wei Luo, Univ. of California, Los Angeles (USA); Samuel Chiang, Tara Kappel, Crystal Mejia, Univ. of California Los Angeles (USA); Derek Tseng, Univ. of California, Los Angeles (USA); Raymond Yan Lok Chan, Univ of California Los Angeles (USA); Eddie Yan, Univ. of California, Los Angeles (USA); Hangfei Qi, Univ. of California Los Angeles (USA); Faizan Shabbir, Haydar Ozkan, Steve Feng, Aydogan Ozcan, Univ. of California, Los Angeles (USA) . . . . . [NIH200-95]

Distal scanning diffractive endoscope for ultrahigh-resolution volumetric imaging of internal organs, Jessica Mavadia-Shukla, Wenxuan Liang, Xingde Li, Johns Hopkins Univ. (USA) . . . . . [NIH200-96]

Surgical margin guidance for breast conserving surgery using sub-diffusive structured light imaging with microCT, David M McClatchy III, Stephen C Kanick, Venkataramanan Krishnaswamy, Jonathan T Elliott, Thayer School of Engineering at Dartmouth (USA); Wendy A Wells M.D., Richard J Barth M.D., Dartmouth Hitchcock Medical Ctr. (USA); Keith D Paulsen, Brian W Pogue, Thayer School of Engineering at Dartmouth (USA) . . . . . [NIH200-98]

Therapeutic femtosecond laser stimulated nonlinear optical effects in corneal tissue: evaluation of novel safety concerns, William R Calhoun III, Ilko K Ilev, U.S. Food and Drug Administration (USA) . . . . . [NIH200-99]

Numerical approaches of metallic nanoclusters interacting with green fluorescent proteins in the visible range, Taerin Chung, Tugba Koker, Fabien Pinaud, The Univ. of Southern California (USA) . . . . . [NIH200-100]

Quantitative receptor concentration imaging for tumor margin assessment in head and neck surgical resection, Kimberley S Samkoe, Geisel School of Medicine at Dartmouth College (USA); Kenneth Tichauer, Illinois Institute of Technology (USA); Jason Gunn, Thayer School of Engineering at Dartmouth College (USA); Eunice Chen, Wendy Wells, Dartmouth Hitchcock Medical Ctr. (USA); P. Jack Hoopes, Geisel School of Medicine (USA); Tayyaba Hasan, Wellman Center for Photomedicine (USA); Brian Pogue, Thayer School of Engineering at Dartmouth College (USA) . . . . . [NIH200-101]

Quantitative imaging of cell signaling for personalized pancreatic cancer therapy, Kimberley S Samkoe, Dartmouth Hitchcock Medical Ctr. (USA); Dianmu Zhang, Oregon Health and Sciences Univ. (USA); Dawn Fischer, Dartmouth Hitchcock Medical Ctr. (USA); Cynthia Yang, Illinois Institute of Technololgy (USA); Kerrington Smith, Dartmouth Hitchcock Medical Ctr. (USA); Kenneth Tichauer, Illinois Institute of Technololgy (USA); Summer Gibbs, Oregon Health and Sciences Univ. (USA) . . . . . [NIH200-102]

Catheter-based optical determination of met-myoglobin content for estimating radiofrequency ablated, chronic lesion formation in atrial tissue, Rajinder P Singh-Moon, Christine P Hendon, Columbia Univ. (USA) . . . . . [NIH200-103]

High spatial frequency modulated imaging for tissue histological evaluations, Zili Cao, Wenzhou Medical Univ. (China); Min Xu, Fairfield Univ. (USA); Weihao Lin, Bixin Zeng, Wenzhou Medical Univ. (China) . . . . . [NIH200-104]

Capitalizing on quantum-confined Stark effect in quantum dots for imaging action potentials, Clare Rowland, Kimihiro Susumu, Michael H Stewart, Eunkeu Oh, Antti Makinen, Thomas O'Shaughnessy, Gary Kushto, Mason Wolak, Jeffrey Erickson, Alexander Efros, Alan Huston, James B. Delehanty, U.S. Naval Research Lab. (USA) . . . . . [NIH200-105]

Flow analyses of microcirculation from sidestream dark-field images, Hideaki Haneishi, Minori Takahashi, Takashi Ohnishi, Chiba Univ. (Japan) . . . . . [NIH200-106]

Miniature line-scanned dual-axis confocal (LS-DAC) microscope for point-of-care pathology, Chengbo Yin, Adam K Glaser, Steven Y. Leigh, Univ. of Washington (USA); Gary Peterson, Sanjeewa Abeytunge, Memorial Sloan-Kettering Cancer Ctr. (USA); Michael J Mandella, Stanford Univ. (USA); Milind Rajadhyaksha, Memorial Sloan-Kettering Cancer Ctr. (USA); Jonathan T Liu, Univ. of Washington (USA) . . . . . [NIH200-107]

Feasibility of evaluation of breast tissue using confocal microscopy strip mosaicing, Sanjeewa Abeytunge, Gary Peterson, Melissa Murray, Milind Rajadhyaksha, Memorial Sloan-Kettering Cancer Ctr. (USA) . . . . . [NIH200-108]

On-chip imaging using synthetic aperture, Wei Luo, Alon Greenbaum, Univ. of California, Los Angeles (USA); Yibo Zhang, Univ of California Los Angeles (USA); Aydogan Ozcan, Univ. of California, Los Angeles (USA) . . . . . [NIH200-109]

Rapid and sensitive detection of waterborne pathogens using machine learning on a smartphone based fluorescence microscope, Hatice Ceylan Koydemir, Zoltan Gorocs, Derek Tseng, Bingen Cortazar, Steve Feng, Raymond Yan Lok Chan, Jordi Burbano, Aydogan Ozcan, Univ. of California, Los Angeles (USA) . . . . . [NIH200-110]

Label-free, non-invasive, ballistic imaging using light from a supercontinuum laser in new NIR windows, Laura A Sordillo, peter p sordillo M.D., Lingyan Shi, Yury Budansky, Robert R. Alfano, The City College of New York (USA) . . . . . [NIH200-111]

Plasmonic nanoparticle assisted on-chip imaging cytometry using optical diffraction, Qingshan Wei, Euan McLeod, Univ. of California, Los Angeles (USA); Hangfei Qi, Univ of California Los Angeles (USA); Zhe Wan, Ren Sun, Aydogan Ozcan, Univ. of California, Los Angeles (USA) . . . . . [NIH200-112]

In-vivo monitoring of mitochondrial dynamics using solely endogenous contrast, Dimitra Pouli, Tufts Univ. (USA); Mihaela Balu, Bruce J Tromberg, Beckman Laser Institute and Medical Clinic (USA); Irene Georgakoudi, Tufts Univ. (USA) . . . . . [NIH200-113]

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Intra-operative dual channel blue/red excitation imaging of protoporphyrin IX during neurosurgical resection of brain tumors provides topographic sensitivity to subsurface malignancy, Stephen C Kanick, Kolbein K Kolste, Jonathan D Olson, Keith D Paulsen, Thayer School of Engineering at Dartmouth (USA); David W Roberts M.D., Dartmouth Hitchcock Medical Ctr. (USA) . . . . . [NIH200-114]

Broadband optical mammography: optical contrast of human breast cancer, Pamela G Anderson, Tufts. Univ. (USA); Jana M Kainerstorfer, Angelo Sassaroli, Nishanth Krishnamurthy, Tufts Univ. (USA); Sirishma Kalli, Shital S Makim, Marc J Homer, Roger A Graham, Tufts Medical Ctr. (USA); Sergio Fantini, Tufts Univ. (USA) . . . . . [NIH200-115]

High-throughput imaging of pathology slides using on-chip microscopy, Yibo Zhang, Univ. of California, Los Angeles (USA); Alon Greenbaum, California Institute of Technology (USA); Alborz Feizi, Ping-Luen Chung, Wei Luo, Shivani R Kandukuri, Aydogan Ozcan, Univ. of California, Los Angeles (USA) . . . . . [NIH200-116]

Needle tip tissue identification by Raman spectroscopy, Jeon Woong Kang, Massachusetts Institute of Technology (USA); T. Anthony Anderson, Massachusetts General Hospital (USA); Ramachandra R. Dasari, Peter T.C. So, Massachusetts Institute of Technology (USA) . . . . . [NIH200-117]

Tunable breast-simulating phantoms for photoacoustic tomography image quality assessment, William C Vogt, Congxian Jia, Keith A Wear, Brian S Garra, Joshua Pfefer, U.S. Food and Drug Administration (USA) . . . . . [NIH200-118]

Facial plethora: modern technology for quantifying an ancient clinical sign and its use in Cushing syndrome, Ali Afshari, National Institutes of Health (USA) . . . . . [NIH200-122]

Diffuse Optical Spectroscopic Imaging (DOSI) of breast density and composition during Tamoxifen treatment, Thomas D. O'Sullivan, Anais Leproux, George P. Philipopoulos, Alice M. Police, Freddie Combs, Min-Ying Su, Bruce J. Tromberg, Univ. of California, Irvine (USA) . . . . . [NIH200-124]

SESSION 7
LOCATION: MASUR AUDITORIUM . . . . . FRI 1:00 PM TO 2:00 PM

Advanced Optical Microscopy

Session Chair: **Jessica C. Ramella-Roman,**
Florida International Univ. (USA)

1:00 pm: **Understanding biomechanics of sickle cell disease at individual cell level** *(Invited Paper)*, Poorya Hosseini, Sabia Abidi, Sarah Du, Ming Dao, Massachusetts Institute of Technology (USA); Geregory Kato, Univ. of Pittsburgh (USA); John M. Higgins, Harvard Medical School (USA); Zahid Yaqoob, Peter T. C. So, Massachusetts Institute of Technology (USA) . . . . . [NIH200-23]

1:20 pm: **Super-resolution imaging using multi-photon and multi-photon-like fluorescence microscopy techniques** *(Invited Paper)*, George H. Patterson, National Institute of Child Health and Human Development (USA) . . . . . [NIH200-24]

1:40 pm: **Multiphoton imaging for clinical endoscopy** *(Invited Paper)*, Chris Xu, Cornell Univ. (USA) . . . . . [NIH200-25]

Coffee Break . . . . . .Fri 2:15 pm to 2:45 pm

SESSION 8
LOCATION: MASUR AUDITORIUM . . .FRI 2:45 PM TO 4:00 PM

Keynotes by SPIE Britton Chance Biomedical Optics Award Recipients

Session Chair: **Fatima A. Chowdhry,**
National Institutes of Health (USA)

2:45 pm: **Redefining the spatiotemporal limits of optical imaging: photoacoustic tomography, wavefront engineering, and compressed ultrafast photography** *(Keynote Presentation)*, Lihong V. Wang, Washington Univ. in St. Louis (USA). . . . . [NIH200-26]

3:20 pm: **Light advances in biomedicine** *(Keynote Presentation)*, Robert Alfano, The City College of New York (USA) . . . . . [NIH200-27]

PANEL DISCUSSION
LOCATION: MASUR AUDITORIUM . . FRI 4:00 PM TO 5:00 PM

Funding and the Future

PANELISTS:

Houston Baker, NCI, National Institutes of Health

Richard Conroy, NIBIB, National Institutes of Health

Behrouz Shabestari, NIBIB, National Institutes of Health

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Journal of Biomedical Optics

Published by SPIE

Lihong V. Wang, Ph.D.
Washington University in St. Louis, USA
Editor-in-Chief

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Recent growth in the use of optics technology for biomedical research and health care has been explosive. New applications are made possible by emerging technologies in lasers, optoelectronic devices, fiber optics, physical and chemical sensors, and imaging, all of which are being applied to medical research, diagnostics, and therapy. The *Journal of Biomedical Optics* publishes peer-reviewed papers that utilize modern optical technology for improved health care and biomedical research.

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TECHNICAL SUMMARIES

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SPIE/NIH Biophotonics from Bench to Bedside

CONTENTS

NIH200-6, SESSION 2

Functional Near Infrared Spectroscopy – History, Advances, Applications *(Keynote Presentation)*

David A. Boas, Athinoula A. Martinos Ctr. for Biomedical Imaging (United States)

The adoption of functional Near Infrared Spectroscopy (fNIRS) continues to grow with the number of publications per year doubling every 4 years. During my talk I will first review some history of fNIRS, focusing on our cross-validation with fMRI. I will then discuss recent advances that are improving the translation and usability of the technology, particularly related to reducing motion artifacts and the confounding influences of the scalp. I will also present examples of potential clinical impact we are exploring at Massachusetts General Hospital, particularly the ability to assess pain in the operating room.

BIOGRAPHY: David Boas is the director of the Martinos Optics Division in the Department of Radiology at Massachusetts General Hospital, and is a full professor of Radiology at Harvard Medical School. He received his BS on Physics at Rensselear Polytechnic Institute and PhD in Physics at the University of Pennsylvania.

NIH200-7, SESSION 2

Quantitative analysis of cerebral hemodynamic oscillations for the study and assessment of the cerebral microcirculation *(Invited Paper)*

Sergio Fantini, Tufts Univ. (United States)

Cerebral hemodynamic oscillations at a given frequency may be described by a set of phasors that represent oscillatory blood flow, blood volume, metabolic rate of oxygen, and cerebral concentrations of oxy-hemoglobin, [HbO], and deoxy-hemoglobin, [Hb]. Quantitative relationships among these phasors are obtained by modeling cerebral autoregulation and the effects of dynamic changes in blood flow and blood volume on [HbO] and [Hb], which are measured non-invasively with near-infrared spectroscopy. Such quantitative analysis led to the new technique of coherent hemodynamics spectroscopy (CHS), which we used to measure the capillary transit time and dynamic cerebral autoregulation in healthy subjects and hemodialysis patients.

BIOGRAPHY: Sergio Fantini is professor of Biomedical Engineering at Tufts University. His research interests are in diffuse optical spectroscopy and imaging of biological tissues, with applications to non-invasive functional imaging and hemodynamic assessment of the brain, quantitative tissue oximetry in vivo, and the development of novel instrumentation for optical mammography.

NIH200-9, SESSION 3

Photodynamic Therapy: does it have a role in Low to Middle Income Countries? *(Invited Paper)*

Tayyaba Hasan, Wellman Ctr. for Photomedicine (United States)

Photodynamic activation (PDA) has the potential of providing a theranostic modality for diagnostics, treatment and therapy. However, the major source of illumination has been lasers which in the early years were expensive making PDA, out of reach for Low to Middle Income Countries (LMICs). With the advent of diode lasers and Light emitting diodes and daylight PDT, the light source issue is likely to be ameliorated. The popularity of smart phones in LMICs provides another avenue for the adoption of PDA-based medical applications. The promise and pitfalls of applying PDA/PDT in LMICs will be discussed in this presentation.

BIOGRAPHY: Tayyaba Hasan, PhD, is a Professor of Dermatology at Harvard Medical School (HMS) and a Professor of Health Sciences and Technology (Harvard-MIT). The focus of her research is in photochemistry and photodynamic therapy of cancer. She is an inventor of the FDA approved photodynamic treatment of Age-Related Macular Degeneration. She directs a NCI funded multicenter P01 grant and a consortium on developing low cost technologies for oral cancer.

NIH200-11, SESSION 3

A see and treat paradigm for cervical cancer *(Invited Paper)*

Nirmala Ramanujam, Duke Univ. (United States)

Cervical cancer is disproportionately prevalent in low resource communities. Women who are most vulnerable to this disease are sex workers who are susceptible to both HIV and HPV infection. However, these women generally lack access to early cervical cancer screening services, and are prematurely diagnosed with advanced lesions as a consequence of this health service gap. Cryotherapy is the most commonly available therapy in these settings and is only effective for low-grade lesions. Cryotherapy of high-grade lesions can actually increase invasive cancer risk. Thus, our efforts focus on developing strategies to enable low cost see and treat paradigms for cervical pre-cancer and cancer for vulnerable populations in low resource settings.

BIOGRAPHY: Dr. Nimmi Ramanujam is professor of Biomedical Engineering, Global Health and Pharmacology at Duke University. She founded the Global Women's Health Technologies Center in 2013. The Global Women's Health Technologies Center reflects a partnership between the Pratt School of Engineering and the Duke Global Health Institute . The center's mission is to increase research, training and education in women's diseases, with a focus on breast cancer, cervical cancer, and maternal-fetal health; and to increase retention of women and underrepresented minorities in Science, Technology, Engineering, and Mathematics (STEM) educational disciplines locally and globally.

NIH200-12, SESSION 4

Optical coherence tomography: development and applications
(Keynote Presentation)

James G. Fujimoto, Massachusetts Institute of Technology (United States)

Optical coherence tomography (OCT) is an example of a medical imaging technology that has been translated from bench to bedside. OCT is now a standard modality in ophthalmology, where it has improved diagnosis and treatment monitoring, with 20-30 million procedures performed worldwide every year. It is also an emerging technology in specialties ranging from cardiology to endoscopy and has had a powerful impact on fundamental biomedical research. The translation of OCT required a complex "ecosystem" of engineering, government support, clinical investigation, VC funding and corporate development. This talk reviews the development of OCT and its translation into clinical medicine.

BIOGRAPHY: James Fujimoto is Elihu Thomson Professor of EECS at MIT. His group and collaborators were responsible for the invention and development of OCT. Dr. Fujimoto's group performs research in OCT technology and applications to ophthalmology, endoscopy and oncology. He is a member of the National Academy of Science and National Academy of Engineering.

NIH200-13, SESSION 4

In vivo vascular biology studies using intravascular OCT: the Massachusetts General Hospital OCT Registry *(Invited Paper)*

Ik-Kyung Jang, Massachusetts General Hospital (United States)

In June 2010, an international collaboration was organized to launch the Massachusetts General Hospital (MGH) OCT Registry. As of August 2015 more than 2700 patients have been enrolled from 21 sites across 6 countries (US, China, Korea, Japan, Singapore, and Australia).

Recent findings from the MGH OCT Registry include: (1) plaque erosion is responsible for 30-40% of patients with acute coronary syndromes (ACS), (2) demonstration of pan-vascular plaque vulnerability in patients with ACS, (3) characterization of the plaque phenotype responsible for ACS, and (4) identification of predictors for adverse outcome after coronary stenting.

BIOGRAPHY: Dr. Jang is a professor of medicine at Harvard Medical School and an interventional cardiologist at Massachusetts General Hospital. For the last 17 years he has pioneered the application of intravascular OCT in patients to study in vivo vascular biology. In 2010 Dr. Jang established an International OCT Registry, which include 21 sites across 6 countries. The registry now has over 2700 patients.

NIH200-28, SESSION PS1

Probing pediatric disease with diffuse optical spectroscopies

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The neonatal brain undergoes substantial development during childhood, generating considerable metabolic demand. For example, in infants with compromised vasculature, the oxygen supply to the brain may be insufficient to meet these demands, leading to irreversible brain damage. Currently, clinicians lack tools to directly monitor cerebral oxygen metabolism and therefore rely on systemic parameters to monitor brain health. Unfortunately, these tools have are not organ specific (e.g., oxygen delivery measured by lactate concentration), require significant extrapolation (e.g., cerebral blood flow measured by blood pressure), or are otherwise inadequate. As children have many decades of expected life ahead of them, repeated use of ionizing radiation is of special concern. Moreover these systemic parameters often change quite slowly, preventing clinicians from dynamically following the efficacy of interventions.

Diffuse optical and correlation spectroscopy provide continuous measurement of cerebral blood oxygenation, volume, and flow without ionizing radiation at a patient's bedside utilizing a diffusion approximation to the radiation transport equation. In this contribution, we review work at the June and Steve Wolfson Laboratory for Clinical and Biomedical Optics at the Children's Hospital of Philadelphia designing, developing, and translating diffuse optical tools into clinical use in the context of the vulnerable pediatric brain. Unlike commercially available cerebral oximeters, we quantify these hemodynamic parameters continuously throughout routine care and interventions. This quantification permits calculation of oxygen metabolism at ~0.1-1Hz.

We have applied these tools to children with severe congenital heart disease, on extra-corporeal membrane oxygenation therapy (ECMO), extremely premature infants, pediatric stroke, and sleep apnea. The unique insights provided by diffuse optical tools have the potential to significantly impact pediatric care.

NIH200-29, SESSION PS1

Post-operative regional cerebral hemodynamics in neonates with critical congenital heart disease

Tiffany S. Ko, Univ. of Pennsylvania (United States)

Non-invasive, functional neuroimaging of the primary motor cortex (M1) is needed to assess psychomotor delays in neonates at high risk for neurologic hypoxic-ischemic injury1,2. Bedside near-infrared diffuse optical techniques provide real-time sensitivity to cerebral tissue oxygen saturation (ScO2), total hemoglobin concentration (THC) and cerebral blood flow index (BFI) 3. This investigation aims to provide regional baseline quantification of cerebral hemodynamics during post-operative recovery and identify the differential impact of cardiac physiology in neonates with critical congenital heart disease (CHD).

Hybrid instrumentation, combining diffuse optical spectroscopy (DOS) and diffuse correlation spectroscopy (DCS), were used to quantify right and left, prefrontal and parietal ScO2, THC and BFI in term CHD neonates (40 ± 4 weeks gestation). Measurements were performed daily from pre-operative recruitment through post-operative MRI. Relative cerebral blood flow (rCBF) was calculated from BFI with respect to first post-operative measurement.

Clinically significant regional differences were not observed (n=14). Dichotomizing by arch integrity (Normal Arch, n=7 vs. Obstructed Arch, n=7), linear mixed-effects models including subject-specific random effects were used to predict mean cerebral hemodynamics as a function of post-operative time. The intercept of ScO2 (48.8±2.3%, $p<0.001$) and THC (41.1±2.5 ?mol/L, $p<0.001$), and log-transformed rCBF slope in both groups (Normal Arch: +11.2 ± 1.96% /day, $p<0.001$, Obstructed Arch: 7.21 ±1.45% /day, $p<0.001$) were highly significant.

Feasibility of regional cerebral hemodynamic measurements were demonstrated in CHD neonates. In the first post-operative week, ScO2 and THC remained constant while significant increases in rCBF were observed; normal arch physiologies exhibited greater increase.

NIH200-30, SESSION PS1

High-resolution myocardial imaging using spectral domain optical coherence tomography (SD-OCT) system with low noise supercontinuum light source

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Heterogeneity in myocardial tissue microstructures may contribute to increased risk of life-threatening cardiac diseases such as arrhythmia and heart failure. Most commercial real-time medical imaging modalities do not have sufficient resolution to visualize cellular level remodeling that occurs during cardiac diseases. We present a high-resolution SD-OCT system at 800nm that has an axial resolution of 2.45μm optimized for myocardial imaging.

We designed a custom spectrometer to accommodate a light spectrum from a low-noise supercontinuum source (NKT) that has 3-dB bandwidth of 160nm centered at 840nm. The system has a measured axial resolution of 2.45?m in air, a lateral resolution of 4.2μm, and an imaging range of 1.5 mm.

Cross-sectional images and 3D volumes were acquired ex vivo on tissue specimens from the right ventricle septum of the human and swine hearts obtained from the National Disease Research Interchange (NDRI) Tissue Bank and Columbia University's tissue sharing program respectively. The penetration depth was measured to be 0.34±0.16mm from 10 right ventricular septum specimens from swine hearts. Analysis of H&E slides showed that with the increased resolution and contrast from the high-resolution system, features such as elastic fibers, fibrosis, Purkinje fibers, and collagen were observed, which were otherwise not shown in our previous work using Thorlabs Telesto system. This shows the promise of high-resolution OCT imaging for applications in assessing ventricular remodeling associated with cardiac arrhythmias and heart failure. We also observed dependence of scanning orientation with respect to the fiber orientation, which may help to differentiate the difference in fiber sheets.

NIH200-31, SESSION PS1

Towards the automatic classification of endomyocardial tissues for intracardiac OCT

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Combining the techniques of computer vision and of machine learning, we present an automated algorithm to classify tissue types from intracardiac optical coherence tomography (OCT) images. Our objective is to automatically identify regions of fibrosis, collagen, scar, and adipose tissue, to assess ventricular remodeling, which can increase the likelihood of arrhythmia.

OCT image volumes were obtained from human heart (n = 15) ex vivo within 48 hours of death (source, NDRI) and were segmented using a graph searching method. The boundary was searched among voxels by minimizing a cost function, which consisted of intensity, gradient, and contour smoothness. In each segmented region, features, including texture analysis, optical properties, and statistical were extracted. Through matching our OCT volumes with Trichrome pathology, we analyzed the optical signatures for all tissue types. A statistical model using relevance vector machine was developed to classify the above tissue types. To validate our method, we applied our algorithm to 144 regions from 77 OCT volumes. The datasets used for validation were manually segmented and classified by investigators who were blind to the automated results based on trichrome guidance for comparison.

The difference between automated segmentation and manual segmentation is 51.78±50.96 μm. Experiments show that optical properties features are significantly different among most of tissue types ($P<0.05$, ANOVA). Importantly, fibrotic tissue shows differences when comparing with normal myocardium in homogeneity and skewness. The tissue types are classified with an accuracy over 80% and are visualized in three dimensions. Our method can potentially aid treatment of atrial fibrillation.

NIH200-32, SESSION PS1

Hyperspectral oximetry of an image-derived, 3D-printed vascular network phantom

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Biomimetic tissue phantoms have the potential to provide novel insights into clinical biophotonic device working mechanisms and bridge the gap between idealized phantoms and in vivo testing. The emerging technique of 3D printing provides a revolutionary way to fabricate objects with arbitrary morphology, including image-defined tissue geometries. 3D-printed phantoms may be used to elucidate factors that influence performance, particularly for techniques such as Hyperspectral Reflectance Imaging (HRI) for oximetry imaging in which signal contrast originates in irregular vascular structures. In this study, we modified a segmented 2D fundus image of the human retina into a vascular network with circular cross sections. The optical properties and morphology of the resulting phantom were characterized with spectrophotometry and micro-CT imaging, respectively. Phantom channels were filled with hemoglobin solutions containing yeast, and imaged with a near-infrared HRI system as the solution exhibited desaturation over a two hour period. Relative concentrations of chromophores including oxy- and deoxy-hemoglobin, water and matrix material were determined using a non-linear least squares approach. Results were analyzed in terms of hemoglobin saturation measurement accuracy, penetration depth and the effect of vessel density on measured parameters. Overall, our results indicated that 3D-printed phantoms may be useful for studying biophotonic system performance and light-tissue interactions, although improvements in printing quality and biological relevance of optical properties would improve the utility of this technique.

NIH200-33, SESSION PS1

Sub-diffuse structured light imaging provides wide-field assessment of tissue microstructure biomarkers

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The onset and progression of cancer introduces changes to the intra-cellular ultrastructural components and to the morphology of the extracellular matrix. Previous work has shown that localized scatter imaging is sensitive to pathology-induced differences in these aspects of tissue microstructure; however, these studies tend to be limited by two factors. First, the time required to image with confocal-level localization of the remission signal can be substantial. Second, localized (i.e. sub-diffuse) scatter remission intensity is influenced interchangeably by parameters that define scattering frequency and anisotropy. This similarity relationship must be broken in order to obtain unique estimates of biomarkers that define either the scatter density or features that describe the distribution (e.g. shape, size, and orientation). This study develops a structured light imaging approach that addresses both of these limitations.

Monte Carlo data were used to model the reflectance intensity over a wide range of spatial frequencies (0-1 [mm^{-1}]), reduced scattering coefficients (0.5-2 [mm^{-1}]), absorption coefficients (0-0.3 [mm^{-1}]), and a metric of the scattering phase function that directly maps to the fractal dimension of scatter sizes (3.6-4.6 [-]). The approach is validated in tissue-simulating phantoms with estimated scattering parameters independent of background absorption. Preliminary data from clinical tissue specimens show quantitative images of both the scatter density and fractal dimension of various tissue types and pathologies. These data represent the first wide-field quantitative maps of microscopic structural biomarkers that cannot be obtained with standard diffuse imaging. Implications for the use of this approach to assess surgical margins will be discussed.

NIH200-34, SESSION PS1

In vivo evaluation of the effect of device/tissue variables in NIRS-based intracranial hematoma detection: Towards standardized cerebral tissue phantoms

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This study is to develop a well-validated phantom-based method to evaluate emerging NIRS devices for intracranial hematomas detection. It includes developing an NIRS system and an in vivo murine model of hematoma to validate the phantom method. The developed polymer phantom can be used to elucidate the effect of NIRS design parameters such as source-detector separation distance, wavelength, tissue morphology/inhomogeneity and lesion size and depth on hematoma detectability. The validated test methods will benefit regulatory review, research, development, and bedside validation of NIRS devices for hematoma detection.

NIH200-35, SESSION PS1

Applications of the Foldscope in eyecare

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Recent work from the PrakashLab1 describes a simple, low cost microscope using folded paper with glass lenses to attain high quality microscopy images. The availability of such a microscope that can work in extreme field conditions opens up many possible applications for clinic care in remote regions.

Two eyecare applications are described here: impression cytology and identification of Demodex mites. Impression cytology is the application of a filter paper to the ocular surface in order to remove the superficial layers of the epithelium. These cells can then be subjected to histological or immunohistological assessment. Applications for impression cytology include diagnosing a wide range of ocular surface disorders ranging from dry eye to staging conjunctival squamous metaplasia. Demodex are ubiquitous and while normally considered commensals, with infestation they are associated with dry eye, blepharitis, and rosacea.

The purpose of this study was to compare standard light microscopy to the Foldscope using impression cytology or eyelash Demodex using standard clinical protocols. We found that the Foldscope can be used as an alternative to standard microscopy both qualitatively (quality of the still and video images) and quantitatively (comparable cell counts).

The Foldscope can be used in eye clinics without access to standard microscopy. In addition, it opens up the possibility of screening for preclinical Vitamin A deficiency using impression cytology2 in remote regions.

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NIH200-36, SESSION PS1

Safety and efficacy of Regadenoson in myocardial perfusion imaging(MPI) stress tests: a review

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Myocardial perfusion imaging (MPI) tests are often used to help diagnose coronary heart disease (CAD). The tests often involve applying stress, such as hard physical exercise together with administration of vasodilators, to the patients. To date, many of these tests use non-selective A2A adenosine receptor agonists which, however, can be associated with highly undesirable and life-threatening side effects such as chest pain, dyspenea, severe bronchocontriction and atrioventricular conduction abnormalities. Regadenoson is a relatively new, highly selective A2A adenosine receptor agonist, suitable for use in MPI tests which exhibits far fewer adverse side effects and, unlike others testing agents, can be used without the necessity of excessive concomitant exercise. In addition, the dose of Regadenoson required is not dependent upon patient weight or renal impairment and it can be rapidly administered by i.v. injection. Regadenoson use in MPI testing thus has the potential as a simplified, relatively safe, time-saving and cost-effective method for helping diagnose CAD. The present study was designed to review several articles on the safety, efficacy and suitability of Regadenoson in MPI testing for CAD. Overall, the combined studies demonstrate that use of Regadenoson together with low level exercise in MPI is a highly effective and relatively safe test for CAD, especially for more severe health-compromised patients.

NIH200-37, SESSION PS1

Pre-treatment protoporphyrin IX concentration in actinic keratosis lesions predicts response to aminolevulinic-acid based photodynamic therapy

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Photodynamic therapy (PDT) using aminolevulinic acid (ALA) as a precursor for protoporphyrin IX (PpIX) is an effective FDA-approved treatment for precancerous skin lesions known as actinic keratosis, but a substantial number of patients do not respond (up to 25%). This study incorporates optical measurements into a pilot clinical study of patients undergoing ALA-PpIX PDT treatments to quantitate PpIX fluorescence. Patients were treated with topical administration of 20% ALA with a 1 hour incubation and a treatment illumination with blue therapeutic laser (BLU-U). Patients (n=70) reported pain on the visual analog scale (VAS) during treatment, and a subpopulation (n=13) assessed pain and erythema 2-3 days after treatment. High inter-patient variability in PpIX concentration was observed, with many patients presenting extremely low values, with 45% of lesions in the bottom 5% of the sampled range [0-1.5] ?M. PpIX concentration was significantly higher in lesions of patients reporting high levels of pain (VAS score ≥ 5) immediately after therapy compared with patients reporting low pain ($p<0.022$), although pain was not an exclusive indicator of PpIX concentration as many patients with low PpIX concentration reported high pain. The follow-up data show that PpIX measured on the day of treatment was strongly correlated with erythema evaluated days after treatment ($r=0.58$, $p < 0.039$). This study discusses the potential causes of variations in PpIX production between different patients, and suggests that quantitative fluorescence measurements of PpIX may be a reliable and objective method to identify non-responding patients at the time of treatment.

NIH200-38, SESSION PS1

Real-time depth control for handheld microsurgery tools based on CP-SSOCT distal sensor

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Precise tool-tip manipulation is critical for successful microsurgery. Here we present a novel intuitive targeting and tracking scheme that utilizes a common-path swept source optical coherence tomography (CP-SSOCT) distal sensor integrated handheld microsurgical tool. A reliable and robust OCT distal sensing method is necessary to achieve micron-order precision control. At the same time, a prediction algorithm is adopted to compensate for the system delay due to the computational, mechanical and electronic latencies. A shifted cross-correlation method is applied for surface detection to improve robustness and accuracy in distal sensing. A predictor based on Kalman filter was implemented to compensate for system delay. The implemented system was evaluated using a dry phantom consisting of stacked cellophane tape and an ex-vivo bovine retina to assess system accuracy and precision. The results demonstrate highly accurate depth targeting with less than 5 ?m RMSE depth locking.

NIH200-39, SESSION PS1

Core biopsy guidance with encoder-based OCT imaging

Nicusor V. Iftimia, Physical Sciences Inc. (United States); **Sharjeel Sabir,** MD Anderson Cancer Center (United States); **Jesung Park,** Physical Sciences Inc. (United States)

We present a novel method, based on encoder feedback OCT imaging, for real-time guidance of core biopsy procedures. This method provides real-time feedback to the interventional radiologist, such that he/she can reorient the needle during the biopsy and sample the most representative area of the suspicious mass that is being investigated. This aspect is very important for tailoring therapy to the specific cancer based on biomarker analysis, which will become one of the next big advances in our search for the optimal cancer therapy. To enable individualized treatment, the genetic constitution and the DNA repair status in the affected areas is needed for each patient. Thus, representative sampling of the tumor is needed for analyzing various biomarkers, which are used as a tool to personalize cancer therapy. The encoder-based OCT enables samping of large size masses and provides full control on the imaging probe, which is passed through the bore of the biopsy guidance needle. The OCT image is built gradually, for every few microns incremental movement of the needle and is independent of the needle speed while advancing through the tissue. The OCT frame is analyzed in real-time and tissue cellularity is reported in a very simple manner (pie chart). Our preliminary study on a rabbit model of cancer has demonstrated the capability of this technology for accurately differentiating between viable cancer and heterogeneous or necrotic tissue.

NIH200-40, SESSION PS1

Non-invasive and minimally invasive strategies for optical detection of cancer and anatomic structures

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ChemImage Corporation, in collaboration with clinicians, has been developing non-invasive and minimally invasive methods based on molecular chemical imaging for the detection of a variety of disease states. For detection of colorectal cancer and pre-malignant colorectal neoplasia in blood serum, we are developing an in vitro diagnostic, the Raman Assay for Colorectal Cancer (RACC), which exploits the high specificity of Raman molecular imaging to distinguish diseased from normal dried blood serum droplets. Pilot Study results from testing of more than 250 biobank patient samples have demonstrated that RACC can detect colorectal cancer (CRC) with sensitivity and specificity approaching 90%. Preliminary test results from an ongoing Clinical Trial that will collect and analyze results from up to 1500 patients will be presented. For anatomic structure imaging and tumor margin detection, ChemImage has been developing and testing visible-near infrared diffuse reflectance molecular chemical imaging technology for use as an intraoperative surgical tool set. In surgical oncology, local recurrence of disease is a critical problem which can often result from incomplete tumor excision during surgery. Currently, tumor margins are identified post-surgery through histological evaluation of the tissue biopsy, and one in four patients who undergo tumor resection surgery will require re-operation in order to fully excise the malignant tissue. We are developing an intraoperative device for detecting tumor margins in real-time which exploits conformal imaging liquid crystal tunable filter technology, a type of compressive sensing. Conformal imaging combines digital imaging with molecular spectroscopy to provide information-rich multivariate hyperspectral images of tissue margins and anatomic structures without the use of reagents in real-time. Test results from ex vivo Human kidney cancer studies will be presented, as well as preliminary results from in vivo animal testing.

NIH200-41, SESSION PS1

Toward clinical endoscopy for upper airway elastography: pressure-dependent porcine trachea deformation via swept-source anatomical OCT

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Children and adults suffering from airway obstruction due to structural or functional abnormalities (such as subglottic stenosis or obstructive sleep apnea) are currently assessed by endoscopy, which is subjective in nature. MRI and CT imaging in these situations suffer from poor spatial resolution and cannot generally capture dynamic collapse events. We investigated the use of anatomical OCT (aOCT) of the airway to provide a quantitative measure of the luminal cross-sectional area (CSA), which enables computational fluid dynamics to predict respiratory function. Furthermore, real-time OCT collected while also measuring air pressure enables elastographic analysis, which can be used to locate regions with high compliance where dynamic collapse occurs.

Here we present new, pressure-dependent results from our endoscopic aOCT system. The aOCT system employs a catheter (0.82 mm diameter) that fits into the bore of a commercial, pediatric bronchoscope and offers an imaging range >10 mm from the catheter tip with <10 dB reduction in signal-to-noise ratio. We investigated changes in CSA as a function of pressure in ex vivo porcine trachea. Static pressures ranging from 0 - 40 cm H20 were applied via a bag valve mask with a port enabling access of the bronchoscope to the trachea for aOCT imaging. Changing CSA as a function of pressure were used to estimate trachea elasticity. CT scans of the tracheas was subsequently performed to validate CSA values at no pressure, while fiducial markers were employed to co-align OCT and CT images for comparison.

NIH200-42, SESSION PS1

Measurement of the deep brain hemodynamics in transmittance mode by time-resolved spectroscopy

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Near-infrared time-resolved spectroscopy (TRS) is an effective method for quantifying mean optical path length, absorption coefficients, and hemodynamics of human tissues. In order to monitor the hemodynamics of the important organs placed in deep regions from the human surface such as the deep brain, we developed a highly sensitive TRS system. This TRS system consists of three-wavelengths of high-power light source called Nanosecond Light Pulsers, a photomultiplier tube (PMT) for single-photon counting, a TRS circuit based on the time-correlated single-photon counting (TCSPC) method, and optical bundle fibers. Compared with a standard TRS system, the sensitivity of this system was approximately 200 times higher. Data analysis was carried in the transmittance mode and assumed that the ratio of reduced scattering coefficients for three-wavelengths constant, enabling to suppress the fluctuation of the absorption coefficients.

Simultaneous measurements on human head were made in transmittance mode (ear-to-ear measurement) by the developed TRS system, and on the left forehead in reflectance mode by the standard TRS system during hyperventilation. The hemodynamic trends observed by the two methods were similar, with the following changes recorded: decrease in oxygenated hemoglobin, increase in deoxygenated hemoglobin, and decrease in tissue oxygen saturation.

In this study, we confirmed that it is possible to monitor the hemodynamics of human head during hyperventilation even in the transmittance measurements by the developed TRS system. We expect that this TRS system will be applied to point-of-care testing device for monitoring the hemodynamics of deep brain tissues and deep biological organs, and diffuse optical tomography.

NIH200-43, SESSION PS1

Real-time monitoring of airway mucus hydration via diffusion of gold nanorods using polarization-sensitive OCT

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Hydration of pulmonary mucus is critical in maintaining respiratory health. In patients with cystic fibroses and COPD, hydration is impaired, resulting in reduced respiratory function and increased risk of infection. Mucus hydration (wt%) has become an increasingly useful metric in real-time assessment of respiratory health. However, available techniques are slow and not easily translatable to in vivo measurements. We previously established a method of rapidly (<0.5 s) assessing the static hydration state of mucus from the diffusion rate of gold nanorods (GNRs) using optical coherence tomography (OCT). Here, we collect an ensemble of sequential Mmode images, from which we obtain GNR diffusion coefficients resolved within depth over time. Human bronchial epithelial cell cultures were prepared by allowing GNRs (83x22 nm) to diffuse through endogenous mucus >6 hours prior to imaging. For each sample, 10μL of either hypertonic saline (HS) or isotonic saline (IS), premixed with GNRs, was topically deposited during Mmode image acquisition. GNR diffusion was measured up to a depth of 600 μm with 4.65 μm resolution and monitored up to 8 minutes in increments of 3 seconds. Both HS and IS were observed to reduce mucus concentration and change layer height (? for HS, ? for IS). Cross-polarized OCT also revealed mucus secretion by cells after HS deposition. This provides a new window into understanding mechanisms of mucus thinning during treatment, and is readily translatable to in vivo measurements, enabling real-time efficacy feedback needed to optimize and tailor treatments for individual patients.

NIH200-44, SESSION PS1

Photoacoustic imaging with alexandrite lasers

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We describe ongoing development of alexandrite lasers for photoacoustic imaging (PAI) applications, and we discuss the benefits of these lasers for cancer screening and diagnostics. PAI targets specific cancer biomarkers to provide functional imaging of soft tissue, from as small as the subcellular scale to as large as the human breast. These applications use <100 ns visible and near-infrared laser pulses ranging from sub-mJ to Joule levels. We compare and contrast different laser technologies used for PAI. Alexandrite lasers are highly attractive for applications requiring mJ-level or higher pulse energies to localize and quantify hemoglobin and oxyhemoglobin chromophores throughout the region of interest. For applications that require Joule-level energies, such as breast imaging, alexandrite lasers provide the robust high-average-power performance that is necessary for clinical use. We present recent breast phantom imaging results using a Joule-level alexandrite laser.

NIH200-45, SESSION PS1

Brain-computer-interface (BCI) and communication in the completely locked-in state

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Person in completely locked-in state (CLIS) due to amyotrophic lateral sclerosis (ALS) has no means of communication even though they have intact cognitive and emotional processing capacities. Brain-computer-interface (BCI) uses brain activity directly without any motor involvement for activation of various external devices. None of the conventional BCI technique has been able to solve the communication problem in CLIS. Hence there is a need to find an alternative neuroimaging technique to design a more effective BCI to help ALS patient in CLIS with communication. Previous researches have shown that near infrared spectroscopy (NIRS) can be successfully used to design BCI; hence NIRS was used to design BCI to help ALS patient in CLIS with communication. Four patients suffering from advanced amyotrophic lateral sclerosis (ALS) two of them in permanent CLIS and two entering the CLIS without reliable means of communication left, learned to answer personal questions with known answers and open questions, all requiring a “yes” or “no” thought (imagining) using fronto-central oxygenation changes measured with NIRS. Each BCI session consisted of 10 questions requiring a “yes” answer and 10 questions requiring a “no”. Three patients completed more than 46 sessions spread over several weeks and one patient (patient W) 20 sessions spread over weeks. Online fNIRS classification using linear support vector machine (SVM) resulted in an average classification accuracy of 70% in all patients. Our results demonstrate that this novel approach of brain-communication is reliable and allowed so far the best communication possible for patients in completely locked-in state.

NIH200-46, SESSION PS1

Fiber-optic techniques towards multiregional, functional brain imaging and perturbation in freely moving animals

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Deciphering the relationships between brain activity and animal behavior of neurodegenerative disease model is a key cornerstone for studying neurological disease mechanism and preclinical studies of potential therapies. Over the last several decades, enormous efforts have been channelized towards comprehensive sampling of cellular activities with the brain disorders during specific animal behaviors, but these efforts have been impeded by the limited access of bench-top microscopes to the freely moving animals. Recent advances in the field of optical imaging through the development of fluorescent markers, which permit tracing and visualization of brain cells in living animals, have greatly advanced our understanding of neurological disorders. In addition, recent developments in fiber optic and miniaturized microscopic techniques enabled optical brain imaging in freely moving animals. However, these optical approaches have so far been applied to a single brain region at a time, and therefore, recording and perturbation of concurrent cellular events from multiple brain regions is yet to be established

In this work, we present various fiber-optic techniques for long-term studying of multiregional, functional cellular network activities to be used in neurodegenerative disease animal models. Our system uses custom designed fiber-bundle imagers capable of brain imaging at cellular resolution. We built a long-term monitoring platform for studying unconstrained mice behaviors and imaging cellular activities for either short or extended periods of time. The outcomes may open doors for new studies on neurological disorders in freely behaving animal models, and lead to advances in our understanding of the functional connectivity in neurological disorders.

NIH200-47, SESSION PS1

Basal cell carcinoma diagnosis and ablation therapy guidance with combined reflectance confocal microscopy/optical coherence tomography imaging

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We present a reflectance confocal microscopy - optical coherence tomography (RCM-OCT) imaging approach that might enable enhanced diagnosis and guidance of laser ablation therapy of BCC basal cell carcinoma (BCC). The combined RCM/OCT imaging approach is uniquely suited for laser ablation therapy guidance due to its capability of resolving both the lateral and depth margins of the tumor. While RCM provides en face images with nuclear-level resolution in superficial skin, to depths of about 200 microns, OCT provides cross-sectional images with structural-level resolution in the deeper skin layers, to depths of at least 1 mm. Tumor lateral and depth extent are o needed to be known prior to performing the ablation procedure in order to precisely determine the size of the area to be ablated and properly choose laser parameters and irradiation time. Our preliminary ex vivo study has demonstrated the suitability of combining these technologies within the same instrument, as well as the clinical value of the complimentary data. Testing on patients will follow soon and is expected to produce new data that will advance our understanding of and define the possibilities for microscopic-level imaging to guide ablation of superficial skin cancers. If successful, the imaging approach may lead (in the long-term) to a new standard-of-care for treatment of superficial skin lesions, pre-cancers and cancers.

NIH200-48, SESSION PS1

Noninvasive diagnosis of middle ear pathologies using phase-sensitive optical coherence tomography

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We report the development of a hand-held functional otoscopy instrument based on phase-sensitive OCT imaging. The handheld otoscopic probe simultaneously acquires en face visible video images, cross-sectional structural images and sound-induced vibrations of the tympanic membrane and of the middle ear ossicles with sub-nanometer sensitivity of the vibratory response. The custom-built handheld otoscopic probe was designed to match the dimensional size of the human middle ear, and mechanically built to assemble three channels including the OCT sample, sound stimulus, and visible light illumination channels. The phase sensitivity of the system was first evaluated on phantoms and then structural and vibrational images were acquired from cadaveric human temporal bone models. The capability of the instrument to retrieve the morphology of the middle ear, as well as measure the vibration of the tympanic membrane, maleus, and incus with subnanomer accuracy was demonstrated.

NIH200-49, SESSION PS1

Optical diagnosis of acute urinary tract infection: a novel approach

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INTRODUCTION AND OBJECTIVES:

The diagnosis of lower urinary tract infection (LUTI) is based on history and clinical symptoms confirmed by positive urine culture. However, reliance on the clinical symptoms and history is problematic in certain clinical scenarios such as in young children and individuals with neurogenic bladder (e.g. spinal cord injury) where history and / or sensation of dysuria are lacking. The purpose of this study was to determine if a quantifiable measure of detrusor oxygen saturation, derived using a transcutaneous near-infrared spectroscopy (NIRS) system could distinguish between subjects with and without LUTI.

METHODS:

A convenience sample of children less than 16 years of age, referred to a urology clinic at a pediatric hospital with an acute LUTI and a matched control group were studied. Diagnosis was confirmed by history, physical examination, laboratory investigations & urine culture. Participants had transcutaneous measurement of TSI% in their bladder wall (BTSI%), and a quadriceps muscle control site (QTSI%), using a wireless SR-NIRS system. With the subject in the supine position, the NIRS device was placed over the bladder (midline 2 cm superior to the symphysis). Following 60 seconds of baseline data collection at 10 Hz with the patient at rest and ready to void, the device was moved to the skin over the right quadriceps (over the vastus lateralis muscle), and a similar one-minute period of data collection made from the control site. Average measures of B.TSI% and Q.TSI% and their differences (TSI.diff) were calculated and compared between those with LUTI & controls by performing a two- way repeated analysis of variance.

RESULTS:

Forty-eight children met the inclusion criteria (24 LUTI and 24 controls). Comparing LUTI to controls B.TSI% and TSI.diff values were significantly higher in the LUTI group. In all LUTI patients the SR NIRS-derived TSI.diff value was equal to or higher than 5.2, while in all control subjects the TSI.diff was lower than 3.9.

CONCLUSIONS:

Optical monitoring of bladder wall oxygenation is feasible in children. There is a significant difference in a SR NIRS-derived measure of absolute oxygen saturation in the bladder wall between children with UTI diagnosed by conventional testing methods, and those in a control group without infection. SR-NIRS monitoring of bladder wall oxygenation may offer a rapid and noninvasive means of bedside screening for LUTI where history and/or clinical signs are not available or adequate.

NIH200-50, SESSION PS1

Diffuse optical monitors of the neonatal brain during extra corporeal membrane oxygenation therapy

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Extracorporeal membrane oxygenation (ECMO) therapy provides a critical bridge to recovery, transplant or long term mechanical support for children and adults with serious, but treatable, afflictions of the heart and/or lungs. In essence, it functions to mechanically circulate externally oxygenated blood into and through the body. Blood pressure optimization is critical to preserve end-organ function during ECMO therapy. However, intrinsic autoregulatory mechanisms for certain end-organs such as the kidney and brain may lead to significant flow discrepancies between systemic and cerebral or renal flow.

Neurological injury remains a debilitating and relatively common complication among ECMO survivors, and current limitations in diagnostic modalities often lead to late diagnosis. Thus, early detection of periods of high risk prior to injury is vital to improve outcomes following ECMO therapy. Currently, clinicians have no tool to directly monitor cerebral oxygen metabolism and instead rely on systemic measurements. A bedside cerebral blood flow monitor could be used, for example, to set appropriate mechanical pump rates to optimize cerebral perfusion. In this contribution we describe our first attempts to utilize diffuse optical and correlation spectroscopies to measure cerebral blood flow and oxygenation during ECMO therapy. We are thus able to explore the effects of variation in ECMO pump rates and assess cerebral blood flow compensatory mechanisms in the extreme pathological state created by extracorporeal circulation through manipulation of ECMO flow rates in a pediatric population on a patient-by-patient basis and as a function of time.

NIH200-51, SESSION PS1

Imaging brain function in children with autism spectrum disorder with diffuse optical tomography

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Autism Spectrum Disorder (ASD) is a common and currently incurable neurodevelopmental disorder defined by impaired social interactions, altered language function, and repetitive behaviors. ASD affects an estimated 1% of children, and engenders enormous personal, social, and economic costs. Investigating the neuroscience of ASD in childhood is vital because early behavioral and educational interventions starting at 18-24 months of age have been shown to improve outcomes. Neuroimaging studies using functional magnetic resonance imaging (fMRI) have identified specific brain regions whose responses to biological motion perception stimuli are correlated with behavioral metrics of ASD; these responses are potential interventional outcome measures. However, current neuroimaging methods (e.g., fMRI) are limited in ASD due to the constrained imaging environment. Our lab has been developing diffuse optical tomography (DOT) methods that overcome ergonomic limitations of fMRI and image brain function with a wearable cap. The wearability of DOT will allow a fuller assessment of brain function in severely affected children with ASD, exceedingly challenging to study with MRI methods. We present here a feasibility study imaging with our high density DOT system school-aged typically developing children (TDC) and sex/age/IQ-matched children with autism (ASD). Both groups of children are able to tolerate imaging for over 30 minutes, and exhibit acceptable raw data quality, and maps of functional brain activity in response to simple language tasks like hearing words and verb generation. Group-matched brain responses of biological motion perception and resting state networks will also be presented.

NIH200-52, SESSION PS1

Non-invasive functional neuroimaging in the mouse using structured illumination diffuse optical tomography

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The study of correlated spontaneous neural and hemodynamic activity in functionally related brain regions using functional connectivity magnetic resonance imaging (fcMRI) has recently allowed comprehensive mapping of distributed brain networks in humans. Extending analogous fcMRI studies to the mouse has been challenging due to technical limitations that preclude high resolution and high signal-to-noise measurements in the small volume of the mouse brain. Instead, optical intrinsic signal (OIS) techniques, which use a simple diffuse reflectance imaging geometry, have provided most of the observations of fc in the mouse brain. While effective and efficient, fcOIS methods require removal of the scalp tissue and are limited to superficial cortical tissues. Diffuse Optical Tomography (DOT) is a non-invasive optical imaging modality, but current systems are either too sparsely sampling or are too slow for capturing functional response in the mouse brain. Here we develop a DOT system that combines the sensitivity and spatial sampling of camera based systems with the rapid-imaging capabilities of structured light illumination to map brain activity in the mouse. With this increased speed and sensitivity, activations in the somatosensory region of the mouse cortex upon electrical stimulation of the forepaw are seen non-invasively, through the intact scalp. Extending the technique to imaging spontaneous activity reveals expected resting state fc within the cortex as previously observed using fcOIS, but with greater depth sensitivity. This new DOT-based mouse neuroimaging technique extends our previous methods to allow imaging through the intact scalp and with increased sensitivity to deeper regions of the mouse cortex.

NIH200-53, SESSION PS1

Mapping large-scale functional connections with ChR2-evoked hemodynamic signals

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Both task-based and resting-state methods have been used to map functional connections in healthy and diseased brain with fMRI in humans. Because functional disruption often precedes clinical symptoms of pathology, understanding why certain resting state networks (RSNs) are more vulnerable to disease requires longitudinally characterizing a functional subunit (cell type or projection pathway) of that RSN. Attempting to map functional subcircuits using hemoglobin alone presents several disadvantages. Evoked and spontaneous hemodynamic fluctuations reflect ensemble activity from several different types of neurons making it difficult to discern excitatory versus inhibitory activity. However, blood-based methods of brain mapping like fMRI remain powerful because hemoglobin provides ubiquitous, endogenous contrast throughout the brain. The ideal functional mapping approach would combine cell-specificity within the point spread function of hemoglobin-based methods to retain the connection to human fMRI results. Optogenetic methods provide a rich array of genetic tools for probing inhibitory and excitatory circuits with cell-specificity. While fMRI in mice is an attractive method for investigating neural activity at the mesoscale, optogenetic-fMRI mapping in mice is challenging due to space constraints, and signal-to-noise limitations preclude comparing cell-specific functional maps to RSNs. We propose to integrate wide-field OIS imaging and optogenetic stimulation to create an OPTO-OIS mapping tool to dissect subcomponents of murine RSNs. Large-scale functional mapping of cell-specific circuits with OPTO-OIS will help answer fundamental questions regarding the cellular basis of intrinsic, spontaneous activity in the brain, and could provide mechanistic insight into pathophysiology to link cellular and functional network alterations to disease manifestations.

NIH200-54, SESSION PS1

Mapping brain function at the bedside during acute stroke recovery using high-density DOT

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Stroke is the fourth leading cause of death in the US and is the leading cause of adult disability. Throughout the acute and sub-acute phases of stroke recovery, early detection of neurological deterioration is essential and close neurological monitoring is critical. Standard clinical care consists of behavioral tests (every 2 hrs) and CT's and/or MRI's, which provide snapshots of brain health. Continuous MRI/CT scans are not feasible due to logistical challenges and high costs. Our lab has developed a portable High-Density Diffuse Optical Tomography (HD-DOT) system that could potentially fill this gap in clinical care by providing more continuous monitoring and imaging.

Ischemic stroke patients (n=19) were scanned within 72 hours of stroke onset. Functional data were obtained for each patient resting quietly, with scan times up to 1 hour. Three dimensional images of hemodynamics, covering the sensory and motor areas were reconstructed from using a subset (48 sources and 34 detectors) of a previously reported system and associated algorithms (Eggebrecht et al. Nature Photonics 2014).

The functional connectivity (fcDOT) analysis was performed for seeds that were raster scanned throughout the DOT field-of-view. Two fc metrics were derived from the full voxel-by-voxel fc-matrix: Asymmetry, which measure how asymmetric the fc maps were, and Similarity, which measures how similar an fc map is to a group-averaged control dataset. Qualitatively, the presence of an infarct disrupted typical homotopic contralateral connectivity patterns and produced significant increases in a patient's asymmetry ($p<0.001$) and decreases in similarity compared to controls ($p<0.001$).

NIH200-56, SESSION PS1

Towards the prediction of preterm birth using full Mueller matrix imaging of cervical collagen

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Although preterm birth is the number one cause of infant mortality and neurological disorders in the world, there is not, yet, a reliable or accurate method for diagnosing women at risk of preterm birth. Cervical collagen is the main component for providing strength and maintaining the weight and structure of the cervis in order for the fetus to gestate. As pregnancy progresses, cervical collagen becomes more disorganized and allows the weakening and opening of the cervix for birth. The changes in cervical collagen may occur prematurely in preterm birth. These changes in collagen organization can be analyzed using Mueller Matrix Polarimetric imaging of the characteristic birefringence of collagen. In this research, we have built a full Mueller Matrix Polarimeter attachment to a standard colposcope to enable imaging and analysis of the quantity and organization of cervical collagen throughout pregnancy.

NIH200-58, SESSION PS1

Novel calibration-free framework for continuous spectroscopic monitoring of blood analytes: pain-free glucose detection

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An outstanding challenge in biophotonics research is to devise a method for continuous, non-invasive monitoring of blood analytes, which constitutes a significant component of critical care and point-of-care diagnostics. Vibrational spectroscopy potentially provides a powerful tool for simultaneous, quantitative and label-free measurement of multiple analytes, due to its intrinsic biochemical specificity. Here, we propose a novel calibration framework that enables spectroscopy-based estimation of analyte information without necessitating extensive a priori concentration information. In a nutshell, a kinetic model of the investigated process provides a guide to the ''missing'' concentration portion of the ill-posed problem of concentration estimation. Using non-invasive blood glucose monitoring by Raman spectroscopy as an illustrative example. We demonstrate the efficacy of this novel approach in predicting glucose concentrations that match closely with the measured values in relation to those generated with conventional calibration methods. In this paradigm, the solution of the model of glucose variation in the human body also enables deeper insight into the physiological lag behavior in response to the initial glucose loading (stimulus) and may offer an alternate route at screening diabetic population. Using our newly developed algorithm, the glucose levels are compared with reference values, and we found that the prediction error is around 2-8% with a single finger stick maintaining clinically acceptable measurement accuracy for a period over one week.

NIH200-59, SESSION PS1

High-resolution retinal imaging: closer to the clinic

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Retinal imaging with cellular resolution is a valuable new tool for clinicians in diagnosis and treatment of many eye diseases. PSI's recently developed compact high-resolution retinal imager is designed for rapid, automated generation of cone photoreceptor density large area maps and retinal structural analysis combining the power of adaptive optics (AO) correction with OCT imaging and PSI's patented line-scanning technology (LSO). This allows clinicians and researchers to resolve and rapidly map photoreceptors and other retinal micro-structures with high resolution dynamically corrected to each subject's eyes. The device has a compact foot-print suitable for clinical deployment.

Numerous new features support clinical research applications, including: (1) a pupil camera for quick patient alignment (x, y and z); (2) an integrated LCD fixation display; (3) a focal plane point-spread function (PSF) monitoring camera for automated calibration and a convenient AO-correction and image quality metric; (4) AO focus control for layer selection and programmed focus; (5) dual-scanner controls with multiple modes for automated montage acquisition; (6) auto-align and auto-calibration routines. A new patient interface eliminates physical motion of the imager and minimizes the need for the operator to chase subjects' head movements. The system has a small electronics module and a computer attached to an adjustable table. These upgrades significantly enhance the capabilities of the AO-LSO-OCT imager, providing the clinician with simultaneously-acquired (registered) en face photoreceptor images and OCT retinal cross-sections.

Retinal targets include cone photoreceptors, vessels and blood flow, nerve fibers bundles, lamina cribrosa and optic nerve head, drusen, edema, lesions, geographic atrophy, and other features of interest.

NIH200-61, SESSION PS1

Imaging birefringent tissues using polarization-sensitive optical coherence tomography and Stokes imaging polarimeter

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Polarized light-based techniques such as polarized light microscopy, optical polarimetric imaging techniques, and polarization sensitive optical coherence tomography (PS-OCT), have shown good sensitivity to the orientation and quantity of birefringent tissue. Combination of these different techniques, which enable different field of view (FOV), sampling rates, and penetration depths, is useful in the characterization of birefringent tissue structures in-vivo. In this study, we introduce one such systems consisting of a custom made polarization-sensitive Fourier domain optical coherence tomography system and an out-of plane Stokes imaging polarimeter. The PS-OCT uses a broadband light source with a center wavelength of 890 nm, a full width at half maximum (FWHM) bandwidth of over 150. Phase sensitive recording of interferometric signals are used to measure and image Stokes vectors of the backscattered light, Mueller and Jones matrix distribution, and fast axis orientation. The maximum FOV of this system is 2 cm x 2 cm with 3.5μm axial and 8.5μm transverse resolution. An out-of-plane Stokes imaging system is integrated with the PS-OCT. The system consists of a narrow band polarized light source attached to a rotating arm illuminating the sample at an incident angle of 49 degrees and an imaging Stokes Vector Polarimeter at the same angle from the sample normal. The out-of-plane polarimeter FOV is 5 cm x 5 cm. Result of the combined system on highly packed structure of birefringent collagen fibers and chicken skeletal muscle is tested versus Monte Carlo models of polarized light transfer with good agreement.

NIH200-62, SESSION PS1

Depth discrimination in coherent hemodynamics spectroscopy

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We are exploring two methods to achieve depth discrimination in coherent hemodynamic spectroscopy (CHS), a new technique for microvascular assessment based on dynamic near-infrared spectroscopy (NIRS) measurements in tissue. These methods are: a) A diffusion model for two-layered media; b) The modified Beer-Lambert law with partial pathlengths through two-layered media. We test and compare these methods with simulated and experimental data in vivo, in an effort to identify the most effective procedure to achieve depth-resolved CHS for the individual characterization of the hemodynamics occurring in superficial and deeper tissue layers.

NIH200-63, SESSION PS1

Oscillations of oxyhemoglobin and deoxyhemoglobin concentrations feature a different phase relationship in the healthy breast and brain

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We used near-infrared spectroscopy (NIRS) to measure hemodynamic oscillations (in the frequency range 0.04-0.08 Hz) in the breast and brain tissue of healthy human subjects. The hemodynamic oscillations were induced by the cyclic inflation (to a pressure of 200 mmHg) and deflation of two pneumatic cuffs placed around the subject's thighs. NIRS allows for the separate measurement of the oscillations of oxyhemoglobin (O) and deoxyhemoglobin (D) concentrations that are associated with the induced oscillatory hemodynamics in breast and brain tissue. We found that O and D oscillated in phase at all frequencies in the breast, whereas they exhibited a frequency-dependent phase difference in the brain. We recently proposed a hemodynamic model that relates the amplitude and phase of O and D oscillations to the dynamics of blood flow, blood volume, and oxygen consumption through a number of physiological parameters such as the blood transit times in the microvasculature and the effectiveness of cerebral autoregulation. According to this model, the in-phase oscillations of O and D in breast tissue indicate that they are dominated by blood volume dynamics, whereas the out of phase oscillations of O and D in brain tissue indicate that they reflect contributions from both blood flow and blood volume dynamics. The frequency dependence of the cerebral O and D oscillations is the basis for the new technique of coherent hemodynamics spectroscopy (CHS), for which we are currently exploring clinical diagnostic or monitoring applications for the injured brain.

NIH200-64, SESSION PS1

Integrated RFA/OCT catheter for real-time guidance of cardiac radio-frequency ablation therapy

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Radiofrequency ablation (RFA) treatment of cardiac arrhythmias would benefit from direct image feedback at the catheter tip. In this paper, we demonstrate feasibility of a radiofrequency ablation catheter with integrated optical coherence tomography (OCT) for direct image-based guidance and monitoring of the RFA procedure in real time. The integrated RFA/OCT catheter is modified from a standard commercial RFA catheter, and includes a newly-designed and fabricated miniature forward-viewing cone-scanning OCT probe. The effective delivery of radiofrequency energy by the integrated probe was verified by comparing the sizes of RFA lesions generated by the integrated catheter with those generated by a standard commercial RFA catheter, and the OCT imaging system was also verified by imaging human skin in vivo. Then the integrated RFA/OCT catheter was demonstrated by monitoring RFA lesion delivery in real time in superfused swine ventricular wedges. The results show that catheter-tissue contact can readily be assessed by the integrated probe, as lack of contact, partial contact, and full contact can be clearly differentiated in the OCT images. RFA lesion formation can be confirmed by the loss of birefringence in the myocardium, and overtreatment with RF energy can also be observed as subsurface tissue disruption in the OCT image. The system may potentially aid RFA therapy of cardiac arrhythmias by providing direct image feedback of the target and treated tissue to the operator in real time.

NIH200-65, SESSION PS1

Development of quantitative biomarkers for wet AMD from OCT imagery

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Retinal imaging is informative for diagnosis and assessment of a both eye and systemic diseases, including melanoma, diabetes, and hypertension. Our research centers on the automated processing and analysis of optical coherence tomography (OCT) imagery for diagnosis and assessment of wet age-related macular degeneration (AMD). We have developed an automated processing pipeline that locates the fovea, evaluates the OCT slices relative to fovea, segments the layers of the retina in each slice, and extracts biologically relevant features from these layers. Due to the effects of advanced AMD on the structure of the retina, the OCT imagery can present a number of challenging conditions that are not evident in healthy subjects. We demonstrate methods for ensuring robust processing and feature analysis in the presence of anomalous features and degraded images. A statistical model quantifies the relationship between the features derived from the imagery and the Best Corrected Visual Acuity (BCVA) observed in a clinical study. Statistical cross-validation quantifies the model's performance. Applying our methods to images collected over time offer an objective method for tracking disease progression and the efficacy of various treatments. We conclude with a discussion of the possible clinical application of our methods to support diagnosis, assessment of treatments, and the potential for targeted therapies.

NIH200-66, SESSION PS1

Monitoring acute cerebral blood flow dynamics during cardiac arrest and resuscitation with laser speckle imaging

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Cardiac arrest (CA) affects over half a million people in the U.S., with neurological injury being the most important prognostic factor. Only 8.3% of initial CA survivors have good neurological recovery, and over 80% reside in a coma, persistent vegetative state, or die within one year. During global brain ischemia, the brain lacks oxygen, glucose, and other nutrients, leading to a cascade of events that cause neuronal injury during ischemia and reperfusion. An important marker for nutrient delivery is cerebral blood flow (CBF). We used laser speckle imaging to investigate CBF dynamics in an established asphyxial CA model. We used varying asphyxial times of 5, 7 and 8min followed by cardiopulmonary resuscitation (CPR), and continued to monitor at 10fps CBF dynamics relative to baseline (mean blood flow during 1-min period immediately prior to onset of asphyxia due to isoflurane washout) for ~2h post-resuscitation. After CPR, 5, 7 and 8min asphyxia durations showed a hyperemic response of ~20, 35, and 50% above baseline, respectively. Furthermore, after each hyperemic response, a sustained stabilization period occurred, where the 5, 7, and 8min asphyxia durations resulted in blood flow ~16% below baseline beginning at 18-min, ~28% below baseline beginning at 20-min and ~77% below baseline beginning at 24-min, respectively. These results suggest that short delays in CPR may have a profound impact on CBF dynamics following CA and resuscitation. Understanding acute cerebral hemodynamics during CA and resuscitation is an important initial step to improve neurological recovery of CA survivors.

NIH200-67, SESSION PS1

A compact instrument for for the monitoring of microcirculation

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We report on the results of implementing a compact, low cost capillary blood flow monitor using diffuse correlation spectroscopy (DCS). The successful commercial implementation of a monitoring and detection system for hemorrhagic shock requires that system components be minimized in size, power draw and cost. We have built a flexible 1-8 channel correlator and associated software, and compared the output to that attained from a commercially available unit on both subjects and phantoms. We are also able to achieve these results short coherence length lasers, and are replacing typical commercial detectors with internally developed Geiger mode APDs to further integrate and miniaturize. Our results represent an exciting approach to a clinically viable DCS system for the monitoring of patients at risk for hemorrhagic shock.

NIH200-68, SESSION PS1

Noncontact FLIR measurement of sweatpore reactivity corresponds with PTSD symptoms

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BACKGROUND:

Non-contact Stress Analysis by FLIR Evaluation (SAFE), developed at the US Army's NVESD Lab, employs high resolution passive thermal video of sweat-pore activation (SPA) on the face and fingers, as surrogates for sympathetic autonomic nervous system (SANS) activity.

METHOD:

SANS activity was measured by skin conductance (SC) response and SPA on the fingers (FiP) and the face (FaP) by SAFE, while a trauma exposed population (10 with PTSD+, 16 without, PTSD-; mean-age 44.08±12.59, 46.2% female) completed a 15-trial loud-tone (LT) test. PTSD symptoms were assessed using CAPS and PCL.

RESULTS:

Multilevel regression analyses examined relationships among SC, FiP, and FaP and to PTSD symptoms. Within-participants association across LT trials was large: SC/FiP (r=.92, p<.003), SCR/FaP (r=.76, p<.005) and FiP/FaP (r=.47, p=.13).

All three responses showed dramatic increases during early LT trials, which flattened out over time. This habituation effect was more substantial for SC (d=-2.97) and FiP (d=-2.34) compared to FaP (d=-1.02). There was a high correlation between the habituation effect for SCR and FiP (r=.76, p<.001). The associations between habituation in SC and FaP (r=.15, p=.454) and in FiP and FaP (r=.29, p=.156) were not significant.

PTSD+ showed larger initial responses compared to PTSD-, with medium effect sizes (d's .44 to .56). The most robust PTSD finding was that reexperiencing symptoms as assessed by PCL significantly predicted initial SCR (d=1.19, p<.001) and FiP (d=.99, p<.02) but not FaP (d=.10).

CONCLUSION:

The findings indicated that this biology-based non-contact SAFE approach could be a useful tool in PTSD studies.

NIH200-69, SESSION PS1

Can the blood-brain barrier disruption be assessed by monitoring of the indocyanine green washout?

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Recently, we reported that the method based on optical monitoring of inflow of indocyanine green (ICG) can be used for assessment of cerebral perfusion at the bedside [1]. The dye reveals high absorption and fluorescence emission in near infrared wavelength range which makes possible to use it in assessment of perfusion in large tissue volumes. Due to the low toxicity of the ICG [2] and small dose of the dye needed [3], the injections can be repeated allowing potentially for frequent measurements of cerebral perfusion in patients with posttraumatic brain injury.

In the present contribution we summarize studies in which time courses of the statistical moments of measured distributions of times of flight of photons (DTOFs) and distributions of times of arrival of fluorescence photons (DTAs) were used for differentiation of patients with various brain perfusion disorders [1]. In these studies a multichannel time-resolved system operating at wavelength of 760 nm was used. It allows for simultaneous monitoring of diffuse reflectance and fluorescence signals from 8 source-detector pairs [4]. The setup is based on semiconductor lasers generating picoseconds light pulses and time-correlated single photon counting for acquisition of DTOFs and DTAs.

Furthermore, we will present results of analysis of the washout of ICG after its intravenous injection. It was observed that the dynamics of the return of the signals to the initial level may depend on the function of the blood-brain barrier. In healthy subjects the increase in absorption caused by inflow of ICG leads to increase in light attenuation, decrease in mean time of flight of diffusely reflected photons as well decrease in variance of the DTOF [5] After initial change these signals return relatively quickly to the initial level (the signals reach 20% of the maximum within 3 min after the maximum). In patients in which blood-brain barrier disruption can be expected (due to cardiac arrest or brain edema) this return is delayed (the signals drop only to the levels between 20 and 50% of the maximum within 3 min after maximum). It was observed that dynamics of these signals return to the initial level differ when various statistical moments of DTOFs and DTAs are analyzed. Analysis of the correlation between parameters of the inflow and washout will be presented which suggests that the two phases of the signal change may contain complementary information.

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NIH200-70, SESSION PS1

Imaging and reconstruction of the neonatal nasal cavity with an optical coherence tomography probe

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The use of non-invasive ventilation has increased dramatically in neonatal care. Respiratory support can now be administered through the nose via nasal prongs. Nevertheless, complications often arise, which can include injury and necrosis of soft tissue and cartilage in the developing neonatal nose. Currently, there is no bedside diagnostic tool that can identify the first signs of nasal trauma. Optical coherence tomography (OCT) is a minimally-invasive imaging modality capable of providing high-resolution, 3D cross-sectional images of biological tissue. The main objective of this work is to construct an OCT probe that is capable of imaging and reconstructing the nasal cavity.

First, a phantom nose was constructed from CT images of a neonatal nasal cavity using 3D Slicer. Next, a side-viewing, helical scanning OCT probe was inserted into a sheath with an outer diameter of 1.01 mm, which is then inserted into the nasal cavity for imaging. After imaging, each cross-sectional OCT image was analyzed in MATLAB. The average cross-sectional area of the nose and area between the nose and sheath are 4.53 mm^2 and 3.73 mm^2, respectively. Data have shown that occlusion of the nasal cavity by the OCT and sheath is not a problem.

Finally, pilot evaluation of human neonates will be attempted. This study will be conducted to discern the different tissue layers of the nasal cavity, such as the epithelium, basement membrane, lamina propria, and cartilage, and detect any irregularity or trauma if present.

NIH200-71, SESSION PS1

Living cells metabolic imaging in tissue by dynamic full field OCT (D-FFOCT)

Claude Boccara, Institut Langevin (France); **Clement Apelian,** Langevin/LLTECH (France); **Fabrice Harms,** LLTech SAS (France)

Without the help of exogenous contrast agents (e.g. fluorescent dyes) or phase-based techniques (interferometry, holography, phase contrast) cells are difficult to observe under microscopic examination. Due to the high scattering level of the surrounding tissue structures like collagen or myelin the backscattered signal from cells is even more difficult to extract. Relying on the fact that cell motility happens at time scales much shorter that the movement of the fibrous structures, we have developed a new approach based on the time dependence of the FFOCT signal. This dynamical signal is able to reveal hidden cellular structures with a micron resolution at timescales of a few ms. We will describe the statistical treatments of the signals from variance analysis to singular value decomposition that not only show hidden cells but can quantify their time response.

Using these signal processing approaches, we will show images of cellular structures of normal or pathologic tissues from different organs of human or animal tissues: liver, brain, breast etc.

We have compared the signal dependence with the wavelength in order to identify which structure is responsible of the dynamical signals: cytoskeleton, mitochondria, fibroblast etc. Blocking specific mechanisms associated to these structures will complete this approach.

In conclusion we will discuss how these weak signals can be increased allowing a full space-time imaging of the cells activities at a subcellular scale and how we forecast to see D-FFOCT paving the way to better intraoperative diagnosis.

NIH200-72, SESSION PS1

Coherent hemodynamics spectroscopy: a new tool to measure cerebral autoregulation

Jana M Kainerstorfer, Carnegie Mellon Univ. (United States); **Angelo Sassaroli, Kristen Tgavalekos, Sergio Fantini,** Tufts Univ. (United States)

Near-Infrared Spectroscopy (NIRS) can measure cerebral concentrations of oxy- and deoxy-hemoglobin, which are determined by cerebral blood volume (CBV), cerebral blood flow (CBF), and metabolic rate of oxygen (CMRO2). We have recently introduced a hemodynamic model, which, in conjunction with induced changes in the systemic mean arterial pressure (MAP), led to a technique that we named Coherent Hemodynamics Spectroscopy (CHS). Such MAP perturbations can be induced by cyclic thigh cuff occlusions or by paced breathing at a set of sequentially controlled frequencies. Systemic MAP changes can also be induced by the fast deflation of two pneumatic cuffs around the subject's thighs after they have been kept inflated for 2 min at a pressure of 200 mmHg. Frequency-resolved measurements of the phase and amplitude of the induced cerebral hemodynamic oscillations, which result in CHS spectra, are quantified by the novel hemodynamic model in terms of physiological and vascular parameters such as the blood transit times in the microvasculature, the autoregulation cutoff frequency, and the microvascular blood volume. Here, we demonstrate how CHS spectra can be used to quantify cerebral autoregulation. Based on CHS measurements on healthy volunteers, in a protocol based on a fast deflation of thigh cuffs, we quantify the enhanced cerebral autoregulation associated with hypocapnia achieved by hyperventilation. In addition, we demonstrate that our hemodynamic model can separate CBF and CBV contributions to measured oscillations of oxy- and deoxy-hemoglobin concentrations, which allows for the quantification of the hemoglobin saturation of volume oscillating compartments.

NIH200-119, SESSION PS1

Solid hemoglobin-polymer composites: stable, realistic phantoms for spectroscopy and imaging

Hyounguk Jang, Univ. of Maryland, College Park (United States); **T. Joshua Pfefer,** U.S. Food and Drug Administration (United States); **Yu Chen,** Univ. of Maryland, College Park (United States)

Tissue-simulating phantoms that exhibit the true spectral absorption characteristics of hemoglobin (Hb) with long-term stability would significantly benefit development and clinical translation of a wide range of biophotonic spectroscopy and imaging devices. We have developed and validated solid Hb-polymer (SHP) composite materials that meet both of these criteria. The fabrication process involves thorough mixing of an oxy-Hb solution – that can be desaturated using yeast – with a liquid silicone base, followed by a curing agent. We describe novel mixing, curing and storage approaches used to preserve Hb spectral features in the final, solidified composites. The absorption coefficients of cured oxy- and deoxy-Hb samples were determined over visible and near-infrared wavelengths (450-1000 nm) using spectrophotometry. Measurements indicated very good agreement with native Hb absorption spectra and minimal optical changes over a period of four months. Hyperspectral imaging and near-infrared spectroscopy measurements of SHP samples embedded in a turbid matrix demonstrate the practical utility of this approach. SHP composites will enable realization of more robust, biologically-realistic phantoms for performance assessment, quality control, and standardization of biophotonic devices for oximetry and other applications.

NIH200-120, SESSION PS1

In search for biomarkers of brain development in early childhood: pilot study using functional near infrared spectroscopy

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To understand the development of brain function there is a crucial need to quantitatively assess brain activation in early childhood, specifically for early intervention of neurodevelopmental disorders. The current brain imaging modalities (such as fMRI or PET), however, make it challenging to study the brain function at a young age, mostly due to patient movement or invasive nature of the study. Functional near infrared spectroscopy (fNIRS) is an emerging non-invasive brain imaging technology that is affordable, compact, and less susceptible to patient movement. Therefore, it becomes suitable for imaging the cortical activation in young cohorts. In this study, we used an fNIRS to assess functional biomarkers, oxy- and deoxy-hemoglobin, based on activation in prefrontal cortex (PFC) using specific tasks. We conducted two studies to compare the functional development of the brain: 1) in typical children from ages of 4-8 performing a Go/No-Go task and 2) in a group of 3-year-old typical and language delay (LD) toddlers watching a video. We introduced a novel parameter, Oxygenation Variability Index (OV index), directly obtained from fNIRS data. This index measures the changes in oxygen saturation in PFC in frequencies related to cerebral autoregulation (<0.1 Hz). In a group of seventeen typical children, our results indicate that the OV index increased significantly with age between 4 and 6 years and decreased afterward, reaching a plateau. In 3 year old toddlers, we noticed a significant difference in OV Index between LD (N=4) and typical toddlers (N=5), with the latter showing a higher level of OV Index in left PFC. Moreover, compared to the typical group, LD toddlers exhibited significant unilateral activation in PFC. These findings for the first time provide preliminary evidence to describe the relationship between the OV index and age in children, and differentiate the brain function at the early stage of neurodevelopmental disorders using fNIRS methodology.

NIH200-121, SESSION PS1

In search of functional biomarkers in human prefrontal cortex for individuals with traumatic brain injury (TBI) using functional near-infrared spectroscopy: a machine learning approach

Nader Shahni Karamzadeh, National Institutes of Health (United States)

We attempted to identify the prefrontal hemodynamic biomarkers that provide the optimum distinction between the TBI and healthy subjects. To achieve this goal, first the hemodynamic response from a group of 31 healthy controls and 30 chronic TBI subjects while performing a complexity task is captured. First, we identified the hemodynamic signals that show task-related hemodynamic activity. To this end, a novel approach for identifying a single trial hemodynamic response that encompasses task-related hemodynamic activity by imposing certain restrictions on a signal's statistical characteristics is presented. It is followed by a hemodynamic feature extraction procedure in which 11 features from oxygenated hemoglobin (HbO) is identified. To determine the optimum biomarkers from the extracted hemodynamic features, we investigated the effectiveness of 11 extracted features from the subjects' prefrontal hemodynamic response in separating TBI and healthy subjects by utilizing a machine learning classification algorithm as a black box to score all possible combinations of features according to their predictive power. The optimum identified feature elements resulted in classification accuracy, sensitivity, and specificity of 85%, 85%, and 84%, respectively. The sensitivity value of 85% suggests that TBI subjects have been successfully characterized for the identified biomarkers with a reasonable accuracy.

NIH200-123, SESSION PS1

Modulation of low frequency hemodynamic oscillations in the TBI population

Victor Chernomordik, National Institutes of Health (United States)

We propose a cost effective and subject friendly method to assess the cognitive functions of Traumatic Brain Injury (TBI) subjects using Healthy Controls (HC) as baseline. Our method uses functional Near Infrared Spectroscopy (fNIRS) as a non-invasive tool to measure changes in oxy-/deoxy-hemoglobin levels which are correlated to brain activation. We applied filters for specific frequency bands on the cerebral hemodynamics signal to assess such physiological processes, as Cerebral Autoregulation (CA). Novel metrics (recently introduced measure of Oxygenation Variability (the OV Index)), extracted from fNIRS data, allows to follow changes in CA in response to mental tasks for a group of adults that included TBI patients along with HC. Participants were responding to an action complexity judgment task with a varying degree of cognitive load, resulting in brain activation. They were asked to evaluate the complexity of daily life activities by classifying the number of steps as “few” or “many”. Our results indicate that OV index can characterize the level of hemodynamic variations in response to complexity mental tasks in the low frequency band, corresponding to CA, revealing a strong parametric effect. We have shown that mean OV indices, corresponding to high complexity tasks, are higher than that of low complexity tasks, implying stronger CA response to more complicated tasks. Comparison between OV indices for TBI patients and HC indicates that such metrics is sensitive to TBI and can potentially be used to separate both subpopulations. Noticeable differences in localization of maximum OV indexes between subpopulations have been observed.

NIH200-16, SESSION 5

Mitochondrial organization of 3D tissues as a diagnostic cancer biomarker *(Invited Paper)*

Irene Georgakoudi, Tufts Univ. (United States)

Mitochondrial organization changes dynamically within cells in response to alterations in metabolic demands. Such changes are also implicated in numerous diseases including cancer, neurodegenerative and cardiovascular diseases. However, characterization of mitochondrial organization has been limited to studies of 2D cultures, which employ approaches that rely on exogenous contrast, are invasive and qualitative. Recently, we have combined endogenous two-photon excited fluorescence imaging and automated Fourier-based image analysis approaches to quantify mitochondrial organization in 3D tissues. We have established correlations in organization with distinct metabolic states and performed studies that demonstrate the potential of using mitochondrial organization as a cancer diagnostic biomarker.

BIOGRAPHY: Irene Georgakoudi is Associate Professor of Biomedical Engineering at Tufts University. Her work focuses on the development of spectroscopic imaging approaches that rely on endogenous optical contrast to characterize tissues. She is interested in the use of these techniques for early cancer detection and monitoring of tissue development and repair.

NIH200-17, SESSION 5

Optical imaging of cellular metabolic heterogeneity in cancer
(Invited Paper)

Melissa C. Skala, Vanderbilt Univ. (United States)

Cancer is a heterogeneous disease, and sub-populations of cells can drive drug resistance. Multiphoton fluorescence intensity and lifetime imaging of the metabolic co-factors NAD(P)H and FAD is used to monitor treatment-induced metabolic heterogeneity on a single-cell level in vivo and in three-dimensional tumor organoids. This approach can be used to test therapies that target treatment-resistant sub-populations of cells in vivo, and to test new drugs and drug combinations in high-throughput ex vivo screens. Eventually, the use of primary patient tumor organoids and cell-level metabolic imaging can be used to optimize treatment strategies for individual patients.

BIOGRAPHY: Melissa Skala received her B.S. in Physics from Washington State University in 2002, her M.S. in Biomedical Engineering at the University of Wisconsin, Madison in 2004, and her Ph.D. in Biomedical Engineering at Duke University in 2007. Her postdoctoral training was also at Duke University in Biomedical Engineering. She has been an Assistant Professor of Biomedical Engineering at Vanderbilt University since 2010.

NIH200-18, SESSION 5

Predicting pre-surgical neoadjuvant chemotherapy response in breast cancer using Diffuse Optical Spectroscopic Imaging (DOSI): results from the ACRIN 6691 study *(Invited Paper)*

Bruce J. Tromberg, Beckman Laser Institute and Medical Clinic (United States); **Zheng Zhang,** Brown Univ. (United States) and The ACRIN 6691 Study Group (United States)

A two-year multi-center ACRIN study enrolling 60 subjects was designed to evaluate whether changes from baseline to mid-therapy in a DOSI-derived Tissue Optical Index (TOI = deoxyHb x %Water/%Lipid) could predict pathologic complete response (pCR) in breast cancer pre-surgical neoadjuvant chemotherapy (NAC). A 40% cutoff was established for the NAC-induced drop in tumor-to-normal (T/N) TOI. Patients were stratified using median baseline %StO2 (77%). Our results show that a combination of these baseline and dynamic DOSI response assessments predict pCR (AUC = 0.83, 95% CI 0.62 to 1.00) and may provide new insight into NAC response. ACRIN receives funding from the NCI through U01 CA079778 and U01 CA080098.

BIOGRAPHY: Dr. Tromberg is a Professor in the departments of Biomedical Engineering and Surgery and Director of the Beckman Laser Institute and Medical Clinic (BLI) at the University of California, Irvine (UCI). He is principal investigator of the Laser Microbeam and Medical Program (LAMMP), an NIH National Biomedical Technology Research Center at UCI.

NIH200-19, SESSION 5

Breaking tissue depth barriers in cancer photodynamic therapy
(Invited Paper)

Samuel Achilefu, Washington Univ. School of Medicine in St. Louis (United States)

Phototherapeutic interventions such as photodynamic therapy (PDT) are currently used in clinics for treatment of various human diseases. The exciting combination of light and photosensitizer (PS) offers a high degree of control to optimize therapy. Despite the promise of PDT, the shallow penetration of light in tissue confines its use to shallow and localized lesions. By spontaneously generating light from within cancer cells, we demonstrate a new therapeutic approach that harnesses the benefits of PDT for treating primary and metastatic tumors, regardless of the anatomical location of the disease. The intracellular light source and PS employed in this study are approved for human use.

BIOGRAPHY: Samuel Achilefu, PhD is professor of Radiology, Biomedical Engineering, and Biochemistry & Molecular Biophysics at Washington University in St. Louis, MO. His research interests are in the development of molecular imaging probes and therapeutic molecules, new methods, and devices for imaging and treatment of cancer and other human diseases.

NIH200-21, SESSION 6

Thermal imaging as a tool for real time feedback for cancer treatment and monitoring *(Invited Paper)*

Israel Gannot, Johns Hopkins Univ. (USA) and Tel Aviv Univ. (Israel)

Temperature changes tissue following energy application holds important information on the status of the tissue treated. Thermal imaging captures temperature mapping of the surface. However, together with proper mathematical algorithms, together with active time dependent energy applications, one can extract data from deep under tissue surface. This data gives information about the efficacy of the treatment in real time as well as enables monitoring healing process following treatment. This talk will describe some recent results from current projects.

BIOGRAPHY: Former chair and professor at the department of Biomedical Engineering, Tel-Aviv University and Research professor at the Electrical and Computer Engineering at Johns Hopkins University. He is a Fellow of SPIE and AIMBE. His field of research is nanoparticles based image and treatment, Functional optical imaging and bio-sensing.

NIH200-22, SESSION 6

Targeted fluorescent surgical tracers in vivo: Affibody-IRDye development for human neurosurgery *(Invited Paper)*

Brian W. Pogue, Thayer School of Engineering at Dartmouth (United States)

Brian Pogue is Professor of Engineering, Physics & Astronomy, and Surgery at Dartmouth College in Hanover, NH. At Dartmouth since 1996, he focuses on novel optical imaging systems for cancer imaging and therapy. This NIH funded research includes a P01 and several R01 grants. He is currently an editorial board member for Physics in Medicine & Biology, Medical Physics, the Journal of Biomedical Optics, and Breast Cancer Research.

NIH200-73, SESSION PS2

Differentiating malignant versus benign breast lesions based on static and dynamic optical contrast during breast compression

Bhawana Singh, Massachusetts General Hospital (United States) and Harvard Medical School (United States); **Bernhard Zimmerman,** Massachusetts General Hospital (United States) and Massachusetts Institute of Technology (United States); **Bin Deng, Qianqian Fang, David Boas,** Massachusetts General Hospital (United States) and Harvard Medical School (United States); **Jayne Cormier, Richard Moore, Daniel Kopans, Mansi Saksena,** Massachusetts General Hospital (United States); **Stefan Carp,** Massachusetts General Hospital (United States) and Harvard Medical School (United States)

Near-infrared diffuse optical imaging offers a non-invasive method for monitoring breast tissue hemodynamics. In this study we exploit differences in the bio-mechanical properties of normal, benign and tumor tissues to differentiate between benign and tumor lesions. Specifically, we measure changes in the blood volume of breast tissue in a time resolved manner after applying mammographic like compression followed by partial decompression using a multi-modal optical-DBT breast imaging platform.

Application of compression (~20-35N) results in transient hemodynamic changes in breast tissue. Based on data from 2 malignant and 3 benign lesion patients, we observed that blood volume decreases faster in tumor tissue vs. the surrounding normal breast tissue, in agreement with our previous results [1]. During subsequent partial decompression it was observed that blood volume recovery in tumor tissue was faster than in surrounding normal tissue. To the contrary, in breasts with benign lesions compression seems to lead to a faster decrease in blood volume from the normal surrounding tissue than in the benign lesion area. Finally, partial decompression blood volume recovery in normal tissue was marginally faster than in benign lesion tissue. Our results indicate that near-infrared optical imaging may offer a safe and portable, non-invasive method for characterizing breast lesions without the use of external contrast agents.

NIH200-74, SESSION PS2

Mimicking H&E stained histology on digitally acquired images via dual modality confocal strip mosaicing microscopy: towards a rapid real time bedside diagnosis of skin tumors

Manu Jain, Sanjee Abeytunge, Gary Peterson, Melissa Murray, Kishwer Nehal, Chin-Shan Jason Chen, Milind Rajadhyaksha, Memorial Sloan-Kettering Cancer Ctr. (United States)

Background: Confocal microscopy (CM) is a promising tool for rapid diagnosis of freshly excised tissues without the need for tissue processing. Despite the high sensitivity and specificity, black and white (grey-scale) and en face images pose a possible barrier in integrating CM in regular diagnostic workflow. To overcome this barrier, we propose confocal strip mosaicing microscopy (CSM-microscopy), equipped with dual-mode Reflectance CM /Fluorescence CM (RCM/FCM) imaging, to digitally mimic H&E sections for a real time rapid bedside diagnosis.

Design: Tumors from Mohs surgery were obtained and bisected. One half of the tumor was imaged with CSM, the other half was submitted for immediate frozen sectioning and routine H&E staining. Images were acquired in two modes: fluorescence and reflectance. Fluorescence images displayed nuclear morphology (similar to hematoxylin) while reflectance images displayed stroma (similar to eosin staining). H&E and confocal images were compared by the study pathologists.

Results: Normal skin structures such as the epidermis and dermis, containing hair follicles, sebaceous glands and collagen were readily recognized. In addition, aggregates of basal cell carcinoma (BCC) tumors displaying nodular, micronodular, and infiltrative subtypes were identified and appeared distinct from normal skin structures. These images correlated well with the histopathology.

Conclusion: CSM potentially provides rapid and non-invasive evaluation of skin tissue. Further, the ability to generate virtual H&E histology sections at bedside using dual-mode RCM/FCM has a great potential to substitute frozen section analysis to assist in real time bedside diagnosis via telepathology portal.

NIH200-75, SESSION PS2

Pulse thermography for search of breast tissue occlusions

Marija Strojnik, Gonzalo Paez, Ctr. de Investigaciones en Óptica AC (Mexico)

The detection of tumors, that may or may not be malignant, is currently accomplished with positron emission tomography (PET), CT (computed tomography) scans, and x-ray trans-illumination. They are all considered highly damaging to the living tissue, to the point of provoking their own class of cancers. The other optical technique that has been studied recently includes trans-illumination in visible-near infrared region, often referred to as therapeutic window. Currently, the best approach in this spectral region recommends supplementing imaging with the established magnetic resonance imaging (MRI).

The IR cameras for laboratory use were engineered in the early seventies. Just about the same time, the "war on cancer" was declared. Researchers started pointing IR cameras at woman's breast to discover subsurface tumors. The possibility of using the infrared (IR) radiation to detect occlusions a few cm within a surface layer would be very welcome as a screening method. It would replace x-ray imaging, performed under somewhat uncomfortable conditions and of still-debated credibility as a viable diagnostic tool. The development of IR detector materials, number of pixels in the focal plane arrays, and their sensitivity are being constantly improved. Sophisticated experimental setups continue to be conceived to extract the relevant information from the specimen. We examine the mechanisms of pulse propagation inside tissue to assess the wavelengths where the pulse might propagate to an occlusion and reflect from its boundary.

The depth of occlusion may be determined upon measuring the time interval during which the input temperature distribution travels to the inclusion, is reflected from it, and returns on the front surface. Diffusivity time constant and speed of pulse propagation may be calculated from the published tissue properties. They may also be calibrated for specific classes of the biological samples. When time of pulse absorption and return are separated by 2tB, they provide depth of occlusion at zB. The traditional sources of visible light are replaced with IR laser pulses.

NIH200-77, SESSION PS2

Research of extending whole slide microscopy capability by using a Darkfield Internal Reflection Illumination (DIRI) for brain and microfluidics applications

Yoshihiro Kawano, Olympus Corp. (Japan) and Department of Biomedical Engineering, Graduate School of Biomedical Engineering, Tohoku Univ (Japan); **Takuji Ishikawa,** Tohoku Univ. (Japan)

Whole Slide Imaging (WSI) produces images that simultaneously provide high resolution and a wide field of observation that can cover the entire section of sample.

We extended the capabilities of WSI system and developed a prototype system for darkfield internal reflection illumination (DIRI). Our DIRI system uses an ultra-thin light-emitting diode (LED) light source to illuminate slide specimens from the edge of the slide.

This system has four main advantages over WSI:

(1) no oil condenser is required for high resolution imaging,

(2) there is less scatter from dust and dirt on the slide specimen,

(3) there is less halo, providing a more natural darkfield contrast image,

(4) the motorized system produces darkfield, brightfield and fluorescence images.

We used DIRI system for brain and microfluidics applications. Whole slide imaging was also conducted successfully using DIRI system.

(1) The diaminobenzidine (DAB) and fluorescent staining are helpful tools for observing protein localization and volume in tissues. DIRI imaging works on the basis of light scattering from refractive index mismatches in the sample.

(2) The DIRI system could clearly produces both microbubbles image and the channel wall image by utilizing brightfield and DIRI illumination simultaneously.

(3) The methodology is useful not only for static phenomena, such as clogging, but also for dynamic phenomena, such as the detection of bubbles flowing in a channel.

(4) The tiling function significantly expands the observing area of microfluidics. The developed system will be useful for a wide variety of engineering including brain and field of microfluidics.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0058344

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116925

NIH200-78, SESSION PS2

A portable near-infrared spectral tomography system for in vivo monitoring of breast tumor response to neoadjuvant chemotherapy

Yan Zhao, Brian Pogue, Keith Paulsen, Shudong Jiang, Thayer School of Engineering at Dartmouth (United States)

Neoadjuvant chemotherapy has been accepted by an increasing number of patients who have locally advanced breast cancer. A portable hybrid frequency domain (FD)-continuous wave (CW) Near-Infrared spectroscopy NIRS system has been developed for quantifying changes in total hemoglobin, oxygen saturation and water content in the breast during neoadjuvant chemotherapy. A customized novel breast-fiber interface was designed to fit all breast sizes. During the imaging sessions, the subject is seated in a reclining position and the breast is surrounded uniformly by the interface of 16 bifurcated fiber bundles. The other 32 ends of these 16 fiber bundles are uniformly connected to a circulating plate of source and detectors. One pair of the two ends is coupled individually to FD and CW light sources while the other ends of pairs of 15 bifurcated fibers are coupled to PMT and PD detectors, respectively. 12 laser diodes, in the wavelength range of 650-1000 nm, have been divided to two groups, and each group contains 3 CW and 3 FD lasers. For each group, FD and CW data at six wavelengths has been acquired simultaneously by digital lock-in detection. Compared with sequential measurements at multiple wavelengths, simultaneous data acquisition reduced the measurement time from 12 min to less than 1min, which enables real-time in vivo monitoring of the patient response to neoadjuvant chemotherapy. A series of blood phantom with varying inclusion to background contrast was imaged. Moreover, a group of normal subjects will be scanned for performance validation of the hybrid system. The study of integrating this system into the workflow of clinical oncology practice is ongoing.

NIH200-79, SESSION PS2

Ongoing clinical experience using quantitative protoporphyrin IX guided intracranial tumor resection

Jonathan D. Olson, Stephen C. Kanick, Kolbein K. Kolste, Jaime J. Bravo, Thayer School of Engineering at Dartmouth (United States); **David W. Roberts, Keith D. Paulsen,** Dartmouth Hitchcock Medical Center (United States)

Ongoing clinical work is investigating the use of animolevulinic-acid induced protoporphyrin IX (ALA-PpIX) as a guide for neurosurgical resection of brain tumors. ALA-PpIX fluorescence can be observed visually in the surgical field; however, its fluorescence emissions are influenced by factors other than the fluorophore concentration. Specifically, fluorescence emissions are distorted by autofluorescence and background absorption and scattering properties of the tissue. Recent work at Dartmouth has led to advanced fluorescence detection methods which return quantitative assessments of PpIX concentration, which are independent of background optical properties, rather than relying on the surgeon's visual perception of the remitted fluorescence intensity. The quantitative fluorescence imaging (qFI) approach has increased sensitivity to residual disease within the resection cavity at the end of surgery that was not visible through the operating microscope.

This study catalogues observations made during an ongoing clinical investigation of ALA-PpIX based guidance of tumor resection. PpIX fluorescence is measured accurately using a point-probe and spatial variations within the surgical field are returned using a hyperspectral imaging system. Data show variations in the measured PpIX accumulation among different clinical tumor grades (i.e. high grade glioma, low grade glioma), types (i.e. primary tumors and metastases) and normal structures of interest (e.g. normal cortex, hippocampus). These results summarize the contrast enhancement and potential clinical benefit offered from quantitative measurements of PpIX concentration during resection of intracranial tumors.

NIH200-80, SESSION PS2

Detection of dermal epidermal junction and its morphology

Kivanc Kose, Memorial Sloan Kettering Cancer Ctr/ (United States); **Christi Alessi-Fox,** Caliber Imaging & Diagnostics, Inc. (United States); **Jennifer G. Dy, Dana H. Brooks,** Northeastern Univ. (United States); Milind Rajadhyaksha, Memorial Sloan Kettering Cancer Ctr. (United States)

We present 2 quantitative algorithms that imitate clinicians' process of detecting the dermal epidermal junction (DEJ) and analyzing morphology in large areas around this level. Locating the DEJ level visually is subject to variability among the clinicians due to lack of contrast and loss of resolution and sectioning around the DEJ level. Our unsupervised classification model uses loss of resolution with respect to depth, to automatically delineate the DEJ level in stacks of reflectance confocal microscopy (RCM) images. When tested on 30 stacks, this approach lead to delineation of DEJ with a precision of 7 ±12 μm in pigmented skin and 10.5 ± 7 μm in fair skin. The delineation step enables qualitative imaging of large fields of view (mosaics of RCM images) at the DEJ level that can be used for diagnostic analysis. Currently the analysis of these mosaics is done visually and quantitatively, and therefore depends highly on the experience of the dermatologist. Our initial feasibility study, shows that morphological formations at the DEJ can be identified in a quantitative way, using a bag of dense sift features based texture representation model followed by hierarchical support vector machine (SVM) classification. Our algorithm can distinguish between meshwork, ring, clod, malignant and background patterns that we encounter in benign conditions and melanomas using their textural properties. Preliminary tests with $80%$ of the data used for training and rest for testing, show results of classification as 80-67% sensitivity and 99-78% specificity in distinguishing these pattern.

NIH200-81, SESSION PS2

Confocal microscopy imaging to guide laser ablation of basal cell carcinomas

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Nehal Kishwer, Anthony Rossi, Memorial Sloan-Kettering Cancer Ctr (United States);
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Laser ablation offers a minimally invasive approach for precise and rapid removal of superficial and early nodular types of basal cell carcinomas (BCCs). However, the lack of histological confirmation after ablation has been a limitation. The use of reflectance confocal microscopy (RCM) imaging, with nuclear level resolution, may address this limitation. RCM imaging, combined with a contrast agent, can provide cellular-level histology-like feedback to detect the presence (or absence) of residual BCC tumors directly on the patient.

However, after ablation, there is a thermal coagulation layer on the surface of the wound. The coagulation must be controlled to allow uptake of contrast agent. We conducted a bench-top study to investigate the appropriate ablation parameters (fluence, number of passes) for removal superficial BCCs while also controlling the underlying thermal coagulation.

The results for an Er:YAG laser (2.9 μm and pulse duration 250us) show that, for total delivered fluence up to 150 J/cm^2 (6 passes of 25 J/cm^2), thermal coagulation can be effectively controlled, to allow both the uptake of acetic acid (contrast agent) and detection of residual BCCs. Confirmation was provided with histological examination. We also obtained similar results for a CO_2 laser (10.6um, pulse duration 720-1160 msec) with fluence up to 22.5J/cm^2 (3 passes of 6.5 J/cm^2)

Initial testing on 35 patients (fixed fluence while varying number of passes with depth) shows that the uptake of contrast agent (aluminum chloride) and imaging quality in vivo is similar to that observed in the ex vivo study. The detection of the presence of residual BCCs or complete clearance was confirmed in 16 wounds with (additional) histology and in 19 lesions with follow-up imaging. Our results indicate that resolution is sufficient but contrast must be enhanced to improve sensitivity and specificity. With further development, RCM imaging of lateral and deep margins directly on the patient may help to guide laser ablation of superficial and early nodular BCCs in the absence of histology, to provide highly localized, less invasive, faster and less expensive approaches.

NIH200-82, SESSION PS2

Cerenkov radiation dose imaging during human breast and skin radiotherapy

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Over the past century, transmission imaging of x-rays has been optimized and adapted to become the most widely adopted method of visualizing inside the body, and scatter imaging with x-rays has just recently been adopted for niche applications of sub-surface imaging. In the past 5 years, x-ray dose imaging has emerged as a way to visualize radiation delivery in radiotherapy, through capture of the small optical signal from Cerenkov emission as the cascade of electrons decelerate in tissue. This video tool is a uniquely important approach to image wide fields of view (>50 cm diameter) tissue dose delivery, with high spatial resolution (0.5-0.1 mm) with the room lights on, so that radiation therapists can visualize the treatment and verify the delivery in each fraction. Cerenkov radiation dose imaging is demonstrated in soft tissue treatment applications of whole breast irradiation, in a 12 subject pilot trial, as well as in total skin electron therapy, in a 3 subject trial. This translational work to visualize dose allows real time tracking of the combined measure of the patient location with the beam delivery, allowing on-patient measurements.

NIH200-83, SESSION PS2

Bioeffects of low intensity laser light interactions with cells and photodynamic drugs

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Civilizations have endeavored to champion the use of light to treat illnesses in the human body.

Laser light has a plethora of applications in medicine from surgery / ablation of tissues, to activation of photodynamic agents, and in optical spectroscopic diagnoses of diseases. Its mechanism of action at low intensity of exposures on cells, tissues, and the body still continues to be controversial after nearly 50 years. In this talk, we present evidence for visible red and near infrared light to enhance generation of an important chemical messenger: hydrogen peroxide. H2O2 is found to govern the stimulatory or inhibitory responses observed due to narrow wavelength band light exposures. High levels of H202 were also shown to be indicative of diseased cells which have been identified and quantified through Raman spectroscopy.

Additionally, we discuss on the remarkable properties of photodynamic agents to become preferentially retained within cancers and the physics behind their activation and mechanisms involved in photodynamic therapy (PDT). Unfortunately, due to the shallow visible light penetration depth (~2 mm to 5 mm) in tissues, the present photodynamic strategy has largely been restricted to the treatment of surface tumors, such as the melanomas. In our discussion we report on a novel non-invasive strategy in utilizing “soft” energy diagnostic X-rays to indirectly activate photodynamic drugs via x-ray down converting micron size particles and the ensuing obliteration.

NIH200-84, SESSION PS2

Development pathway for Affibody-fluorescence guided neurosurgery for EGFR-positive tumors

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Molecular guidance for surgical resection has been emerged as a tool to aid in a wide variety of surgical procedures using indocyanine green contrast agent for vascular function, tissue perfusion, and lymphatic track imaging. Current listings on clincialtrials.gov show hundreds of clinical surgical trials ongoing, yet the vast majority of these are using FDA approved non-specific agents. This is partly because there are major financial barriers to advancing agents into clinical trials with commercial backing. The development of new agents along the biological therapeutic paradigm is not financially viable, due to the high up front financial investment needed and the limitations in the revenue models of contrast agents. The hypothesized solution to this problem is to develop small molecular biologicals tagged with an established fluorescent reporter, through the chemical agent approval pathway, targeting a phase 0 trials initially, such that the initial startup phase can be completely funded by National Institutes of Health grants. In this way, fast trials can be completed to de-risk the development pipeline, and advance the idea of FGS reporters into human testing. As with biological therapies the potential successes of each agent are still moderate, but this process will allow the field to advance in a more stable and productive manner, rather than relying upon isolated molecules developed at high cost and risk. The pathway proposed and tested here uses peptide synthesis of EGFR-binding affibody molecules, uniquely conjugated to IRDye 800CW, developed and tested in academic and industrial laboratories with well-established records for GMP production, fill & finish, toxicity testing, and early phase clinical trials with image guidance.

NIH200-85, SESSION PS2

A generalizable videomosaicing method for creating panoramic reflectance confocal microscopy images

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Clinicians and pathologists prefer to image large areas of tissue in order to (i) avoid sampling errors, and (ii) examine cellular formations and morphological patterns, which is typically necessary for making diagnostic decisions. Therefore, rapid imaging of large areas is necessary in clinical settings. We present a mosaicing framework for reflectance confocal microscopy (RCM) that enables the user to visualize larger field of views by stitching together individual images of small fields of view. Current mosaicing methods for microscopy, are mostly limited to rigid transformation and prone to blurring due to blending during stitching. Our technique is capable of handling non-rigid transformation, robust against blurring as we use a graphcuts based stitching method. We borrow techniques from 3D scene reconstruction literature and panoramic imaging framework to handle non-rigid deformations, which can easily occur among frames of RCM videos due to effect of tissue deformations on the offered high resolution optical sectioning. We first register the individual images using feature matching and affine transformation estimation. Then use a graphcut based method to find stitching borders among registered overlapping frames. The frames are then stitched along these borders, instead of blending, therefore blurring at overlapping regions is avoided. We tested our technique on in-vivo RCM videos of intact skin with several conditions (e.g. benign melanocytic lesions, lentigo maligna melanoma) as well as videos captured intra-operatively at in MOHS surgical wounds of residual basal-cell carcinomas. The current version of the algorithm is capable of stitching 7 fps RCM videos with ~50% overlapping frames, which corresponds to a coverage of 240 mm2 area per minute.

NIH200-86, SESSION PS2

Mucin 1 antibody-conjugated dye-doped mesoporous silica nanoparticles for breast cancer detection in vivo

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The development of novel methods for tumor detection is a burgeoning area of research. In particular, the use of silica nanoparticles for optical imaging in the near infrared (NIR) represents a valuable tool because their chemical inertness, biocompatibility, and transparency in the ultraviolet-visible and NIR regions of the electromagnetic spectrum. Moreover, silica nanoparticles can be modified with a wide variety of functional groups such as aptamers, small molecules, antibodies and polymers. Here, we report the development of a mucin 1(MUC1)-specific dye-doped NIR emitting mesoporous silica nanoparticles (MUC1-NIR-MSN) platform for the optical detection of breast cancer tissue overexpressing human tumor-associated MUC1. We have characterized the structural properties and the in vitro performance of this system. The MSN-based optical imaging probe is non-cytotoxic and targets efficiently murine mammary epithelial cancer cells overexpressing human MUC1. Moreover; in vivo experiments, with non-tumor bearing female C57BL/6 mice, demonstrated that this platform is non-toxic under the experimental conditions used in this study. Finally, the ability of MUC1-NIR-MSN contrast imaging agent to selectively detect breast cancer tumors overexpressing human tumor-associated MUC1 was successfully demonstrated in a transgenic murine mouse model. The NIR imaging experiments on tumor-bearing animals showed specific accumulation of the MSN-based probe in human MUC1-positive tumors and small signal in control tumors. We envision that this MUC1-specific MSN-based optical probe has the potential to greatly aid in screening prospective patients for early breast cancer detection and in monitoring the efficacy of drug therapy.

NIH200-87, SESSION PS2

YC-27 urea compound for detection of prostate cancer using photoacoustic imaging

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Photoacoustic imaging (PAI) is an emerging functional imaging technique that can detect and diagnose cancer based on the near-infrared (NIR) optical absorption of either endogenous tissue constituents or exogenous contrast agents. Our goal is to develop prostate cancer (PrCa) specific contrast agents for PAI to provide enhancements in specificity, sensitivity and determine their toxicity. To enhance the application of PAI for the detection of early stage PrCa, we have performed multispectral evaluation of different NIR contrast agents. A selective NIR contrast agent YC-27 comprised of IRDye800CW conjugated to a urea that recognizes prostate specific membrane antigen (PSMA) receptors, was chosen to target the PrCa cells. PrCa cells lacking (PC3) and presenting (C4-2) the PSMA cell surface protein were used for testing the photoacoustic signal from the synthesized urea compound that binds to PSMA. These two PrCa cell lines were incubated with 4 micromolar urea compound, washed thoroughly and centrifuged. Centrifuged cell pellets were tested using a commercial fluorescence system to confirm the binding of the imaging agent to the cells and then tested using our PAI system. The average photoacoustic intensity of the C42 cells was ~6 fold higher than PC3 cells, and was highly correlated with the fluorescence data.

NIH200-88, SESSION PS2

Feasibility of intraoperative imaging with reflectance confocal microscopy to potentially guide Mohs surgery

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PURPOSE

Mohs surgery for the removal of non-melanoma skin cancers (NMSCs) is performed in stages, while being guided by the examination for residual tumor with frozen pathology. However, preparation of frozen pathology at each stage is time-consuming and labor-intensive. Reflectance confocal microscopy (RCM) imaging, directly on patients, may be utilized to detect residual tumor (or, confirm clearance) in Mohs surgical wounds. Our study tests feasibility of real-time intraoperative RCM imaging for rapid detection of residual tumor directly in surgical wounds on Mohs patients.

METHODS

We report initial results on twenty-five patients, who presented with superficial surgical wounds at the MSKCC Dermatology service. RCM imaging, using 35% AlCl3 for nuclear contrast, was performed with the Vivascope 3000 (Caliber ID). Imaging was performed in quadrants in the wound, to simulate the Mohs surgeon's examination of pathology. Images and videos were taken at the epidermal and deep dermal margins. Mohs surgeon assessed all images, videos and video-mosaics for quality and correlation to histology.

RESULTS:

Overall, RCM imaging with aluminum chloride in shave excision and Mohs surgical wounds is feasible. RCM images, videos, and video-mosaics of the epidermal and dermal margins were found to be of clinically acceptable quality. Seventeen (68%) of 25 surgical wounds could be observed with acceptable imaging quality, resolution and contrast. Bright nuclear morphology was identified at the epidermal margin. The presence of residual BCC/SCC tumor and normal skin features could be detected in the peripheral and deep dermal margins. We observed correlation between the RCM images/videos and the corresponding histology for presence of tumor in 15 wounds (12 BCC, 3 SCC) and absence of tumor in 8 wounds that showed normal skin. In two wounds, the presence of residual tumor was not detectable in the corresponding RCM images and videos (i. e. false negatives).

CONCLUSIONS

Intraoperative RCM imaging may enable detection of residual tumor, directly on Mohs patients, and may serve as an adjunct for frozen pathology. However, a stronger source of contrast (possibly, in fluorescence) will be necessary to improve sensitivity and specificity, and also a smaller device with an automated approach for imaging in the entire wound in a rapid and controlled manner for clinical utility.

NIH200-89, SESSION PS2

Two-photon fluorescence lifetime endomicroscopy for metabolic imaging

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Two-photon fluorescence intensity and lifetime microscopy of NADH and FAD redox states has been proved valuable for early disease (such as cancer) detection. To translate these methods to in vivo clinical studies, an endoscopic implementation of two-photon fluorescence lifetime microscopy (2p-FLIM) is necessary. Most reported two-photon endomicroscopes so far haven't manifested sufficient signal-to-the-noise level as required for fast FLIM. We recently developed a two-photon endomicroscope which achieves high signal collection efficiency and low background noise, therefore fast 2p-FLIM can be undertaken together with high-resolution 2p fluorescence intensity imaging. Lifetime measurement is performed through time-correlated single-photon counting (TCSPC), which not only fulfills efficient photon utilization, but also enables phasor lifetime analysis of fluorescence decay with multiple exponential components. Our endoscopic system could measure lifetime information accurately with fine spatial resolution of ~0.7 x 6.5 μm (lateral x axial) at a speed of ~3 frames/second on both stained and unstained biological samples, as verified by experiments. Specifically, through phasor analysis of NADH autofluorescence lifetime, the cellular metabolic status and its change can be assessed in vivo; by dual-channel detection of both NADH and FAD signal, the redox ratio of unstained internal tissues (including renal tubules and intestinal villi) can be calculated in vivo at subcellular resolution in real time. Our endomicroscopy technology has demonstrated promising potential for both structural and functional metabolic imaging, and investigation of its application on precancerous animal models is underway.

NIH200-90, SESSION PS2

Angle-resolved low coherence interferometry for the detection of cervical dysplasia in vivo

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Cervical cancer is the fourth most common female malignancy worldwide. Within the United States, implementation of cervical screening programs have resulted in a significant decrease in incidence and death in recent years. However, these screening techniques, including Pap smears and colposcopy-guided biopsy are greatly limited in their sensitivity and specificity, prone to inter-observer variability, dependent on observer experience, and require multiple clinical visits. As an improvement, we seek to develop angle-resolved low coherence interferometry (a/LCI) as a non-invasive optical biopsy technique for detecting cervical dysplasia. a/LCI provides depth-resolved nuclear morphology measurements of epithelial tissue and has been shown effective for early detection of dysplasia in esophageal and colonic epithelium. Recently, we completed an a/LCI pilot study of ex vivo tissue from 20 subjects undergoing cervical cone biopsies or hysterectomies, which showed significant nuclear differences between dysplastic and normal tissues. Now, we assess the feasibility of detecting cervical dysplasia with a/LCI in vivo. An a/LCI system was modified to accommodate in vivo cervical imaging, and a clinical a/LCI study was conducted in 40 women from the University of California, San Francisco (UCSF) Gynecologic Dysplasia Clinic and HPV cohort. The nuclear diameter was determined from the a/LCI scans using two analysis techniques: a Mie theory based inverse light scattering analysis and a recently developed wavelet transform analysis which demonstrated a significant speed improvement compared to traditional analysis techniques. The nuclear data from the a/LCI scans were compared to histopathological results and the processing speed and accuracy of the two algorithms were compared.

NIH200-91, SESSION PS2

Influence of cell penetrating peptide branching on cellular uptake of quantum dots

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To overcome the liabilities associated with traditional, systemic drug delivery, research efforts have focused on utilizing nanoparticle mediated drug delivery systems. These systems employ nanoparticle platforms for the assembly of complex theranostic structures which have poorly understood cellular interactions. Semiconductor quantum dots (QDs) can be incredibly valuable as a platform for understanding the intricacies of how nanoparticles are taken up by cells and their ultimate intracellular fates. Because a number of different functional moieties, such as targeting moieties and drugs, must be attached to the nanoparticle surface for efficient drug delivery and monitoring, the number of internalization peptides necessary for efficient uptake should be minimized. To accomplish this, we have designed a range of branched polyarginine peptides (1 to 16) into the backbone of a dendritic wedge employing WP9G2H6. These dendrimers were attached via metal affinity coordination to the surface of 550 nm CdSe/ZnS QDs at ratios ranging from 0.5 up to 5 peptides per QD. Prior to peptide attachments, QDs were surface functionalized with DHLA-PEG750-Ome ligands to render them colloidally stable. The efficiency and amount of QD uptake was quantified over time (up to 24 hrs). Increasing the number of polyarginine branches per peptide correlated with a higher degree of cellular uptake which was most noticeable at the lowest ratio of peptide (R= 0.5) and shortest time point tested (30 min). By increasing the polyarginine branching in the internalization peptide, more room becomes available on the nanoparticle surface for other functional moieties while still achieving efficient cellular uptake.

NIH200-92, SESSION PS2

Dynamic light scattering for detection of alpha crystallin lens protein as a new biomarker for cataract and aging

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Purpose: To use Dynamic Light Scattering (DLS) to detect and measure changes in alpha crystallin lens protein, a molecular chaperone, in association with development of aging related cataracts.

Methods: We studied the lenses of patients at the Eye Clinic of the Wilmer Eye Institute of Johns Hopkins Hospital under an IRB approved study and followed them every 6 months. All patients gave informed consent and underwent a comprehensive eye exam including grading the the lens using the AREDS cataract grading system and measurement of the alpha crystallins using the DLS device, expressed as the alpha crystallin index (ACI), the primary end point. We determined the association between changes in alpha crystallins and development of age related nuclear cataract using a random effects statistical model.

Results: We studied 66 eyes from 45 patients ages 34-79 years and with lens opacities ranging from 0-3.0 (full range 0-4). We found that as ACI levels in the lenses decreased, there was progression of nuclear cataracts. Eyes that had the lowest baseline ACI also had the fastest cataract progression. Eyes which lost ACI at the highest rates also had the fastest progression of cataracts.

Conclusion: Loss of alpha crystalins lead to development of age related nuclear cataracts. Hence DLS can be used to study and document risk of cataract progression in patients. Those with highest levels of ACI had lower risk of cataract development. DLS measurement of ACI may be used as a biomarker to study cataractogenesis and aging effects on the lens.

NIH200-93, SESSION PS2

In vivo mesoscopic voltage-sensitive dye imaging of brain activation

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The functional mapping and real-time monitoring of brain activity are important steps in understanding the functioning of the neural network. The whisker system of rodents is an excellent object to study peripherally evoked neural activity. Our previous study indicates that angled illuminationand detection configurations can improve both resolution and penetration depth. In this paper, we applied angled FLOT (aFLOT) imaging system to record 3D neural activities evoked in the whisker system of nocturnal rodents by deflection of a single whisker in vivo. A 100μm capillary and micro-electrode were inserted to mouse brain to test the capability of the imaging system. The results show that it is possible to obtain 3D functional maps of the sensory periphery in brain and the approach can be broadly applicable to functional imaging of other brain structures.

NIH200-94, SESSION PS2

Two photon and confocal imaging of postnatal development of the blood-brain barrier in rat motor cortex and auditory brainstem

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The blood–brain barrier (BBB) is a unique structure between the cerebral blood circulation and the delicate neural environment. Despite its importance in regulating the movement of molecules and ions involved in brain development and function, little is known about the physiological rates of BBB solute permeability during development in vivo. We tested the hypothesis that variations in the timing of astrocyte development correlate with different permeability properties of the BBB in different brain regions. We used a combination of two-photon microscopy, immunohistochemistry and Confocal 3D imaging analyses to determine BBB properties during postnatal development in rat primary motor cortex (M1) and medial nucleus of the trapezoid body (MNTB) in the auditory brainstem. We performed direct measurements of BBB permeability to TRITC-dextran 155 kD (an inert solute with molecular weight representative of humoral polypeptides), quantified changes of total vessel volume, and quantified interactions between astrocyte end feet processes and endothelial cells between birth (P0) and P20. We found that in the second postnatal week the BBB permeability decreased significantly in microvessels (diameter < 10?m) to adult-like levels, while vascular structure and astrocyte end feet coverage of microvessels increased significantly in both M1 and MNTB. Our studies provide the first high-resolution measurements of BBB permeability during development in vivo and suggest a unique relationship between BBB permeability, angiogenesis and astrocyte-endothelial cell interactions, independent of brain region.

NIH200-95, SESSION PS2

Mobile-phone based microscopy for imaging and sizing of single DNA molecules

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Single DNA detection and imaging in general require expensive and bulky benchtop instruments that are not readily available in developing countries or resource-limited settings. By leveraging the recent advancements in consumer electronics devices such as mobile-phones and digital cameras, we demonstrated a fluorescence microscopy system based on a smartphone that allows fluorescent imaging and sizing of single DNA molecules. This cost-effective and field-portable imaging device relies on a 3D printed opto-mechanical attachment that is integrated onto the smartphone camera module. This attachment creates a high signal-to-noise ratio darkfield imaging condition based on a high incident angle illumination (~75o) configuration. With this mobile imaging platform, we demonstrated imaging of individual fluorescently labeled and linearly stretched lambda bacteriophage DNA (48 kilobase-pair, kbp) over a 2 mm2 field-of-view, which is two orders of magnitude larger than that of a benchtop fluorescence microscope with a 100x objective. This mobile device also has a custom-developed smart application interface which transmits the acquired cellphone images to a remote server for rapid processing and measurement of the length of each DNA molecule. By testing over five different DNA samples (5, 10, 20, 40, and 48 kbp), we demonstrated the length sizing accuracy of this mobile-phone based device to be <1 kbp for 10 kbp or longer DNA strands. This mobile DNA imaging and sizing platform can useful for various point-of-care applications including for example measurements of copy-number variations in human genome, early detection of cancers, or drug resistance in infectious diseases such as TB and malaria.

NIH200-96, SESSION PS2

Distal scanning diffractive endoscope for ultrahigh-resolution volumetric imaging of internal organs

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Traditionally 3D volumetric endoscopic OCT has been able to be performed at 1300 nm with the axial resolution limited to 5-20μm. By taking advantage of the quadratic dependence of central wavelength on the axial resolution, we can increase the axial resolution to below 3μm. Here we present an ultrahigh-resolution, distal scanning, spectral-domain endoscopic OCT system operating at a central wavelength of ~830nm. 3D volumetric imaging was performed using an endoscope that features a miniature micromotor less than 1 mm in diameter able to achieve high-speed scanning (up to 200 rotations/second) and avoids the challenge of a rotatory joint in handling a broad spectrum around 830 nm. A customized diffractive lens is used in the focusing optics of the endoscope to accommodate chromatic aberrations for a broad-bandwidth light source. The combination of the light source and customized diffractive element allowed us to achieve an axial resolution of 2.4μm with a home built Ti:Sapphire light source of a 3dB spectral bandwidth of 150 nm The distal scanning mechanism enabled us to increase the overall frame-rate of the imaging system to 17 frames-per-second limited only by the sampling density requirement and the A-scan rate of the CCD in the home built linear-k spectrometer of 70 kHz. 3D volumetric imaging of ex vivo guinea pig colon was performed, where fine structures can be clearly identified including the mucosa, muscularis mucosa, submucosa and tunica muscularis and mucosal crypts, demonstrating the ability of this system to visualize microstructures with enhanced contrast. We plan to employ this endoscopic platform to study the early development of malignant polyps in a murine colorectal cancer model. Improved resolution and imaging contrast achieved by the 800nm ultrahigh-resolution OCT endoscope also facilitate image segmentation and other processing to enable optical histology staining.

NIH200-98, SESSION PS2

Surgical margin guidance for breast conserving surgery using sub-diffusive structured light imaging with microCT

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With the recent widespread adoption of neoadjuvent chemotherapy and also with developments in breast cancer screening technologies, an increasing number of breast cancer patients are undergoing breast conserving surgery (BCS) in lieu of a full mastectomy. However, 20-40% of BCS procedures are incomplete resections and require a follow up surgery. In order to curb this high re-excision rate, an intraoperative surgical guidance tool is proposed utilizing both near infrared (NIR) structured light imaging for superficial sensitivity and also X-ray computed tomography (CT) for volumetric visualization of the tumor core. The development of this device is through a collaboration between PerkinElmer and Dartmouth College funded by an Academic Industrial Partnership grant from the NIH. The CT is completely shelf shielded and the size of a standard cart as the specimen rotates axially with a stationary X-ray source-detector. The NIR structured light imaging will be integrated above the specimen allowing for CT-NIR image overlays.

With NIR structured light imaging, the penetration depth can be varied by modulating the spatial frequency of the structured light pattern. Comparing the demodulated reflectance to Monte-Carlo simulations, maps can be created for the absorption coefficient, reduced scattering coefficient, and sub-diffusive phase function parameter, which describes the fractal dimension of scatter sizes. These optical parameter maps will be shown for freshly resected breast tissue with co-registered Hematoxylin and Eosin (H&E) slides, with Receiver Operator Characteristic analyses between different breast tissue pathologies. In addition, the CT resolution and preliminary overlays between CT volumes and NIR superficial images will be presented for 3D heterogeneous tissue phantoms.

NIH200-99, SESSION PS2

Therapeutic femtosecond laser stimulated nonlinear optical effects in corneal tissue: evaluation of novel safety concerns

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Femtosecond lasers (FSL) afford unmatched levels of precision in ophthalmic surgical procedures. They are replacing many manual surgical steps and are generating new solutions that weren't previously possible in a broad area of ophthalmic applications such as FSL-assisted in-situ keratomileusis (LASIK), keratoplasty (corneal transplantation) and cataract surgery. The success of the therapeutic FSL effect has drawn attention away from other well-known, nonlinear optical effects commonly induced by ultrashort pulsed lasers such as harmonic generation (HG). FSLs induce second (SHG) and third harmonic generation (THG) in the corneal stromal collagen resulting in green and UV light production. As both of these spectral regions are capable of causing photochemical damage to collateral tissues, quantifying HG effects, understanding how laser and tissue parameters influence HG and determining ocular safety are important tasks. In this study, we have quantified HG produced by single FSL pulses using a range of FSL pulse energies. We also examined the role of FSL polarization in HG in corneal tissue. The results show HG peak power in the kW range and a strong dependence on laser polarization. Based on these results, a FSL radiation hazard analysis was performed for the most susceptible ocular tissues during worst case scenario exposures. The analyses revealed that the newest generation of FSLs may produce HG that exceeds maximum permissible exposures.

Numerical approaches of metallic nanoclusters interacting with green fluorescent proteins in the visible range

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Metallic nanoclusters with optical properties are receiving increasing attention for biological sensing applications including SERS. Their biocompatibility, sub-nanometer scale resolution, and considerable electromagnetic field enhancement giving rise to localized surface plasmons. We present the numerical approaches exploring the optical phenomena of proteins (specifically, enhanced green fluorescent proteins (EGFP)) attached to various shape of gold nanoparticle clusters via three-dimensional numerical FDTD modeling technique. EGFPs over metallic nanoparticles are physically modeled as a cylindrical shape with estimated refractive index depending on the molecular concentration of solvent solution. Electromagnetic field distributions in the vicinity of metallic nanoparticles and attached EGFPs provide insightful spatial field information with respect to each component (x, y, z) of the electric field profile at the corresponding wavelength. In particular, two coupled gold nanoparticles present distinct spectra in the visible and the NIR range with regard to the interparticle distance, the so-called nanogap. When the interparticle distance is shorter than 3 nm, quadrupolar resonance dominates over dipolar resonance. As the nanogap length increases beyond 3 nm, dipolar resonance prevail over quadrupolar resonance. Hot spot intensity at the nanogap of coupled gold nanoparticles are acutely associated with incident wavelength and polarizability. Those factors are directly attributed to the sensitivity as a function of resonant wavelength in response to variations of the surrounding refractive index. To achieve controllable hot spots and SERS signal in metal hybrid Raman nanoprobe system, the spatial optimization of metallic nanoclusters using EGFPs is presented.

NIH200-101, SESSION PS2

Quantitative receptor concentration imaging for tumor margin assessment in head and neck surgical resection

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Ninety percent of patients with head and neck squamous cell carcinomas (HNSCC) have overexpression of epidermal growth factor receptor (EGFR), which is correlated with poor prognosis. Complete surgical resection of HNSCC tumors has a large impact on patient survival, where detection of tumor at or close to surgical margins increases the risk of death at 5-years by 90%. In addition, large surgical margins can greatly increase the morbidity experienced by the patient due to functional and cosmetic damage of oral and facial structures. Single fluorescence targeting agents are often used for tumor detection in in vivo pre-clinical imaging; however, the arising signal is qualitative at best because it is a complex mixture of vascular perfusion, vascular leakage, inhibited lymphatic clearance, and receptor binding. In vivo receptor concentration imaging (RCI) allows quantification of receptor expression (hence identification of cancerous tissue) by utilizing co-administered paired-agents consisting of a targeted agent and non-targeted perfusion agent to reference the plasma delivery and leakage. A panel of HNSCC tumors with varying levels of EGFR expression (SCC-15 > SCC-25 > SCC-09) have been imaged using ABY-029, a clinically relevant anti-EGFR affibody labeled with IRDye 800CW, and affibody control imaging agent labeled with IRDye 680RD. The RCI threshold parameters for distinguishing tumor from normal tissues (skin and muscle) and the accuracy of margin detection in these tumors will be presented. RCI surgical resection will be further developed using a novel multi-channel, gated fluorescence-guided surgery (FGS) imaging system that is capable of performing RCI in normal room light.

NIH200-102, SESSION PS2

Quantitative imaging of cell signaling for personalized pancreatic cancer therapy

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Pancreatic ductal adenocarcinoma (PDAC) is a difficult cancer to treat. Molecular targeted therapies toward epidermal growth factor receptor (EGFR) have largely failed, even though the majority of pancreatic cancers overexpress EGFR. It is thought that this failure stems from both genetic mutations in EGFR and downstream signaling proteins as well as convoluted intracellular cross-talk between signaling pathways. In order to assess these issues, we developed a high-throughput screen that utilizes xenograft patient derived (PDX) tumors grown on the chicken chorioallantoic membrane (CAM) and the fluorescence-based Quantitative Protein Expression Tracking (QUIET) technique to enable prediction of patient response to molecularly targeted therapeutics in as little as a week following tumor resection. QUIET allows intracellular signaling protein quantification by monitoring three types of fluorescently labeled small molecule imaging agents: cell membrane permeable targeted and untargeted small molecule paired-agents, in addition to an untargeted tumor perfusion agent. Preliminary results demonstrated the ability to quantify the intracellular binding domain of EGFR in vitro using cell permeable agents (erlotinib-FITC and control isotype-TRITC) and in ovo using patient derived xenograft (PDX) CAM models with the same erotinib paired-agents and IRDye 700DX carboxylate (perfusion agent). It is anticipated that the QUIET method could be extended to image up to four intracellular proteins simultaneously using a multispectral tissue imaging system that allows for spectral unmixing (Nuance EX, Perkin Elmer). The development of high-throughput QUIET technology for robust protein quantification using PDX tissues will bridge the gap between genomics and proteomics, linking patient outcomes to provide truly individualize therapy.

NIH200-103, SESSION PS2

Catheter-based optical determination of met-myoglobin content for estimating radiofrequency ablated, chronic lesion formation in atrial tissue

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Single-procedure success of radiofrequency ablation (RFA) therapies has been largely limited by an inability to characterize lesion sufficiency. Momentarily successful conduction blocks may not be indicative of long-term sustained electrical blockage due to transient effects of edema. Studies have shown that the necrotic lesion core exhibits increased ferric content consistent with a rise in tissue met-myoglobin, as compared to viable tissue. Thus, we hypothesize that diffuse reflectance spectroscopic assessment of tissue met-myoglobin content could be used to reliably estimate chronic lesion extent.

A fiber-optic integrated RFA catheter was used to obtain broadband (500-650 nm) diffuse reflectance measurements at a source-detector separation of 0.8 mm at the catheter tip. Atrial samples were excised from two fresh swine hearts and supraperfused in warm (37oC) phosphate buffered saline. Optical measurements were taken for three RFA-treated tissue groups: untreated (n=7), mildly treated (n=3), and moderately treated (n=4). An inverse Monte Carlo scheme was used to invert diffuse reflectance spectra to recover concentrations of oxy-myoglobin(MbO), deoxy-myoglobin(Mb), and met-myoglobin (Mmb). Comparisons across the groups revealed significantly greater Mmb concentrations ($p<0.0001$) in the moderately treated group as compared to the other two. Additionally, an increasing trend in Mmb concentration was observed for increased tissue treatment.

Results from this study indicate that met-myoglobin quantification can serve as an important marker for estimating increased tissue treatment. Furthermore these measurements can be facilitated by real-time optical measurements made at the RFA catheter tip. On going experiments are aimed chemical validation of ferric content, histological correlation, and optimization of optical geometries.

NIH200-104, SESSION PS2

High spatial frequency modulated imaging for tissue histological evaluations

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Spatial-frequency domain imaging (SFDI) can be used to quantify the optical properties of turbid media over a large area. SFDI modulated with a high spatial frequency (HSFDI) offers a few advantages including: 1) improvements in the spatial resolution of imaging, 2) reduction in the boundary effects in extracting the optical parameters from measurements, and 3) the potential of characterizing the phase function of light scattering. The challenge of HSFDI is the lack of an appropriate model capable of describing analytically light reflectance at high spatial frequency. We have recently developed such an analytical model which incorporates the small-angle scattering approximation (SAA) to radiative transfer for sub-diffusive light reflectance and expresses the dependence of the light reflectance on the phase function of the scattering medium in a closed form. This analytical light reflectance model allows us to use a much higher spatial modulation frequency than that in a typical SFDI and extract the parameters relating to the phase function of the turbid media in addition to the scattering and absorption coefficients. These high resolution optical property maps can be potentially applied for large area tissue histological evaluations.

In this presentation, we first outline the analytical model describing light reflectance at an arbitrary source-detector separation covering both sub-diffusive and diffusion regimes for forward-peaked scattering media such as biological tissue. We then present the procedure and the results of extracting the whole set of optical properties from SFDI modulated at both low and ultra high spatial frequencies. The feasibility of SFDI for large area histological evaluations is addressed at the end by imaging both tissue phantoms and tissue specimens.

NIH200-105, SESSION PS2

Capitalizing on quantum-confined Stark effect in quantum dots for imaging action potentials

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Burgeoning interest in quantum dots (QDs) stems from their size-tunable bandgaps, which result in photophysical properties with potential application in areas as diverse as solar cells, sensing, and imaging. The tunable emission profile of QDs coupled with their physical robustness, high absorption cross sections, resistance to photobleaching, and the ability to functionalize their surfaces have drawn particular attention for application in biological imaging. Changes in QD emission as a result of applied electric fields, including a decrease in photoluminescence (PL) intensity and broadening and red-shifting of the emission profile, are collectively termed the quantum confined Stark effect (QCSE). Taken together, the effects of QCSE provide an intrinsic means of detecting changes in electric fields, an attribute which can be readily applied in imaging action potentials.

Here we examine the effects of electric fields on the PL of both Type I and Type II QDs in field strengths comparable to those found across a cell membrane. Using both static and time-resolved PL techniques, we ascertain how the field influences the emission profile, and pairing experimental observations with theoretical treatment, we are able to conclude that the PL quenching originates from ionization of the QDs. Finally, exploring the rapidity of response of the QD PL to the applied field, we are able to demonstrate changes amply able to capture the millisecond timescale of cellular action potentials.

NIH200-106, SESSION PS2

Flow analyses of microcirculation from sidestream dark-field images

Hideaki Haneishi, Minori Takahashi, Takashi Ohnishi, Chiba Univ. (Japan)

We are developing an SDF probe for microcirculation imaging. It consists of two band LED and a CCD camera. One aim of this camera is to estimate the oxygen saturation of microcirculation. That topic is under study although one outcome has been published in this may in Biomedical Optics Express. In this paper, we focus on to the blood flow analysis. One noticeable point is the introduction of L+S component decomposition to the optical blood flow. This technique can visualize the blood flow even from the very low contrast image. We can demonstrate this technique can be applicable to many other motion picture analysis in the bio photonics field.

NIH200-107, SESSION PS2

A miniature line-scanned dual-axis confocal (LS-DAC) microscope for point-of-care pathology

Chengbo Yin, Adam K. Glaser, Steven Y. Leigh, Univ. of Washington (United States); **Gary Peterson, Sanjeewa Abeytunge,** Memorial Sloan-Kettering Cancer Ctr. (United States); **Michael J. Mandella,** Stanford Univ. (United States); **Milind Rajadhyaksha,** Memorial Sloan-Kettering Cancer Ctr. (United States); **Jonathan T. Liu,** Univ. of Washington (United States)

Through recent advances in optical design and the miniaturization of components, handheld and endoscopic confocal microscopes have been developed to provide point-of-care analyses of tissue micro-anatomy and molecular markers of disease. We are currently developing a hand-held line-scanned dual-axis confocal (LS-DAC) microscope, with MEMS-based scanning, for high-speed (>15 Hz) microscopic imaging of superficial (<150-microns deep) tissue surfaces. The line-scanned DAC architecture enables fast frame rates to mitigate motion artifacts during handheld clinical use. Validation studies, performed with reflectance targets and fluorescently stained fresh tissues, show that this device has the potential to significantly impact patient outcomes by enabling early detection and surgical guidance. Future clinical applications include the examination of suspicious lesions in the oral cavity as well as for guiding the resection of brain tumors.

NIH200-108, SESSION PS2

Feasibility of evaluation of breast tissue using confocal microscopy strip mosaicing

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Background: Confocal Sstrip Mosaicing microscopy (CSM-microscopy) provides three-micron optical sectioning and one-micron lateral resolution, which allows for imaging of nuclear and morphological detail in freshly excised tissue. We conducted a preliminary investigation of the feasibility of this technology for the evaluation of breast tissue from surgical excision specimens.

Design. We imaged 74 human breast tissue specimens from 39 patients and correlated with H&E histopathology. Fresh tissue specimens were imaged in two modes: fluorescence and reflectance. Fluorescence images display nuclear morphology while in reflectance images display stroma. Using the two modes, images were colorized to mimic H&E histology in appearance. The use of fluorescence to highlight nuclei provides staining similar to hematoxylin, and the use of reflectance highlights stroma that is similar to eosin staining in pathology. Specimens were subsequently fixed in formalin and routinely processed to obtain H/E stained sections. H/E and confocal images were compared by the study pathologist.

Results: Invasive carcinomas were identified in the CSM-microscopy images and correlated well with the histopathology. In confocal images invasive and in situ carcinoma as well as benign ducts and lobules were distinguished from surrounding stromal tissue. Limitations that are typically encountered in standard histology, such as distinguishing low grade ductal carcinoma in situ (DCIS) from lobular carcinoma in situ (LCIS) or atypical proliferations were encountered in the grayscale confocal images as well.

Conclusion: CSM potentially provides rapid and noninvasive evaluation of breast parenchyma, and has a potential application for intraoperative margin assessment of resected breast specimens.

NIH200-109, SESSION PS2

On-chip imaging using synthetic aperture

Wei Luo, Alon Greenbaum, Univ. of California, Los Angeles (United States); **Yibo Zhang,** Univ of California Los Angeles (United States); **Aydogan Ozcan,** Univ. of California, Los Angeles (United States)

High-resolution imaging across a wide area is critical in various biomedical applications. Conventional lens-based microscopes are partially hindered for such tasks because of the trade-off between resolution and field-of-view (FOV). As a promising alternative, lensfree on-chip microscopy provides sub-micrometer resolution across a wide FOV that equals the area of the image sensor's active region. However, to achieve even higher resolution, previous lensfree on-chip microscope designs are challenged by the signal-to-noise ratio (SNR) deterioration and pixel-induced aberrations that high spatial frequencies experience. Here we report lensfree on-chip imaging using synthetic aperture (LISA), which mitigates some of these challenges in detection of high spatial frequencies. In LISA, the sample that is placed on an image sensor-chip is illuminated sequentially at different angles. Each oblique illumination introduces phase modulation on the specimen, shifting part of the high frequencies into lower frequencies that experience less attenuation and aberrations. Using a source-shifting based pixel super-resolution technique, we then obtain high-resolution diffraction patterns at each illumination angle. Feeding these diffraction patterns into an iterative synthetic aperture algorithm, we can reconstruct both amplitude and phase images of the specimen over a FOV of >20 mm2 at a half-pitch resolution of e.g., 250 nm, which corresponds to an effective numerical aperture of 1.4 at ~700 nm illumination wavelength. LISA also achieves robust phase recovery/retrieval, allowing us to image dense and transparent specimen including breast cancer tissue and unstained Pap smear samples.

NIH200-110, SESSION PS2

Rapid and sensitive detection of waterborne pathogens using machine learning on a smartphone based fluorescence microscope

Hatice Ceylan Koydemir, Zoltan Gorocs, Derek Tseng, Bingen Cortazar, Steve Feng, Raymond Yan Lok Chan, Jordi Burbano, Aydogan Ozcan, Univ. of California, Los Angeles (United States)

We present a field portable and cost-effective smartphone based platform for rapid and sensitive detection of Giardia lamblia cysts, one of the most common waterborne pathogens across the world. This mobile platform is composed of a disposable sample-processing cassette, a fluorescence microscope, and a custom-developed Windows based application for machine learning based specific detection of Giardia cysts. It enables screening of large volume water samples (e.g., 10 mL) and identification of fluorescently labelled G. lamblia cysts within ~1 hour, including sample collection, labelling, filtration, and automated detection. This compact device that is integrated on a mobile-phone weighs only ~205 g and utilizes a filter membrane (5 μm pores) to concentrate the labeled Giardia cysts on the surface of the porous membrane. Our fluorescence microscope that is integrated on a Windows phone allows capturing of the image of this membrane surface over a large field-of-view (~0.8 cm^2). This captured image is then transmitted to our servers through the wireless network of the smartphone for digital identification and enumeration of the cysts that are captured on the membrane using a custom-developed machine learning based detection algorithm. The result of this processing is sent back to the screen of the smartphone within ~2 min per test. The limit of detection of this handheld platform has been validated to be ~1.2 cysts/mL. We believe that this cost-effective and field-portable design that is integrated on a smart-phone could be quite useful for screening of water quality in field settings and resource limited environments.

NIH200-111, SESSION PS2

Label-free, non-invasive, ballistic imaging using light from a supercontinuum laser in new NIR windows

Laura A. Sordillo, Peter P. Sordillo, Lingyan Shi, Yury Budansky, Robert R. Alfano, The City College of New York (United States)

We have developed a label-free, non-invasive, ballistic imaging system which utilizes a compact Leukos 40 picosecond supercontinuum (SC) laser light source (model STM-2000-IR) with wavelengths in the first (650 nm to 950 nm), second (1,100 nm to 1,350 nm), third (1,600 nm to 1,870), and fourth (2,100 nm to 2,300 nm) NIR optical windows, with InGaAs (Goodrich Sensors Inc. SU320-1.7RT) and InSb (Teledyne Technologies) detectors. Due to minimal absorption by water, oxyhemoglobin and deoxyhemoglobin, a reduction in photon scattering at longer NIR wavelengths (inverse wavelength power dependence 1/?n, n≥1), and a greater number of ballistic photons from the SC laser (200 - 500 microwatt/nm power), this system can be used to image through thick tissue. Recently, we imaged through 10 mm thick animal tissue to reveal hidden abnormalities beneath tissue. Potential applications with this system include imaging through tissue to show bone disorders such as microfractures and non-displaced fractures. The tibia, for example, an area under constant pressure and at high risk for a major bone beak, could be monitored (repeated tests) for microfractures using images from this system. Boney areas such as the skull, hip, shoulder blade, elbow, thigh or waist could also be monitored. In addition, this system could provide information on brain activities and functions in live animals. The SC laser light source and IR-CCD detectors imaging system provides an easy method for instantaneously assessing abnormalities and remote areas in the body such as the brain and may be useful part of determination of the individual patient's optimal treatment protocol.

NIH200-112, SESSION PS2

Plasmonic nanoparticle assisted on-chip imaging cytometry using optical diffraction

Qingshan Wei, Euan McLeod, Univ. of California, Los Angeles (United States); **Hangfei Qi,** Univ of California Los Angeles (United States); **Zhe Wan, Ren Sun, Aydogan Ozcan,** Univ. of California, Los Angeles (United States)

Cell counting/analysis usually relies on flow cytometers that are in general bulky and expensive, partially limiting their use and applications in point-of-care medicine. Here, we demonstrate a compact and cost-effective imaging cytometry method that is based on plasmon-resonant nanoparticle assisted lensfree on-chip holography. This platform consists of a CMOS image sensor chip and a compact lensfree/lensless holographic imaging design, which uses partially coherent light to illuminate the specimen over a large field-of-view (FOV) of ~20-30 mm^2, where the diffracted optical field interferes with the background light to create in-line holograms of each cell of interest within the same sample FOV. These digital lensfree holograms are then rapidly reconstructed, providing sub-micron lateral resolution images of the cells. To introduce cellular contrast to this lensfree on-chip imaging platform, we modulated the optical extinction spectra of target cells using plasmonic nanoparticle labeling. To statistically learn the multi-spectral diffraction signatures of labeled and unlabeled cells and be able to differentiate them apart, we used machine learning approaches based on principle component analysis (PCA) and support vector machine (SVM). To demonstrate the proof-of-concept of this on-chip imaging cytometry approach, we used gold and silver nanoparticle labeling for CD4+ and CD8+ T cells, respectively, achieving an overall cell characterization accuracy of >95%. We believe that this cost-effective and compact on-chip imaging cytometry platform could be very useful for point-of-care diagnostics applications especially in resource-limited or remote settings.

NIH200-113, SESSION PS2

In-vivo monitoring of mitochondrial dynamics using solely endogenous contrast

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Mitochondria are key supporters and regulators of cellular processes. Little is known though about the physiological or pathophysiological role of mitochondrial dynamics, especially in 3-dimensional tissues, as the organization of the mitochondrial machinery is traditionally studied in two-dimensional cell cultures, using exogenous stains. In this study, we apply an automated, quantitative analytical approach to two-photon excited fluorescence (TPEF) endogenous images acquired in-vivo from human squamous stratified epithelia and assess changes in their mitochondrial dynamics non-invasively.

In-vivo depth-resolved TPEF images were acquired from the epidermis of a healthy volunteer during arterial occlusion and reperfusion, using a multiphoton microscopy-based clinical tomograph (MPTflex, Jenlab) at 790nm excitation and 410nm-650nm emission. Measurements were conducted according to an approved institutional protocol. The acquired TPEF images were processed in Matlab to firstly isolate features emanating predominantly from mitochondria and then extract, by a Fourier-based approach described previously, information related to mitochondrial dynamics over time.

The fast temporal analysis demonstrates rapid mitochondrial organization changes occurring in the epithelial layers that follow the hypoxia induction from the arterial occlusion. Further the mitochondrial dynamics occurring in the upper versus the deeper epithelial layers in response to arterial occlusion and reperfusion are distinctly different, implying a stronger dependence of the deeper layers to vascular oxygenation.

In conclusion, we show that fast temporal monitoring of mitochondrial dynamics is feasible within three dimensional tissues of human subjects. Our approach offers the potential to observe dynamically, in a non-invasive and quantitative manner, subtle changes in mitochondrial organization in response to treatment in vivo.

NIH200-114, SESSION PS2

Intra-operative dual channel blue/red excitation imaging of protoporphyrin IX during neurosurgical resection of brain tumors provides topographic sensitivity to subsurface malignancy

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Successful outcome of surgical resection of malignant glioma (MG) is related to the extent of tumor removed during surgery. While aminolevulinc-acid induced protoporphyrin IX (PpIX) based fluorescence-guidance enhances contrast between primary malignant and normal tissue, clinical determination of the boundaries of the resected volume is limited to an assessment of the surface of the exposed surgical margin. This is because standard fluorescence imaging techniques match the excitation wavelength with the maximum absorption band of PpIX, which is 30-folder higher in the blue (at 405 nm) relative to red (at 635 nm). However, hemoglobin absorption is 600-fold greater in the blue compared with red, so absorption-based attenuation causes blue excited PpIX fluorescence images to be much more superficial than those collected using red excitation. This study investigates the use of dual-channel excitation of PpIX fluorescence to gain sensitivity to tumor located at depth.

Monte Carlo simulations were used to characterize the depth of origin of PpIX fluorescence sampled by red and blue excitations. Measurements in tissue-simulating phantoms revealed the sensitivity of blue and red excited PpIX images to variations in the depth of fluorescence inclusions. Preliminary clinical intra-surgical images also show substantial differences in blue and red PpIX maps in the brain, which are interpreted using co-registered MRI assessment of tumor location. These data suggest that coupled interpretation of blue/red PpIX fluorescence could provide a simple approach to evaluate the subsurface topography of tumors, information that cannot be detected by standard monochromatic source fluorescence imaging techniques.

NIH200-115, SESSION PS2

Broadband optical mammography: optical contrast of human breast cancer

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Using a continuous-wave, broadband optical mammography system (650-850 nm), we have collected optical mammograms in a transmission geometry with the breast placed between two parallel plates. Implementing a model based on diffusion theory, we generate breast maps of the concentrations of deoxy-hemoglobin, [Hb], oxy-hemoglobin, [HbO], water, and lipids. Hemoglobin saturation (SO_2) defined as [HbO]/([Hb]+[HbO]), is another parameter measured, which is indicative of the perfusion and metabolic activity of breast tissue. We have examined 25 healthy patients, 35 patients with benign lesions, and 26 patients with cancer, and recorded images of [HbO], [Hb], water, lipids, and SO2. We investigated the asymmetry between the right and left breasts, the spatial heterogeneity of the chromophore concentrations, and how the choice of a "normal" reference tissue may impact the contrast measured for breast lesions. For the 26 breast cancer patients measured, when considering the reference tissue to be the healthy tissue in the ipsilateral breast, cancer was found to feature an average increase of 1.2 μM in [Hb], 1.1 μM in [HbO], and 7% in [water] and a decrease of 8% in [lipid] and 5% in SO_2. We are currently imaging breast cancer patients undergoing neoadjuvant chemotherapy and monitoring changes of the chromophore concentrations and hemoglobin saturation within the diseased and healthy breast. We characterize the impact of using different reference tissues in either the ipsilateral or contralateral breast in the definition of tumor contrast. Additionally, we aim to determine the most effective optical parameters for distinguishing pathologic complete responders from non-complete pathologic responders.

NIH200-116, SESSION PS2

High-throughput imaging of pathology slides using on-chip microscopy

Yibo Zhang, Univ. of California, Los Angeles (United States); **Alon Greenbaum,** California Institute of Technology (United States); **Alborz Feizi, Ping-Luen Chung, Wei Luo, Shivani R Kandukuri, Aydogan Ozcan,** Univ. of California, Los Angeles (United States)

Bright-field microscopy is one of the standard tools used in pathology to assist the observation of cell abnormalities and diagnosis of diseases. However, the bulkiness, high cost, relatively small field-of-view (FOV) and the requirement for focus adjustment make the conventional microscope less ideal to be used at point-of-care offices and resource-limited-settings. Lensfree on-chip microscopy based on digital holography helps us mitigate some of these drawbacks, achieving high-resolution and wide FOV in a low-cost and field-portable setup. Here we demonstrate lensfree pathology slide imaging over a large FOV (>20 mm^2) enabled by a multi-height based on-chip imaging scheme in combination with transport-of-intensity equation for improved reconstruction speed, digital tilt correction for automatic removal of sample tilt related aberrations, and colorization algorithms. To demonstrate the performance of this platform, we imaged breast cancer tissue, Papanicolaou smears (consistent with a high-grade squamous intraepithelial lesion) and sickle-cell disease blood smears. A board-certified pathologist examined these lensfree images and compared them to conventional microscope images of the same specimen, confirming the agreement of clinically relevant features between the two imaging modalities. To quantify the diagnostic accuracy, 75 different regions of breast tissue taken from benign, atypical/DCIS and invasive carcinoma samples were imaged by both our lensfree microscope and a conventional lens-based microscope, and these images were sent blindly to a pathologist for evaluation, resulting in an overall diagnostic accuracy of ~99% using the lensfree microscope. This on-chip microscope design is promising to meet the high-throughput, low-cost and mobile imaging needs even in resource-limited-settings.

NIH200-117, SESSION PS2

Needle tip tissue identification by Raman spectroscopy

Jeon Woong Kang, Massachusetts Institute of Technology (United States); **T. Anthony Anderson,** Massachusetts General Hospital (United States); **Ramachandra R. Dasari, Peter T.C. So,** Massachusetts Institute of Technology (United States)

Many medical procedures use a blind, or semi-blind, approach for needle tip placement. These procedures include epidural catheter placement, laparoscopic surgery trocar placement, tissue biopsies, joint injection, lumbar puncture, and fluid collection aspiration. Complications related to these procedures can be serious and are commonly a result of needle tip misplacement. There is a tremendous need for devices which allows identification of tissues at the tip of needles in vivo. Each year, 2.4 million epidural catheters are placed for labor and delivery. An equal number are placed for postoperative acute pain control annually as well. There is a high rate of obesity in surgical patients and this population is associated with a greater number of epidural blockade complications. The failure rate for epidural catheter analgesia is 12-13% due to the failure to accurately locate the epidural space.

Multi-modal spectroscopy using Raman spectroscopy, diffuse reflectance spectroscopy, and intrinsic fluorescence spectroscopy can measure biochemical and morphological information about tissues non-destructively. MMS has previously been shown to differentiate between cancerous and normal tissues and to enable identification of atherosclerotic plaques. We have shown that Raman spectroscopy can differentiate the tissues overlying the epidural space (skin, fat, muscle, supra-/intra-spinous ligament, ligamentum flavum) and those beyond it (epidural fat, dura mater, spinal cord) in an ex vivo animal model. By decomposing tissue Raman signal into five basis spectra, all eight tissues were successfully differentiated.

NIH200-118, SESSION PS2

Tunable breast-simulating phantoms for photoacoustic tomography image quality assessment

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Photoacoustic Tomography (PAT) is a rapidly emerging imaging modality with strong potential for applications such as lymph node localization and cancer detection, especially in breast tissue. Standardized testing can expedite clinical translation of medical products, and well-developed methods exist for established medical imaging technologies (CT, MRI). Therefore, as PAT matures, there is an increasing need for well-validated phantom-based methods for quantitative, objective image quality characterization. Standard phantoms for PAT must exhibit biologically-realistic optical and acoustic properties, including sound speed and acoustic attenuation, that are uniform across the imaged region and highly stable over time. All prior published phantoms fail to provide at least one of these characteristics. Therefore, we have developed novel, robust tissue-simulating phantoms based on PVC plastisol (PVCP) with tunable optical and acoustic properties and implemented them as a demonstration of their utility. Breast-mimicking phantoms were fabricated which contained blood vessel-mimicking tubes of varying size and depth, which contained bovine blood at different states of oxygen saturation. This phantom was imaged using a custom PAT system based on a tunable pulsed NIR OPO laser source and a research-grade ultrasound system capable of supporting commercial ultrasound transducers with different operating parameters. Quantitative metrics such as penetration depth, low-contrast detectability, contrast-detail analysis, and uniformity were determined for optical wavelengths of 700-900 nm and radiant exposures of 5-20 mJ/cm^2. Results demonstrate the suitability of our realistic bi-modal PVCP phantom and indicate that phantom-based test methods can facilitate characterization of essential performance in PAT systems.

NIH200-122, SESSION PS2

Facial plethora: modern technology for quantifying an ancient clinical sign and its use in Cushing syndrome

Ali Afshari, National Institutes of Health (United States)

Facial plethora is a clinical sign described since ancient times for a variety of diseases. In the 19th century, it was linked to increased blood volume or flow but this has never been proven. Facial plethora is also one of the early described clinical features of Cushing's syndrome (CS). This study aimed to quantify FP changes in CS as an early assessment of cure following surgery using new technology. Non-invasive multi-spectral near-infrared imaging (MSI) was performed on the right cheek of patients before and 4.9 ± 3.1 days after surgery. Clinical data obtained from 34 patients indicate that a decrease in facial plethora after surgery as evidenced by a decrease in blood volume fraction is linked with cure of CS. This novel technology for the first time identified a physiologic mechanism associated with an ancient clinical sign. Furthermore, as a proof of principle, MSI is a promising early marker of cure in patients with CS that compliments biochemical and clinical data.

NIH200-124, SESSION PS2

Diffuse Optical Spectroscopic Imaging (DOSI) of breast density and composition during Tamoxifen treatment

Thomas D. O'Sullivan, Anais Leproux, George P. Philipopoulos, Alice M. Police, Freddie Combs, Min-Ying Su, Bruce J. Tromberg, Univ. of California, Irvine (United States)

Several studies have shown that hormonal therapies given to reduce the risk of breast cancer are most effective when accompanied by a reduction in mammographic breast density. These results suggest that change in breast density is a surrogate endpoint of hormonal therapy response and could guide personalized treatment. With that goal in mind, we present the design and preliminary data from an ongoing multi-site prospective study designed to assess whether these changes can be measured by DOSI - a safe, noninvasive, and portable optical imaging tool. Preliminary data demonstrate that breast water and lipid composition correlates with MRI-measured breast density.

NIH200-23, SESSION 7

Understanding biomechanics of sickle cell disease at individual cell level *(Invited Paper)*

Peter T. C. So, Massachusetts Institute of Technology (United States); **Poorya Hosseini, Sabia Abidi, Sarah Du, Ming Dao,** Massachusetts Institute of Technology (United States); **Geregory Kato,** Univ. of Pittsburgh (United States); **John M. Higgins,** Harvard Medical School (United States); **Zahid Yaqoob,** Massachusetts Institute of Technology (United States)

Sickle cell disease (SCD) is an inherited blood disorder where the sickle hemoglobin polymerizes when deoxygenated, leading to vaso-occlusion and restricted blood flow in capillaries and small vessels. To this end, we are developing state-of-the-art label-free optical imaging assays combined with microfluidics to quantify biomechanical and morphological changes at single cell level. High-throughput measurement of above-mentioned biophysical properties together with established biochemical markers will advance our understanding of SCD and that of the pharmaceutical mechanisms of existing as well as new drugs in the pipeline, and set path for future monitoring of individual patients to avoid sickle cell crisis.

BIOGRAPHY: Peter So is a professor in the Department of Mechanical and Biological Engineering in the Massachusetts Institute of Technology. His research focuses on biomedical optics with applications ranges from infectious diseases to neurobiology. He is the Director of the MIT Laser Biomedical Research Center, a NIH NIBIB P41 research resource

NIH200-24, SESSION 7

Super-resolution imaging using multi-photon and multi-photon-like fluorescence microscopy techniques *(Invited Paper)*

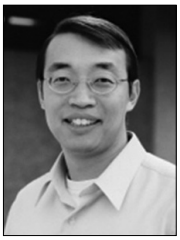
George H. Patterson, National Institute of Child Health and Human Development (United States)

Multi-photon microscopy provides deeper tissue imaging capacity than most linear fluorescence imaging techniques but often suffers relatively high illumination intensities required for nonlinear excitation. We will discuss "two-step" fluorescence microscopy, a new approach to nonlinear imaging requiring orders of magnitude less light than conventional multi-photon excitation. This technique is based on positive reversible photoswitchable fluorescent probes, such as Padron, which display behaviors necessary for the "two-step" approach. These require that the fluorescent molecule photoswitch or ideally rapidly equilibrate to a non-fluorescent state, that the probe photoswitch to an active fluorescent state, and that the same wavelength used to turn on the probe also excite the active state to produce fluoresce. Since both activation and excitation are linear processes requiring sequential absorption processes, the total fluorescent signal is proportional to the square of the illumination dose. Thus, two-step microscopy is similar in principle to two-photon microscopy but with orders-of-magnitude better cross-section.

BIOGRAPHY: George Patterson received a B.S. from the University of North Alabama in 1992. He received a Ph.D. for studies with David Piston at Vanderbilt University in 1999. His post-doctoral studies at NIH were performed in Jennifer Lippincott-Schwartz's lab. Currently, his lab in NIBIB focuses on fluorescent protein development for imaging.

NIH200-25, SESSION 7

Multiphoton imaging for clinical endoscopy *(Invited Paper)*



Chris Xu, Cornell Univ. (United States)

Imaging intrinsic tissue fluorescence and harmonic generation is an area that showcases the unique advantages of multiphoton microscopy. The primary engineering challenge of translating this advantage for clinical application lies in miniaturizing bulky microscope components into a small diameter flexible probe without comprising imaging performance. In this talk, we will show that multiphoton imaging of intrinsic molecules and harmonic generation in living tissue revealed similar resolution and details of standard histology, but without tissue removal or the use of exogenous stain. We will present our effort on developing miniature multiphoton endoscopes that are capable of high-resolution imaging in live animals.

BIOGRAPHY: Chris Xu is Professor of Applied and Engineering Physics, Cornell University. Prior to Cornell, he was a member of technical staff at Bell Laboratories. He received his Ph.D. in Applied Physics, Cornell University. His current research areas are fiber optics and biomedical imaging, including endoscopy and deep tissue optical microscopy.

NIH200-26, SESSION 8

Redefining the spatiotemporal limits of optical imaging: photoacoustic tomography, wavefront engineering, and compressed ultrafast photography *(Keynote Presentation)*

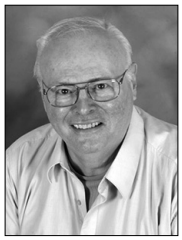
Lihong V. Wang, Washington Univ. in St. Louis (United States)

Photoacoustic tomography (PAT), combining optical and ultrasonic waves via the photoacoustic effect, provides in vivo functional, metabolic, molecular, and histologic imaging. PAT has the unique strength of high-resolution imaging across the length scales of organelles, cells, tissues, and organs with consistent contrast. PAT has the potential to empower multiscale biology research and accelerate translation from microscopic laboratory discoveries to macroscopic clinical practice. PAT may also hold the key to the earliest detection of cancer by in vivo label-free quantification of hypermetabolism, the quintessential hallmark of cancer. Broad applications include imaging of the breast, brain, skin, esophagus, colon, vascular system, and lymphatic system in both humans and animals.

BIOGRAPHY: Beare Distinguished Professor. Editor-in-Chief of JBO. 425 journal articles with an h-index of 99 (>38,000 citations). 430 keynote/plenary/invited talks. OSA Mees Medal, NIH Director's Pioneer and Transformative Research Awards, Goodman Book Award, IEEE Technical Achievement and Biomedical Engineering Awards, Britton Chance Biomedical Optics Award. Honorary doctorate from Lund University, Sweden.

NIH200-27, SESSION 8

Light advances in biomedicine *(Keynote Presentation)*



Robert Alfano, The City College of New York (United States)

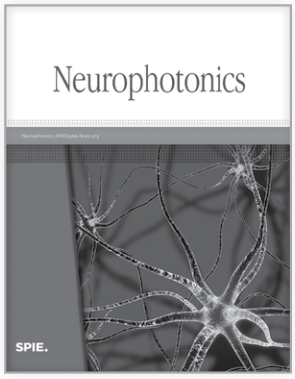
The talk presents advances in novel state-of-the-art non-invasive spectroscopic methods to detect the onset and progression of cancer, including pre-malignancy, malignancy, and most important native label-free markers such as Tryptophan that can denote aggressive cancers of tissue and cells for future translation into the clinical setting. The presentation will discuss applications of 3 unused Near Infrared optical spectral windows (900 nm to 2500 nm) in biological tissues for deeper imaging of brain and breast achieved by reduced light scattering and image blurring. In multiphoton microscopy deeper images of brain blood vessels and neurons may be obtained by selecting excitation and emission wavelengths of upper S2 state of contrast agents (dye, quantum dots) to fall within optical windows of tissue. It will allow better view of optical signatures from normal and diseased tissues, understand the underlying biochemical and structural changes of tissues and cells responsible for the observed spectroscopic signatures associate with cancer. In the past only the therapeutic window from 700 nm to 950 nm was widely used due to available Silicon based photo imagers. The advent of photo imagers for 900nm to 1800nm spectral zone based on InGaAs allows the used in the imaging in the new NIR zones . Spatial frequencies of images from absorption or emission from stained and unstained tissue slices can be analyzed to create a new approach for optical histology. This presentation covers a wide array of well-established label-free optical biopsy techniques and novel approaches to diagnose tissues changes, including in vivo and ex vivo fluorescence spectroscopy, Stokes shift spectroscopy, Raman spectroscopy, and multiphoton methods .

BIOGRAPHY: Distinguished Professor of Science and Engineering at The City College of New York, has contributed significantly to the field of ultrafast laser science and is a pioneer in the application of light and photonics technologies to the study of biological, biomedical and condensed matter systems. His crowning research achievements include discovery of supercontinuum, development of new tunable Cr^{3+}/Cr^{4+} lasers, advance of laser spectroscopic and optical imaging techniques for condensed matter and biomedical photonics, and study of ultrafast optical pulse propagation and imaging in scattering media. He is a fellow of APS, OSA, IEEE, NY Academy of Science, and Alfred P. Sloan fellow. He has received his Ph.D. in physics from New York University. He spent 8 years at GTE Labs (now Verizon) from before joining CCNY. He has received OSA Charles Hard Townes Award in 2008, SPIE Britton Chance Biomedical Optics Award in 2012, and APS Arthur L Schawlow Prize in Laser Science in 2013.

Neurophotonics

Published by SPIE

David A. Boas
Massachusetts General Hospital
Harvard Medical School
Editor-in-Chief



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Aims and Scope

At the interface of optics and neuroscience, *Neurophotonics* covers cutting-edge technological advances and the impact on neuroscience and clinical applications.

Novel optical technologies for imaging and manipulation of brain structure and function span from visualization of intracellular organelles and protein assemblies to noninvasive macroscopic investigation of cortical activity in human subjects. The methods and applications are growing rapidly and are driving profound advances in understanding brain phenomena such as electrical excitability, neuroglial partnership, neurovascular signaling, metabolic activity, and hemodynamics in health and disease.

Indexed in PubMed

Neurophotonics publishes peer-reviewed papers on a broad range of topics highlighting the impact of novel optical methods in the neurosciences including:

- Microscopic methods
- Super-resolution nanoscopic methods
- Optogenetics and other optical methods of manipulating cellular behavior
- Synthetic and genetically encoded optical reporters and actuators
- Optical clearing methods
- Methods to investigate neuroglial and vascular physiology
- Methods to investigate cellular energetics
- Noninvasive methods of measuring and imaging brain function and physiology
- Photoacoustic methods spanning from optical to acoustic resolution
- Clinical and translation applications
- Computational methods relevant to understanding and interpreting optical measurements.

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GENERAL INFORMATION

NATIONAL INSTITUTES OF HEALTH

National Institutes of Health
Masur Auditorium, Building 10
10 Center Drive
Bethesda, MD 208922

NIH Visitor Information Center is located near the Natcher Conference Center (Building 45). NIH Visitor Information Center phone number is 301-496-1776, and fax number is 301-402-0601. Go through the main entrance on South Drive; Building 45 is located south on Center Drive near Rockville Pike. Entering the main lobby, the NIH Visitor Information Center is located left of the dining services area.

LOCAL TRANSPORTATION

Metrorail Transportation (Washington Metropolitan Area Transit Authority) Metrorail is the clean, safe, easy-to-understand rail transit system serving the Washington, D.C. area. Metrorail serves 78 stations along 96 miles of track, using 5 color-coded lines that intersect at various points enabling passengers to change trains.

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Each passenger must have a farecard, which can be purchased for any amount. At each station, fares and approximate times to all other stations are posted. In addition to farecards, Metro offers a variety of passes that are good for both bus and rail travel. The farecard stores the value paid and deducts your fare when you leave the system. Rates are subject to change. For more information, visit the website:

http://www.wmata.com/

Metrorail from the Doubletree Hotel to NIH

The closest Metrorail Station to The DoubleTree Hotel & Executive Meeting Center - Bethesda is the Medical Center Metro Stop on the red line and you can get there by complimentary shuttle. The hotel has a complimentary shuttle that runs every hour from 7:00 am to 10:00 pm. The shuttle stops at the Medical Center Stop (red line).

Metrorail from the Doubletree Hotel to Reagan International

From the Medical Center Stop (red line) above, you can catch the Metrorail to Reagan International (DCA). You will need to transfer to the blue line at Metro Center Stop. The blue line will take you to the Reagan National Airport stop. The Metrorail station at the Reagan airport is directly adjacent - walking distance into the airport. It is 15 miles to the airport from the DoubleTree Hotel & Executive Meeting Center - Bethesda, and the trip to the airport takes approx. 45 minutes to 1 hour traveling time.

SUPERSHUTTLE

From REAGAN WASHINGTON NATIONAL to NIH

From DULLES to NIH

From BALTIMORE to NIH

Book Online or call 1-800-BLUE VAN (1-800-258-3826) at least 24 hours before your departure. Rates are subject to change.

Taxi Fare to the Natcher Center (Building 45) National Institutes of Health

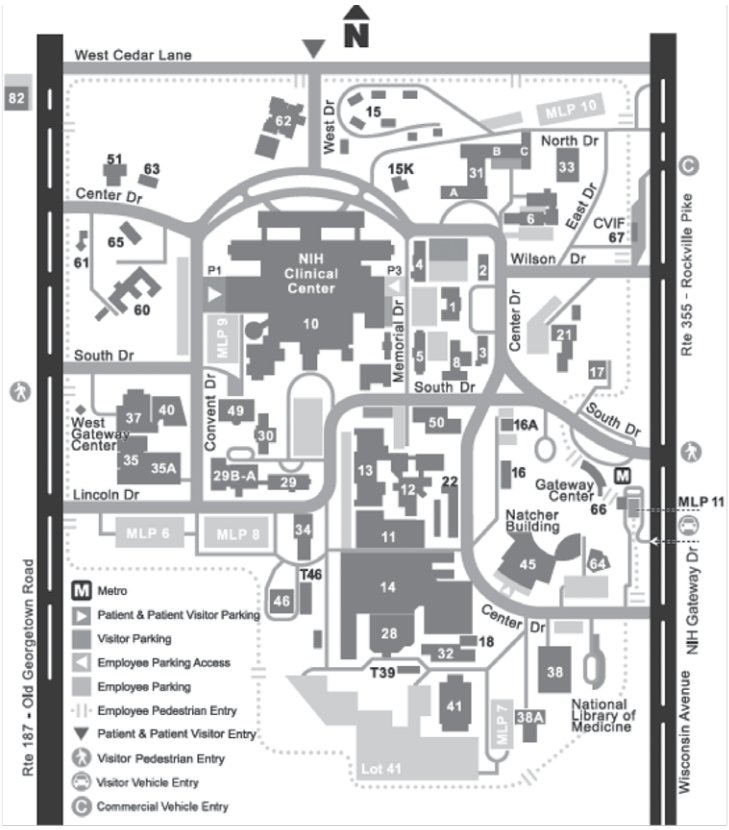
(Rates are subject to change)

From Reagan Airport from $30 (15 miles)

From Baltimore Washington Int'l Airport from $92 (34.5 miles)

From Dulles Int'l Airport from $55 (26.2 miles)

NIH VISITOR MAP



PARKING AT NIH

Visitor Parking is extremely difficult to find at NIH, so if at all possible, take public transportation.

There are NEW SECURITY MEASURES in place at NIH for all visitors.

COMPLIMENTARY SHUTTLE TO NIH

The Doubletree has a complimentary shuttle that runs every hour from 7:00 am to 10:00 pm. The shuttle stops at the Medical Center Metro Station Stop (red line). The shuttle will continue on to the NIH and stops at Natcher Center and then at Building #10, meeting location.

Shuttle schedule available online.

Hertz Car Rental has been selected as the official car rental agency for this event. To reserve a car, identify yourself as an NIH Workshop Conference attendee using the Hertz Meeting Code CV# 029B0020. Note: When booking from International Hertz locations, the CV # must be entered with the letters CV before the number, i.e. CV029B0020.

• In the United States call 1-800-654-2240.

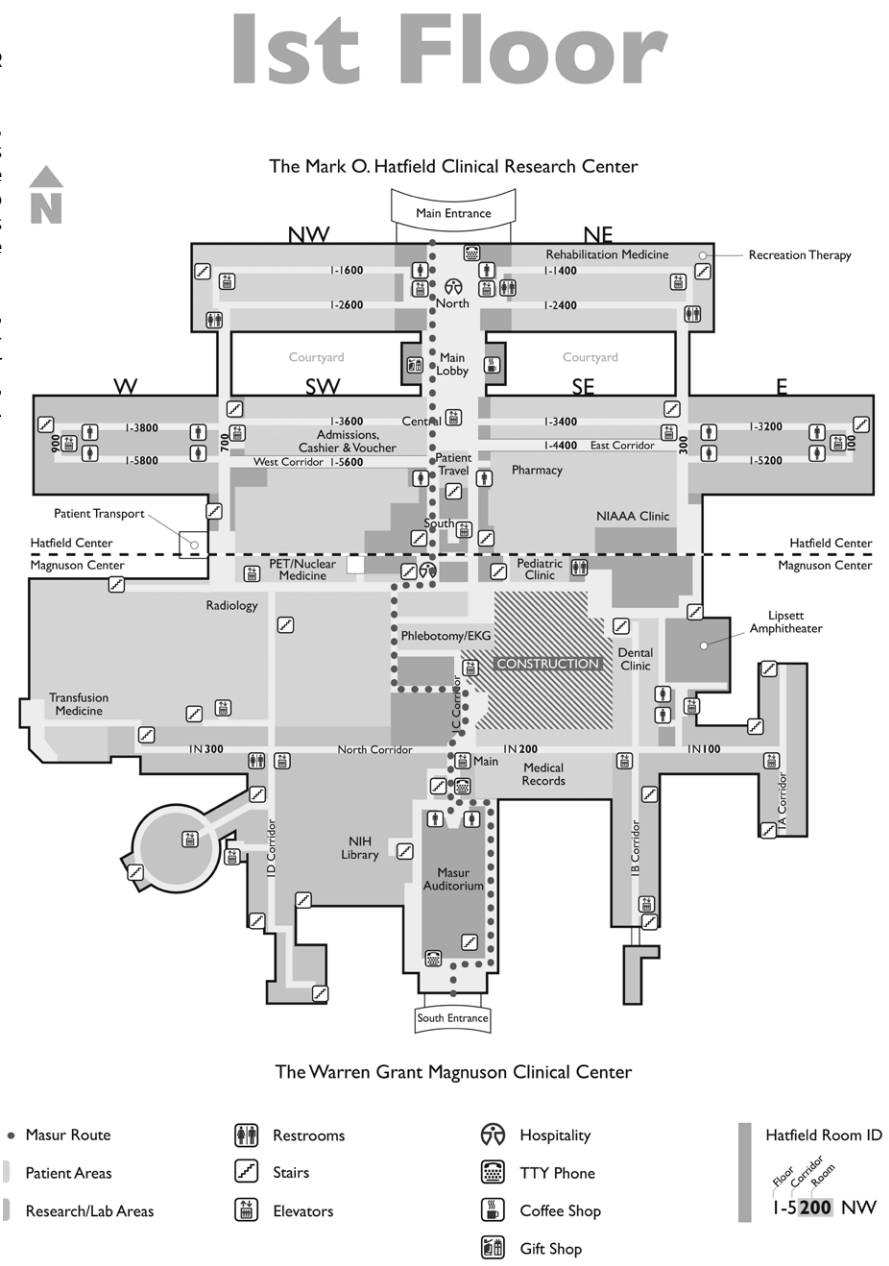
Book Online at www.hertz.com.

MEETING LOCATION

FIRST FLOOR OF THE CLINICAL CENTER (BUILDING 10)

From the North lobby entrance: From the lobby, proceed down the right side, passing Admissions on your right. Continue straight through the sliding glass doors, following posted signs to the Masur. Continue to follow the 'Detour' signs to the Masur. The auditorium is just past the main elevators.

From the South lobby entrance: From the lobby, take either the left or right hallway up a slight incline until you come to the entrance of the Masur Auditorium. When the two hallways converge, you will be standing in front of Masur Auditorium.



HOTEL INFORMATION

NOTE CONCERNING HOUSING

The following is a list of hotels that are located near the NIH. This list is a suggestion of the nearest hotels to the facility.
Special hotel rates have not been negotiated.

Hyatt Regency Bethesda
7400 Wisconsin Avenue, Bethesda, MD 20814

Bethesda Marriott
5151 Pooks Hill Road, Bethesda, MD 20814

Doubletree Hotel Bethesda
8120 Wisconsin Avenue, Bethesda, MD 20814

Hilton Garden Inn Bethesda
7301 Waverly Street, Bethesda, MD 20814

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Registrants for paid elements of the event, who do not provide a method of payment, will not be able to complete their registration. Individuals with incomplete registrations will not be able to attend the conference until payment has been made. SPIE accepts VISA, MasterCard, American Express, Discover, Diner's Club, checks and wire transfers. Onsite registrations can also pay with Cash.

Authors/Coauthors

By submitting an abstract, you agree to the following conditions:

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Conferences, courses, and poster sessions: For copyright reasons, recordings of any kind are prohibited without prior written consent of the presenter or instructor. Attendees may not capture or use the materials presented in any meeting/course room or in course notes on display without written permission. Consent forms are available at Speaker Check-In. Individuals not complying with this policy will be asked to leave a given session and/or asked to surrender their recording media.

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Unauthorized solicitation in the Exhibition Hall is prohibited. Any non-exhibiting manufacturer or supplier observed to be distributing information or soliciting business in the aisles, or in another company's booth, will be asked to leave immediately.

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For the health and consideration of all attendees, smoking, including e-cigarettes, is not permitted at any event elements, such as but not limited to: plenaries, conferences, workshops, courses, poster sessions, hosted meal functions, receptions, and in the exhibit hall. Most facilities also prohibit smoking and e-cigarettes in all or specific areas. Attendees should obey any signs preventing or authorizing smoking in specified locations.

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