Óbuda University

PhD Thesis Booklet

Investigation of optrodes for infrared stimulation in the deep tissue

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Abstract

During my PhD work, I developed a single-crystalline silicon-based, Michigan-type (in-plane) infrared (IR) optrode capable for simultaneous deep-brain electrophysiological recording and temperature sensing. Although the discovery of IR-induced modulation of cellular activity dates back to the early 2000s, such an integrated, multimodal, long neural probe has never been created. Thanks to this compact investigation tool, further knowledge about the interaction of IR light and deeper regions of the neural tissue can be extended *in vivo* in a minimally invasive way.

At the beginning of my dissertation I give an overview of related fields in the literature of neural microdevices. I briefly introduce some neuroscientific aspects of the applications and the contemporary opportunities of the rich field of implantable neural microdevices with integrated optics. Then I sum up the mechanism of optical and thermal stimulation methods of the nervous system. I introduce the optrode device through the description of its

expected functionalities and the details of its design and fabrication process. All of the fulfilled test methods of the optrode's functionalities are also introduced: benchtop tests of the device development, calibrations of individual products, functional tests *in vitro* and *in vivo* validation as well.

Összefoglaló

Doktori kutatásom során kifejlesztettem egy egykristályos szilíciumalapú, planáris (Michigan típusú) infravörös (IR) optródot, amely optikai stimuláció mellett képes mélyagyi elektrofiziológiai jelelvezetésre és hőmérséklet érzékelésre is. Bár az infravörös idegi ingerlés első leírása a 2000-es évek elejére tehető, máig nem készült még ilyen, több funkciót egyetlen hosszú, idegszövetbe implantálható eszközbe integráló megoldás. E kompakt eszköznek a segítségével az IR fény mélyebb agyterületekre gyakorolt hatásával kapcsolatos ismereteink oly módon gyarapíthatók, hogy közben minimalizáljuk a kísérleti állatot érő hátrányos külső hatásokat.

Doktori értekezésem elején áttekintem az idegi implantátumok kapcsolódó szakirodalmát. Röviden bemutatom az integrált optikát is tartalmazó idegi implantátumok alkalmazásának idegtudományi szempontjait és e gazdag tudományterület kortárs lehetőségeit. Összefoglalóan bemutatom az idegrendszer optikai és hőmérséklet általi ingerlő módszereit és mechanizmusukat. Bemutatom az optród eszköz elvárt funkcióinak tervezését, megvalósítását. Továbbá ismertetem az optród funkcionális tesztelésének módszereit az eszközfejlesztési szakaszban, az egyes eszközpéldányok kalibrációjakor, valamint *in vivo* kísérleti körülmények között is.

I. Introduction

1. Theory

Neural microdevices can be classified based on various aspects: e.g. human or animal purpose; central or peripheral nervous system is targeted; chronic or acute, cortical or deep-tissue application. They can provide sensing or stimulating functions or both. The development of deep-brain implants that are simultaneously able to

monitor neural activity and to stimulate the same tissue environment is advantageous to gain comprehensive information on the behaviour of cooperating neuronal population. Means of modulation of neuronal activity are acting through electrical (Rizzone et al. 2001), (Temperli et al. 2003), (Owen et al. 2006), (Fisher et al. 2010), (Chen et al. 2018), pharmacological (Martinoia et al. 2005), (Oldfield, Keating, and Perry 2007), (Nitsche et al. 2012), (Liu et al. 2013), (Borbély et al. 2016) or optical intervention (Vandecasteele et al. 2014), (Son et al. 2015), (Wang et al. 2019). Among clinically relevant stimulation methods (Rizzone et al. 2001), (George et al. 2007), (Eljamel and Slavin 2013), photo stimulation is a promising tool, since electrical crosstalk effects, which contaminates recorded brain signals during electrical stimuli, are limited (Shoham and Deisseroth 2010). The most often used technical term for these devices, which can deliver light to neurons and can record evoked potentials, is optrode (Iseri and Kuzum 2017), (S B Goncalves et al. 2017). Typically, optrode devices are used for optogenetic applications, during invasive methods. A special field of optical neuromodulation

applies infrared (IR) light for several beneficial reasons (Chernov and Roe 2014). It is simple, as does not require any genetic transformation (Shapiro et al. 2012); its longer wavelength provides superior penetration in tissues (Jacques 2013) and facilitates artefact-free recording of electrophysiological signals (Wells et al. 2005), (Cayce et al. 2014).

It is proved that the thermal sensitivity of certain ion channels of neurons (TRPV4) plays a fundamental role in stimulating effect of IR illumination (Albert et al. 2012). Thermal stimulation is suitable in view of invasiveness of the stimulating methods: as visible light required for optogenetics has to be delivered through a transcranial waveguide element, thermal “signals” can be delivered in a non-invasive way through external stimulus. Its simplest way is ambient warming which is lacking cell specific selectivity. IR illumination is still promising, because its penetration depth in tissues is more favourable than visible light’s one (Bashkatov et al. 2005; Jacques 2013). Although penetration depth of light is strongly wavelength-dependent (Tanya V.F. Abaya et al. 2014) and

also depending on the examined tissue, effective deep-brain application of IR light still needs penetrating waveguides.

2. Available devices of nowadays

Before optrodes have been introduced, bulky optical fibres implanted in the tissue were only used to stimulate neuronal population using light in spatially confined manner (Aravanis et al. 2007), (Adamantidis et al. 2007), (Zhang et al. 2010), (Anikeeva et al. 2012). The key advantage of optrodes is that they provide multiple functions in a single device, which helps to mitigate the extent of cellular damage otherwise induced using standalone recording and stimulation devices. Such multifunctional tool also provides precise relative location of recording and stimulation spots eliminating the complicated positioning of individual devices (Warden, Cardin, and Deisseroth 2014). The state-of-the-art optrodes can be divided in two main groups: passive and active optrodes. Passive optrodes contain a passive microoptical element, which delivers light coupled into the system from an external light source (optical fibre,

waveguide). In active optrodes, light is generated through integrated sources (like microLEDs) located on the probe (Schwaerzle, Paul, and Ruther 2017), (Wang et al. 2019), or even on its shaft (Cao et al. 2013), (Wu et al. 2015), (S. Beatriz Goncalves et al. 2018). All these abovementioned implantable microdevices with integrated optics are developed for visible light applications. The only available deep-brain implantable optical microdevice for IR light application is a developed version of the long-used Utah-type (out-of-plane) array (T.V.F. Abaya et al. 2012), however, their system is only a technological demonstration, and was never applied in living tissue.

II. Objectives

The Michigan-type IR optrode in question is made of single-crystalline silicon and developed for acute *in vivo* experiments in deep-brain tissue of rodent subjects. The aim of the present device development was to create an implantable optical stimulation device, which is able to deliver IR light through its embedded bulk waveguide and holds sensors, which monitor the optically evoked electrical and thermal response of the irradiated tissue. The

relevance of this device development – as far as I know – is that this is the first Michigan-type, multimodal, deep-brain microimplant which simultaneously holds sensory and stimulating functionalities integrated into a single needle-like device by the application of IR waveguiding, thermal measurement and electrophysiological recording which is validated during *in vivo* experimental conditions. This miniaturized investigation tool is beneficial for brain researchers as they do not need to injure the experimental animal with disjunct tools and probes just one small, multimodal needle to get further knowledge about the impact of IR light on deeper regions of the neural tissue *in vivo*.

III. Methods

1. IR optrode device

I introduce the IR optrode device from its layout design through its MEMS manufacturing technology to its manual assembly. The Si substrate is not only the mechanical carrier of the functionalities, but it is the IR waveguide as well. IR light is coupled into the Si bulk from an optical fibre through a cylindrical lens which is

formed by deep reactive ion etching (DRIE). To achieve a good efficiency waveguide, the sidewall of the Si is further polished to reduce its roughness caused by DRIE. The elongated, needle-like shaft part of the optrode chip holds right at the tip, the electrophysiological recording sites and a meander-shape resistance temperature sensor filament as close as possible to them. Both are made of Pt thinfilm.

2. Electrode functionality

The electrical performance of the optrode is tested by electrochemical impedance spectroscopy. The similar arrangement was used to test the long-term integrity of the layer structures in wet environment (soaking test). The impedance of the electrophysiological recording sites is reduced by exploiting the enhanced specific surface of electroplated porous Pt (black-Pt).

3. Waveguiding functionality

To determine the optical properties of the optrode, I used two measurement setups. One of them relies on a CMOS beam profiler, which was used to evaluate the shape of the IR light emitted from the tip of the optrode. The other one comprises of a laser power meter (with an IR sensor head),

which provided quantitative information on optical power. During my PhD work, I used different types of IR laser light sources. All of them was a laser diode operated in constant current (continuous wave, CW) mode. In the initial stages an un-cooled, 5 mW diode was chosen. Later, when higher light intensity was required, it was replaced with a 30 or 40 mW laser diode. The latter types needed cooled environment, so they were placed in a custom designed Al holder, which also supported the focusing and collimation of IR light to the front facet of the optical fibre. All of them operate at wavelength of 1310 nm. The fourth IR light source is a pigtailed laser diode with 50 mW and 1550 nm operating power and wavelength, respectively. I made optical measurement on chip scale and with fully functional, assembled optrodes as well. In latter case, I observed not only IR light intensity distribution emitted from the blunt tip of the Si chip (beam size, shape, waveguide efficiency) but the divergence angle of emitted beam and absolute optical power as well.

4. Thermal aspects of the IR optrode

I fulfilled the calibration of the optrode's integrated temperature sensor through a series of simultaneous measurement with an industrial aluminium-oxide negative temperature coefficient thermistor used as reference.

It was essential to determine the spatial distribution of heat around the tip of an illuminating optrode to avoid any harmful overheating of the tissue in later *in vivo* conditions. This test of temperature distribution due to optical heating was performed in a 2 ml polyethylene cylinder filled with 1.7 ml room temperature saline. The shaft of two Si probes were immersed in the liquid medium. One was the heating source (optrode) and another one was used to measure the temperature change in different positions from the end facet of the optrode (reference point of the coordinate system). First, the heating power (the level of supply current of the IR laser diode) was changed at a fixed position of the immersed shafts. This calibration procedure provided relation between temperature elevation and coupled optical power, which is an essential input information to design *in vivo*

tests. After that, the spatial distribution measurements were made at a selected optical power level and at multiple locations along the axis of the shaft (x) and also in perpendicular direction (y) with 100 μm resolution set by a micropositioner.

5. *In vivo* validation

The optrode's suitability was validated in animal model. The primary aim of the *in vivo* experiment was to test concurrent IR stimulation and electrical recording in the deep neural tissue of anesthetized rat in acute experiments. The optrode was implanted in the targeted depths from the superficial layer of the somatosensory cortex down to the CA1 region of the hippocampus. Another commercial linear silicon probe was implanted in 18° as a calibration tool for neural activity recording modality of the optrode. These surgeries were made in cooperation with colleagues in the Research Centre for Natural Sciences (RCNS). One stimulation cycle was composed of 2 min long laser-ON, and 4 min long laser-OFF periods. The latter was aimed to provide enough time for the temperature of the stimulated region to return to baseline temperature. To check the

reproducibility of the stimulation patterns in the electrophysiological traces, 10-15 trials were performed in a random fashion for different input power (temperature) based on the *in vitro* tests of the temperature distribution and the literature. Furthermore, to check the stability of the stimulating power and to ensure the validity of the evoked neural and temperature response, absolute optical power measurements were performed before and after the *in vivo* implantation. Extracellular electrophysiological recording was performed through the integrated Pt sites of the optrode and those of the commercial linear silicon probe as well. An additional screw electrode implanted over the cerebellum served as a reference. All signals were sampled at 20 kHz by a preamplifier connected to an Intan Evaluation Board. Raw local field potential (LFP) channels were band pass filtered between 0.4-7 kHz, and multi-units were detected with an absolute threshold. The unit activity was combined from multiple neighbouring channels, downsampled to 1 kHz and smoothed with a 10 ms moving average filter. This data was used for calculation of peri-stimulus time histogram (PSTH) of

heating events. Single unit detection was made by a simple thresholding method, followed by a manual clustering.

IV. Results

1. Novel multimodal deep-brain implant – Thesis 1.

I developed a microfabrication process to create an implantable, multifunctional, silicon-based microprobe capable of both optical stimulation and interrogation of neural activity (infrared optrode, IR optrode). The optrode consists a monolithically integrated optical waveguide, a temperature sensor and four platinum sites. Platinum recording sites are integrated to record electrophysiological response evoked by the infrared irradiation delivered through the waveguide of the probe. [1], [2]

2. Electrochemical performance of recording sites – Thesis 2.

I determined the electrical characteristics of the electrophysiological recording sites of the IR optrode by electrochemical impedance spectroscopy. The initial impedance of the recording sites measured at 1 kHz can be

reduced to 46±9 kΩ from 678±198 kΩ by electroplating porous platinum on top of the sputtered platinum sites. Utilizing long-term soaking tests, I proved that the applied dielectric layer structure can provide stable insulation of the platinum wiring. I determined that the average impedance values of the electrophysiological recording sites measured on a daily basis at 1 kHz changed less than 18% around the mean value of 1031 kΩ during a 16-day-long stability test in phosphate buffer solution. [2], [3]

3. Optical performance of integrated waveguides – Thesis 3.

I developed an experimental arrangement to characterize the absolute optical power and beam profile emitted from the end facet of the waveguide integrated on the optrode chip. In the case of chip-scale measurements, I showed that the waveguiding efficiency of the optrode chips is 32.04±4.10%, using a light source with 1310 nm wavelength. I developed an encapsulation process to facilitate the testing of all integrated functionalities of the chips. Due to the precision of the assembly method, the repeatability of optical measurements increased, the

standard deviation was reduced below 4% in case of individual assembled devices. The overall optical efficiency of the assembled optrodes can be as high as 41.5±3.29%. [1], [2], [4]

4. Properties of the optical heating functionality of the IR optrode – Thesis 4.

I developed an automated environment to measure the effective cross-section of optical heating induced by optical absorption in liquid medium. I determined that the full width half maximum of the effective cross-section in perpendicular to the axis of the probe shaft is 1020±184 μm considering a 2.17–3.5 mW optical power range. I proved that the temperature increase (1–4 °C) in the thermally affected region shows a linear dependence on the optical heating power (between 3–9 mW). [3]

5. *In vivo* validation of optrode functionality – Thesis 5.

I carried out the *in vivo* validation of the device to test all functionalities of the IR optrode. I proved that the recording sites are able to capture single unit activity, and the operation of optical stimulation, concurrently with recording of neuronal signals, causes no electric artefact in

the electrophysiological data. I determined that operating a light source of 1550 nm wavelength coupled to the optrode at an optical power between 2.8–13.4 mW, modulation of the spike rate of particular neurons is possible in a safe and, repeatable manner. [3]

V. Potential applications and benefits

Some recent studies in the literature has shown similar observations, however, these experiments were limited to *in vitro* subjects (Xia and Nyberg 2019), (Shibasaki et al. 2007), (Hedrick and Waters 2011), (Radzicki et al. 2013). For example, in our experiments, the activity of CA1 neurons was recorded during *in vivo* stimulation. There is a growing literature debating the expression, presence and function of thermosensitive receptors and ion channels in the hippocampus (Kim and Connors 2012), (Hurtado-Zavala et al. 2017), however, the in-depth investigation of the underlying phenomena and sensitivity to temperature was out of the scope of my work. Nevertheless, the very recent results of Xia et al (Xia and Nyberg 2019) suggests that safety limits are far beyond the range we used, therefore the toolset based on the IR optrode in question is

definitely able to address questions on cell excitability modulated with tissue temperature.

Besides the above works on the response of brain cells to hyperthermia, studies on infrared neural stimulation (INS) and infrared neural inhibition (INI) may also benefit from the use of this photonic microdevice. In particular, the above introduced results indicate that low-energy (in the range of a few mW) irradiation of the intracortical and hippocampal neurons is able to either boost or suppress the firing activity of neurons without creating high spatial or temporal gradient of temperature increase. Nevertheless, the degree of inhibition (decrease in firing rate) in our case of infragranular cells are in the same range as demonstrated *in vitro* by Xia et al at 1550 nm with continuous wave laser light (Xia and Nyberg 2019) and *in vivo* by Cayce et al at 1875 nm with pulsed infrared irradiation (Cayce et al. 2011).

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VI. References

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VII. Scientific publications related to theses

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