Cuff Electrodes for Very Small Diameter Nerves – Prototyping and First Recordings *In Vivo* –

Juan S. Ordonez, *Member IEEE*, Victor Pikov, Harvey Wiggins, *Member IEEE, Craig Patten, Member IEEE,* Thomas Stieglitz, *Senior Member IEEE,* J. Rickert, Martin Schuettler, *Member IEEE*

***Abstract*— A fabrication method for cuff electrodes to interface small nerves was developed. Medical grade silicone rubber conforms the body of the cuff and insulation of the wires, platinum was used as metal for the embedded wiring and contacts. Planar electrode arrays where fabricated using a picosecond laser and then positioned into a carrying tube to provide the third dimension with the desired inner diameter (Ø 0.3 – 0.5 mm). The post preparation of the cuffs after structuring allows the fabrication of a stable self-closing flap that insulates the opening slit of the cuff without the need of extra sutures. Basic for the success of the cuff is the laser-based local thinning of both the silicone rubber and the metal at defined sections. This is critical to permit the PDMS' body to dominate the mechanical properties. Finite element modeling was applied to optimize the displacement ability of the cuff, leading to design capable of withstanding multiple implantation procedures without wire damage. Furthermore, the contact's surface was roughened by laser patterning to increase the charge injection capacity of Pt to 285 µC/cm^2 measured by voltage transient detection during pulse testing. The cuff electrodes were placed on a small sympathetic nerve of an adult female Sprague-Dawley rat for recording of spontaneous and evoked neural activity in vivo.**

I. Introduction

The use of cuff electrodes has emerged as probably the most appropriate method to interface nerves in the animal peripheral nervous system (PNS). A cuff electrode is usually manufactured to encompass the nerve and has the advantage of being non-invasive to the nerve, different to other PNS interfaces (e.g. inter- or intrafascicular electrodes) [1]. The aim of the cuff design is to create an insulated environment which allows the signal detection from the enclosed nerve without interference signals from the surrounding tissue (e.g. muscular activity). It has been shown that even small defects in the seal along the cuff's length can compromise the ability to detect low amplitude neural activity [2]. Furthermore, it is advantageous to have an inner diameter as close to the nerve diameter as possible in order to prevent current shunting through body fluids within the cuff, which leads to reduced recording amplitude and/or increased stimulation thresholds. At the same time the cuff must not compress the nerve, leading to reduced blood circulation of the small peripheral nerve blood vessels. Despite initial suggestions that the cuff's inner diameter should be up to 1.5 times larger than the nerve's diameter in order to avoid damage caused by compression of a mechanically irritated, hence swollen nerve, studies by Naples et al. and Agnew et al. have shown that neural trauma is not directly related to the diameter ratios [3-6]. Most cuff electrodes require sutures to close the cuff's opening slit and hold the electrode in place, making compression levels difficult to control. An additional requirement on the cuff is the use of material that minimizes mechanical and chemical hazards to the nerve. From the electrochemical point of view, the actual electrode contacts should be of low impedance in order to reduce to minimize the electrical high-pass behavior as well as thermal noise. In turn, the contacts of stimulating cuff electrodes should permit large charge densities to provide sufficient charge for neural stimulation without triggering corrosion and hydrolysis. Both demands are difficult to meet for wire-based cuff contacts [7], which tend to be uncoated or smooth and thus very limited in electrochemically active surface area.

Regardless of all advantages and disadvantages of different cuff electrode types and technologies for fabricating the same, common manufacturing methods for tube cuffs [7] reach their handling limit at very small sizes, and providing tailored and stable contacts with the integration of thin wires in a small piece of tubing is just inaccurate and suboptimal for proper recording or stimulating electrodes.

To enable a proper interface to small nerves the authors investigated a method to fabricate cuff electrodes with small inner diameters (0.3 – 0.5 mm). A strong focus was set on the mechanical conception of the device, without restricting the electrical properties required for stimulation applications. We opted for a silicone rubber based approach and laser-aided structuring to define the embedded contacts and wiring.

II. Methods

A. Design considerations a-priori

Silicone rubber (polydimethylsiloxane (PDMS)) is an elastic material that allows fabricating flexible probes with good electrical insulating properties but it has one big disadvantage: different to thermoplastic polymers (e.g. polyimide) it cannot be reshaped after curing with thermal treatment. This makes it difficult to think of 3D PDMS devices carrying precise embedded wiring. To circumvent this, we decided to fabricate the electrodes and the embedded wiring on a planar substrate, take advantage of precise laser patterning to define the structures and mount the flexible planar array on the inner side of a silicone tubing (Fig. 1).

J.S. Ordonez, M. Schuettler and T. Stieglitz are with the Laboratory for Biomedical Microtechnology at the Department of Microsystems Engineering (IMTEK, University of Freiburg, 79110 Freiburg, Germany, (+49(0)761 2037297; fax: +49(0)761 2037472; ordonez@imtek.de).
V. Pikov is with the Huntington Medical Research Institutes (HMRI, Pasadena, CA, USA, (pikov@hmri.org)
H. Wiggins and C. Patten are with Plexon Inc, Dallas, TX, USA, (harvey@plexon.com, craig@plexon.com)
J. Rickert and M. Schuettler are with the CorTec GmbH, 79110 Freiburg, Germany (rickert@cortec-neuro.com, schuettler@ieee.org)

978-1-4244-7929-0/14/$26.00 ©2014 IEEE

The predefined shape of the tubing offers the required force to return the cuff into the sealed position after implantation.

A very important consideration is the fact that very large inner curvatures are inherent to small cuffs. Having the very thin planar electrode attached into the inside of a PDMS tubing shifts the metallic leads from its neutral axis (embedded in a symmetrical PDMS coating) towards the position of maximum curvature in the system. Stress is directly proportional to the change in curvature, so a change from the neutral position of the closed cuff towards a planar position (as during implantation of spiral cuffs) would introduce too large stresses in the metallic layer. A wiring's design that does not break during implantation (max. stress when opening of the cuff) is indispensable (see next section).

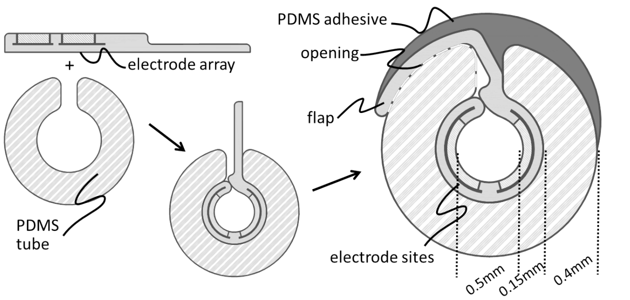

Figure 1: Cross-sectional representation of the static-spiral cuff design. A laser structured electrode array is attached to a PDMS tube. PDMS adhesive defines the structure of the flap.

A further disadvantage that arises from miniaturization using silicone rubber is the variation in the metal-to-silicone rubber ratio. The metallic tracks and contact pads have an elastic modulus over a thousand times larger than silicone rubber ($E_{Pt} \approx 170$ GPa; $E_{PDMS} \approx 1$ Mpa). Thus, for small devices even what would seem a thin layer of metal foil could define the structural behavior of the cuff. Optimally, the elastic silicone rubber should govern the overall mechanical properties of the cuff to counteract plastic deformations of the metallic wiring during implantation to avoid improperly sealed cuffs. The thickness of the embedded leads and contacts within the cuff's body has to be minimized. The contacting pads for wire attachment to the amplifying electronic however, should remain thick for a reliable interconnection to work. Localized laser thinning (publication in preparation) allows a thickness adaptation at desired sections. We choose resistance welding as a slim but tough interconnection between wires and the cuff's contacts.

B. Design

The mechanical load on the embedded wiring during the implantation procedure and probably in post-implantation is a critical issue. The wiring and the stimulation/recording sites have to be able to withstand flexural stresses without rupture. In the following 2D FEM simulations, two cases are demonstrated: Firstly, a tube cuff (in cross-section) with a continuous metal contact embedded in PDMS. The second simulation shows a cuff with two metal contacts (split contact). The model simulates the opening of a cuff at the slit in x-direction. The models were simulated using the structural mechanics module from Comsol Multiphysics™ by applying a prescribed displacement of 500 µm in each direction (± x) at the opening edges of the simplified cuff (no flap) in PDMS. For the continuous metal model, the stress maxima are located within the metal foil perpendicular to the opening (Fig. 2 – top). Avoiding fractures in the metal can be achieved by splitting the metal and creating an elastic PDMS joint at the inner bottom of the cuff (Fig 2 – bottom).

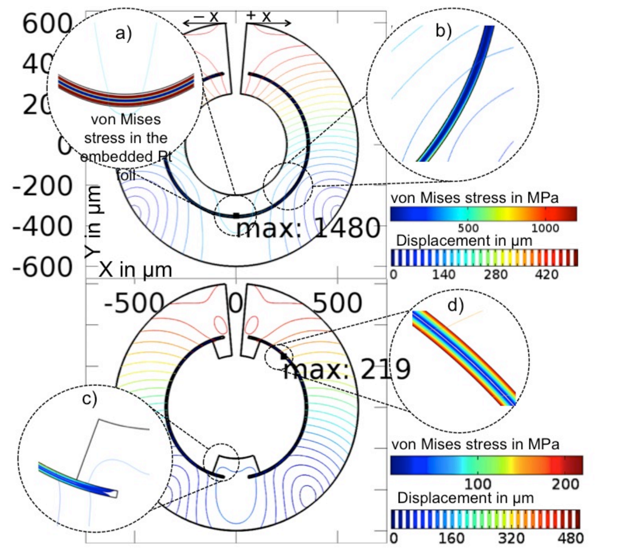

Figure 2: 2D FEM of embedded Pt foil in PDMS (Cuff's cross section). The contour plot represents the displacement field for a prescribed displacement at the opening of 500 µm. The insets show the von Mises stress within the foil, demonstrating how maximum stress is concentrated at the opposite side of the opening (a) and vanishes out along the circumference of the cuff (b). Splitting the metal allows stress cancelation at the opposite side of the opening (bottom, inset c) by permitting the elastic deformation. The stress from a change in curvature during deformation is presented in d). Data below 10 MPa is not represented.

For an identical displacement study, the stress is reduced to the (unavoidable) stress induced from a change in curvature at a vertex away from the neutral axis. It demands mentioning that the presented maximum values (1480 MPa and 219 MPa for the circumferential and the split model, respectively) assume a perfect adhesion between the two layers. The stress would probably initiate a detachment at the interface before triggering rupture of the metal after its plastic deformation. However, of importance is the magnitude of stress reduction achieved by simple splitting of the contacts.

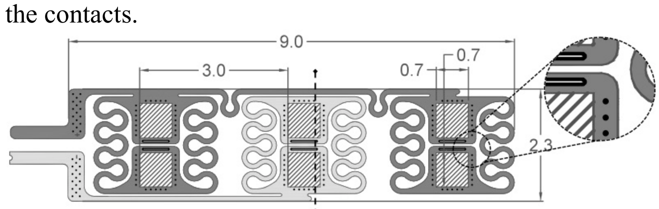

Figure 3: Design of the embedded metal layer shown for quasi-tripolar cuffs of the second generation with dimensioning in millimeters. The dashed line represents the cross-section simulated on Fig. 2 (bottom).

To retain the position of the metal during elastic deformation, riveting perforations along the edges (Fig. 3 – zoom circle) permit the PDMS to hold the metal in place. To avoid a circumferential wire positioning (similar to the effect in Fig. 2 – top) a stretchable meander track is used to contact both sides of the split-electrode. In general, reducing the embedded metal in a volume unit of silicone, will reduce the stress in the metal, as the surrounding elastic material will undergo deformation at lower stress levels. Two connecting wires were designed, fabricated and tested mechanically (see experimental section and results). Design (a) (Fig. 4 d) consists of a single meander attached at the inner side of the split contacts on each side. Design (b) attaches a multi-meander structure at the outer side of the split contacts (Fig. 3 & Fig 4 c). These wires are redundant as long as no denser contact integration is required.

C. Fabrication procedure

Similar to Schuettler et al. 2012 [8], the electrode arrays are manufactured using restricted medical grade PDMS (MED-1000, Nusil, Carpinteria, CA, USA) and platinum foil with a nominal thickness of 12.5 µm (99.5% Pt, Goodfellow, Friedberg, DE). A passively mode-locked Neodymium-Vanadate (Nd:YVO_4) picosecond laser with a third harmonic oscillator at 355 nm wavelength (Lumera Rapid10, Coherent Inc. CA, USA) is used for structuring. The process is aided by a 2” x 2 ” alumina substrate (Rubalit 708s, Ceramtec, DE) which acts as a carrier throughout the process coated with self-adhesive tape (No. 4124, tesa AG, Hamburg, DE) working as a release layer at the end of the process. PDMS is diluted in a 1:1 ratio with n-heptane and a 100 um thin layer is spin-coated onto the taped carrier. After some hours initial curing, a trench is cut into the first layer of PDMS. This allows a two-sided removal of the PDMS at the interconnection pads used for resistance welding later on. Platinum foil is manually laminated onto the silicone surface. The metal is thinned down locally to 6 µm to reduce the stiffness and subsequently structured to create the desired structures in the foil. Using tweezers, the excess material is manually peeled off the surface. Kapton tape (type 5431, 3M, Neuss, DE) is used to cover the top side of the intercconection pads. A second layer of diluted PDMS is deposited and the metallic wires are embedded in rubber. The inner diameter of the cuff can be tailored by adapting the thickness of this layer. Again, the laser is used to cut the outline of the contact openings and the contour of the array including the masking at the interconnection pads. The PDMS is manually removed from the contact openings. Subsequently, the surface of the same is laser-patterned to increase the surface area. Similar to the metal, the PDMS is thinned down to 100 um at the end which will become the cuff’s flap (Fig. 1 left). Residues from the laser process are removed using a microbrush and ethanol. Finally, the electrodes are removed from the carrier substrate.

USP-Class VI silicone rubber tubing (Ø 0.8 mm ID, Ø 1.6 mm OD, Deutsch und Neumann GmbH, Berlin, DE) is cut to length (3 mm for monopolar and 9 mm for tripolar cuffs). With a scalpel blade facing up, a straight slit is cut perpendicular to the center. Diluted PDMS is dispensed into the inner of the tube using a blunt cannula (Ø 0,31 mm OD F560016-1/4, Vieweg GmbH, Kranzberg, DE). Kapton tape is wrapped around the cannula, which is then used as stylus to equally insert the electrode array through the slit into the tube. A half-pipe mold (Ø 1.8 mm) is used to hold the device while the rubber adhesive cures. Finally, the flap is wrapped around the tube and diluted PDMS is deposited on top to retain the position of the flap and provide the mechanical closing system. Colored PDMS (MED-1000 + MED-45502-4) is used as to mark the end of the flap. PtIr wires can be attached either before mounting into the tube or at the end of the process. The cuff-wire contacts are also coated with PDMS.

III. Experimental

A. Electrochemical characterization

Impedance spectroscopy was carried out in phosphate-buffered saline solution (PBS, pH = 7.4, room temperature) in a 3-electrode setup (RE: Ag/AgCl, CE: Pt) electrode applying a 10 mV_{pp} sinusoidal excitation. Single contacts and shorted (double) contacts within the quasi-tripolar configuration were characterized.

An electrode was subjected to a voltage transient measurement (pulse test), using a custom-made current source with real-time subtraction of the iR drop (voltage across the electrolyte and metal conductors) from the generated voltage transients, providing just the voltage across the phase boundary (V_{PB}) [9]. Pulse testing was done within a three-electrode configuration (RE: Ag/AgCl, CE: stainless steel). The excitation stimulus was a biphasic (cathodic phase first), symmetrically rectangular and charge balanced current pulse (200 Hz frequency) with a fixed pulse width of 200 µs and an interpulse phase of 10 µs. The current’s amplitude was increased manually until the cathodic component of V_{PB} reached the lower limit of the water window (-800 mV). The maximum injected current was recorded to determine the safe injection limits for the laser-structured surface. Because of the limitations of the current source, a test electrode with a diameter of Ø 250 µm was fabricated and its surface was identically roughened as with the cuffs.

B. Mechanical loading

A loop of thread was glued to both ends of the cuff which was then manually pulled apart under a microscope until a break in a track was detected. The distance at break was recorded.

C. First in-vivo trial

The stimulating (tripolar) and recording (monopolar) cuff electrodes (design 1) were placed on the exposed splanchnic sympathetic nerve of an anesthetized adult female Sprague-Dawley rat. A reference Pt electrode was placed in adjacent muscle tissue and the ground Pt electrode was placed on the moist skin of the shaved animal’s back. The wires from the recording cuff, reference, and ground electrodes were connected to a custom-made low-noise (< 1 µV RMS) headstage (HS). The HS was DC coupled to reduce the common-mode rejection (at the expense of producing some electrochemical offset voltage, multiplied by the HS gain). The HS has a one-pole high-pass filter at 10 Hz and the gain of 100. The output from the HS was digitized at the 24-bit by the analog input channel of the National Instruments data acquisition board (PXI-4461). First, the spontaneous nerve activity was recorded for 5 min, and the electromagnetic artifacts from the cardiac and pulmonary muscle activity were removed offline by digital high-pass filtering at 200 Hz. Then, the rectangular biphasic charge-balanced current pulses at the amplitude of 0.1 to 10 mA and phase duration of

0.4 ms were generated by the analog output channel on the same National Instruments board and applied to the stimulating cuff, placed proximal to the recording cuff. Simultaneously, the evoked compound action potentials (CAPs) were recorded for 100 ms with the recording cuff, and the records containing the cardiac or pulmonary muscle activity were removed from analysis. The amplitude and latency of the CAP peaks were calculated.

IV. Results

A. Fabrication, Design and Mechanical Properties

Cuffs with desired elastic properties with inner diameters of 320 µm and 500 µm were successfully fabricated (Fig. 4). Inserting thicker cannulas up to 300 µm larger than the nominal value (300 µm or 500 µm) still provided a sealed flap with no direct contact of the inner and outer environment.

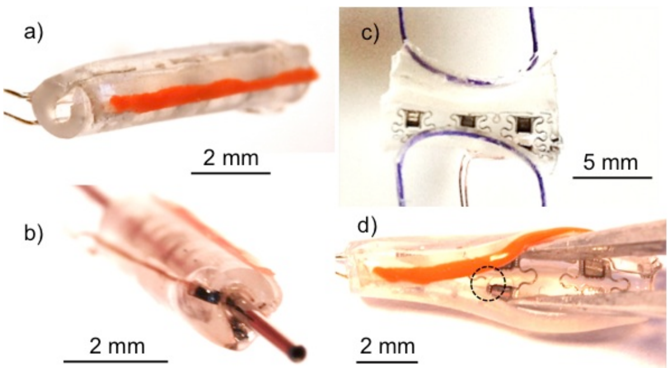

Figure 4: a) tripolar cuff's front view b) back side view at interconnection sites with a Ø 500 µm cannula showing the fitting c) cuff under mechanical test d) the dashed circle denotes the place of wire breakage with design 1 at ~900 µm extension.

Opening the cuffs with a pair of tweezers as demonstrated in Fig. 4-d often resulted fatal for the cuff. Design 1 failed mainly at the joint between the wire and the contact at openings of approximately 0.8 mm (Fig 5 d, dashed circle). Design 2 was capable of displacements up to 1 mm without any crack detection. Further pulling resulted in detachment of the thread. No plastic deformation after loading was visible on the cuffs after loads below these limits.

B. Electrochemical Characterization in vitro

The access impedance at 1 kHz was recorded to 0.9 – 4 kΩ, with an average cut-off frequency at 250 kHz. Tripolar cuffs with outer contacts shorted to one showed the lower range impedances. Using a Ø 200 µm electrode, a charge of 140 nC was delivered at -800 mV. The charge injection capacity (CIC) of 52 $\mu C/cm^2$ and 285 $\mu C/cm^2$ were calculated for the plain Pt reference and the laser roughened surface, respectively.

C. In-vivo recordings

Spontaneous spiking activity was detected in the nerve with an average signal-to-noise ratio of 4.5 and the noise RMS level of 1 µV, indicating a proper sealing of the cuff. Upon the electrical stimulation, the CAP activity was evident at the nearly constant latency after the stimulus pulse. To confirm the neural origin of the recorded evoked activity, the nerve was cut between the stimulating and recording cuff, and all evoked activity was abolished.

V. Discussion and Conclusions

The laser-based process and the tailored thickness of the metal is probably the key to success in the fabrication of the presented small cuff electrodes. Same applies for the thinning on the PDMS flap, which allows the fabrication of a tight flap without the memory effect of the thicker silicone rubber. The use of diluted PDMS is also of significant importance, as the n-heptane diffuses into the previously cured rubber, expanding the polymer structure and allowing reshaping of the same to a certain extent. The laser roughening of the electrode sites provides an increase in the safe charge injection limits, which is required if larger amounts of current are needed. The manual process of combining the electrode and the tube is however prone to misalignment and relies on a rather subjective evaluation of the success of each step. Nonetheless, the right tools and methods can reduce human mistakes during fabrication. We prototyped cuffs for two diameters, however, adapting the tubing size or the thickness of the electrode array allows tailoring the cuff's inner diameter to the size of the targeted nerve. Long-term *in vivo* studies will demonstrate the structural compatibility and the chronic acceptance of these cuffs. Also, whether thicker nerves remain undamaged if the diameter is smaller than the nerve should be carefully investigated. The design is also of importance for the stability of the system. Even though good *in vivo* results were obtained with design 1, we expect design 2 to provide a device capable of rougher handling and multiple implantations. The wire technology remains under close investigation. PtIr is tough against mechanical loads, but also stiff, which could cause damage to the nerve similar to previous reports [6]. However, the initial prototypes and their test results are encouraging and we are confident that these can provide a proper tool for interfacing small nerves in the PNS.

References

[1] J. Badia, T. Boretius, D. Andreu, C. Azevedo-Coste, T. Stieglitz, and X. Navarro, "Comparative analysis of transverse intrafascicular multichannel, longitudinal intrafascicular and multipolar cuff electrodes for the selective stimulation of nerve fascicles.," *J Neural Eng*, 8(3), p. 036023, 2011.

[2] Andreasen L. N. S., and Struijk, J. J., "On the importance of configuration and closure of nerve cuff electrodes for recording," *Engineering in Medicine and Biology Society. IEEE EMBS*, 6, pp. 3004–3007, (1998)

[3] Naples GG, Mortimer JT, Scheiner A, Sweeney JD. „A spiral nerve cuff electrode for peripheral nerve stimulation" *IEEE Trans Biomed Eng*, 35, pp. 905–916, (1998)

[4] Agnew WF, McCreery DB, Yuen TGH, Bullara LA. Histologic and physiologic evaluation of electrically stimulated periph- eral nerve: Considerations for the selection of parameters. *Ann Biomed Eng, 17*, 39–60 (1990)

[5] Agnew WF, et al. Safe stimulation of the central and peripheral nervous systems for neural prostheses. Quarterly progress report no. 3, *Neural Prostheses Program, National Institutes of Health*, Bethesda, MD, Contract no. NO1- NS-2-2323, (1992)

[6] Grill, W. M., Mortimer, J. T., "Neural and connective tissue response to long-term implantation of multiple contact nerve cuff electrodes," *J Biomed Mater Res*, 50(2), pp. 215–226, (2000).

[7] Loeb, G. E., Peck, R. A., "Cuff electrodes for chronic stimulation and recording of peripheral nerve activity.," *J. Neurosci. Methods*, 64 (1), pp. 95–103, (1996)

[8] Schuettler, M, Ordonez J.S., Henle, C., Meier, W., Kohler, F., Stieglitz, T. "Laser-Fabrication of Neural Electrode Arrays", *Proc. Neural Interfaces Conference* p.157 (2012)

[9] Schuettler M, Franke M, Krueger T.B, Stieglitz T, "A Voltage-Controlled Current Source With Regulated Electrode Bias-Voltage for Safe Neural Stimulation," *J Neurosci Meth*, 171(2) pp. 248-252, 2008