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Optical Techniques in Neurosurgery, Neurophotonics, and Optogenetics II

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Introduction

While light has been used for several decades for non-contact stimulation and manipulation of cells, optogenetics adds to the innovative optical toolkit for optical control of cells. Optogenetics refers to the use of optics and genetics together for controlling activity of proteins and cellular function. Optogenetics present cell-specific optical control of the functioning of genetically-targeted/modified cells. The use of optogenetics has exploded in last few years and has given rise to great advances in basic and applied research. The cellular functions that can be controlled with optogenetics include stimulation/inhibition of cells, gene activation, intracellular signaling, and migration. Many different cells including neurons, cardiac cells, stem cells and cancer cells can be controlled by optogenetic modulation. Optogenetics technologies could eventually form the basis for vision restoration, psychiatric treatment and pain-control. Photonic technologies are playing crucial role in both delivering light for cellular control, and, in some cases, for imaging the consequences of this control. The conference was divided into four major sessions spread over two days.

Innovative schemes for delivery and control of light irradiation, including miniaturized light sources, fiber optics, waveguides and special beams can potentially transform optogenetic approaches. Prof. John Rogers (UIUC) described the advancement on implantable, wireless optoelectronic systems for optogenetics, as part of the opening keynote lecture. Results of chronic optogenetic stimulation and recording across cortical areas in non-human primates using high-density micro-electrocorticography were presented in this session. Further, ultra-compact multi-channel implantable optical neural probes for deep brain optogenetic stimulation using visible array waveguide gratings or multipoint light emitting optical fibers were described in several talks. Prof. Patrick Ruther (Univ. of Freiburg) presented an invited talk on "Highly compact MEMS-based optrodes with integrated light sources" in which he reviewed the state-of-the-art technologies for optrodes enabling simultaneous illumination and electrical recording from brain. Together, these talks depicted the role of nanophotonics and electronics in successful implementation of optogenetic technologies.

Prof. Edward S. Boyden (MIT) gave the second Keynote lecture on "Optical tools for mapping and engineering the brain". His talk described his recent work on high-resolution imaging of brain using expansion microscopy. Further, he presented advancement in the development of new opsins in his lab providing red-shifted activation. With development of near-infrared light controllable proteins, cellular systems can be modulated in a minimally-invasive manner. Yawo group presented use of up-conversion of near-infrared light by lanthanide nanoparticles to activate channelrhodopsins for manipulating neural activities. Researchers from Mohanty Laboratory presented development of multi-opsin and use of broad-band light for ambient white-light based restoration of vision in photodegenerative retinal diseases. While molecular biology researchers will continue to engineer more efficient opsins having unique temporal, functional, and spectral characteristics, there is also a need to develop new molecular probes and imaging method for mapping cellular activation. Label-free optical polarimetric detection of cellular activation by optogenetic excitation was presented in this conference. A representative from industry (AXXAM, Italy) presented the use of different light-gated actuators and sensors in the generation of novel cellular recombinant assays, in order to prove their robustness and adaptability for drug discovery assays.

Several studies on *in-vivo* optical stimulation and optical/electrical read-out from neural circuits in non-human primates and rodents were presented. In a keynote lecture titled "Playing the piano with neural circuits: simultaneous 3D all-optical imaging and activation of neurons in vivo", Prof. Yuste (Columbia University) reviewed the efforts of his group in developing optical methods to perform two-photon imaging and photostimulation of neuronal populations using spatial light modulators, PSF engineering and a variety of optical, optogenetic and optochemical sensors. He also delivered a talk on "Simultaneous Imaging of Neural Activity in 3D" as part of BiOS hot topics. Detection and modulation of spatiotemporal patterns of neuronal activity in primary visual cortex from awake behaving mice was presented. Dr. Nassi (Salk Institute) presented measurement on the causal effects of locally-generated excitation and inhibition on spontaneous and visually-evoked responses in visual cortex of alert, fixating macaque monkeys. Prof. Augustine (KIST and Duke) presented an invited talk on optogenetics to map the spatial organization of local circuits.

Innovations in optical techniques hold significant promise for advancing optogenetic technologies. The introduction of non-linear optics has allowed precise and in-depth spatial control of optogenetic stimulation with (sub)cellular resolution. *In vivo* all-optical interrogation of neurons in mice using two-photon optogenetic stimulation and calcium imaging with two-photon fluorescence microscopy was presented by researchers from Canada. Prof. Shoham (Israel Institute of Technology) presented an invited talk on "Distributed optogenetic interfacing with retinas, optonets and brains: photonics and potential applications". Researchers from UIUC described the use of a photonic crystal fiber pumped by Ytterbium laser as a broadband femtosecond source for two-photon optogenetics and imaging. Researchers from Europe presented Spatio-angular light control in microscopes using micro mirror arrays for precise, localized activation of optogenetic probes or the activation and deactivation of signaling cascades using photo-activated ion-channels. An automated laser tracking and photothermal/optogenetic manipulation system for studying social behaviors in multiple freely moving fruit flies was described in an invited talk by Dr. Lin (National Tsing Hua Univ). Researchers from Mohanty Laboratory described use of ultrafast NIR laser microbeam for delivery of opsin-encoding genes and impermeable actin-staining molecules into spatially-targeted neurons enabling visualization of neuronal network and their activation.

Besides control of light-activatable ion-channels, optogenetics encompasses controlling activity of other proteins and cellular functions. The varieties of cellular functions that can be controlled with optogenetics include stimulation/inhibition of cells, gene activation, intracellular signaling, and migration. Prof. Hahn (UNC at Chapel Hill) presented a keynote lecture on "Engineering proteins for visualization and control of signaling networks in vivo". He described new tools to visualize and manipulate signaling in cells, using Rho family GTPase networks and cell motility as test beds. Further, methods to direct activated kinases to specific targets and control sequestration of proteins at intracellular membranes with light was described. Prof. Lin (Stanford) described optogenetic control of protein activity with photodissociable fluorescent proteins. Such fluorescent light-inducible proteins enabled optical control over guanine nucleotide exchange factor and protease domains, and can be generalized in future to other protein families including kinase and DNA nuclease. Studies on optomechanical and photothermal manipulation of cells were also presented by various researchers. Scientists from Japan presented work on "Laser-induced perturbation into molecular dynamics localized in neuronal cell" using optical trapping dynamics of synaptic vesicles or neural cell adhesion molecules. Further, dielectrophoretic trapping using metal coated chemically etched fiber was proposed for cell manipulation and isolation. At the end of the conference, Prof. Mohanty presented all-optical approach for construction (by optical tweezers, and axonal guidance), and manipulation (laser nanosurgery and optoporation) as well as modulation (optical or optogenetic) and detection (calcium and quantitative phase imaging) of neural activities.

While looking forward, we believe applications of optogenetic and other optical modulation of cells will have wide-variety of basic research and biomedical applications. Though representatives from industry also participated in the conference, more active role of the photonics industry in developing novel source and imaging platforms for optical activation and detection of cellular activities will be crucial for the successful development of this area. We hope that reading the talks presented in the annual Optogenetics and Optical control of cells conference and abstracts/articles provided in this volume will convey the knowledge and excitement of this exciting field. We look forward to your participation as authors and presenters in this conference next year. In addition to the travel support provided by SPIE to selected students, we were able to partially support selected speakers. We believe that we will be able to support more participants next year with support from the sponsors.

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