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Chronic Intracortical Implantation of Saccharose-coated Flexible Shaft Electrodes into the Cortex of Rats

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Abstract— **Within this study, polyimide based shaft electrodes were fabricated and dip-coated in molten saccharose to stiffen them for insertion into the brain tissue. These electrodes were then implanted successfully into the cortex of whistar rats and the insertion force during implantation was recorded. Electrochemical impedance spectroscopy was performed immediately after implantation and in regular time intervals up to 201 days after implantation to monitor the tissue response to the implanted electrodes. Depending on the measured electrode pairs and the rats, the impedance spectra behaved different over time. Either they showed a constant decrease in impedance at 1 kHz, or they showed an initial decrease to increase again later. Furthermore, physiological signal recording was performed by stimulating the rats with acoustic signals and simultaneously recording the response on the different electrode sites. Multi-unit activity was detected until 37 days after implantation with an averaged signal-to-noise ratio of 2 to 4.**

I. Introduction

Neural interfaces to the CNS can be helpful tools to treat several diseases like Parkinson's disease, depression, epilepsy or chronic pain, in the near future. But for this application, the devices have to selectively interface a high quantity of neurons reliably over a long time period to ensure an accurate performance.

While planar epicortical electrode arrays already work well for pre-surgical epilepsy diagnostics [1], an increased selectivity is necessary for more complex interactions and this is only feasible with intracortical electrodes. Researchers already developed micromachining techniques to fabricate these penetrating electrodes with a large number of electrode sites. The "Michigan Probe" [2] and the "Utah Array" [3] are the best known among them. These arrays have a good performance in acute *in vivo* experiments, but they tend to fail in chronic experiments the longer they are running. The possible reason for this failure is probably the high stiffness of the silicon shanks [4]. The brain tissue is much softer than the silicon shanks and hence micromotion of the brain due to breathing and the heart beat constantly injures the brain tissue, resulting in an increased tissue response that triggers the formation of a glial scar, also called a "kill zone" for neurons around the probe [5-7]. The glial scar acts as insulation layer and makes it harder to record signals or to stimulate the tissue.

There are several approaches to overcome this problem [8], either by developing new materials for electrode sites, to increase the charge transfer [9], or by using softer polymeric materials as substrate material, like polyimide or parylene C [10]. The latter would minimize the injury of brain tissue due to micromotion and hence may minimize the formation of a glial scar [4]. Furthermore, there are approaches to develop devices with sub-cellular structures [11] or substrates with variable stiffness [12]. Since tissue reaction around the electrodes alters the transfer functions of the electrodes due to the glial scar, electrical impedance spectroscopy has been proposed as in vivo evaluation method for monitoring purposes [13].

This paper presents the results of an approach using polyimide as substrate material and saccharose as a thin coating layer to stiffen the electrode for insertion.

II. Materials And Methods

A. Electrode Design

The electrode (Fig. 1a) consists of a 1.7 mm long tip, with six electrodes sites (40 µm in diameter) distributed over the whole length of the tip to interface the different cortical layers. A 5 mm long cable was integrated between the electrode tip and the soldering pads for the connector, to improve the handling properties and to mechanical decouple the later implanted tip from the connector.

B. Electrode Fabrication

The electrodes were fabricated according to the standard MEMS processing of polyimide electrodes [14], using polyimide as substrate material and platinum as electrode sites and tracks. After soldering the connectors directly to the electrode, the solder joints were encapsulated with epoxy resin (UHU plus endfest 300, UHU GmbH & Co. KG,

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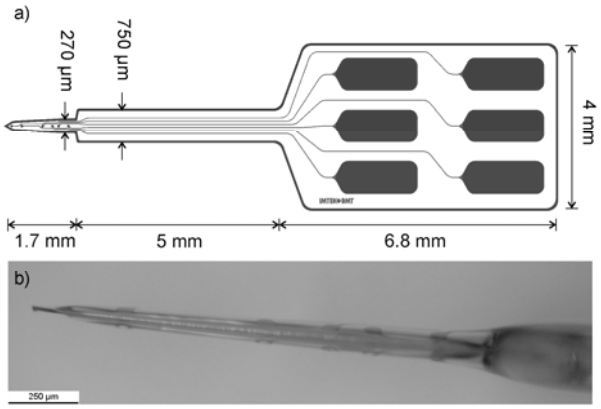

Fig. 1. Electrode design (a) and saccharose-coated electrode tip (b).

Bühl/Baden, Germany). The electrode tips were then dip-coated in molten saccharose to attach a thin layer (about 75 µm) to the tips to increase the stiffness of the flexible electrodes (Fig. 1b). Afterwards, the electrodes were stored in a vacuum desciccator until they were used for implantation.

C. Implantation

All experimental procedures were in accordance with the German law on animal research, which includes every possible attempt to minimize animal suffering.

The electrodes were implanted into the cortex of 3 month old female whistar rats, 200 g in weight. The anesthesia was introduced with isoflurane gas and afterwards deepened and maintained with a mixture of ketamine and xylazine. The rat's head was fixed in a stereotactic frame and after shaving the head, a sagittal incision was made and the skull was opened locally with a dentist's drill. The saccharose coated electrode tip was then implanted with an insertion speed of $v = 166$ µm/s, using a custom made inserter system (Fig. 2), that simultaneously recorded the insertion force (Precision Load Cell 8432-2.5, burster praezisionsmesstechnik GmbH, Gernsbach, Germany) during implantation. The final position of the electrode was fixed by applying Kwik-Sil

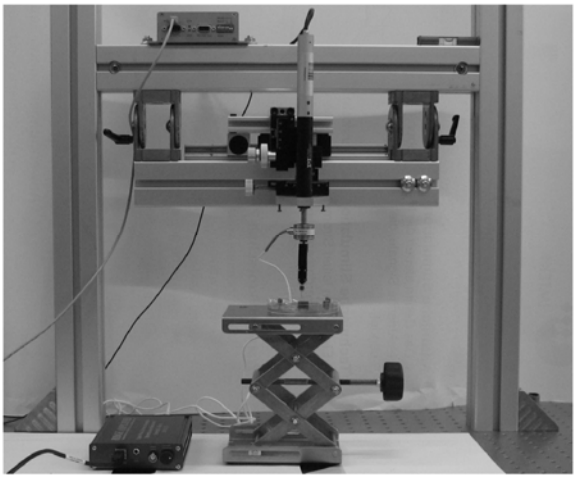
Fig. 2. Custom made, motorized inserter system with integrated force sensor. Insertion depth and insertion angel can be adjusted.

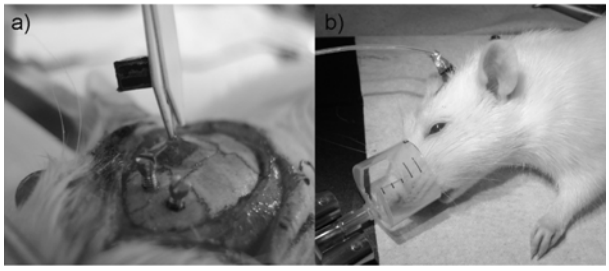

Fig. 3. Implantation of saccharose-coated electrode into the rats's cortex (a) and impedance spectroscopy of anesthetized rat (b).

(World Precision Instruments, Inc., Sarasota, FL, USA) to the overlaying end of electrode tip. The Kwik-Sil also closed the hole in the skull (Fig. 3a). After a drying period of 10-20 minutes, the electrode connector was removed from the insertion holder and placed on top of the skull. Two screws were drilled into the scull, serving as an anchor for the dental cement that was applied on top of the skull, too, to fixate the connector. To protect the connector from moisture and dirt, a cap was placed on top of it.

D. Impedance Spectroscopy

Electrochemical impedance spectroscopy was performed immediately after implantation and in regular time intervals up to 201 days after implantation, while the rats were anaesthetized with isoflurane (Fig. 3b). The impedance spectra were recorded using a portable potentiostat (Ivium Stat, Ivium Technologies B. V., Eindhoven, Netherlands). A two-electrode setup was used, recording the impedance between two adjacent electrodes, in a frequency range of 10 Hz to 100 kHz with a voltage amplitude of 50 mV.

E. Signal Recording

Physiological signals were recorded randomly up to 37 days after implantation to verify, if the electrodes could detect usable signals. This was performed by stimulating the rats with a stochastic acoustic signal and simultaneously recording the signals with a 4-channel recording system (Medusa, Tucker Davies Technologies, Inc., Alachua, FL, USA), using one of the non-recording electrode sites as reference electrode.

III. Results

A. Insertion Force

The saccharose coated electrodes easily penetrated the cortex of the rats without bending. Figure 4 shows the insertion forces of five different implantations.

The forces increased with insertion depth, until the electrodes were in final position, and decreased afterwards to further stabilize between 0.5 and 2.5 mN. The peak forces varied between 1 and 6 mN.

B. Impedance Spectroscopy

Impedance varied over the implantation period. Figure 5 shows the development of the impedance spectra between electrode 1 and 2 of rat no. 6 over time. Immediately after

implantation and six days afterwards, the impedance spectra showed an almost capacitive behavior. The impedance at 1 kHz was approx. 2 MΩ right after the implantation and decreased to 1 MΩ after six days. Between day 12 and day 54 after implantation only minor changes happened. The impedance at 1 kHz stayed at about 1 MΩ, but the impedance at lower frequencies decreased and the spectra showed a more resistive behavior there. At day 97, the impedance at 1 kHz further decreased to 250 kΩ and remained stable until the last measurement 201 days after implantation.

Figure 6 shows the development of the impedance spectra between another electrode pair (3 and 4) of rat no. 6 over time. Immediately after implantation and six days afterwards, the impedance spectra showed an almost capacitive behavior, too. The impedance at 1 kHz was about 1 MΩ right after the implantation and decreased to 800 kΩ after six days, 700 kΩ after 12 and 26 days, and reached a minimum of 400 kΩ after 33 days. On day 54, the impedance at 1 kHz increased again to 1.5 MΩ and remained stable until 201 days after implantation. From day 12 on, the spectra became generally more resistive at lower frequencies, but were subject to fluctuations.

The impedance spectra of the other electrode pairs (also recorded on other rats), behaved either similar to the first pair or similar to the second, and were therefore not additionally presented.

C. *Signal Recording*

First recordings, 2 weeks after implantation, showed a response to the acoustic stimulation which was clearly visible on all four channels with an averaged signal-to-noise-ratio of 2-4. The signal quality did not decrease over time. It was still possible to detect multi-unit activity until 37 days after implantation, where the last recordings were performed (Fig. 7).

IV. Discussion

The flexible polyimide electrodes were successfully coated with a thin layer of saccharose, which did not enlarge the electrode tip's dimensions too much but made the electrodes stiff enough to be able to penetrate the cortex of rats. The variety in the insertion peak forces can be explained by the heterogeneity of the brain tissue and the coating procedure, which resulted in slightly different coating thicknesses. However, the low insertion forces indicated, that the electrodes were thin enough to keep the injury of the brain tissue as low as possible.

The saccharose coating started almost immediately to dissolve after the the tip came in contact with the brain fluid. Hence, the position adjustment of the electrode, prior to implantation, had to be performed under maximum care to prevent a too early loss of the coating. The fast dissolving of saccharose is one major disadvantage with respect to the handling properties. However, if the tip already penetrated

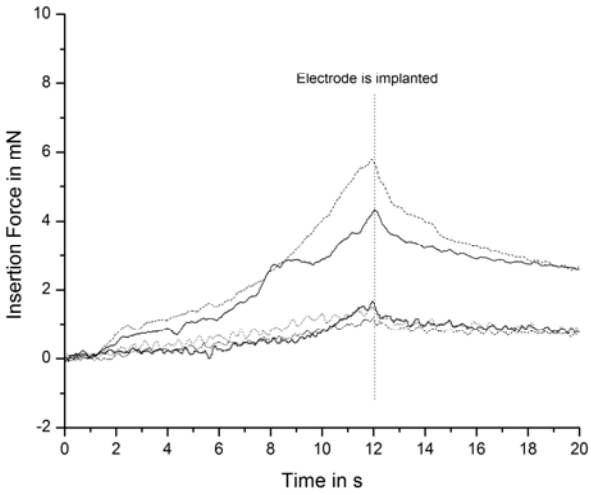

Fig. 4. Insertion force of five different implantations of saccharose coated polyimide electrodes into a rat's cortex.

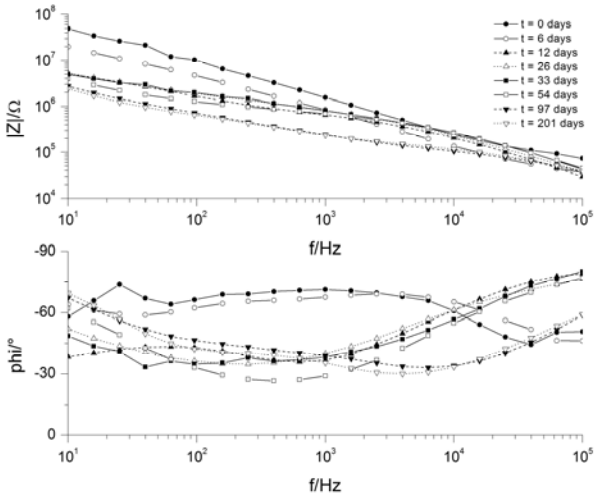

Fig. 5. Development of the impedance spectra over time of rat no. 6, between electrode 1 and 2.

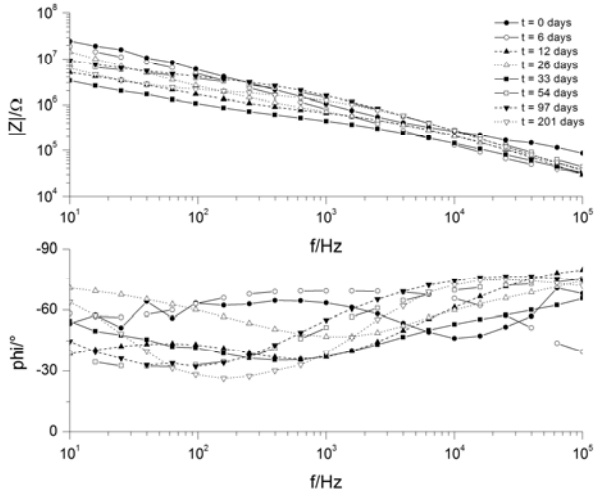

Fig. 6. Development of the impedance spectra over time of rat no. 6, between electrode 3 and 4.

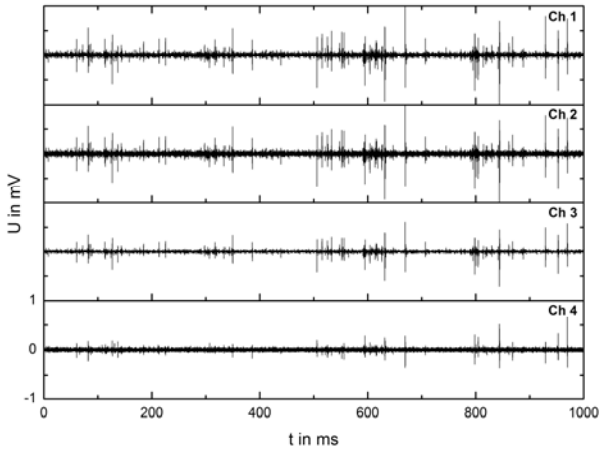

Fig. 7. Example of a 4-channel recording of rat no. 2, 37 days after implantation.

the brain tissue, the fast dissolving of the coating did not complicate the further penetration. In contrast, this behavior could be helpful because it prevented that too much saccharose could collect inside the cortex, which may have led to an increased tissue response. Furthermore, the final thickness of the implanted electrode was lower compared to other uncoated polyimide electrodes [15] that require a certain thickness to be able to be inserted.

The results of the impedance spectroscopy were not consistent. The development over time varied from electrode pair to electrode pair and from rat to rat. Either the impedance decreased with time and stabilized after different time periods, or it decreased initially to increase again afterwards. This behavior can be partly explained by the fact that the width of the electrode is not constant over the whole length. It is smaller at the end of the tip and hence the initial injury of the brain tissue at this position should be smaller. Another influence could be the insertion depth. Maybe the response to a foreign body in deeper regions is different to the response to a foreign body which is located closer to the cortex surface. Additionally, the variability of the response of the immune system of each single rat might cause these variations as well as the implantation procedure itself. To evaluate the results of the impedance spectroscopy, histology is needed, which is currently under work. Histology together with impedance spectroscopy will be a helpful tool to monitor the tissue response to implanted electrodes.

Despite the fact that the impedance spectra changed with time, physiological signals were recorded successfully, without a loss of signal quality over time. However, 37 days are only a short time period compared to the lifetime that is required for interfaces, which are intended for chronic medical use. Further and longer studies are required to evaluate the usability of these electrodes.

V. Conclusion

It was shown that saccharose coated polyimide electrodes were stiff enough to penetrate the brain tissue. Only low forces were required, what indicated that the injury of the brain tissue was kept as low as possible. These electrodes were also able to record multi-unit activity. To verify the results of impedance spectroscopy, histology is needed, which is currently under work. Furthermore, different electrode coatings will be examined and their *in vivo* behavior will be compared to the results of this study.

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