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EDITORIAL

Special issue on optical neural engineering: advances in optical stimulation technology

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Guest Editors

Neural engineering, itself an 'emerging interdisciplinary research area' [1] has undergone a sea change over the past few years with the emergence of exciting new optical technologies for monitoring, stimulating, inhibiting and, more generally, modulating neural activity. To a large extent, this change is driven by the realization of the promise and complementary strengths that emerging photo-stimulation tools offer to add to the neural engineer's toolbox, which has been almost exclusively based on electrical stimulation technologies. Notably, photo-stimulation is non-contact, can in some cases be genetically targeted to specific cell populations, can achieve high spatial specificity (cellular or even sub-cellular) in two or three dimensions, and opens up the possibility of large-scale spatial–temporal patterned stimulation. It also offers a seamless solution to the problem of cross-talk generated by simultaneous electrical stimulation and recording.

As in other biomedical optics phenomena [2], photo-stimulation includes multiple possible modes of interaction between light and the target neurons, including a variety of photo-physical and photo-bio–chemical effects with various intrinsic components or exogenous 'sensitizers' which can be loaded into the tissue or genetically expressed. Early isolated reports of neural excitation with light date back to the late 19th century [3] and to Arvanitaki and Chalazonitis' work five decades ago [4]; however, the mechanism by which these and other direct photo-stimulation, inhibition and modulation events [5–7] took place is yet unclear, as is their short- and long-term safety profile. Photo-chemical photolysis of covalently 'caged' neurotransmitters [8, 9] has been widely used in cellular neuroscience research for three decades, including for exciting or inhibiting neural activity, and for mapping neural circuits. Technological developments now allow neurotransmitters to be uncaged with exquisite spatial specificity (down to a single spine, with two-photon uncaging) and in rapid, flexible spatial–temporal patterns [10–14]. Nevertheless, current technology generally requires damaging doses of UV or violet illumination and the continuous re-introduction of the caged compound, which, despite interest, makes for a difficult transition beyond *in vitro* preparations. Thus, the tremendous progress in the *in vivo* application of photo-stimulation tools over the past five years has been largely facilitated by two 'exciting' new photo-stimulation technologies: photo-biological stimulation of a rapidly increasing arsenal of light-sensitive ion channels and pumps ('optogenetic' probes [15–18]) and direct photo-thermal stimulation of neural tissue with an IR laser [19–21].

The *Journal of Neural Engineering* has dedicated a special section in this issue to highlight advances in optical stimulation technology, which includes original peer-reviewed contributions dealing with the design of modern optical systems for spatial–temporal control of optical excitation patterns and with the biophysics of neural–thermal interaction mediated by electromagnetic waves. The paper by Nikolenko, Peterka and Yuste [22] presents a compact design of a microscope-photo-stimulator based on a transmissive phase-modulating spatial-light modulator (SLM). Computer-generated holographic photo-stimulation using SLMs [12–14, 23] allows the efficient parallel projection of intense sparse patterns of light, and the welcome development of compact, user-friendly systems will likely reduce the barrier to its widespread adoption. The paper by Losavio *et al* [24] presents the design and functional characteristics of their acousto-optical deflector (AOD) systems for studying spatial–temporal dendritic integration in single neurons *in vitro*. Both single-photon (UV) and two-photon (femtosecond pulsed IR) AOD uncaging systems are described in detail. The paper presents an excellent overview of the current state of the art and limitations of this technology, which is increasingly being applied for both photo-stimulation and imaging [25, 26]. Finally, the paper by Pikov *et al* [27] studies the modulatory biophysical effects exerted by low power millimeter waves on neuronal excitability and membrane properties of cortical pyramidal neurons *in vitro*. These extensive neuro-modulatory effects seem to include a thermal component (related to the photo-thermal effects observed under laser illumination [28]) as well as a more specific effect exerted by these lower frequency (sub-THz) electromagnetic waves.

These new contributions augment five previous manuscripts published by the journal on optical stimulation technology, which reported the development of a fiber-based system for *in vivo* optogenetic cortical stimulation [29], patterned stimulation systems based on computer-generated holography [23] and on arrays of micro-LEDs [30] designed for an optical retina neuroprosthetic [31], and an integrated system for optical stimulation with microelectrode array recording [32]. Without doubt, many more will quickly follow as neural engineers and neuroscientists increasingly tackle the many challenges that this exciting area poses. We can all expect to hear much more in the near future about the biophysics and implementation of photo-physical neural-interaction mechanisms, the design of new optogenetic probes and patterned-stimulation systems (including stand-alone and implantable systems), further integration of electrodes and optical components into electro-optical neurostimulation systems, and rapid progress towards multiple medical applications for alleviating neurological disabilities and improving human health.

References

[1] Durand D M 2006 What is neural engineering? *J. Neural Eng.* **4** (4)

[2] Niemz M H 2007 *Laser-Tissue Interactions: Fundamentals and Applications* 3rd edn (Berlin: Springer)

[3] Arsonval A D 1891 La fibre musculaire est directement excitable par la lumiere *C. R. Soc. Biol.* **43** 318–20

[4] Arvanitaki A and Chalazonitis N 1961 Excitatiory and inhibitory processes initiated by light and infra-red radiations in single identifiable nerve cells *Nervous Inhibition* ed. E Florey (New York: Pergamon) pP 194–231

[5] Fork R L 1971 Laser stimulation of nerve cells in Aplysia *Science* **171** 907–8

[6] Allegre G, Avrillier S and Albe-Fessard D 1994 Stimulation in the rat of a nerve fiber bundle by a short UV pulse from an excimer laser *Neurosci. Lett.* **180** 261–4

[7] Hirase H, Nikolenko V, Goldberg J H and Yuste R 2002 Multiphoton stimulation of neurons *J. Neurobiol.* **51** 237–47

[8] Callaway E M and Yuste R 2002 Stimulating neurons with light *Curr. Opin. Neurobiol.* **12** 587–92

[9] Ellis-Davies G C 2007 Caged compounds: photorelease technology for control of cellular chemistry and physiology *Nat. Methods* **4** 619–28

[10] Shoham S, O'Connor D H, Sarkisov D V and Wang S S 2005 Rapid neurotransmitter uncaging in spatially defined patterns *Nat. Methods* **2** 837–43

[11] Nikolenko V, Poskanzer K E and Yuste R 2007 Two-photon photostimulation and imaging of neural circuits *Nat. Methods* **4** 943–50

[12] Lutz C, Otis T S, DeSars V, Charpak S, DiGregorio D A and Emiliani V 2008 Holographic photolysis of caged neurotransmitters *Nat. Methods* **5** 821–7

[13] Nikolenko V, Watson B O, Araya R, Woodruff A, Peterka D S and Yuste R 2008 SLM microscopy: scanless two-photon imaging and photostimulation with spatial light modulators *Front. Neural Circuits* **2** 5

[14] Zahid M, Velez-Fort M, Papagiakoumou E, Ventalon C, Angulo M C and Emiliani V Holographic photolysis for multiple cell stimulation in mouse hippocampal slices *PLoS One* **5** e9431

[15] Boyden E S, Zhang F, Bamberg E, Nagel G and Deisseroth K 2005 Millisecond-timescale, genetically targeted optical control of neural activity *Nat. Neurosci.* **8** 1263–8

[16] Zhang F, Aravanis A M, Adamantidis A, de Lecea L and Deisseroth K 2007 Circuit-breakers: optical technologies for probing neural signals and systems *Nat. Rev. Neurosci.* **8** 577–81

[17] Gradinaru V, Zhang F, Ramakrishnan C, Mattis J, Prakash R, Diester I, Goshen I, Thompson K R, Deisseroth K 2010 Molecular and cellular approaches for diversifying and extending optogenetics *Cell* **141** 154–65

[18] Zhang F, Gradinaru V, Adamantidis A R, Durand R, Airan R D, de Lecea L and Deisseroth K 2010 Optogenetic interrogation of neural circuits: technology for probing mammalian brain structures *Nat. Protoc.* **5** 439–56

[19] Wells J, Kao C, Mariappan K, Albea J, Duco Jansen E, Konrad P and Mahadevan-Jansen A 2005 Optical stimulation of neural tissue *in vivo Opt. Lett.* **30** 504–6

[20] Izzo A D, Richter C P, Jansen E D and Walsh J T Jr 2006 Laser stimulation of the auditory nerve *Lasers Surg. Med.* **38** 745–53

[21] Richter C P, Izzo A D, Wells J, Jansen E D and Walsh J T Jr 2010 Neural stimulation with optical radiation *Laser Photonics Rev.* available at doi:10.1002/lpor.200900044

[22] Nikolenko V, Peterka D S and Yuste R 2010 A portable laser photostimulation and imaging microscope *J. Neural Eng.* **7** 045001

[23] Golan L, Reutsky I, Farah N and Shoham S 2009 Design and characteristics of holographic neural photo-stimulation systems *J. Neural Eng.* **6** 066004

[24] Losavio B E, Iyer V, Patel S and Saggau P 2010 Acousto-optical laser scanning for multi-site photo-stimulation of single neurons *in vitro J. Neural Eng.* **7** 045002

[25] Duemani Reddy G, Kelleher K, Fink R and Saggau P 2008 Three-dimensional random access multiphoton microscopy for functional imaging of neuronal activity *Nat. Neurosci.* **11** 713–20

[26] Grewe B F, Langer D, Kasper H, Kampa B M and Helmchen F 2010 High-speed *in vivo* calcium imaging reveals neuronal network activity with near-millisecond precision *Nat. Methods* **7** 399–405

[27] Pikov V, Arakaki X, Harrington M, Fraser S E and Siegel P H 2010 Modulation of neuronal activity and plasma membrane propertiess with low-power millimeter waves in organotypic cortical slices *J. Neural Eng.* **7** 045003

[28] Liang S *et al* 2009 Temperature-dependent activation of neurons by continuous near-infrared laser *Cell Biochem. Biophys.* **53** 33–42

[29] Aravanis A M, Wang L-P, ZhangF, Meltzer L A, Mogri M Z, Schneider M B and Deisseroth K 2007 An optical neural interface: in vivo control of rodent motor cortex with integrated fiberoptic and optogenetic technology *J. Neural Eng.* **4** S143–56

[30] Grossman N *et al* 2010 Multi-site optical excitation using ChR2 and micro-LED array *J. Neural Eng.* **7** 016004

[31] Degenaar P, Grossman N, Memon M A, Burrone J, Dawson M, Drakakis E, Neil M and Nikolic K 2009 Optobionic vision—a new genetically enhanced light on retinal prosthesis *J. Neural Eng.* **6** 035007

[32] Zhang J *et al* 2009 Integrated device for optical stimulation and spatiotemporal electrical recording of neural activity in light-sensitized brain tissue *J. Neural Eng.* **6** 055007