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Faculty of Information Technology and Bionics

OTDK Report

Characterisation of infrared optrodes with a micromirror needle tip

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Abstract

Previous experiments have shown that changes in body temperature affect the electrical activity of nerve cells and metabolic processes in the nervous system. The implantable microsystems developed at the Faculty are designed to explore these connections.

The Research Group for Implantable Microsystems, at PPKE-ITK has been developing deep brain implants that perform multiple functions in a single device for many years. The experience gained from in vivo experiments with infrared optrodes so far has stimulated research into the development of a new needle tip geometry: the shape of the waveguide needle tip has a great influence on the shape of the infrared light spot that influences the electrical behaviour of the neurons, and thus on the direction and area of the modulation of the electrical activity of the targeted neuron group relative to the stimulation site (i.e. the needle tip).

In my research, I investigate micromirror tip optrodes fabricated for infrared neuro-modulation through optical, thermal and electrical measurements.

Primarily, based on the basic properties of Infrared Neural Stimulation (INS) and the multimodal silicon optrode learned from literature, the setup and procedure of the measurement was designed.

The main points of my report include the analysis of the integrated functions of micromirror-tip infrared optrodes: measuring the impedance of extracellular electrophysiological recording sites; studying the optical properties of light exiting the micromirror tip; and the spatial distribution of the heating effect of infrared light in the needle tip environment and its dependence on the driving power.

The results obtained will be compared with the corresponding parameters of previous device versions prepared by the research team, providing useful data for the design of a future in vivo application. The results may also open up the possibility to formulate new research directions.

Acknowledgements

Throughout my work, I owe a huge gratitude and thanks to my supervisor Ágoston Csaba Horváth, who carefully monitored my work all the way. In addition to his continuous support, I received a lot of advice and knowledge from him.

I am also grateful to my consultant Zoltán Fekete, who granted me the opportunity to join the research team. He also gave me a lot of support and advice to achieve my results.

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Contents

Abstract	iii
Acknowledgements	iv
1 Introduction	1
1.1 The structure of my report	2
2 Scientific background	3
2.1 Neuromodulation	3
2.1.1 Phenomenon	3
2.1.2 Techniques	4
2.2 Infrared neuromodulation	5
2.2.1 Phenomenon	5
2.2.2 Advantages	6
2.2.3 Challenges	7
2.2.4 Inhibition	7
2.3 Intracortical infrared optrodes	8
2.3.1 Structure	8
2.3.2 Fabrication	10
3 Techniques	13
3.1 Thermal measurements	13
3.1.1 Experimental setup	13
3.1.2 Steps of the measurement	15
3.1.3 4-wire resistance measurement	15
3.1.4 The basis of temperature calculations	15
3.1.5 Expected results	16
3.2 Optical investigations	16
3.2.1 Tools	16

3.2.2	Experimental setup	18
3.3	Impedance of electrophysiological recording sites	18
3.3.1	Experimental setup	19
4	Results	21
4.1	Thermal measurements	21
4.1.1	Spatial distribution of optical heating	21
4.1.2	Dependence of optical heating on supply current	26
4.2	Optical investigations	28
4.3	Impedance of electrophysiological recording sites	32
5	Conclusion	33
5.1	Task	33
5.2	Results	33
5.2.1	Thermal characteristics	33
5.2.2	Optical characteristics	34
5.2.3	Electrical characteristics	34
5.3	Future plans	34
	Bibliography	37

Chapter 1

Introduction

As it has been shown by previous studies, the shape of the waveguide needle tip has a strong influence on the shape of the infrared light spot that influences the electrical behaviour of the neurons, and thus on the direction and area of the modulation of the electrical activity of the targeted neuronal group relative to the stimulation site (i.e. the needle tip). The in vivo experiments carried out so far encourage the development of a new, micromirror-tip needle tip geometry.

The aim of my work was to make steps in the characterization of optrodes used for infrared neural stimulation. A precisely designed optrode transfers infrared light to the neurons. The characteristics of the light exiting the tip of the probe can be controlled by the geometry of the optrode. In our studies, micromirror tip silicon optrodes were used. This type of needle tip geometry is designed to locate the maximum of the optical heating closer to the silicon (Si) needle, where the electrophysiological recording sites are placed.

The basic concept behind the design is that the infrared light exiting the needle tip should emerge not only straight from the tip, but orthogonally, to its left side as well.

As this is a completely new and uncharted optrode design, the full mapping of its properties is obviously needed. The methods mentioned in my report attempt to provide a basis for this brand-new micromirror-geometry needle tip behaviour. To achieve this, the results of independent measurements of the micromirror needle tip are compared with our previous knowledge of different tip geometries.

During my work I mapped the electric, thermal and optical characteristics of the device. The final aim is to make assumptions about how this new type of implanted optrode would work in the biological environment.

I completed my work at the Research Group for Implantable Microsystems, at the

1.1. The structure of my report

Scientific background The basic concept and forms of neuromodulation. Infrared neuromodulation, introducing the phenomenon with its advantages and challenges. The structure and fabrication of intracortical infrared silicon optrodes. Optical dummies and functional optrodes.

Techniques A summary about the setup, the steps and the expected results of measurements. 4-wire resistance measurements of a MEMS temperature sensor to investigate the thermal characteristics of our device. Optical investigations of different types of optrodes with integrating sphere. The measurement of the impedance of electrophysiological recording sites with NanoZ device.

Results The basis of the calculations. Results in the three different aspects of my measurements.

Conclusion Finally all the achieved results are concluded. Future plans are introduced.

Chapter 2

Scientific background

2.1. Neuromodulation

Neuromodulation is the process of using an external source to alter the firing of neurons in the peripheral nervous system (PNS) or the central nervous system (CNS). It is a very useful tool in both research and clinical use. Although the most common method for neural stimulation is by electrical means, it is proven that action potentials can be generated in neurons using many different stimuli including electrical, mechanical, magnetic, thermal, and chemical techniques. The application fields of neurostimulation include pain relief in case of spinal cord injuries, the treatment of Parkinson's disease and other movement disorders. It can also be used for the monitoring of cortical surfaces in case of tumor resection, but also to map deep brain structure before electrode implantation. [1]

2.1.1 Phenomenon

In principle, the generation and propagation of action potentials in neurons have been explained by electrical stimulation based on transmembrane ion exchange. This occurs when the transmembrane voltage potential rises over a threshold value as a result of which the opening of sodium channels occurs. The typical threshold for this phenomenon is around -50 mV. Another concept of neuron activation is that a small amount of free energy coming from chemical reactions is required for repeated induction of action potentials. Wells et al. published very similar results using infrared light to generate the formation of action potentials. [1]

2.1.2 Techniques

Electrical stimulation

The best-known method of influencing brain function is to manipulate the neural circuitry with electric currents through implanted electrodes. [2] It comes with many advantages. The stimulation parameters can be easily controlled and quantified. Furthermore, the electrodes used for stimulation can be manufactured with a well established fabrication process. On the other hand, electrical stimulation has some drawbacks as well. Microelectrodes, which are used to target specific cells, are not always suitable for long-term implantation in human or animal nervous tissue. Moreover, the signal recorded by the electrodes may be contaminated by the electrical artifacts of the background. By electrical stimulation, all cells are affected, therefore it is not a selective method. This property of the phenomenon can cause side effects. [1]

Electricity-focused measurements in the past have encountered many obstacles. First, the brain is a 3-dimensional structure, so to investigate deeper levels we need to implant an external object into the living tissue. These implants can damage the brain under certain conditions, so their use is limited. Second, the electrodes are not able to properly target different nerve cells within the same area. Third, the electrical stimulus and its spatial extent are two interdependent factors. The stronger the stimulus in a particular area, the greater the chance of unwanted activation of surrounding areas. To solve these problems, research has begun into optical alternatives to electricity-focused techniques, which could be used to access neurons using light beams. These methods include Infrared Neuromodulation.[2]

Magnetic nerve stimulation

Magnetic nerve stimulation (MNS) is a new method for the noninvasive stimulation of neuromuscular tissue. This technique does not rely on the passage of electric currents through electrodes and the skin. The mechanism starts when a pulse of magnetic field passes into the body. As a result, an electric field is induced, which causes ions to flow and results in stimulation. MNS has some disadvantages compared with electric stimulation. The equipment is more expensive. The magnetic stimulator has a much larger extent and relies on electric power instead of simple batteries. Moreover it has a lower stimulus repetition rate, although it can be overcome. Also, the site of stimulation is not well defined, than in case of electric stimulation.

On the other hand it has many advantages as well. MNS is able to stimulate the human brain without discomfort. This is possible due to the fact that magnetic fields penetrate the skull without any attenuation. By this technique, deep peripheral nerves and facial nerves can also be accessed. Previously, this was only possible by using needle electrodes. Finally, there is no mechanical contact needed with the body, magnetic fields can pass through air without decay. [3]

2.2. Infrared neuromodulation

2.2.1 Phenomenon

When light rays enter any absorbing environment, they can change it in several ways based on wavelength and optical pulse shape. Light can break molecular bonds, accelerate chemical reactions or even generate shock waves that travel at the speed of sound in tissues. All these effects can alter neural activity.[2]

Based on experiments performed by Jonathan D. Wells' research group neurons can be stimulated successfully by exposing the neural tissue to infrared light. [1] The aim of Infrared Neural Stimulation (INS) is to induce temperature gradients in neurons, which can lead to action potentials. Infrared light is able to change a cell's firing rate. In case of excitable cells, a capacitive current is generated by the increasing temperature. This current depolarizes the cell membrane, which causes the formation of action potentials. Another theory, that supports the capacitive concept, is that the conductance of ion channels is changed by the growing temperature, being extremely sensitive to thermal changes. [4] Nowadays, the most common INS techniques use bulky fiber optics to conduct light to the neurons. These create a beam with such a large radius, that a huge field of inhibitory neurons can be activated in layer I. and II. of the cortex. As a result the synaptic connections in neural networks are suppressed, that causes a lower firing rate in the cortical layers. The concept of infrared neural stimulation is shown on figure 2.1. [5]

Due to the fact that biological tissues contain a high proportion of water, Jansen's research team used it as an absorber during the investigation of the properties of INS. Using a free-electron laser, they demonstrated in frog and rat models that infrared light induced the formation of an action potential [6]. The absorption capacity of water changes as a function of wavelength. Jansen's results show that the optimum wavelength for INS is such that it can generate the rapid thermal transient in the nerve needed to induce an action potential. This value may vary depending on the form of use. It is still under

investigation which wavelengths of infrared light are the most suitable for the different forms of application. [2] The threshold value for INS to induce neural responses is quite various. The reason for this, is that by in vivo experiments it is hard to accurately determine the beam's spot size. [5] Moreover, this stimulation is wavelength dependent, explained on Fig. 3. in ref [1]

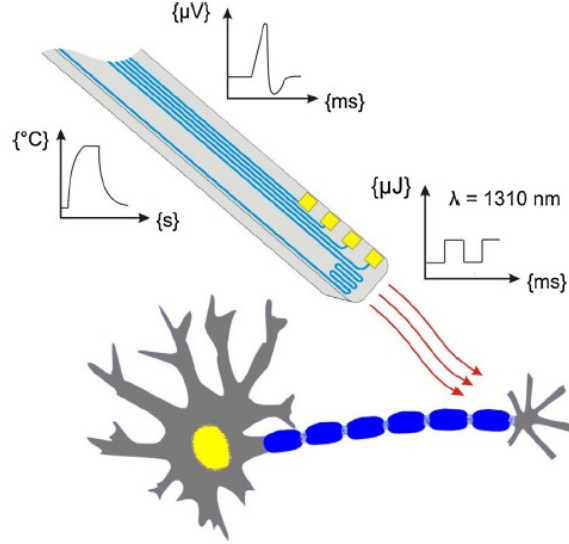


Figure 2.1: The concept of infrared neural stimulation via an implant that integrates multiple functionalities. Due to thermal changes, action potential is generated. [5]

2.2.2 Advantages

Compared to electric stimulation infrared neural stimulation (INS) has great advantages. Using INS, stimulation artifacts do not appear in the recorded electric signal, therefore the recording can be performed close to the stimulation in space and time. The spatial distribution of the stimulation can be controlled by adjusting the wavelength, intensity and light beam shape (e.g. by using optrodes with different tip geometry), which are design parameters of the system. Different wavelengths of infrared light have different penetration depths in the tissue and different absorption efficiencies. [7]

In addition, INS can be applied without the genetic integration of any light sensitive opsins. Therefore it provides a much flexible and easier application.[8]

In contrast to electrical stimulation, INS has a very high spatial accuracy, the stimulation is only in the illuminated areas. Its precision is about 100 to 400 microns in extent. This property appears in the results discussed later in this report. The superficial cortical areas can also be stimulated through a transparent membrane, without the need for any kind of implantation. The exact location of stimulation can be easily changed by moving

the light beam. Another great advantage of INS is that it is compatible with magnetic resonance imaging (MRI). [2]

Experiments have shown that a short duration (0.2 s) of INS activates the neuronal response. [9] On the other hand, much longer INS stimulation can lead to an accumulation of heat in the tissue, resulting in a delayed but significant astrocytic response. This demonstrates the ability of INS to detect neuronal architectures in the cerebellar cortex. It also supports the spatial accuracy of the process and its utility as a tool for studying cortical circuits. In addition, the different effects of short and long INS pulses underline the importance of the precise choice of stimulation parameters.[2]

2.2.3 Challenges

The thermal damage caused by INS has a threshold below 0.4 J/cm^2 per pulses. Pulses above this threshold resulted in distinguishable lesions in the brain. [10] The reason for the narrow safety region of INS can be explained by the fact that radiant exposure used for the stimulation of neural cells show a large variability. It is also questioned whether INS can be repeated. Experiments show, that the reproducibility of INS is around 23%. [11] It is also a challenge, that at a greater pulse rate the generated heat can not dissipate completely, therefore there is a thermal accumulation in the tissue that can cause further damages. [12] The accumulated heat leads to a delayed but significant astrocytic response.[2]

2.2.4 Inhibition

It was shown during researches in recent years, that INS can change the GABAergic neurotransmission. This means that besides stimulation, infrared light can also be used for the inhibition of neural cells. The blockage of the propagation of action potentials can be related to the rise of the baseline temperature. Laser-induced inhibition is assumed to be caused by the non-linear increase of temperature-dependent frequencies in the Hodgkin-Huxley gating mechanism. It causes the reversible block of the formation of action potentials. Infrared Neural Inhibition needs much less energy than Infrared Neural Stimulation, thus uses less radiant exposure.[13] [8]

2.3. Intracortical infrared optrodes

2.3.1 Structure

The intracortical infrared optrodes used for our experiments were made of silicon (Si). They are designed to efficiently conduct infrared light into the neural tissue, to record electric signals and to perform infrared stimulation. Figure 2.2 presents the structure of the microelectrode. The electrophysiological recording sites, made of platinum (Pt), can be found on the tip of the probe. (Figure 2.3.) The distance between two sites is $100\text{ }\mu\text{m}$, and the extent of these is $900\text{ }\mu\text{m}^2$. The shaft of the probe is 5 mm long, $170\text{ }\mu\text{m}$ wide and $190\text{ }\mu\text{m}$ thick. The probe is covered with silicon-dioxide acting as an electrical insulator of the Pt wiring. A glass fiber is embedded into the base of the probe, where a coupling lens is also incorporated. (Figure 2.4) This helps with the collimation of the divergent light rays so they can travel through the needle tip. A parabolic mirror is fabricated on the tip of the optrode to control the emitted beam shape thus the volume of the stimulated tissue. [5] [7] The fully assembled optrode is introduced in figure 2.5.

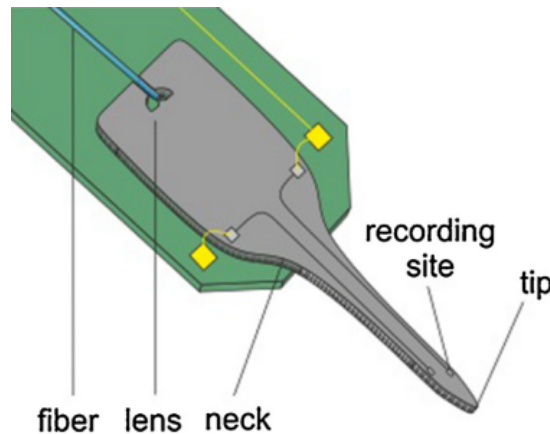


Figure 2.2: The structure of the silicon microelectrode that provides infrared stimulation and records the electrical activity of neurons simultaneously [7]

Fiber and Waveguide-based Approaches

A very important feature of optrodes is that they are capable of light delivery and the recording of electrical neural activity simultaneously. The usage of waveguides aims to make these processes more convenient. Based on this method the light is delivered to the required deep brain areas from an external source.[14]

The advantages of using waveguides include the use of an external light source. It

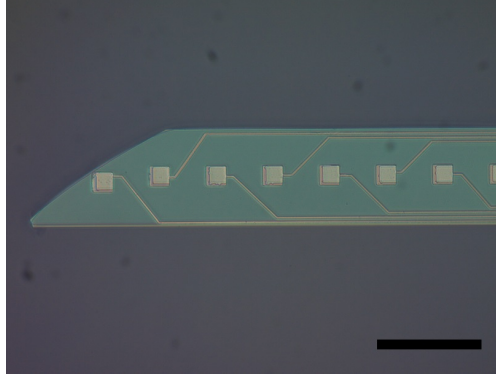


Figure 2.3: Optical microscopy image of the optrode tip. The scale bar represents 200 μm .

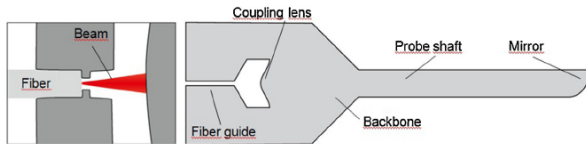


Figure 2.4: The layout of the silicon optrode, showing the internal positioning of the glass fiber and the coupling mirror. [7] In our case the core diameter of the fiber is 105 μm and its numeric aperture is 0.22 respectively.

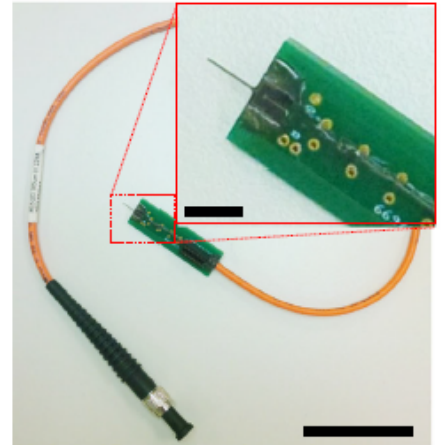


Figure 2.5: Photo of an assembled optrode device. (Scale of the image with smaller and larger magnification are 3 cm and 5 mm respectively.)[8]

reduces the heating effect, thus maintains the tissue temperature at a safe level. These types of devices are also capable of a controlled, multipoint illumination.[14]

Despite their benefits they also hold some drawbacks. Their power efficiency is lower than in case of implanted μ LEDs. Additionally, the tethered design of fiber optic cables restrict free movements of in vivo subjects.[14]

Challenges

Several complicating factors can occur when using optoelectronic electrodes. For example, achieving and delivering the right power to the desired brain area. Care must be taken during the process, as tissue can be damaged.[14]

It is very important that incident light has enough energy to successfully activate or inhibit neurons. The threshold required for this is around $1mW/mm^2$. Light exiting the needle tip must travel a certain distance in the tissue before reaching the targeted cells. During this pathway, the light energy may decrease due to the scattering effect. Biological tissues are also able to absorb light with a higher refractive index than air and are also optically inhomogeneous. [14]

2.3.2 Fabrication

In the following section, the process steps of fabrication of two particular sample types will be described: optical dummy samples (seen on figure 2.9.) that do not hold any other functionalities on top of light delivery and fully functional optrodes (seen on figure 2.8.) capable of light delivery and electric recording. Optical dummies are mainly used for experiments in order to investigate the thermal and optical properties of a given tip geometry. Functional optrodes are designed to be implanted to rat models.[15]

The infrared optrodes used for the measurements presented later in this report were fabricated by a Si-based MEMS process. The wet chemical polishing step at the back-end of technological sequence aims to reduce the surface roughness of the electrode sidewalls, caused by deep reactive ion etching (DRIE). The final purpose of this is to increase the efficiency of IR light coupling and waveguiding efficiency. Figure 2.6. summarizes the main steps of the fabrication sequence of implantable infrared optrodes. [16]

Functional optrodes

The process starts with SiO_2 and Si_xN_y deposition on both sides of the wafer. It is followed by low temperature oxide (LTO) deposition, and the front-side gets covered

with a photoresist (PR) layer for protection. In the third step of the process HF etch is carried out to remove LTO layer from the bottom. After that, the PR is removed. Next, the nitride and the oxide are removed from the backside of the wafer. In the fifth step Ti/Pt layer deposition and shaping are made by lift-off, which is followed by another LTO deposition, so the metal layer of electrode functionality between dielectric insulation layers is done. Then deposition, photolithography and etching of the Al mask are carried out for the first DRIE process. During this DRIE some parts of the dielectric stack with the Al mask is removed in a wet etchant. In the next step another Si_xN_y layer is deposited on the surface to finish dielectric insulation of the metal layer. After that the deposition, photolithography and etching of Al mask happens with a backside PR protective layer. This is followed by deep silicon etching in DRIE to form the needle-like electrode shape on the wafer. Then, the Al mask and the protective PR layer on the backside are removed and the structure is polished by a wet chemical process. Lastly, the obtained device goes through HF etching and Si_xN_y removal in phosphoric acid to open the dielectric insulation just above the electrophysiological recording sites and wire bonding pads. [16] The process flow of the fabrication of functional optrodes is summarized by figure 2.6.

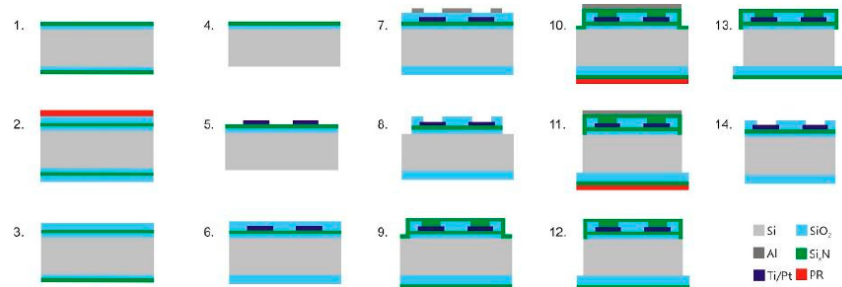


Figure 2.6: A schematic summary about the general fabrication process of the functional silicon optrode. [16]

Optical dummies

Although the fabrication process for optical dummies is very similar to that of implantable functional optrodes, it also differs from it in a few ways.

The micromachining starts with SiN_x deposition and SiO_2 masking. Then SiN_x is removed from the backside of the wafer by wet etching. In the next steps, an Al mask and an additional PR cover is used as a hard mask during dry etching, that forms the chip's contour and the fiber guide groove. Finally, the Al and PR layers are removed in acetone and in nitric acid. The planarization of the probe sidewall is achieved by

immersing the wafer in a polishing mixture of HF:HNO₃:H₃PO₄. The microfabrication process is supplemented with another nitride etching in phosphoric acid in case of bare Si samples. [15] The process is summarised by figure 2.7.

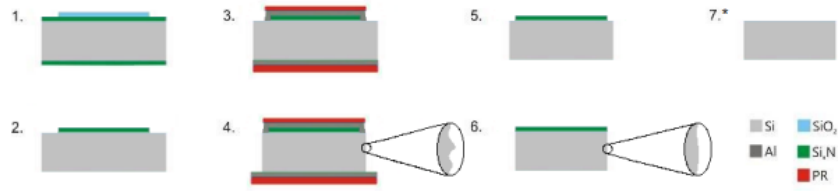


Figure 2.7: A schematic summary about the general fabrication process of the optical dummy.[15]

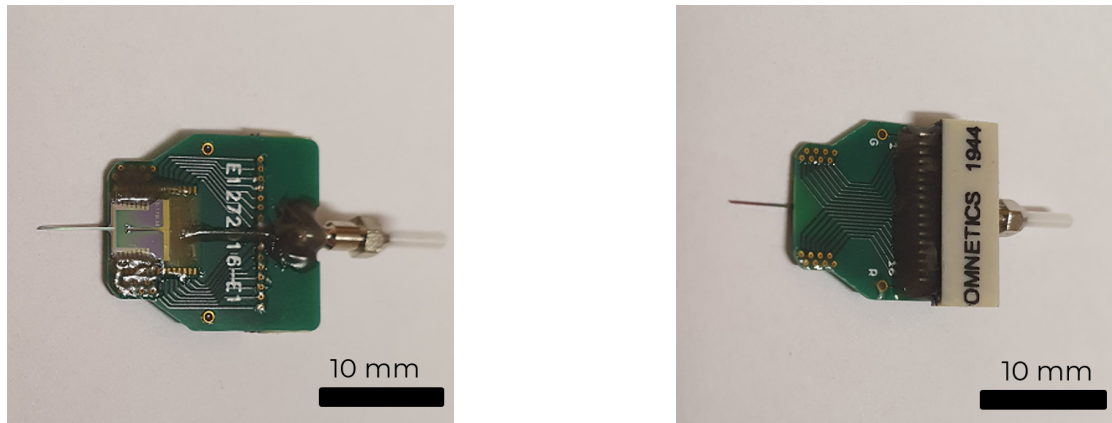


Figure 2.8: The implantable functional optrode from front (left side) and back (right side). It can be connected to the glass optical fiber manually with the connector seen on the right side of the optrode.

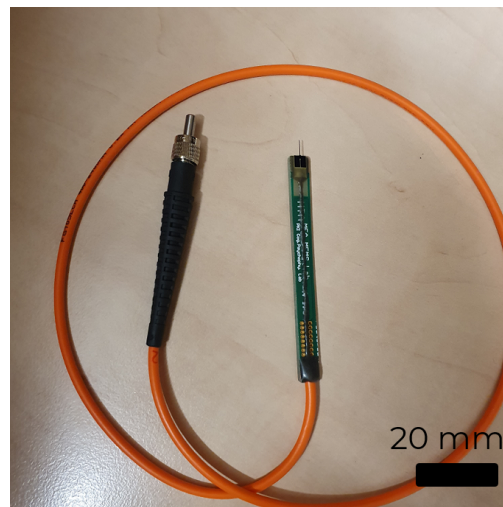


Figure 2.9: The optical dummy on the PCB with the inserted glass optical fiber.

Chapter 3

Techniques

3.1. Thermal measurements

To characterize the thermal properties of the micromirror tip optrode many measurements were performed, during which the temperature changes of water were examined in different positions of the optrode delivering the infrared light and a thermal sensor.

3.1.1 Experimental setup

The setup of the measurement is shown in figure 3.1. A MEMS temperature sensor was placed diagonally onto a 1D translation stage on one side of a measuring bench. On the other half, a micromirror tip needle-like Si sample (implantable optrode or optical dummy) was inserted, into which infrared light was guided by a glass fibre. The two probe tips were brought close together so that the ends of the two needle tips went under the surface of a small cup of water in the middle of the table. The distance between them was first set to 0 μm . This was the origin in the imaginary coordinate system.

The measurement was taken in several predefined positions along the x- and y-axes. Figure 3.3 and 3.2 demonstrate the setup from the top and side view. The volume of water medium (about 2 ml) was chosen to approximate the size of the brain of rodents. [17] The axis directions are also represented.

Our measurements were performed from three different points of view. According to the first one the y directional distance is fixed at 0, the x directional distance between the probes is increased from 0 μm to 600 μm , with 50 μm and 100 μm steps. In the second type of measurements the x directional distance is fixed at either 100 μm or 200 μm , the thermal sensor is moved between -2000 μm and 2000 μm along the y direction. In the third type of measurements a fixed position is used based on previous results. The aim

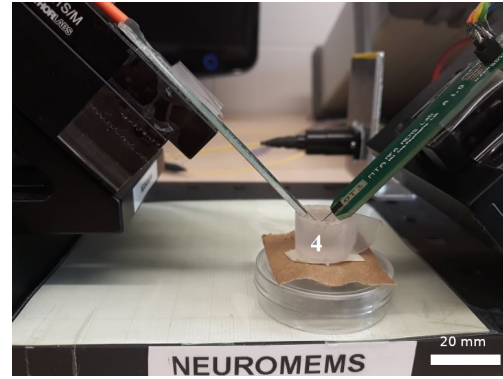
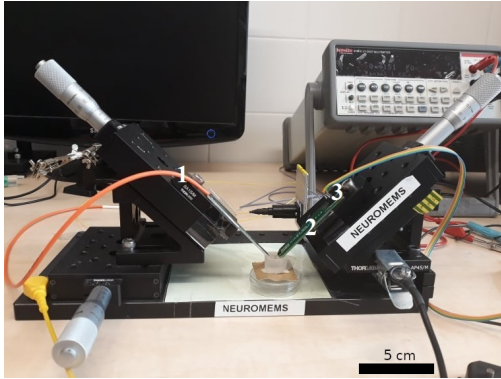


Figure 3.1: The setup of the measurement: (1) The micromirror tip needle-like Si sample (implantable optrode or optical dummy) placed onto a 1D translation stage of the measuring bench. (2) The MEMS thermal sensor placed onto 1D translation stage on the other side of the measuring bench. (3) 4-lead resistance measurement connection. (4) The cup of water (about 2 ml), into which the two shafts are set.

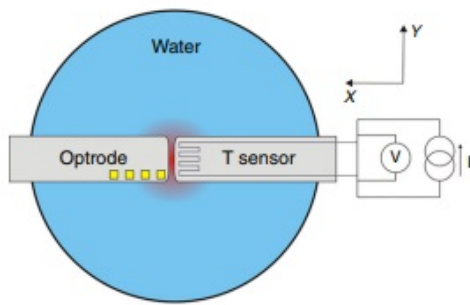


Figure 3.2: A schematic drawing of the setup of optically induced heating measurement from the top view[8]

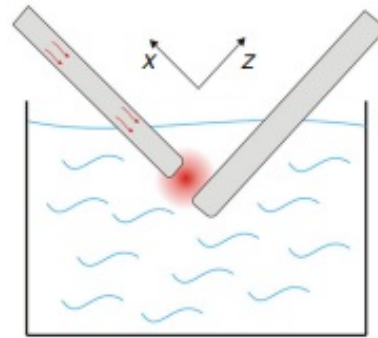


Figure 3.3: A schematic drawing of the setup of optically induced heating measurement from the side view[8]

of this latter type of measurement was to check the interdependence of the heating effect and the magnitude of the supply current, at the position of maximal heating. Only the supply current is changed from 100 mA to 400 mA. During these types of measurements the X position was 200 μm and the y position was -400 μm .

3.1.2 Steps of the measurement

The measurement consisted of 5 phases in total. Each phase consisted of a 1 minute ON phase and a 1 minute OFF phase.

During the ON phase, the Keithley 2611B Sourcemeter [18] was switched on and generated a current between 380 mA and 420 mA, based on the pre-settings. During these ON phases, infrared light was passed through the glass fibre into the optrode and the light emitted from the tip of the optrode generated heat at the tip of the needle through its absorption in water. In the OFF phases, the infrared radiation was eliminated, thus let the environment cool almost back to its original state.

Each measurement started with a half-minute OFF state to measure the initial temperature of the water. There was also a few seconds of attenuation time after the last OFF state was completed. The average duration of a measurement was 638 seconds.

3.1.3 4-wire resistance measurement

The MEMS temperature sensor is a platinum wire integrated on the surface of a Si needle. Thermal sensing is realized by 4-wire resistance measurement. The advantage of this setup is that the resistance of connected wiring does not affect the measurement of the measurand (i.e. the temperature dependent resistance of the sensor), so quite accurate resistance measurements can be made. The resistance measurement was carried out by a Keithley 2100 6 $\frac{1}{2}$ -digit multimeter and was controlled via Matlab. The supply current was provided by the Keithley 2611B Sourcemeter [18], controlled by Test Script Builder (TSB) Integrated Development Environment.

3.1.4 The basis of temperature calculations

The resistances measured on the thermal sensor were saved to 'csv' files. From this the data was processed for each individual setup. Using the measured resistance, the temperature values were calculated using the following formula:

$$T = \left(\frac{R_T}{R_0} - 1 \right) \cdot \frac{1}{TCR}$$

where R_T is the actual temperature dependent resistance measured in the timepoints, R_0 is the constant resistance parameter of the thermal sensor and TCR is the sensitivity of the integrated temperature sensor. The number of timepoints and the duration of the measurement were also recorded.

3.1.5 Expected results

Based on the literature and the research team's experiences with other optrode tip geometries, the following results were predicted.

For the measurement along the x axis, the largest temperature rise was expected to be at a distance of about 200 μm or closer.

For measurements along the y axis, a larger heating effect is expected on the left side of the optrode due to the asymmetric geometry of the micromirror tip.

For measurements in which the optrode position is fixed and only the supply current is changed, a linear increase is expected in the thermal change around the infrared optrode.

3.2. Optical investigations

In order to get information about the power of infrared light exiting the optrode tip, some optical power measurements were performed. Based on their results, the performance of three types of optrode tips can be compared. In addition to micromirror-tipped optrodes, the performance of blunt-tipped and sharp-tipped optrodes were also investigated.

3.2.1 Tools

Integrating sphere

For the optical investigation of the infrared optrode a Thorlabs 145C integrating sphere (shown in figure 3.4.) was used. It is an excellent tool to use for accurate optical power measurements because the results will be independent of beam uniformity, divergence angle, beam shape.

This integrating sphere is designed for a wide range of different wavelengths from 350 to 2500 nm. The sphere has a black covering in order to minimize reflected light around the entrance aperture. Sensors use different photodiodes based on the range of detection. A silicon photodiode is used for detection in the 350-1100 nm range. For wavelength



Figure 3.4: The Thorlabs 145C integrating sphere [19]

ranges between 800-1700 nm, 900-1650 nm, or 1200-2500 nm an InGaAs photodiode is used. [19]

PM400 Optical Power and Energy Meter

The PM400 console (shown in figure 3.5.) is designed to be used together with Thorlabs' power sensors to read out measured data. It has a capacitive touchscreen on which we can easily prepare the properties of the measurement.

The display screen of the device contains all the necessary information about the setup and the measurements, including NIST-traceable responsivity curves, sensor types, and model numbers, the operating wavelengths and power or energy ranges for each sensor.

During its setup, we can choose the appropriate operating wavelength. For our optical power measurements 1552 nm wavelength was used.

As a first step of each measurement, it was important to zero our device. This way we could get rid of all the negligible light rays, which were coming from the outside, but were recorded by the sensor of the integrating sphere (background noise). [20]



Figure 3.5: The Thorlabs PM400 optical power and energy meter [20]

3.2.2 Experimental setup

The optrode was mounted in front of the inlet of the optical power meter. The origin point is fixed where the needle tip is in line with the entrance aperture of the integrating sphere. The first measurement point was 7 mm forward from this origin, because that is where the measuring layer starts. The optical power measurements were taken at seven equidistant points with $500\mu\text{m}$ steps from each other, starting from the origin to $3000\mu\text{m}$ distance. The supply current was increased in 50 mA steps from 100 mA to 400 mA. The measurement was also performed with 3 different types of optrodes, ending in a blunt tip, a symmetric sharp tip and a micromirror tip. In all cases measurements were made in both horizontal and vertical alignment (showed in figure 3.6.). This allowed us to check whether the instrument gave the same result regardless of the angle of rotation. Finally, the performance of the glass fibre without the optrode was also measured. This is important in the estimation of how much light actually passes from the fibre optic to the optrode.

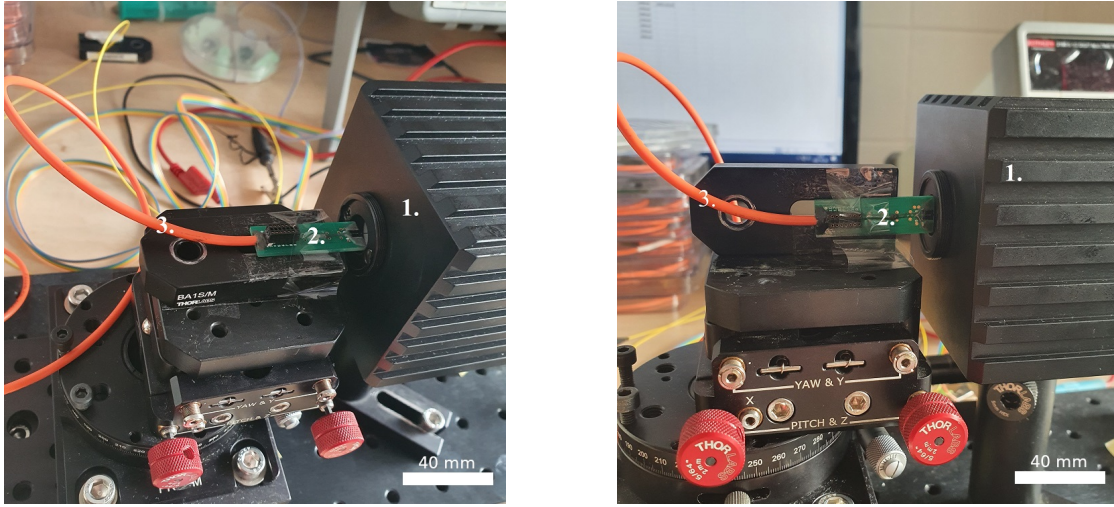


Figure 3.6: The horizontal (left side) and the vertical (right side) alignment on the functional optrode. (1) Thorlabs integrating sphere. (2) Functional optrode. (3) Glass optical fiber.

3.3. Impedance of electrophysiological recording sites

The electrophysiological recording sites of the implantable optrodes were characterized using NanoZ device. The impedance of the electrode was measured at a frequency of 1 kHz, which aligns with the frequency of the formation of spikes. According to the literature, at 1 kHz frequency the impedance of in vivo electrodes should be between 50

k Ω and 100 M Ω . [21] This range is the most suitable for the desired applications. [22] The 1 kHz frequency value is an arbitrary choice by the research community, which is conventionally used to describe the impedance of recording brain electrodes. [21]

3.3.1 Experimental setup

Figure 3.7 summarizes the experimental setup. The optrode is connected to the NanoZ device, the needle tip is put into a phosphate buffered saline (PBS) electrolyte solution with an Ag/AgCl reference electrode.

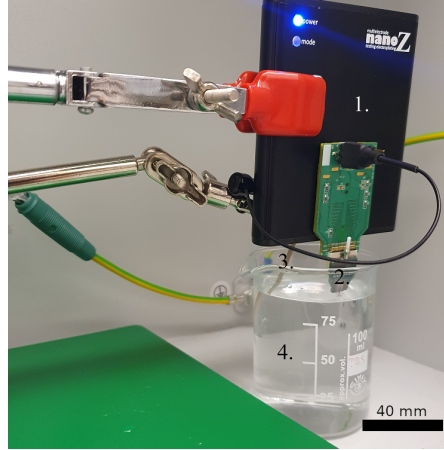


Figure 3.7: The measurement setup of electrochemical impedance testing. (1) The NanoZ Tester. (2) Functional optrode. (3) Ag/AgCl reference electrode. (4) PBS electrolyte solution.

NanoZ

This device is designed for multichannel electrode arrays. It is capable of measuring impedance or electrode impedance spectroscopy (EIS) featuring extremely low currents. It comes with many built-in electroplating modes for automated electrode impedance matching, activation and cleaning. For measuring impedance, it uses a voltage divider circuit. (figure 3.8.)[23]

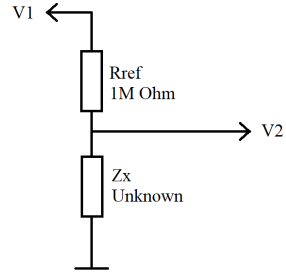


Figure 3.8: The basic principle of how nanoZ works. It has a single measurement circuit, including the generator voltage $V1$, the amplifier for $V2$, and a reference resistor R_{ref} . Different channels, having different electrode impedances Z_x , are connected to this circuit via a non-board 64-to-1 analog multiplexer. [23]

Chapter 4

Results

4.1. Thermal measurements

Thermal measurements were performed to get knowledge about the heating effect of micromirror tip infrared optrodes. The experiments were repeated for optical dummies and implantable functional optrodes as well.

From the diagram shown in figure 4.1, the durations of the consecutive cold (OFF), phases and the warm (ON) were examined. Based on the timepoints given, the average temperature per phase, then the temperature change per pulse were calculated, finally the 5 results were averaged to form a numeric value as the result of each particular setup.

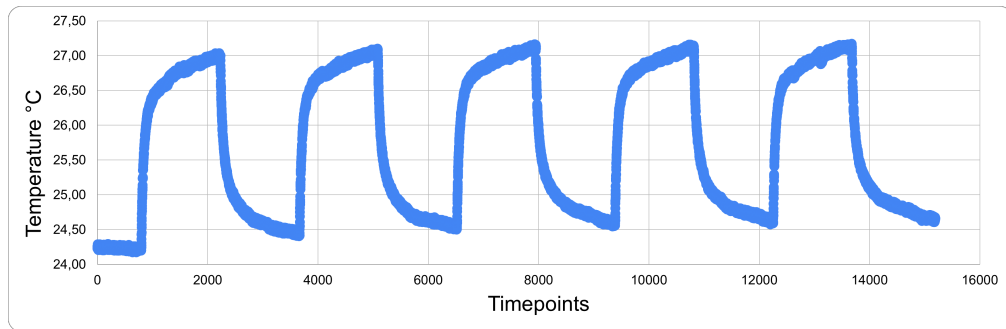


Figure 4.1: The temperature measured in each timepoint was illustrated on a diagram. On the horizontal axis, the timepoints are shown, the vertical axis represents the temperatures in °C

4.1.1 Spatial distribution of optical heating

Mentioned axes in the followings are shown in figures 3.3. and 3.2. above.

Along x axis

In case of the measurements along the x axis, the position of the temperature sensor was fixed. The setup was initialized by positioning the tip of the infrared waveguiding sample on top of the tip of the thermal sensor. This state is referred to as 0 μm distance or origin. From this distinct measurements were performed, each with 50 μm steps, until the 400 μm distance mark was reached. After that the step size was doubled to 100 μm until the final measurement at 600 μm . The same measurement was repeated for 4 different copies of optical dummies and 2 different copies of functional optrodes, as well. The supply current was set to 380-420 mA, based on the performance of each sample.

Results of the optical dummies

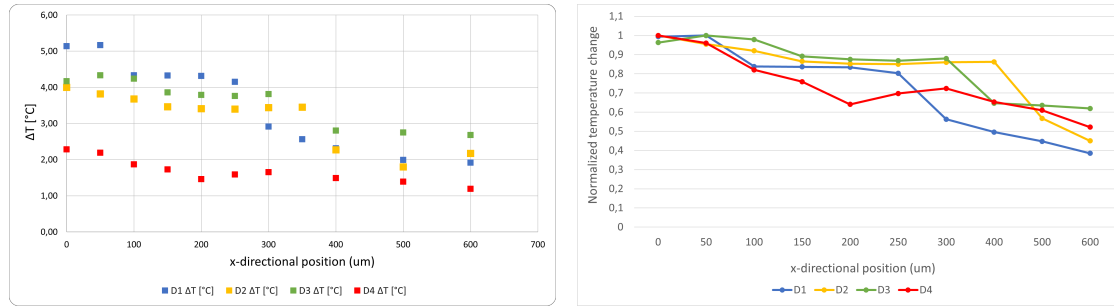


Figure 4.2: Results of the measurements with micromirror tip optical dummies. On the left side the original values of the temperature change are shown in $^{\circ}\text{C}$ as a function of x-directional position. On the right the normalized temperature change is represented, also as a function of position along x. Each measurement point on the diagrams is derived from one 5-peak graph seen on figure 4.1.

From figure 4.2. it can be seen, that although the different samples may show different maximal heating value, the normalized temperature change has the same pattern for all samples. The maximal temperature change is at 0 - 50 μm x-directional distance. Between 100 μm and 300 μm there is a plateau with 80% heating efficiency. Over 300 μm distance there is a greater decline in the heating effect.

Results of the implantable optrodes

Based on figure 4.2. and figure 4.3. it is seen that the overall heating efficiency is lower in case of implantable optrodes. This can be the result of the difference in types of connection of the glass optical fibres of the different optrode versions. Optical dummies have a glass optical fibre implanted and fixed to the inlet of the optrode which fibre has

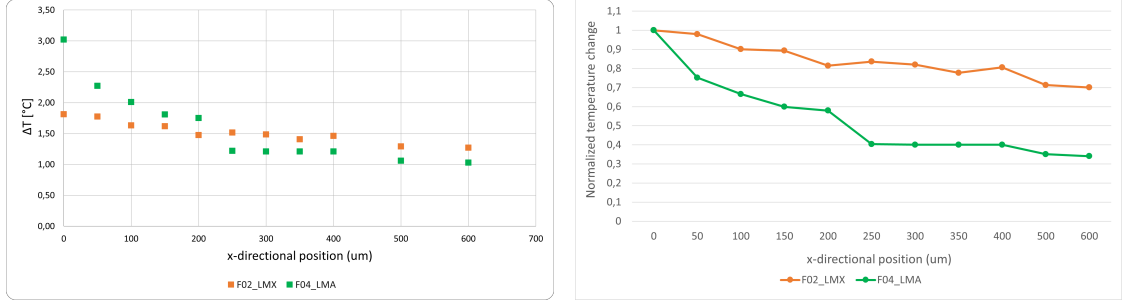


Figure 4.3: Results of the measurements with implantable micromirror tip optrodes. On the left side the original values of the temperature change are shown in °C as a function of x-directional position. On the right the normalized temperature change is represented, also as a function of position along x.

an SMA optical connector. In case of implantable optrodes the glass optical fibre has an LC optical connector which has reduced sizes and reduced coupling performance as well compared to the SMA type.

Looking at the normalized graphs it can be noticed that the optrode named FO2_LMX shows similar results as the optical dummies. On the other hand optrode FO4_LMA declines at a lot closer distance in heating efficiency. To investigate this difference more thoroughly and to get a more confident picture about implantable optrodes, further measurements are needed.

Comparison of micromirror tip optrodes with different tip geometries

Results in figure 4.4. show different heating properties for optrodes with different tip geometry. Sharp- and micromirror tip optrodes have their maximal heating effect at 0-50 μm distance. The results confirm the expectation that the location of the maximum temperature change is even closer to the needle tip for the micromirror-tip optrode, with a steeper decay than for the sharp one. The sharp-tip optrode also decays later, but not as fast as the micromirror one. Meanwhile optrodes with blunt tip geometry have their maximal heating effect at 300 - 350 μm distance.

Along y axis

In case of the measurements along the y axis, the position of the infrared optrodes was fixed with either a 100 μm or a 200 μm distance along the x axis. Then, only the thermal sensor was moved along the y axis, along a symmetric ± 2 mm interval. The step size between two measurement points were 200 μm . On the following diagrams the negative y position values represent the left side of the probe.

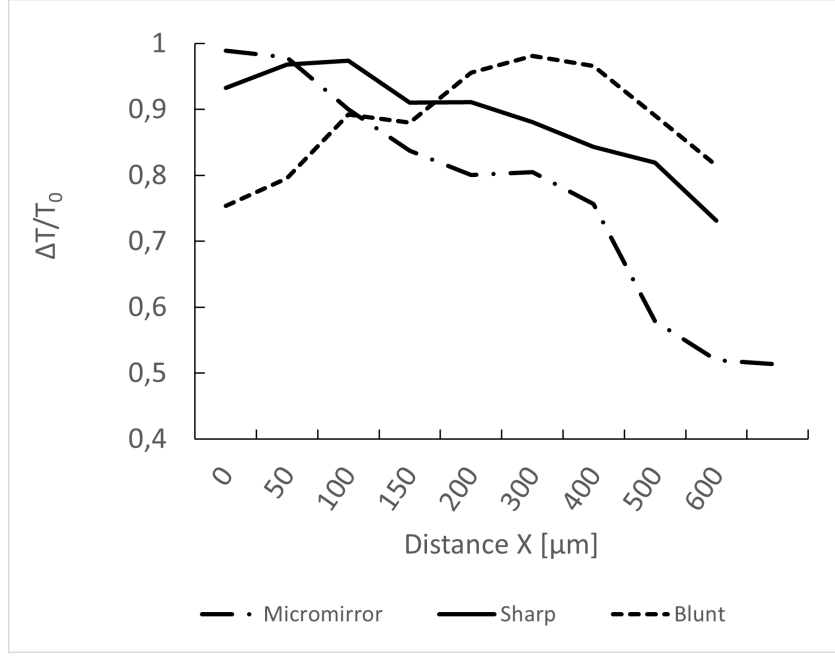


Figure 4.4: The normalized values of the heating effect of optrodes with different tip geometry: micromirror-, sharp- and blunt-tipped optrodes. On the horizontal axis, the x-directional distances are shown. Based on Fig. 2F in [24]

Results of the optical dummies

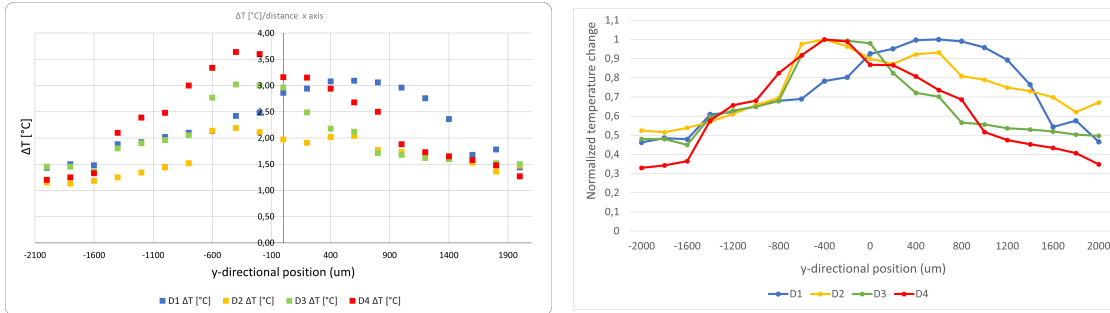


Figure 4.5: Results of the measurements with micromirror tip optical dummies. On the left side the original values of the temperature change are shown in °C as a function of y-directional position. On the right the normalized temperature change is represented, also as a function of position along y. The x-directional distance was set to 200 μm .

Looking at the normalized values at figure 4.5. it can be seen that the majority of the optical dummies have their maximal heating effect at the left side of the probe.

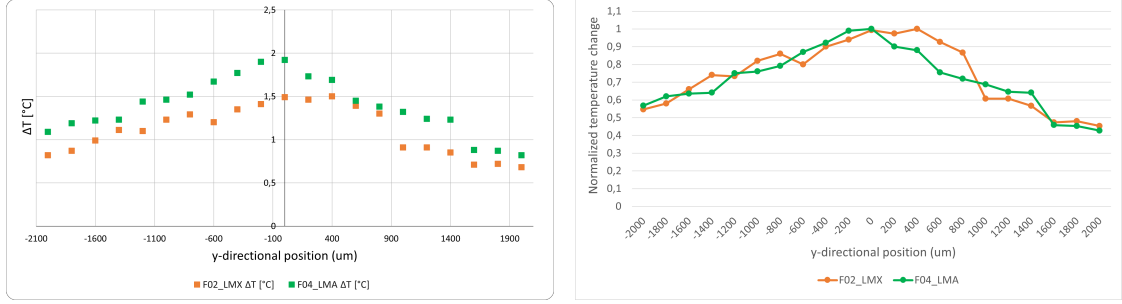


Figure 4.6: Results of the measurements with implantable micromirror tip optrodes. On the left side the original values of the temperature change are shown in $^{\circ}\text{C}$ as a function of y-directional position. On the right, the normalized temperature change is represented, also as a function of position along y. The x-directional distance was set to $200\text{ }\mu\text{m}$.

Results of the implantable optrodes

In case of implantable optrodes, the maximal heating was around the tip of the probe, at $0\text{ }\mu\text{m}$ distance. However, it is not what was first expected, it can be helpful to look at the mean values from the results of the two different implantable optrode samples. Observing

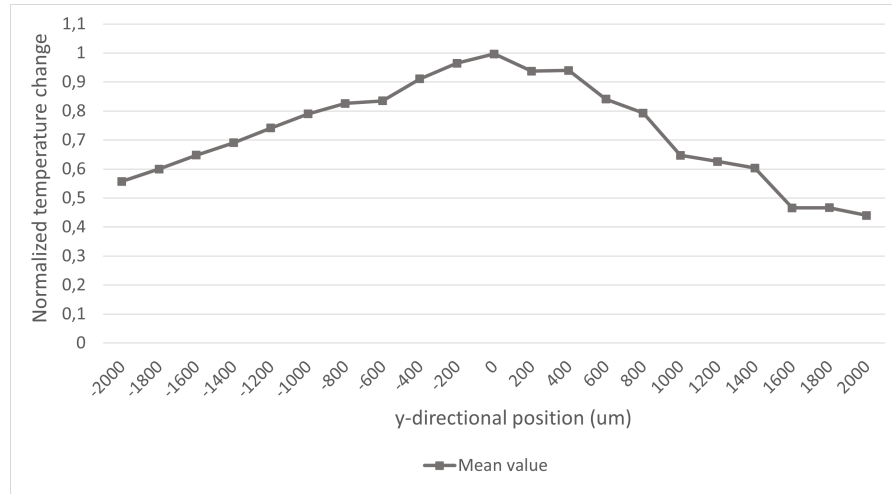


Figure 4.7: The mean values from the two implantable micromirror tip optrode samples used for the measurements.

figure 4.7. it is noticeable that the left (negative y) values have higher and more uniform for thermal heating, than on the other side of the optrode. As only 2 samples were measured, more data are needed for a more accurate and reliable conclusion.

Comparison of micromirror tip optrodes with different tip geometries

Finally, results from micromirror-tip optrodes were compared again with previous results from experiments with optrodes with different tip geometry.

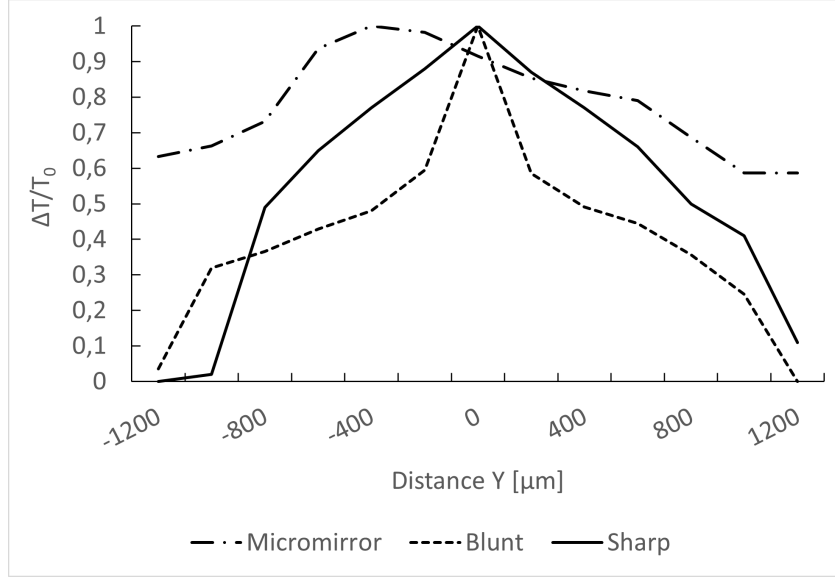


Figure 4.8: The normalized values of the heating effect of optrodes with different tip geometry: micromirror-, sharp- and blunt-tipped optrodes. On the horizontal axis, the y-directional distances are shown. Based on Fig. 2G in [24]

As figure 4.8. demonstrates, all three types of optrodes show different heating property along the y axis. While the micromirror-tipped optrode has its maximum value at $-400 \mu\text{m}$, the blunt and sharp optrodes have a symmetric heating property around the shaft (around the $0 \mu\text{m}$ mark). The blunt-tipped optrode shows a faster decay around the tip, than the micromirror- and sharp-tip optrode.

4.1.2 Dependence of optical heating on supply current

For the third type of measurements only the supply current of the infrared light source was changed between two measurement setups. Based on the results of measurements along the x and y axes, a fixed measurement position was chosen at $x = 200 \mu\text{m}$ and $y = -400 \mu\text{m}$. The supply current was increased from 100 mA to 400 mA with 20 mA steps. The aim of it is to investigate how the increasing magnitude of supply current influences the heating effect at a given point.

Results of the implantable optrodes

This type of measurement was only performed on implantable optrodes. Figure 4.9 introduces the results. The graph for both implantable micromirror tip optrode samples shows a fairly linear tendency, with equations 4.1 for FO4LMA and 4.2 for FO2_LMX:

$$y = 0.0451x + 0.2705 \quad (4.1)$$

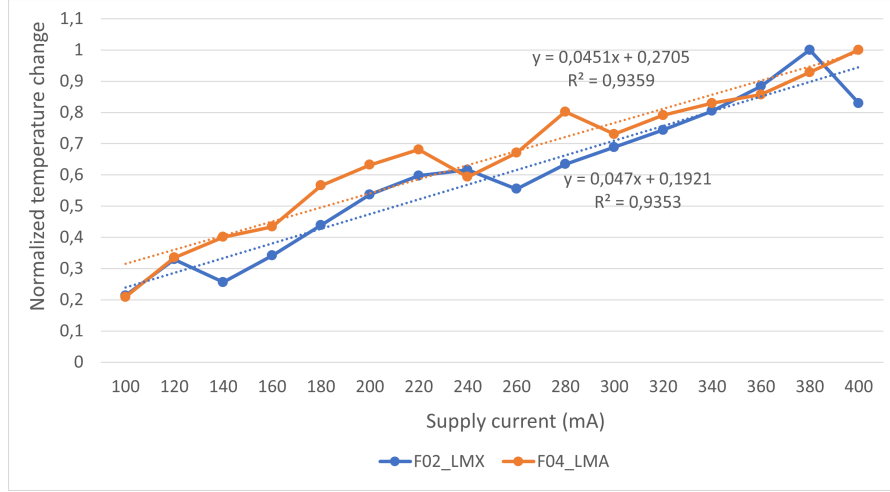


Figure 4.9: The normalized values of temperature change around implantable micromirror tip optrodes with different supply current showed on the horizontal axis.

$$y = 0.047x + 0.1921 \quad (4.2)$$

To get an overall image of the efficiency of optically induced heating at different supply current values, the results received from the implantable micromirror tip optrodes were averaged and compared to the previously mentioned other types of optrodes (symmetric sharp tip and blunt tip ones). As represented on figure 4.10. all the used types of

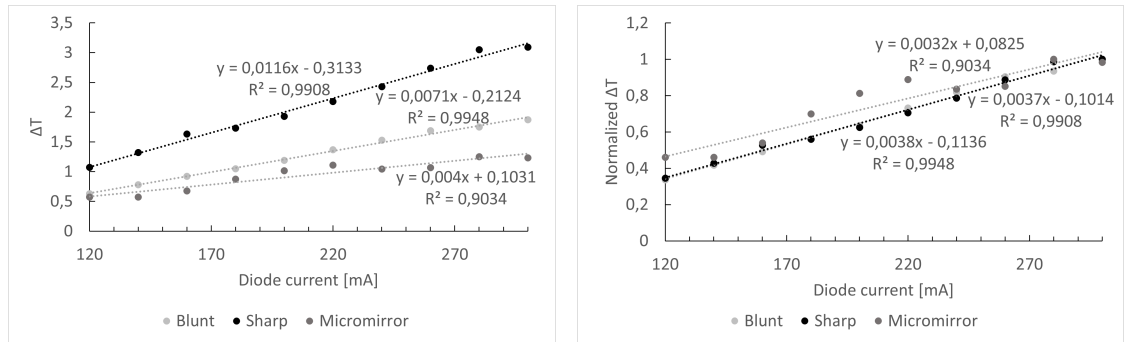


Figure 4.10: Dependence of optical heating on supply current in case of blunt-, sharp- and micromirror-tipped optrodes. The horizontal axes represent the current values in mA, while the vertical axes show the temperature change. The diagram on the left shows the original, while the diagram on the right side shows the normalized values. Based on Fig. 2E in [24]

optrodes produce linear increase in temperature change as a function of supply current. The equations for the results of the three different optrodes are eq. 4.3 for the sharp-tip

optrode, eq. 4.4 for the blunt-tip optrode and eq. 4.5 for the micromirror-tip optrode:

$$y = 0.0116x - 0.3133 \quad (4.3)$$

$$y = 0.0071x - 0.2124 \quad (4.4)$$

$$y = 0.004x + 0.1031 \quad (4.5)$$

Looking at the right diagram on figure 4.10. it can be stated that there is little difference between the three kinds of optrodes, thus the linear increase in temperature as a function of supply current is not affected by the shape of the needle tip.

The equations of the linear approximation are eq. 4.6 for the sharp-tip optrode, eq. 4.7 for the blunt-tip optrode and eq. 4.8 for the micromirror-tip optrode:

$$y = 0.0037x - 0.1014 \quad (4.6)$$

$$y = 0.0038x - 0.1136 \quad (4.7)$$

$$y = 0.0032x + 0.0825 \quad (4.8)$$

4.2. Optical investigations

Besides thermal measurements optical investigations were also performed to get information about the optical power of light exiting the needle tip.

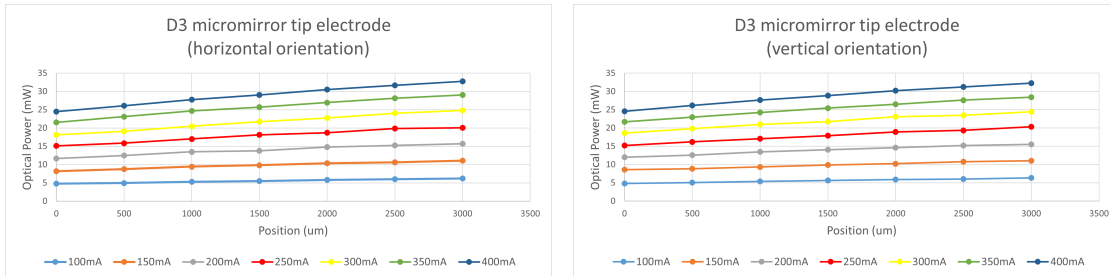


Figure 4.11: The optical power of the D3 micromirror-tipped optical dummy sample as a function of position in the integrating sphere. The horizontal orientation is showed on the left and vertical is showed on the right side. (Orientations are explained in figure 3.6.) The x axis of the diagrams represent the position of the needle tip starting from the origin. The ordinate axis shows the optical power in mW.

The diagrams in figure 4.11. imply that the sample placement does not affect the measured optical power. It is worth averaging the values and looking at the power values from different angles side by side to support the comparison. (cf. figure 4.12.)

It can also be seen from figure 4.11. that the magnitude of the supply current affects the power of the infrared light emitted from the needle tip. In addition, the power at any supply current increases with the same, $y = 0.0017x + 15$ equation as a function of position.

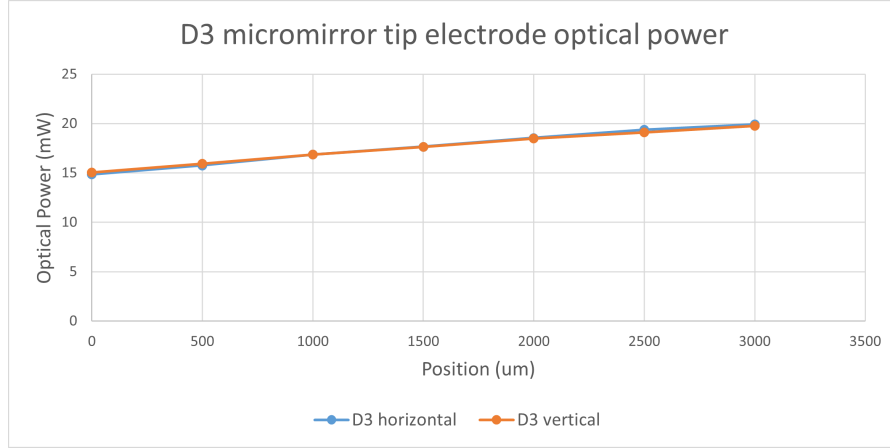


Figure 4.12: The comparison of optical power of D3 micromirror-tipped optical dummy sample from different orientations.

It can be seen that the optical power increases by an average of 33% in the innermost position of the micromirror-tipped optical dummy sample.

As we have seen above, in case of micromirror tip samples, the measured optical power of the infrared optrode does not depend on its orientation, and we see a similar rate of increase for all supply currents. In the next section the results of sharp-tip optrodes are discussed. The averaged results are shown on figure 4.13. Figure 4.13. summarizes the results of measurements with the SMA18 sharp-tipped optrode sample. For the SMA18 30° pointed symmetric-tip optrode, results are very similar to the micromirror-tip case. The position-dependent power increase is about 30%, with a power of 15 mW at the origin and 19.5 mW at the innermost position, 3000 microns from the starting point (origin).

The results of measurements with the SMA1 blunt-tipped optrode sample can be seen in figure 4.14. Out of the 3 different tip types tested, the blunt-tipped optrode shows the largest difference between the horizontal and vertical alignment. Compared to the previous ones, this one shows the smallest difference in performance between the starting and the ending point of the measurement, only 6.5%. A further difference compared to the micromirror and the sharp cases is that much higher optical power values were

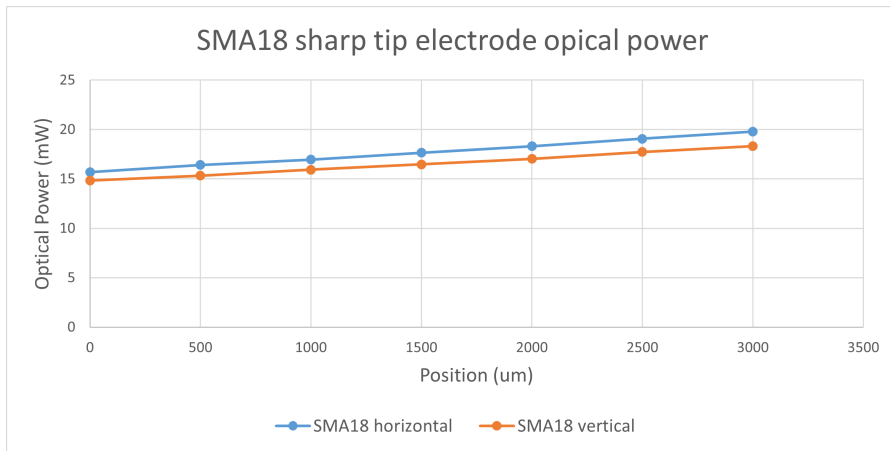


Figure 4.13: The comparison of optical power of SMA18 sharp-tipped optrode sample from vertical and horizontal orientations.

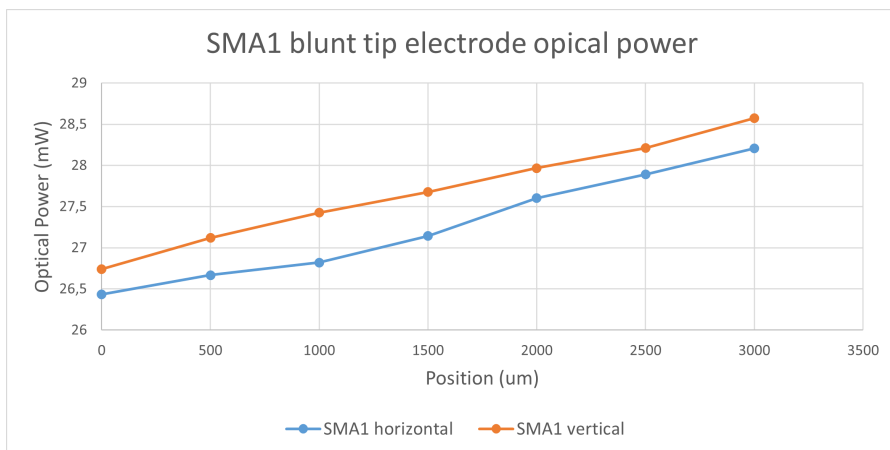


Figure 4.14: The comparison of optical power of SMA1 blunt-tipped optrode sample from vertical and horizontal orientations.

measured.

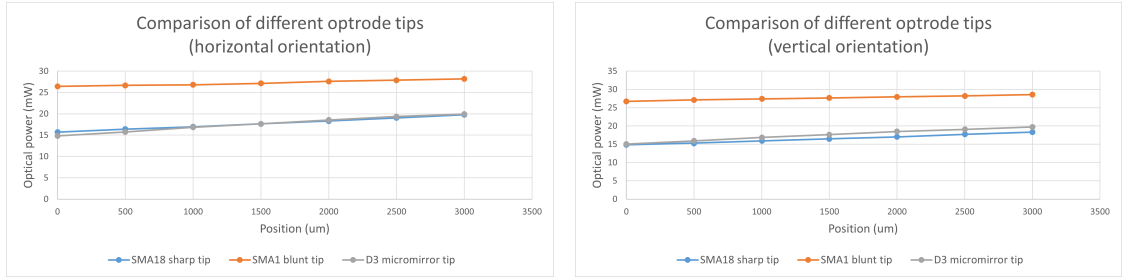


Figure 4.15: The comparison of the optical power of three different types of optrodes: sharp-, blunt, and micromirror-tipped. On the left side the results from the horizontal orientation are shown. The diagram on the right side represents the results from the vertical orientation.

Figure 4.15. summarises the results measured on 3 different optrodes. In all three cases, as the optrode was moved further into the integrating sphere, the measured power increased. The horizontal and vertical alignment gave similar results in cases of micromirror- and sharp-tip optrodes. The measurement is independent of the rotation for needle tips with these geometries. From both diagrams in figure 4.15. it can be seen that for the blunt-tipped optrode, values were about 75% higher than in the other two cases. The difference between the sharp- and the micromirror-tipped cases is negligible.

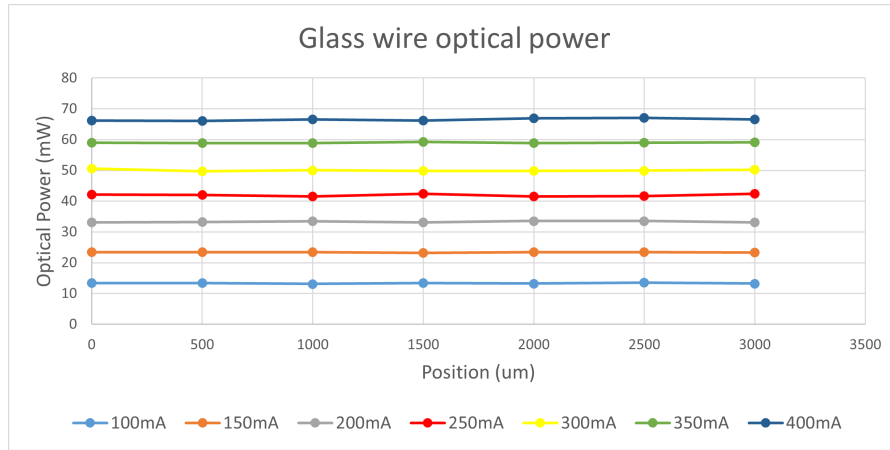


Figure 4.16: The optical power of the glass optical fiber as a function of position in the integrating sphere. (mW)

From figure 4.16. it can be seen that for the glass optical fiber, similar optical powers are obtained at different measurement points for any supply current. Comparing this with the results of the optrodes, we conclude that the light output from the glass optical fiber does not depend on its position inside the integrating sphere. As we observed in chapter 4.1.2 there is a linear increase in optical power change as a function of supply

current, with equations 4.1 - 4.8.

Based on the previous diagrams, the amount of infrared light injected into the glass optical fibre that passes through to the optrode was also investigated. The average optical powers of different optrodes were divided by the average optical power of the glass optical fiber. For micromirror-tip optical dummies and sharp-tip optrodes this ratio is 43%, in case of blunt-tipped optrodes it is 66%.

4.3. Impedance of electrophysiological recording sites

As mentioned in chapter 3.3, the electrophysiological recording sites of the implantable optrode were characterized using NanoZ device. In the literature, the impedance of in vivo recording electrodes at 1 kHz typically range between 50 k Ω and 1 M Ω . The amplitude value of the impedance at 1 kHz is $|Z| = 995 \pm 25k\Omega$. This average value with standard deviation is derived from the measurement of 16 different recording sites on a micromirror-tip optrode, at 1 kHz. The variability among the sites is less than 7%. Nevertheless, this impedance is sufficiently low for many in vivo applications, which aims to record the activity of single neurons.

Chapter 5

Conclusion

5.1. Task

Infrared light is proved to be able to stimulate or inhibit the formation of action potentials in the nervous tissue. The spatial characteristics of the effect greatly depend on the incident radiation what is affected by the geometry of the applied silicon microelectrode. The experiments of our research group aim to explore all the optical, thermal and electrical properties of these optrodes.

5.2. Results

5.2.1 Thermal characteristics

The thermal characteristics of micromirror-tip optrodes were examined in two different points of view. In the first one the spatial characteristics of heating were observed in case of optical dummies and functional optrodes as well. Measurements were performed along both the x and the y axes. Results suggest, that in the x direction, heating is the strongest at the origin. On the other hand in case of the y axis, the strongest heating affect was observed on the left side of the shaft.

The other parameter that was investigated was the dependence of heating on supply current. It was observed that the magnitude of the supply current is in linear relation with the thermal performance of an optrode. In the measured results there was little difference between the three kinds of optrodes, thus the linear increase in temperature as a function of supply current is not affected by the shape of the needle tip.

Finally, the results gained from measurements with micromirror tip optrodes were compared with previous results of optrodes with different tip geometries.

5.2.2 Optical characteristics

Results from 3 different needle tip geometries showed that as opposed to blunt tip optrodes the measurement with sharp- and micromirror tip optrodes is independent of the angle of rotation. The difference between the optical power of light coming from these two types of needle tips is negligible. Through the measurements we observed that no light leaks from the glass fibre, whereas light leaks out along the shaft of the Si optrodes, more from sharp and micromirror-tip optrodes and less from the blunt-tip optrodes. Since we did not insert the whole optrode in any cases, we could not measure all the light leaks.

5.2.3 Electrical characteristics

Electrical impedance measurements were performed at 1 kHz frequency. The impedance measured at 16 points on the functional optrodes fell within the expected range of $50\text{ k}\Omega$ - $1\text{ M}\Omega$. Thus, sufficiently low values were obtained for in vivo use. The electrode is suitable for implantation in animals.

5.3. Future plans

My plan for the future is to extend my findings on the introduced, new type of micromirror-tipped optrodes. I plan to measure the thermal and optical properties in several planes to get an idea of the spread and shape of the light emerging. Furthermore, I plan to perform electrochemical impedance spectroscopy (EIS) on functional optrodes to investigate the impedance of extracellular recording sites over a wider frequency range.

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