Boston University Neurophotonics Center

Annual Report 2017-2018

BU Neurophotonics Center

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Message From the Director

I am extraordinarily pleased to describe here the activities of the Boston University Neurophotonics Center during its inaugural academic year, 2017-2018. This was an action-packed time, to say the least. While the Center started in July of 2017 as a construction site, it finished the academic year with 7 optical bays, a surgical suite, mechanical and electrical shops, and human subject testing space actively used by 34 faculty of the Neurophotonics Center and the members of their labs. The main Center laboratory space is situated in the Life Science and Engineering Building at 24 Cummington Mall with additional activities in the Cognitive Neuroimaging Center in the Kilachand Center for Integrated Life Sciences and Engineering at 610 Commonwealth Ave, amongst the neuroscience and photonics faculty of the Boston University Charles River Campus.

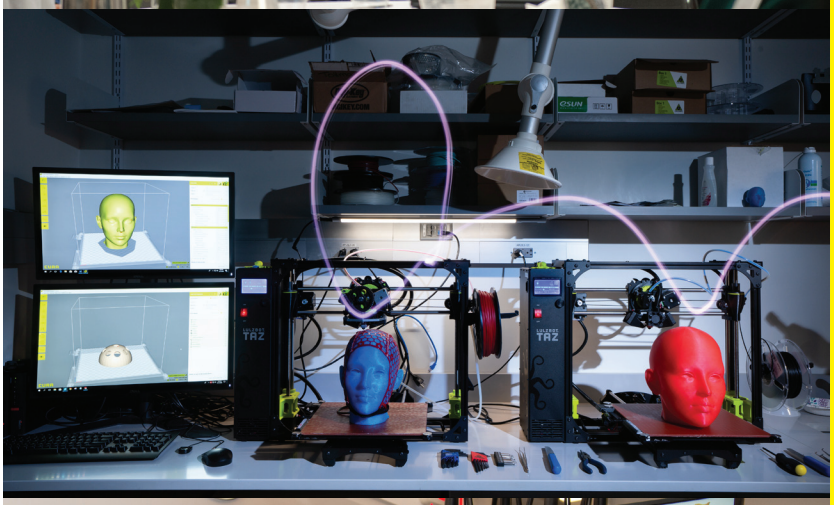
An overwhelming strength of the Center is the community of students, fellows, staff, and faculty who all actively contribute to realizing the *Center's mission: to build and support an interdisciplinary community that can develop and broadly deploy impactful photonics technologies in the neurosciences to advance our understanding of how the brain works in health and in disease.* Fortuitously, the launch of the Neurophotonics Center coincided with a $3M Neurophotonics NSF Research Training Grant to foster growth of the community and promote graduate traineeships. In its first

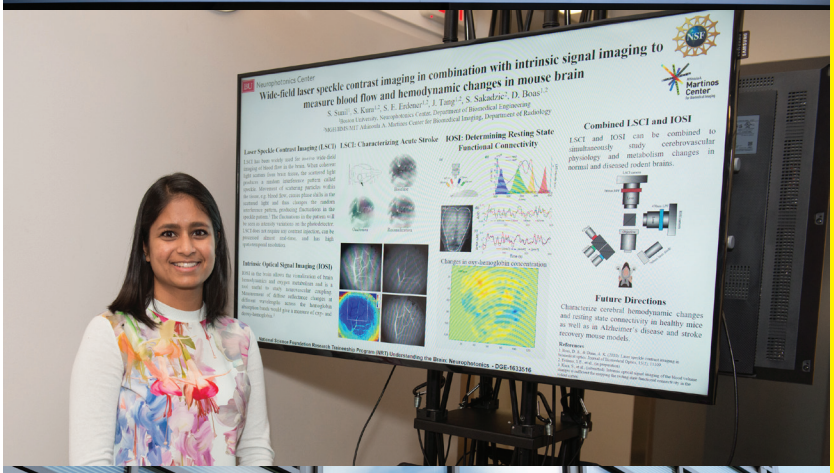
year, this community has identified and launched 11 projects to further the Center's mission. The projects include investigating a novel laser for 3-photon microscopy for imaging deeper into the brain, supporting the advancement of wearable micro- and meso-scopes to image neural activity in freely moving animals, increasing the volumetric imaging rate of confocal microscopy to image voltage indicators with millisecond temporal resolution, and developing wearable functional near infrared spectroscopy for measuring brain activity in freely behaving humans. These projects—just a few of the many under way—are detailed in the following pages.

We have many people to thank for this tremendous ramp-up of the Center. The BU construction manager Mike Ragusa, Architect Joe Gibbons, and the Shawmut construction company were a highly professional and friendly team of people who managed to complete the complex project on time, enabling us to start performing neurophotonic studies the week of the Neurophotonics Symposium on November 30, 2017. I am forever grateful to Juliette Selb, whom I worked with for 15 years, who followed me from Massachusetts General Hospital to assist with the launch of the Center during these first 6 months before moving on to the next phase of her professional career. I cannot imagine two more talented colleagues than Kıvılcım Kılıç and Anderson Chen to manage the collaborative research activities of the Center. They are exceptional at their jobs and exceedingly friendly and generous with their time supporting the many Center members. And of course, I must thank and acknowledge the vision and generous support of College of Engineering Dean Ken Lutchen, Photonics Center Director Tom Bifano, and Vice-President of Research Gloria Waters in launching the Neurophotonics Center.

It is a great pleasure working with the phenomenal group of faculty, students, fellows, and staff at Boston University. We look forward to realizing the many goals set in Year 1, and to the continued growth of Center activities in the coming years. Thank you for your interest in our activities. I invite you to read further here and at our website bu.edu/neurophotonics, and look forward to meeting you at one of our Center events.

David Boas
Director, Boston University Neurophotonics Center





At a Glance

34
Faculty Members

44
Students in NRT

11
Projects Supported

10
New Collaborations Started

18
External Speakers

Events

The Neurophotonics Center offers an exciting array of events throughout the year to engage the community and offer enriching opportunities to BU, Boston area universities and local companies. These events foster interdisciplinary discussion and encourage faculty and students to collaborate with a variety of professionals on fundamental research. Check out our website at http://www.bu.edu/neurophotonics/events for upcoming events.

Research on Tap, Illuminating How the Brain Works

Sponsored by the University, the Neurophotonics Center organized a Research on Tap event on November 29, 2017 to officially launch the Neurophotonics Center. Twelve Center faculty each gave a 4 min presentation of their work to a packed, stand-room only, conference room.

21st Annual Photonics Symposium

The Neurophotonics Center organized the 21st Annual Photonics Center Symposium focused on the topic of Neurophotonics. The symposium, held on Nov 30, 2017, drew 200 attendees from BU, other academic institutions, and industry. The agenda for this year's symposium featured presentations by researchers from leading academic institutions.

Dr. Kwanghun Chung, MIT
Dr. Yves De Koninck. Laval University
Dr. Anna Devor, UC San Diego
Dr. Maria Franceschini, Harvard University
Dr. Fritjof Helmchen, University of Zurich
Dr. Elizabeth Hillman, Columbia University
Dr. Na Ji, UC Berkeley
Dr. Alipasha Vaziri, Rockefeller University
Dr. Chris Xu, Cornell University

At the conclusion of this year's conference, a reception and electronic poster board session was held where participants, students and speakers discussed their research in an informal setting.

Seminar Series

The Neurophotonics Center organizes a monthly seminar series, generally in coordination with affiliated Departments and Centers.

October 26, 2017
Mark Andermann, Harvard Medical School
"Imaging visual information flow from retina to amygdala"

March 1, 2018
Spencer Smith, University of North Carolina Chapel Hill's Neuroscience Center
"Advancing multiphoton imaging technology for neuroscience"

April 9, 2018
Brenda Bloodgood, University of California San Diego
"Deconstructing neural activity with an immediate early gene"

April 23, 2018
David Kleinfeld, University of California San Diego
"How blood flows throughout cortex"

fNIRS Symposium

January 16, 2018 we organized a day long symposium to launch functional Near Infrared Spectroscopy research activities at BU. In addition the 6 external speakers, the symposium also had three engaging panel discussions, a poster session, and reception. It was a great opportunity for networking with other developers and users of fNIRS from the regional area and beyond.

The speakers included:
David Boas, Boston University
Meryem Yücel, Boston University
Ioulia Kovelman, University of Michigan
Katherine Perdue, Boston Children's Hospital
Joy Hirsch, Yale School of Medicine
Hasan Ayaz, Drexel University
Ted Huppert, University of Pittsburgh

The day after, on January 17, 2018, we then hosted a fNIRS hands-on training bootcamp for 20 interested BU students and faculty who wanted to start utilizing fNIRS for their own research projects.

Neurophotonics Social

A monthly social is held in CILSE in the 8th floor lounge to bring together students and faculty to meet and catch up on the latest activities in their labs.

Faculty

David Boas
Professor (BME, ECE)
Director, Neurophotonics Center

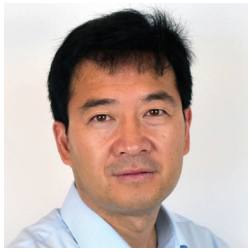
Neurophotonics; Biomedical Optics; Oxygen delivery and consumption; Neuro-vascular coupling; Physiological Modeling

Thomas Bifano
Professor (ME, MSE, BME)

Deformable mirrors; Microelectromechanical systems (MEMS); Adaptive optics; Biphotonic microscopy; Astronomical telescope instrumentation; Laser wavefront control

Irving Bigio
Professor (BME, ECE)

Medical application of optics, lasers and spectroscopy; Biophotonics; Nonlinear optics; Applied spectroscopy; Laser physics



Ji-Xin Cheng
Professor (ECE, BME)

Molecular spectroscopic imaging technologies; Label-free microscopy; Medical photonics; Neurophotonics; Cancer metabolism; Photonics for infectious diseases

Jerry Chen
Assistant Professor of Biology

Large-scale neuronal networks; Sensorimotor integration; Decision making; Neurodevelopment; Non-linear microscopy

Alice Cronin-Golomb
Professor, Psychological & Brain Sciences

Neural correlates of perception and cognition in aging and age-related neurodegenerative disease

Alberto Cruz-Martin
Assistant Professor of Biology

Neural circuits; Sensory processing; Visual pathways

Ian Davison
Assistant Professor of Biology

Pheromones and innate social behaviors; Cortical computations and plasticity

Allison Dennis
Assistant Professor, (BME, MSE)

Nanobiotechnology; Fluorescent biosensing; Fluorescence resonance energy transfer (FRET); Quantum dot chemistry; Fluorescence microscopy; Single molecule sensing/imaging

Helen Fawcett
Research Assistant Professor, ME

Biodetection; Optics; Nanoscale lithography and imaging; Photonics applications

Chris Gabel
Assistant Professor, Physiology & Biophysics

Femtosecond laser surgery and optical neurophysiology for the study of the nervous system of the nematode worm C. elegans

Timothy Gardner
Associate Professor of Biology

Neural circuits; Vocal learning; Time-frequency analysis; Brain-machine interfaces

Lee Goldstein
Assoc. Professor (Neurology, BME, ECE)

The role of abnormal protein aggregation in chronic degenerative disorders of aging

Xue Han
Assoc. Professor, Biomed. Engineering

Neurotechnology; Optical neural modulation; Optogenetics; Neural prosthetics; Neural network dynamics; Brain rhythms; Neurological and psychiatric diseases; Cognition

Michael Hasselmo
Director, Center for Systems Neuroscience

The role of oscillatory dynamics and neuromodulatory regulation in cortical mechanisms for memory-guided behavior

Mark Howe
Assistant Professor, Psychological & Brain Sciences, College of Arts & Sciences

Basal ganglia circuit mechanisms for learning and action

Melissa Kibbe
Assistant Professor, Psychological & Brain Sciences

Representation of information about objects (e.g., perceptual features, animacy, group statistics, numerosity, verbal labels)

Swathi Kiran
Professor, Department of Speech, Language, and Hearing Sciences

Bilingual aphasia; Aphasia rehabilitation; Functional neuroimaging; Language recovery; Impairments in naming, reading, writing

Sam Ling
Assistant Professor, Psychological & Brain Scientists

Imaging human behavior to explore how the brain mediates between the "buzzing confusion" of the visual world and our limited processing power

Jerome Mertz
Professor (BME, ECE)

Development and applications of novel optical microscopy techniques for biological imaging

Tim Otchy
Res. Assist. Prof., Biology

Experiments in probing, manipulating and modeling the neural circuits involved in song learning and production

Siddharth Ramachandran
Professor (ECE, MSE)

Optical physics of guided waves; Micro- and nano-structured optical fibers; High-power fiber lasers and fiber sensors; Biomedical imaging and microscopy with optical fibers

Steve Ramirez
Assistant Professor, Psychological & Brain Sciences

Revealing the neural circuit mechanisms of memory storage and retrieval, and artificially modulating memories to combat maladaptive states

Darren Roblyer
Assistant Professor, BME

Optical functional imaging; Diffuse optics and spectroscopy; Monitoring of therapies in oncology; Non-invasive monitoring of tumor metabolism

Faculty

Michelle Sander
Assistant Professor (ECE, MSE)

Femtosecond lasers; Ultrafast photonics and nonlinear processes; Fiber and integrated optics; Frequency combs; Infrared spectroscopy and biomedical applications

Kamal Sen
Associate Professor, (BME)

Neural coding of natural sounds; Neural discrimination; Population coding of natural sounds

Barbara Shinn-Cunningham
Professor, Biomedical Engineering

Auditory attention; Spatial hearing; Neuro-electric imaging; Neural coding; Plasticity and learning in auditory tasks

Robert Stern
Professor, Neurology

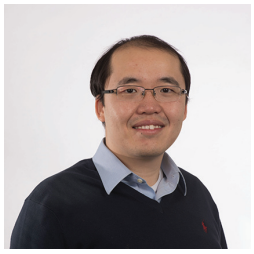
Director of the Clinical Core of the BU Alzheimer's Disease Center

Chantal Stern
Professor, Psychological & Brain Sciences

Using fMRI to study how the normal brain encodes, stores and subsequently recognizes visual, spatial and verbal information

Helen B. Tager-Flusberg
Director, Center for Autism Research

The phenotypic characteristics of the language, communication and associated social-cognitive deficits in autism (ASD) and other neurodevelopmental disorders

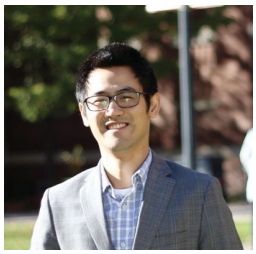


Lei Tian
Assistant Professor (ECE)

Computational imaging and sensing; Gigapixel, 3D microscopy; Compressive imaging; Phase retrieval; Imaging through complex media; X-ray phase imaging

John A. White
Professor & Chairman (BME)

Mechanisms of episodic memory; Pathophysiology of epilepsy; Computational neuroscience; Design of real-time instrumentation; Imaging of activity in neurons and astrocytes



Ji Yi
Assistant Professor, Medicine

Development of novel optical techniques for fundamental research and clinical applications with a focus on cancer detection, glaucoma, and aging

Meryem Yücel
Research Assistant Professor (BME)

Functional neuroimaging (fNIRS, fMRI, EEG); fNIRS signal processing; cognitive neuroscience

Photo by Bernhard Zimmermann


DESICCATOR

NUEROPHOTONICS CENTER BUILDOUT
Summer - Fall 2017

The Neurophotonics Center labs occupy 2,700 square feet of space on the second floor of the Life Science Engineering building on the BU campus. Designed from the ground up to meet the needs of Center faculty and their groups, the space is home to electronic and mechanical shops, a wet lab facility. and seven optical bays with advanced technologies including wide-field imaging; two-photon microscopy, fluorescence lifetime imaging microscopy, and more.

Construction began in June 2017, after about eight months in the planning stages, and continued through mid-November, when Center researchers moved in to the new space.

BU Neurophotonics Center Launches With 'Research on Tap' Talks

During the inaugural event, Center faculty described a number of projects already under way in a host of different research areas

The BU Neurophotonics Center opened its doors to the public with a series of events highlighting both the work of its faculty and the latest advances in the field generally.

On Wednesday, November 29, Center faculty joined the BU "Research on Tap" series for a rapid-fire series of talks: "Illuminating How the Brain Works—With the Help of BU Neurophotonics." The next day was witness to the 21st annual Photonics Center Symposium, with researchers from across the U.S. and abroad shining a light on neurophotonics and the many ways it can boost a host of applications.

The Wednesday event was an especially apt kick-off as it introduced much of the work already in progress in the Neurophotonics Center, and in doing so demonstrated both the depth and the breadth of the research taking place under its roof. In all, 12 of the 34 faculty affiliated with the Center spoke about their work, representing an array of departments within BU: Biomedical Engineering, Psychological & Brain Sciences, Medicine, and more.

Not surprisingly, given the diversity of the speakers, the talks described both technology development and applications studies. On the technology development front, for example, Jerome Mertz, Professor of Biomedical Engineering, spoke about his group's efforts to tackle the problem of dynamic range, particularly with the imaging modality two-photon microscopy. Their solution to the problem: an "adaptable" microscope that changes laser power as it is scanning, so it is delivering power only where and when it is needed. This yielded an extraordinary 16,000-fold increase in dynamic range, he said, surely a welcome improvement for the neurobiologists who use two-photon microscopy.

Michelle Sander, Assistant Professor of Electrical & Computer Engineering, addressed another longstanding concern in the instrumentation realm. Particular ultrafast lasers offer exceptionally high spatial resolution but, unfortunately, often don't overlap with the

desired "biological windows"—the wavelength ranges where the laser light optimally penetrates biological tissue. To right this imbalance, she and her group worked to develop a fiber laser system based on the thulium materials that overlaps well with biological windows, and have begun to explore its potential for infrared nerve stimulation, an important emerging application.

The goal of technology development, of course, is to help researchers approach problems in innovative ways and from novel perspectives—to see the problems, both literally and figuratively, as they never have before. Many of the talks on Wednesday pulled back the curtains to show how this is happening in the Center. For instance, Meryem Yucel, Research Assistant Professor in Biomedical Engineering, described an emerging optical monitoring technology—functional near-infrared spectroscopy (fNIRS)—and the myriad ways it can be put to use. Not least among these: she and colleagues are exploring its potential for research and clinical applications in Alzheimer's, autism and stroke.

Some of the applications discussed in the talks sounded almost futuristic in their scope. Steve Ramirez, Assistant Professor of Psychological & Brain Sciences, described his group's successful efforts to suppress painful memories and prevent a "fear response" in mice by artificially activating positive memories with light. They achieved this, he said, by identifying the neurons underlying those memories and genetically engineering them to respond to light. This, naturally, could have profound implications especially for the treatment of psychiatric disorders.

Artificial intelligence also made an appearance. Jeffrey Gavornik, Assistant Professor of Biology, spoke about using calcium imaging to investigate the neural basis of learned temporal relationships. This is particularly relevant for the ongoing development of AI, he said. Today, AI is not actually a true representation of how the brain works; it doesn't fully replicate the mechanisms by which the brain processes new information on a temporal level. Better understanding how this happens will help in bringing about the next stage of the AI revolution.

Neurophotonics trainees pitch research to Canadian counterparts

The "Research on Tap" event wasn't the only occasion that day to hear about what is happening in the Neurophotonics Center. A few hours before the event, trainees in the Neurophotonics National Science Foundation Research Traineeship Program (NRT) at BU had a virtual research exchange with graduate students at Laval University's Neurophotonics Center in Quebec City, Canada. Students from the two campuses exchanged 15- to 90-second research pitches, using techniques adapted from abbreviated Alan Alda Science Communications training they received from the Program Coordinator of the NRT, Helen Fawcett.

The first cohort of NRT trainees

The goal of this research exchange was for the students to communicate their research without resorting to scientific jargon, paving the way for future discussions and potential collaborations between the two centers. More exchanges between faculty and students, both virtually and in person, will take place over the coming year. Just one example: two trainees from the BU program will attend Laval's Frontiers in Neurophotonics Summer School, where several neurophotonics faculty from BU have and will continue to give lectures.

fNIRS Comes to Boston University

The Neurophotonics Center is partnering with researchers throughout the university to incorporate the burgeoning imaging modality into their work

Dr. Helen Tager-Flusberg has made tremendous strides over the years in shedding light on language and social communication impairments in autism and other neurodevelopmental disorders. Director of the Center for Autism Research Excellence at Boston University, she has devoted herself to understanding the roots of these impairments and exploring interventions designed to help in the development of language and social communication skills.

In her work with autism Tager-Flusberg has taken advantage of behavioral and developmental approaches, study paradigms based on the observation of subjects interacting with their environment. She has also sought to probe the brain mechanisms underlying the development of language and social communication skills. Applying the tools typically used for this—neuroimaging technologies such as functional MRI—can be challenging in the populations with which she's working. Now, though, through a collaboration with the Neurophotonics Center at Boston University, she is initiating a study with an emerging imaging modality, one that will allow her to delve more deeply into the brain and begin to uncover the many mechanisms at work.

Functional near-infrared spectroscopy—more commonly known as fNIRS—takes advantage of the properties of light to measure the amount of oxygen in the blood. Because of the tight coupling between blood oxygenation levels and activity in the brain, the technology allows researchers to monitor such activity, and in doing so begin to answer a host of questions about the brain in both health and disease. fNIRS is noninvasive and portable—imaging is done by way of a lightweight cap tethered to a larger device with fiber-optic cables, so subjects can move around and perform tasks during imaging. Thus, it can overcome some of the limitations of other neuroimaging technologies.

David Boas, director of the Neurophotonics Center and a pioneer of the technology, introduced in the mid-1990s, has been collaborating with researchers throughout the university to apply fNIRS to a broad range of studies. Because of its many unique capabilities, the approach can benefit these studies in new and exciting ways.

For example, in partnership with Boas and others in the Neurophotonics Center—including Meryem Yücel and Xinge Li —Tager-Flusberg launched a pilot fNIRS study of the mirror neuron system in autism. Mirror neurons are a type

BU researchers Helen Tager-Flusberg and Swathi Kiran are working with the Neurophotonics Center to incorporate functional near-infrared spectroscopy into their work.

Opposite: The Center's Meryem Yucel leads a workshop at the fNIRS symposium.

of brain cell that responds to a stimulus in the same way whether a person encounters it him or herself or simply observes others encountering it, suggesting a neurological basis for empathy. Many researchers believe that dysfunction of the mirror neuron system can negatively impact social communication skills in people with autism.

Thanks to its portability and flexibility, fNIRS opens up the study to a broader population than Tager-Flusberg could access with other imaging modalities. "I've done a little bit of work with much older and more verbal individuals using fMRI," she says. "However, fNIRS offers the opportunity to look at the brain in a wider group of individuals with autism, particularly young children, who we can't put into an fMRI scanner, and older individuals who have more challenging behavior."

Researchers are applying the technology with other populations as well. Dr. Swathi Kiran, director of the Aphasia Research Laboratory at Boston University, studies which parts of the brain can recover function after stroke, particularly as they pertain to language. Aphasia refers to difficulty in understanding or expressing speech as a result of brain damage. In her work she has used functional MRI and other, related multimodal approaches, but measurements with these approaches can suffer from motion artifacts—a loss in data quality due to the subject moving during the measurements.

Because its design allows for motion during imaging, fNIRS is already proving an important addition to the tools used for the studies. "With functional MRI, if there's any motion in the scanner, we've pretty much lost all of the data," Kiran says. "fNIRS provides a means to circumvent some of these methodological issues, and it provides a different way of looking at the problem."

Sharing the many benefits of the technology

On a brisk day in January the Neurophotonics Center hosted a daylong symposium devoted to fNIRS. Held in the Kilachand Center for Integrated Life Sciences & Engineering on the BU campus, the symposium brought together fNIRS developers, users and potential users to explore best practices and the latest advances in the field. The topics covered included fNIRS as an objective measure of pain, applications in developmental neuroscience, probe design, data analysis, and more.

With six invited talks, a contributed poster session, panel discussions, a lunch and an evening reception, the symposium gave researchers interested in adopting fNIRS a wealth of opportunities to learn about the advantages the technology offers. Tager-Flusberg and Kiran both were there, as were a number of other faculty, students and postdoctoral fellows from throughout the university. All were clearly inspired by the possibilities of the technology.

"We couldn't be more excited to introduce fNIRS to the BU community on such a broad scale," Boas says. "The researchers with whom we're partnering are already doing incredible work. Now, with access to this burgeoning imaging modality and the support of Neurophotonics Center staff, they can explore even further into the many problems at hand and tell us more about the brain both in healthy subjects and in a range of disorders."

Training the Next Generation of Neurophotonics Researchers

With a background in electrical engineering, Jenny Sun had little experience with neurophotonics—with neuroscience, generally—when she entered the "Understanding the Brain: Neurophotonics" training program at Boston University just about a year ago. Now, Sun, a second-year graduate student at BU, is designing and building an advanced ultrafast wide-field microscope for imaging of neurons in mouse models.

Sun's story might seem an anomaly, something of a quirk in a world where, historically, researchers are highly specialized and seldom cross over into other fields. In fact, bridging disciplines like this is one of the major goals of the program. "I hadn't been exposed to a lot of biology before I signed up but I had always been fascinated by how the brain works," Sun says. "With this program, I saw an interesting opportunity to learn more about the brain, and to explore the intersection of neuroscience and what I was already studying."

Launched just two years ago, the National Science Foundation (NSF)-funded research traineeship program—better known at BU as the NRT program—brings together Ph.D. students in biology, neuroscience, biophysics, and engineering who are interested in using photonics to explore the role of the brain in a variety of human activities. The mandate of the program is to train students to adopt a broader perspective and work with collaborators from across the research spectrum to achieve their many goals.

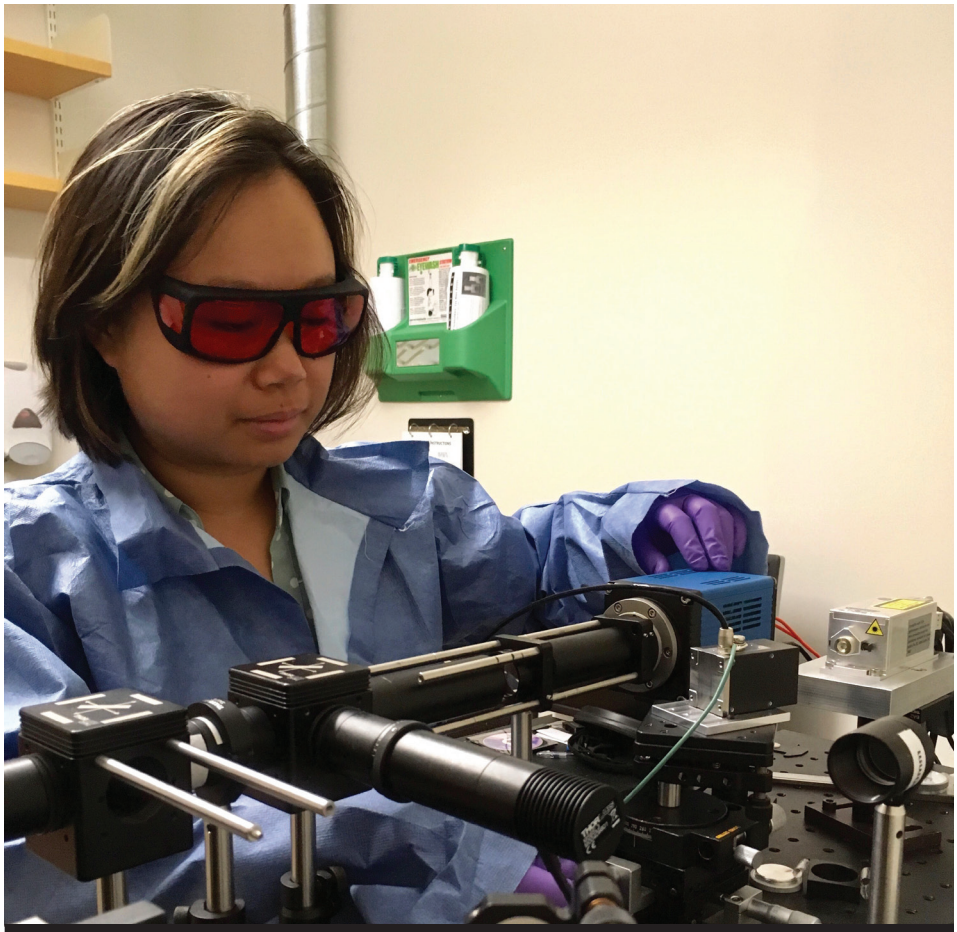
"The idea was to create a program where students from different backgrounds are immersed in and thrive

in an interdisciplinary environment," says Helen Fawcett, program coordinator with the NRT who also played an integral role in developing the program. "Photonics is the enabler; we are using light to group all of these students together."
A second, complementary goal is to support women and underrepresented minorities seeking training in interdisciplinary studies. The program's target enrollment is 40 percent women and 20 percent underrepresented minorities; a total of 20 students receive fellowships.

Preparing students for a career in research

The five-year NRT program provides unparalleled opportunities to explore neurophotonics and work with some of the most accomplished researchers in the field. Trainees take part in immersive hands-on training and lab rotations with world-class faculty, interdisciplinary coursework and research for their Ph.D. dissertation, and professional development mentoring. They can also learn from the many neurophotonics events and additional training opportunities held throughout the year. Among these are seminars, an annual symposium, summer school workshops and more.

Students' tenure in the program officially begins with the aptly named Boot Camp. Over the course of three days each July the newest NRT cohort assembles for a series of crash courses in the fundamentals—neurophotonics and neuroscience more broadly—as well overviews of select topics in relevant areas of inquiry. The latter have included core courses in microscopy, fluorescent markers and optogenetics. Boot camp is designed to bring trainees up to speed, so they begin with a baseline understanding of the material. This is integral to the success of the NRT. Thus far, 63 percent of new trainees have not had photonics training prior to entering the program; 31 percent have not had any neuroscience training at all.



NRT trainee Jenny Sun

"With this program, I saw an interesting opportunity to explore the intersection of neuroscience and what I was already studying."

The NRT Boot Camp also includes a modified version of the Alan Alda Communicating Science training program, which helps researchers improve their communication skills so they can better explain their work to family and friends as well as to colleagues. An ability to communicate the esoteric and complicated concepts explored in the NRT program is especially important because neurophotonics is such an interdisciplinary field; trainees will need to break down what they are doing so collaborators, for example, can easily understand it. It can also help with team building and community development within the program, Fawcett says, by facilitating robust interactions among the trainees.

This focus on communication is woven throughout the entire program, and indeed throughout the sciences at the university. BU is one of 17 schools chosen by the National Institutes of Health (NIH) to participate in its Broadening Experience in Scientific Training (BEST) program, which offers professional development curricula designed to help Ph.D. students and postdoctoral trainees explore career paths in the biomedical sciences both inside and outside academia. These curricula include the full-blown version of the Alan Alda Communicating Science program. So not only is the focus on communication embedded in the culture of the sciences at the university, instructors trained by the Alan Alda program are on staff and available to work with the NRT.

"The program has opened up avenues that I hadn't considered before with respect to my career."

Revealing new opportunities

Students enrolled in the NRT are already seeing the benefits of the interdisciplinary program and the broader perspective it provides. Scott Knudstrup was introduced to the NRT during his first year in BU's Graduate Program in Neuroscience, and though he was working with two-photon imaging in the lab of Jeff Gavornik he had "virtually no prior experience" working with microscopes. Now, he is wielding advanced photonics technology to image the primary visual cortex of mice in order to study how cortical populations change during learning.

"The program has opened up avenues that I hadn't considered before with respect to my career," he says. "My background was entirely

NRT trainee Scott Knudstrup

in theoretical and/or computational studies, and NRT has enabled me to get more into experimental work by giving me the tools to work with and understand sophisticated instrumentation."

And this, of course, is just one of the many benefits the program offers. Knudstrup points to the many opportunities it affords to meet and develop relationships with researchers from diverse backgrounds. "NRT facilitates connections between people that span many disciplines and are at very different stages in their careers," he says. "It's especially great to have access to the NRT talks because it gets everyone under the same roof. In addition to the great lecturers that span many topics, these events make the process of forging personal connections with people outside of your immediate lab or research area much easier than they would be otherwise."

The Guiding Hand of the NRT

Helen Fawcett is the not-so-secret secret weapon of the NRT. A mechanical engineer by training, with a wealth of additional experience in putting together interdisciplinary programs, she was the perfect person to help design and develop the NRT program. After the grant was awarded, she stayed on as program coordinator, recruiting and guiding trainees in the NRT and working with the associated academic departments at BU to ensure that the program offers an enriching experience without adding to the trainees' total time to degree.

Fawcett is delighted to be working with the Neurophotonics Center to provide the best possible training environment for the students. "The Neurophotonics Center is an exciting place to be and the NRT program has been an opportunity to include the students in a central and key role of developing the neurophotonics research community," she says. "I have had the distinct pleasure of being able to develop this foundation for them, meet and engage with all of the students during recruitment and participation in the NRT program itself and welcome this coming year to guide the students into becoming more active drivers of the program."

Why the Free Bird Sings

Wireless miniature microscope opens up new applications

A team of investigators at Boston University has designed a miniature microscope that allows them to monitor brain activity in freely behaving animals – including the pint-size songbird. The microscope uses an open-source approach so researchers can build it themselves, adapting the design to suit their specific needs.

The project was a response to a growing need in neuroscience: an ability to perform optical imaging in unconstrained animals, to see what's happening at the cellular level as they go about their daily business.

"Most of the interesting things that animals do involve running around and exploring and interacting with other animals," says Daniel Leman, a researcher at BU and one of the developers of the technology. "We wanted to be able to watch this but the commercially available microscopes didn't have all the features we needed, and their closed design meant we couldn't tweak them to offer those features."

Specifically, Leman and colleagues wanted to study a particular region of the brain in zebra finches – an especially loud and spirited species of songbird. Their goal: to track individual neurons over weeks and months as the birds performed their songs time and time again, so they could better understand learning-related changes in that part of the brain.

The team advancing the miniature microscope includes: (top, L-R) Anderson Chen, Tim Otchy, Ian Davison, Kıvılcım Kılıç; (bottom L-R) Jasmine Clevenger, Will Yen, Dan Leman.

The researchers knew they had several options for the study. One was to use a conventional microscope, with the birds restrained to enable accurate monitoring. Here, though, they would have needed to train the birds – since few will sing unprompted when they cannot move freely – while the use of constraints might have precluded study of motor activity in the brain.

This led them to try miniature microscopes, which would allow them to study the finches' behavior in "the most authentic way possible." They tested a couple of commercial instruments they had borrowed from other labs in BU's Department of Biomedical Engineering but these didn't offer all of the features they needed. So they did what any good engineer would do: they decided to design their own.

A tinker set for biomedical researchers

The researchers described their microscope in a Journal of Neural Engineering paper published earlier this year; Will Liberti, who originally cooked up the idea for the microscope, is the first author of the paper. Developed for single-photon fluorescence imaging in freely behaving animals, the instrument includes all of the features the researchers wanted. It is light enough (less than 1.8 grams) to use

with zebra finches, it is flexible, and it can be used either wirelessly or in conjunction with active commutators. Importantly, it was designed so other research groups could make their own instruments, both inexpensively and relatively easily.

To this end, the researchers came up with a design that uses off-the-shelf components and 3D-printed parts. The off-the-shelf components used in the microscope are especially affordable thanks to advances in consumer-grade electronics in the cellular and telecommunications industries, which have driven costs down across the board. The use of a 3D-printed parts means the microscope body can be built inexpensively and to the users' precise specifications.

And with the open-source approach, users can download the initial design from the web and then tweak it as need be. "It's all very customizable, all very hack-able," says Ian Davison, a researcher at BU and another of the microscope's developers. "I like to think of it as a tinker set. We provide the materials and people can toggle it as they see fit to answer their own questions." It doesn't take much to assemble a microscope. After a little bit of practice, users can do so in maybe half an hour.

A huge step forward in wearable technologies

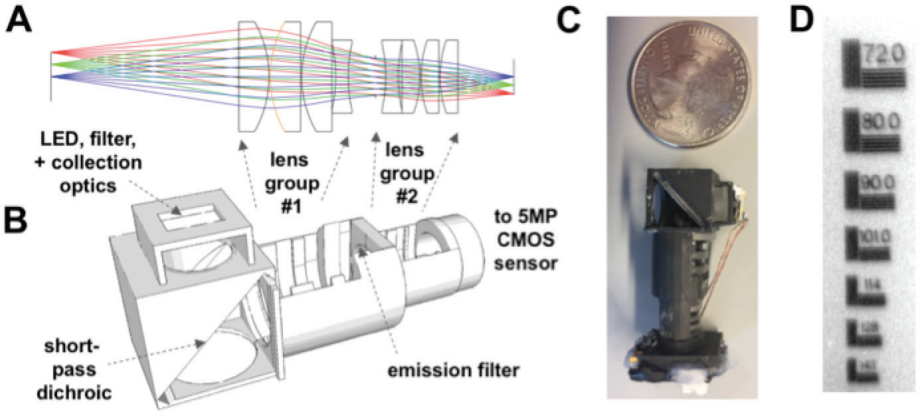
The miniature microscope has already fulfilled its promise for the BU group. Using what amounts to birdsong-triggered data acquisition, the researchers have been able to perform around-the-clock studies in the zebra finches, collecting anywhere from 400 to 1,000 song motifs per day and building a rich longitudinal sample of brain activity at cellular resolution. This data will go a long way toward advancing our understandings of how the brain codes for the learning behaviors.

The potential applications extend well beyond the study of birdsong, though. The miniature microscope really represents a huge step forward in the evolution of wearable technologies, technologies that can help to answer a host of questions that were previously essentially unanswerable.

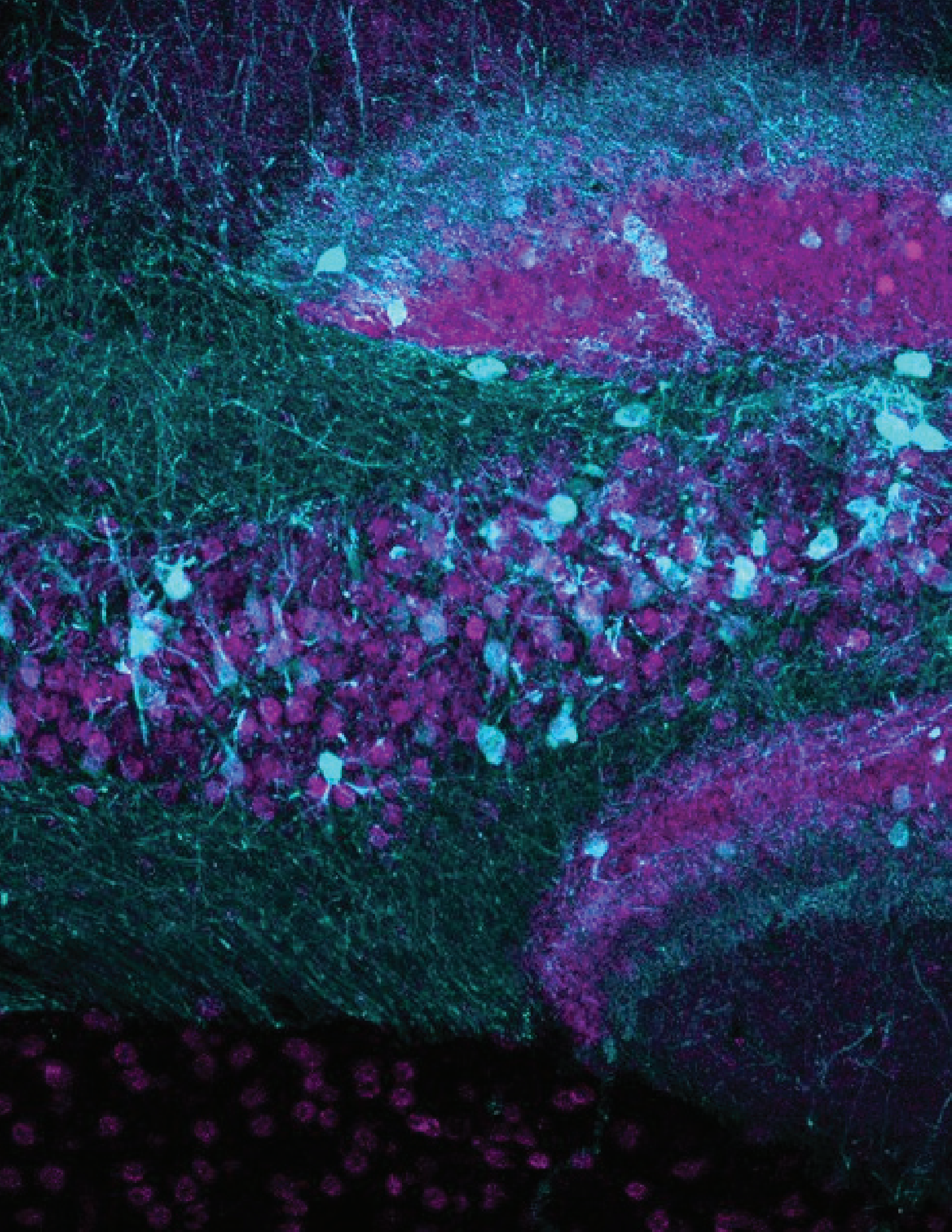
Davison describes, for example, a burgeoning interest in olfactory processing. In rodents, many social behaviors – those that involve the animals smelling each other to intuit gender, reproductive status, etc. – are often mediated by chemicals. The challenge in studying these processes has always been how to image the relevant part of the brain while the animals are engaging in these behaviors.

The researchers didn't just stop with designing the microscope. Supported by a grant from NIH, they are also actively working to disseminate the technology, to get it into the hands of other groups so those groups can use it to tackle their own unique sets of challenges. They have been offering training sessions at BU – three different labs in the Department of Biomedical Imaging are now using the microscopes in their work – and sharing the technology with other group across the country, including groups at Harvard, MIT and Duke University.

Now, the Neurophotonics Center is supporting the broader dissemination of the wearable technology, both across BU and beyond. Further, the Center is working with Davison, Gardner and other faculty to expand its capabilities, including improving the spatial and temporal resolution and cellular specificity. Advances in several different areas of interest are expected in the near future, such as two-color imaging, patterned illumination and wearable multi-photon microscopy.



A large-field miniscope system for imaging across brain areas as large as 3mm X 4mm. (a) Zemax schematic of optical path maintaining high resolution and collection efficiency (F/2.27). (b) Diagram of housing indicating placement of various components. (c) Fully assembled widefield miniscope. (d) Images of a resolution target demonstrating resolution of approximately 10 µm.

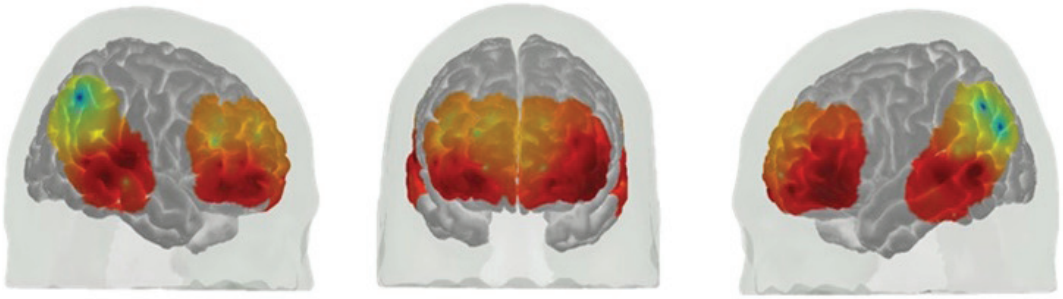


Neurophotonics Center-Supported Research Projects

Supporting new research directions between faculty is an important component of the *Center's mission: to build and support an interdisciplinary community that can develop and broadly deploy impactful photonics technologies in the neurosciences to advance our understanding of how the brain works in health and in disease.* Neuroscientists are dependent on new technologies that enable them to measure previously inaccessible aspects of brain function and structure. Scientists advancing photonics methods are on the lookout for impactful applications to motivate and direct their technological developments. The Center aims to connect the technology developers with the users to accelerate the advancement and early adoption of novel photonic methods. The following pages describe seven such innovative efforts that the Center is supporting.

Image by Steve Ramirez

Functional NIRS (fNIRS)



The Neurophotonics Center has been performing several functional near infrared spectroscopy (fNIRS) studies with BU faculty. First, Center investigators have been collaborating with Dr. Tager-Flusberg from the Autism Center of Excellence, using fNIRS to investigate mirror neuron system (MNS) dysfunction in autism spectrum disorder (ASD). MNS activates during the observation and execution of the same actions and plays a key role in action understanding. Converging neuroimaging evidence has postulated a link between MNS dysfunction and ASD symptoms. Given that fNIRS is relatively robust to motion artifacts and allows participants to perform hand actions with relatively large and flexible limb movements, it is well suited to study the activation in MNS regions. Thus far, Center researchers and Dr. Tager-Flusberg have completed a pilot study on healthy adults and found interesting results in which MNS showed a significantly stronger and ipsilateral activity in response to the execution and even observation of complex hand actions compared with simple hand actions. More recently, the team has launched a study in which they are performing fNIRS measurements of the MNS activity of ASD children. The aim of this study is to compare the MNS activity of children with ASD with that of typically developing children – the children in both groups were 3 to 4 years old – to see how MNS activity differs between the groups.

The Center has also been working with Dr. Swathi from the College of Health & Rehabilitation Sciences: Sargent College to probe the brain function of stroke patients. Together, the investigators have initiated both cross-sectional and longitudinal fNIRS studies of stroke patients, each of whom has a brain lesion on one of their language areas. They designed language tasks--e.g., picture naming and semantic judgement--and other cognitive tasks to use with the studies. fNIRS is well suited suitable to perform language studies, in particular, as it can provide a measurement environment with little noise. The cross-sectional study aims to investigate how lesions in language areas affect the brain function of stroke patients. The longitudinal study seeks to determine how the patients' brain function changes during their language and cognition recovery programs.

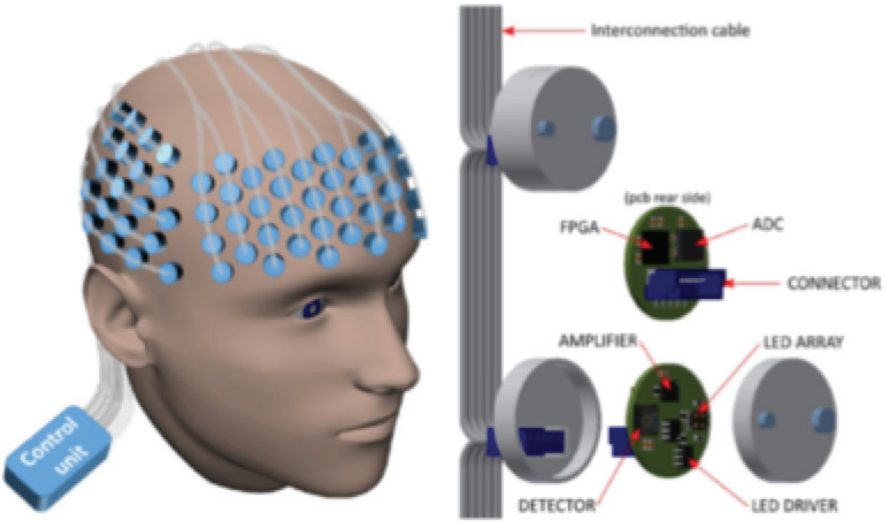
In another study, the Neurophotonics Center has been collaborating with Dr. Stern from the Alzheimer's Disease Center at BU's medical campus to study the brain compensatory mechanism of patients with mild cognitive impairment (MCI). The primary objective of this study is to determine the utility of fNIRS as a screening tool to distinguish MCI from early stages of AD. The investigators have already completed a pilot study on healthy adults, in which they utilized fNIRS to monitor the adults' brain activity asn they performed cognitive tasks (e.g., paired-associate memory task, stroop task and contextual task). They have already published results from the memory task.

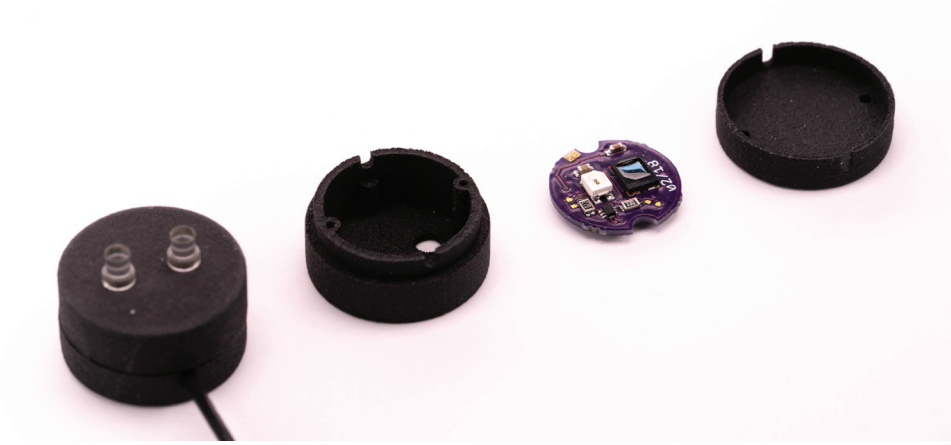
Expected Outcomes

The adoption of fNIRS by BU faculty and their research groups is progress very well because of support from Center personnel in performing the pilot studies and training others to perform the measurements themselves and to analyze the results. It is expected that an additional three groups will adopt fNIRS in the coming year.

Wearable functional NIRS Systems

Advances in wearable fNIRS are transforming the technology, not only enabling studies of brain activity associated with natural behaviors in natural settings, but also dramatically reducing the cost of fNIRS systems. The past decade has seen a growing effort by several research groups and fNIRS companies to develop wearable systems. Because they typically replace the bulky optical fibers of conventional systems with light-weight electrical wires, by placing light emitters and receivers directly on the scalp, wearable devices are much lighter and more flexible than conventional fNIRS equipment. While most wearable systems have been restricted to fixed source-detector separations and to forehead measurements, novel approaches have appeared in more recent years, allowing multi-channel high dynamic range acquisition with promising results.





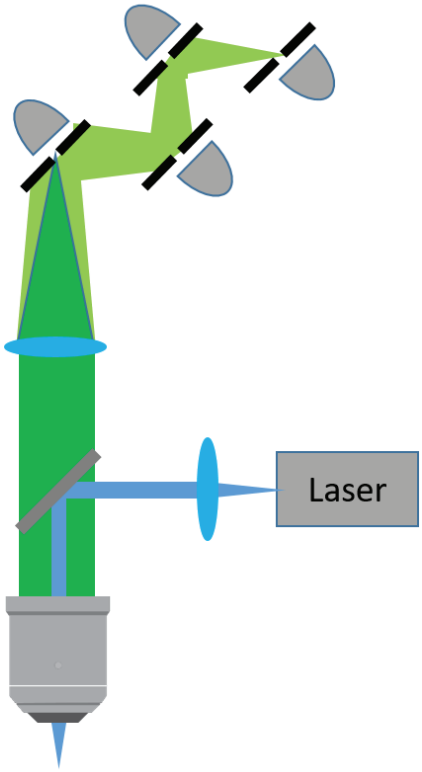
Building on these recent advances, the Neurophotonics Center is developing a wearable, fully scalable and modular system based on a new compact optode (see Fig. 1). Each optode consists of one dual wavelength LED (730 nm and 850 nm) and one photodiode (7.5 mm2 active area) 5 mm away, on a circular printed circuit board (PCB) of 14.9 mm diameter. Each optode PCB is encapsulated in a 3D printed case where light pipes guide the light from the LED to the scalp, and from the scalp to the photodiode. Multilevel LED output power and high dynamic range detection allow the photodiode to act both as short-separation detector for the source on the same optode and as longer separation detector for surrounding optodes. When completed, the system will be functional with as little as 2 optodes and can easily be expanded to as many as 128 optodes. This truly scalable approach will allow users to begin with a very simple low-cost device and from there, if needed, extend to high density whole-head coverage with complete flexibility to design probe arrays specifically relevant to given applications.

Expected Outcomes

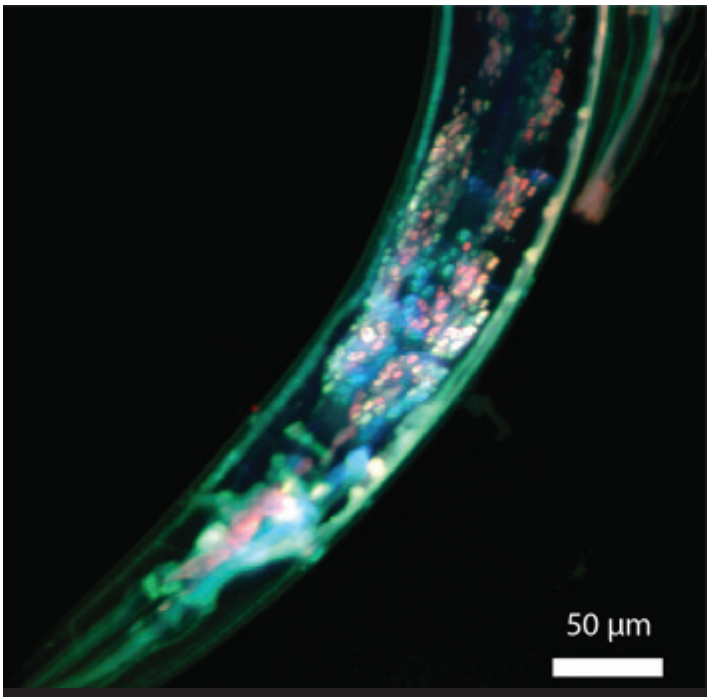
fNIRS measurements are presently being performed in the Neuroimaging Facility in the CILSE building. Upon completion of this wearable technology, it will be possible to fabricate several fNIRS systems and provide them to BU research groups to instead perform measurements in their own labs. It is anticipated that this will accelerate the adoption and impact of fNIRS at BU, and more broadly.

Sheet-scan Multi-Z Confocal Microscopy for Large-scale Voltage Imaging

Neuronal signals can vary on millisecond timescales, with communicating neurons often separated by hundreds of microns. Imaging such fast dynamics over extended volumes presents a challenge for standard fluorescence microscopes. This is becoming a major imaging challenge as a new generation of genetically encoded voltage indicators are becoming available whose response times are on the order of milliseconds. To address this challenge, Dr. Jerome Mertz and colleagues are seeking to develop a new type of microscope that can perform near-1kHz-rate large-scale volumetric imaging. The proposed solution, called Multi-Z confocal microscopy, is based on two key ideas. First, it combines high-numerical aperture (NA) detection with low-NA illumination. The former leads to high signal collection efficiency; the latter leads to axially extended illumination over an extended range of Z depths. Second, it uses light-sheet illumination and detects multiple signals from this extended depth range using multiple confocal slits that are axially distributed. The slits are reflecting, so signal rejected by one slit is sent to the next and so forth. Thus no signal is lost, and signal collection efficiency remains high. Dr. Mertz's goal is to perform in-vivo voltage imaging in mouse brains with novel voltage indicators. The ability to image large-sample volumes at 1kHz rates can be broadly impactful in a range of application areas. Dr. Mertz's group is building this microscope in Center space to facilitate its adoption by other Center faculty for neuro-biological studies.



Schematic of the Multi-Z confocal microscope



Video-rate image of GCaMP-labeled neurons in a live c-elegans (courtesy of Chris Gabel). Different colors are separated by 25um.

Expected Outcomes

The targeted microscope specifications are volumetric (optically-sectioned multiplane) imaging at 850Hz over a 1x1x0.2mm scale, with collection efficiency sufficient to observe voltage signals in behaving mice using fast voltage indicators. Other Center faculty's research efforts will likely benefit from utilizing this novel microscope to measure these fast neuronal signals.

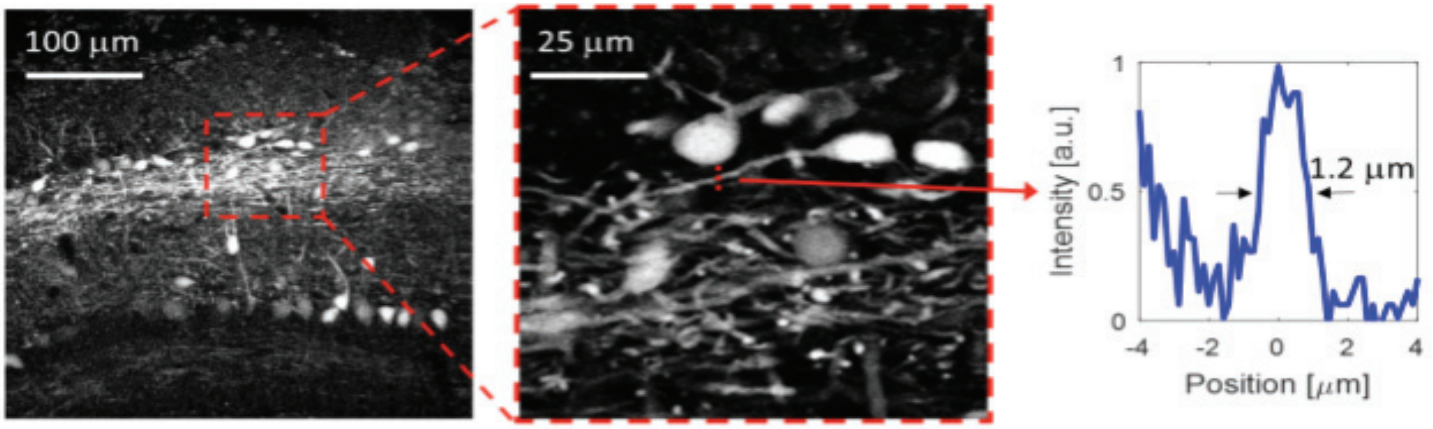
Three-Photon Microscopy

The Siddharth Ramachandran lab at BU is working to develop and validate the advantages of a new type of laser specifically adapted for 3-photon microscopy (3PM), which may be more attractive than commercially available lasers. Commercial lasers for 3PM are based on two-component systems involving pump lasers and optical parametric oscillators. An alternative strategy, proposed by the Ramachandran lab, is to develop a laser with similar performance using a different technology based on fiber optics. The researchers in the lab have already built a prototype laser and shown that it outperforms commercial lasers in terms of its capacity to produce 3P excitation. What remains is to integrate this laser into a microscopy platform, and demonstrate its effectiveness at imaging neuronal tissue in vivo.

The Neurophotonics Center is aiding in the development of a home-built microscope for this project. The microscope is initially being built in the Ramachandran lab. The Center is supplying assistance from Center Personnel and ancillary microscope equipment. Jerome Mertz is providing advisory expertise on the building of the microscope. Once completed, the performance of the 3PM will be validated with demonstrative neurobiology experiments designed by the John White group and executed with assistance from Center Personnel. To date, the microscope has been designed and constructed. Full characterization of the microscope design is scheduled to be completed Summer 2018. Three photon microscopy images have been obtained on brain slices (see figure) and reveal the generation of three photon excited fluorescence and near diffraction limited operation.

Expected Outcomes

In the event that the project is successful, and other Center faculty express interest in pursuing studies with three-photon microscopy, then the Center will endeavor to replicate the system to provide a work horse three-photon microscope advanced user facility for faculty to use to reach deeper regions of the brain for their neurobiology studies. This can also lead to a 3 photon microscopy earlier-adopter facility for incorporating photonic advances including adaptive optics and optimized scan procedures, for instance. The Center would support faculty in utilizing these facilities.



3-photon imaging of fluorescent labeling in genetically defined olfactory bulb neurons. Conditional YFP expression was targeted to projection neurons, mitral/tufted cells, using adeno-associated viruses encoding DIO. YFP in a Tbet-Cre mouse line. Left, view of mitral (bottom) and tufted neurons (center), along with dendritic processes that receive sensory input in histological sections. Zoomed view shows tufted neurons in external cell layers including both cell bodies and dendritic processes. Right, shows a linecut of the zoomed view.

Computational Miniature Mesoscope (CM^2)

The goal of this project is to develop a computational miniature mesoscope (CM^2) for imaging fluorescent procedures across multiple cortical areas. Dr. Lei Tian will develop prototype versions of CM^2 in the following manner.

1) Miniaturization: Optical microscopy is an invaluable tool for neuroscientists to record neural activity in the brain. Standard microscopes are bulky, which limit their scope and scale in brain imaging. A recent trend is towards miniaturization, e.g., miniscope, which has demonstrated new capabilities in high-speed recording of fluorescence and tracking of individual neural dynamics in freely behaving animals. The device should be thin (the total height<20mm, measured from the cortex to the top of the device) and lightweight (<4g), so as to be applicable to head mounting studies.

2.) Wide-FOV: Dr. Tian envisions that a miniaturized mesoscopic brain-mapping device, i.e., miniature mesoscope, will be a pivotal advance that will facilitate whole-brain recording on freely behaving animals and provide multiscale spatiotemporal data. Such miniature mesoscopes should provide wide-FOVs (~10x10mm^2), single-neuron resolution (~10μm), and high light-throughput to allow fluorescent imaging of neural firing events over a large area of the cortex. Unfortunately, such miniature mesoscopes cannot be constructed by simply modifying existing miniscopes. In fact, simultaneously achieving all of the requirements eludes any conventional optical instrumentation.

3.) Computational Optics: Dr. Tian proposes a Computational Miniature Mesoscope (CM^2), that uses computational optics to bypass conventional limitations. Specifically, his team will first collect wide FOV images using a microlens array (MLA) directly placed in front of a CMOS sensor. Next, high-resolution will be reconstructed using a deconvolution algorithm that performs the synthetic aperture procedure to combine information from multiple MLAs.

4.) Fluorescent Imaging: The CM^2 will be developed with the ability to image the vasculature labeled with FITC-dextran and neuronal activity with GCaMP calcium indicators. Experiments will be performed on both head-fixed and freely moving mice to benchmark the performance of the proposed device. Genetically modified mice that express GCaMP in neurons or wild type mice that are injected with FITC-dextran to label the vasculature will be used. These mice will undergo a surgical procedure to install a curved glass replacement to the dorsal cranium, which will provide a 8x9mm^2 viewing area and 10mm radius of curvature. The proposed mesoscope will provide ~1mm depth-of-field, so it can tolerate the window curvature. First, imaging on head-fixed animals will validate all the performance metrics of the device. Next, experiments will demonstrate the technique on freely moving mice.

The technology is being developed by Dr. Lei Tian (ECE) with guidance from Dr. Ian Davison (Biology) and from the Neurophotonics Center (NPC). Dr. Tian has received a Dean's Catalyst Award to provide support personnel from his lab and Dr. Davison's lab. The NPC is providing additional support in terms of personnel and supplies. An NIH R21 has been submitted, and a BRAIN Initiative R01 is in preparation.

Expected Outcomes

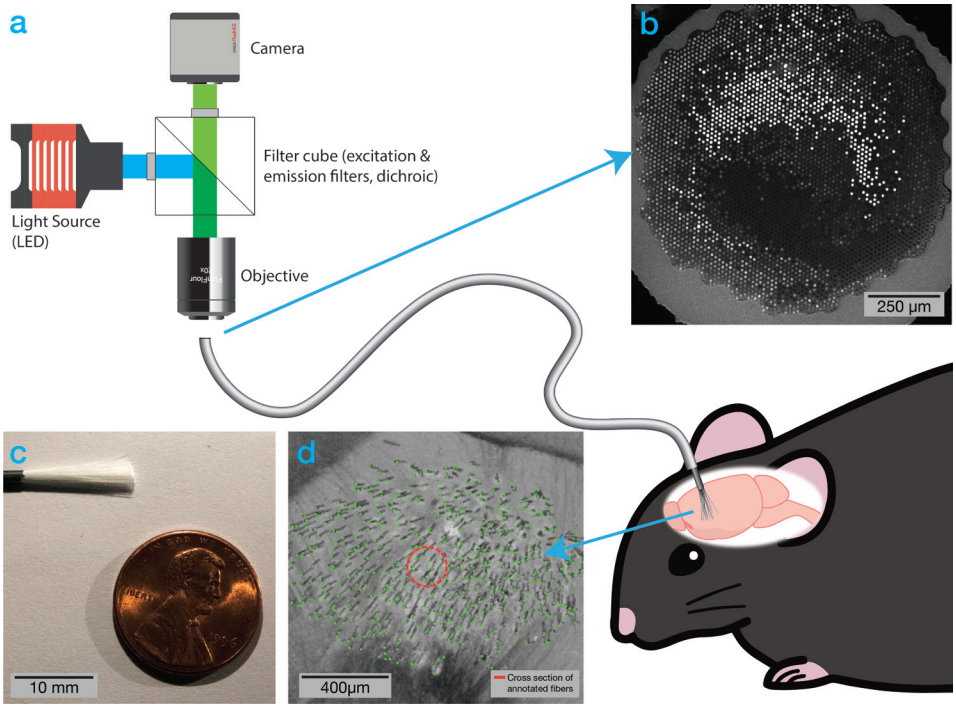
It is anticipated that the development of a computational miniature mesoscope will open up many new neuroscience applications by providing a wide-field brain mapping capability with single-neuron resolution. In particular, the miniaturized design will enable large-scale head-mounted recording that can be flexibly distributed to many animals in-parallel.

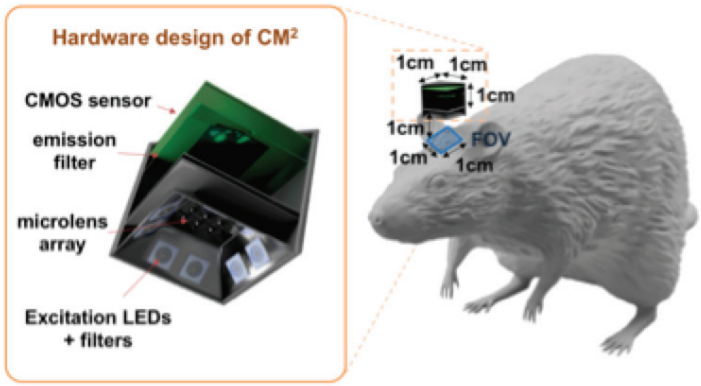
Opposite: Miniaturized CM2 hardware. The 1x1cm^2 FOV is provided by a 3x3 microlens array (MLA). A ring of LEDs and filters below the MLA deliver direct excitation, and emission filters reside between the MLA and CMOS sensor. The entire device will be ~1cm^3 in volume, and weigh ~3.2 grams.

Splaying optical fiber implants for neural sensing and modulation

In order to achieve a high channel count interface with deep brain regions, Dr. Nathan Perkins and Dr. Timothy Gardner developed a novel form of fiber photometry that uses hundreds or thousands of optical microfibers to record or stimulate neurons throughout a 3D volume. The individual fibers have diameters as small as 8 µm. As the fibers are inserted into the tissue, each fiber moves independently, spreading through the target brain region; each fiber provides an optical interface with a small region of tissue near the tip. Histology shows the fibers consistently spread during insertion, and find NeuN-stained neurons in close proximity to the fiber tips. Outside the brain, the fiber bundle comes together as a polishing imaging surface held in a ferrule. Early recording trials have recorded cortical spreading depolarizations and sensory signals evoked by forepaw stimulation through a traditional fluorescence microscope, but traces have a low signal to noise ratio.

The researchers are now seeking to optimize the microscope design and configuration to improve the ability to couple with the fibers and to record fluorescent indicator activity through the splaying fiber bundles. The new microscope configuration will aim to a) increase excitation light delivery, b) achieve a better NA match between the objective and the fibers to maximize coupling of excitation and emission light, c) streamline securing and aligning the fiber for interfacing both in acute, anesthetized animals and chronically implanted animals, and d) realize the potential to deliver bulk stimulation light via the fibers.





Expected Outcomes

The researchers anticipate that the revised microscope will improve the signal quality of data acquired through the bundles of splaying optical microfibers and enable initial stimulation experiments; these steps will further establish the optical microfibers as a technique for recording and stimulating deep brain regions. Faculty members performing calcium imaging may benefit from this work. These faculty include Dr. Ian Davison, Dr. Mark Howe and Dr. Jeffrey Gavornik. The ability to independently record or stimulate neurons at hundreds or thousands of points throughout a 3D volume in a deep brain region will enable interrogation of network dynamics underlying complex behaviors, such as olfaction, visual pattern matching and memory recall.

Functional Ultrasound

Being able to image large brain volumes with high spatio-temporal resolution is an important need that is not fully meet in the functional neuroimaging field. Functional Ultrasound (fUS) is a newly commercialized technology that has recently shown great potentially for extending capabilities for high spatio-temporal resolution imaging over large volumes in rodents. In the last two years, the application of functional Ultrasound in the neurosciences has rapidly spread because of the availability of commercial systems that provide high spatial temporal resolution (approximately 100 μm and 20 ms/frame) imaging in the rodent brain (up to depths of 15 mm). The next evolutionary step with the technology is to utilize a functional ultrasound research system to quantify and image brain activity with unprecedented spatial and temporal resolution in conjunction with synergistic technologies including photoacoustic imaging and optical coherence tomography. Photoacoustic imaging takes advantage of using the ultrasound signal to detect optical absorption, providing higher spatial temporal resolution to deeper tissues than achieved by optical imaging alone (~100 μm, 100 ms/frame, ~10 mm deep). In addition, by choosing an appropriate excitation wavelength, photoacoustic imaging can selectively image the distribution and functional information of targeted endogenous and exogenous chromophores, such as oxyhemoglobin, deoxyhemoglobin, and neural targeting agents. The acquisition of an ultrafast ultrasound research system can serve for both functional ultrasound imaging and photoacoustic tomography imaging. These two systems can be used across a wide range of biomedical applications by BU faculty.

David Boas, Professor, Biomedical Engineering

Dr. Boas studies cerebral blood flow and oxygen delivery, but is limited in the imaging penetration depth while maintaining high spatial resolution. fUS is analogous to the OCT imaging of blood flow that he has been utilizing for the last 10 years, and greatly improves the penetration depth. fUS will allow high spatial-temporal resolution measurements of cerebral blood flow alterations, for instance, associated with stroke and peri-infarct spreading depressions. In addition, photo-acoustic imaging can be integrated with the fUS to provide measurements of hemoglobin oxygenation throughout the entire extent of the rodent brain with 0.1 to 1.0 mm resolution. These capabilities will greatly enhance Dr. Boas' research program by permitting studies of cerebral blood flow and oxygen delivery to extend from the top 1 mm of the brain to the entire rodent brain.

Thomas L. Szabo, Research professor, Biomedical Engineering

Dr. Szabo and his teams are developing ultrasound methods to detect disease by characterizing the dynamic, nonlinear and viscoelastic properties of tissue and biofluids. Chronic disease or inflammation is often associated with changes in microstructure or biochemistry or mechanical response. Dr. Szabo's group is investigating methods to characterize these abnormalities in vivo using a combination of physics, signal and image processing and biofluid assays. The Verasonics system provides a unique combination of arbitrary waveform transmission, advanced receive filtering and onboard signal and image processing needed for these projects.

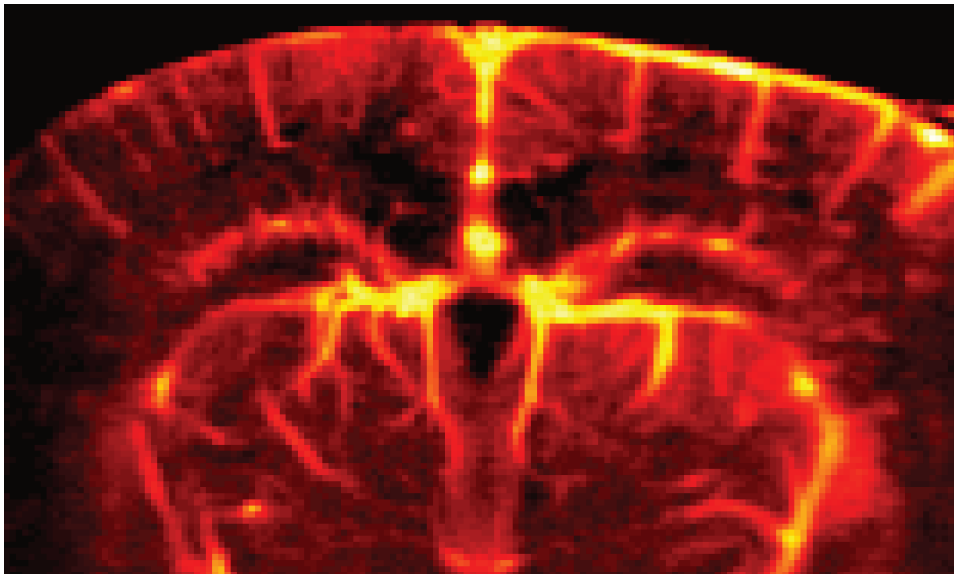
Jerome Mertz, Professor, Biomedical Engineering

Dr. Mertz and his team have recently developed an optical imaging technique, called oblique-back illumination microscopy (OBM), that provides phase contrast in arbitrarily thick tissue. The technique is simple, robust, and free of speckle noise. The drawback of this technique is that it provides only limited depth penetration in tissue, undermining its potential relevance for clinical applications. Because of the close analogy between optical and acoustical imaging, they believe the technique of OBM can be directly translated to the acoustical domain. They will test this idea using the Verasonics platform.

Kathleen G. Morgan, Professor, Health Sciences

Dr Morgan and her collaborators are focused on the topic of vascular dementia. Current funding supports studies in an aging mouse model. The central hypothesis be-

ing tested is that many individuals diagnosed with Alzheimer's Disease are primarily suffering from vascular problems in the brain. They are targeting vascular protein-protein interfaces with microbubble-packaged, cell permeant, decoy peptides that, in preliminary data, prevent aging-induced vascular damage. This ultrasound system will greatly aid their studies in which microbubble-loaded peptides are introduced into whole mice and image brain vascular status before and after microbubble bursting.



Tyrone Porter, Ph.D. Associate Professor Mechanical Engineering, Biomedical Engineering, Materials Science and Engineering

Dr. Porter has several projects that will benefit from the Verasonics system. Using microfluidic devices, the team is producing lipid-coated microbubbles (LCMB) which serve as contrast agents for diagnostic ultrasound imaging. The team has recently discovered that the onset of nonlinear bubble oscillations can be dictated by the lipid shell composition. Combining custom-engineered LCMB with appropriate pulsing and processing schemes will enable nondestructive subharmonic imaging with unprecedented contrast enhancement in diagnostic ultrasound images. The nonlinear response of the LCMB can be utilized for focal and reversible opening of the endothelium lining blood vessels. This strategy can be leveraged for delivery of therapeutic agents through the blood-brain barrier for treatment of a broad spectrum of brain disorders, delivery of biologics and macromolecules to smooth muscle cells proximal to blood vessels, and enhanced delivery of chemotherapeutics to solid tumors.

Paul Barbone, Professor, Mechanical Engineering

Dr. Barbone studies inverse problems related to elastography. His recent work shows evidence of a mechanical response to neurostimulation (MNS). That is, brain tissue seems to become locally and temporarily stiffer when it is stimulated, an effect that is measurable in vivo by elastography. The Verasonics Engine is the standard research imaging system in ultrasound shear wave elastography (SWE). The availability of this piece of equipment in the Neurophotonics Center provides an ideal opportunity to evaluate the MNS, corroborate with other functional approaches, and to investigate MNS mechanisms

Joyce Y. Wong, Professor, Biomedical Engineering

Dr. Wong's lab studies the use of microparticles in the diagnosis and treatment of disease including a current project that seeks to develop a microbubble based targeted ultrasound contrast agent with the specific goal of imaging and diagnosing fibrinous post-surgical adhesions in the peritoneum. The resolution and features available in the Verasonics system allow for the detail and imaging options necessary to complete preliminary in vivo experiments needed for grant applications, as well as to motivate future experiments showing and improving the clinical effectiveness of the microbubble system.

Darren Roblyer, Assistant Professor, Biomedical Engineering

Professor Roblyer studies the metabolism and microenvironment of tumors. His group currently uses diffuse optics and intravital multiphoton imaging in small animal tumor models. These modalities provide functional information (diffuse optics) and molecular imaging (multiphoton), but these modalities lack the ability to provide structural and microvascular information at imaging depth greater than 1mm. fUS will allow Dr Roblyer's group to correlate structure and function within tumor during growth and treatment for the study of chemoresistance. Additionally, the photoacoustic ability would accelerate Dr. Roblyer's research into antivascular therapeutic response by providing hemoglobin contrast at high resolution throughout the tumor, providing a link between molecular imaging and clinical imaging.