A Novel Microchannel Electrode Array: Towards Bioelectronic Medical Interfacing of Small Peripheral Nerves

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***Abstract*— Bioelectronic medicine is an emerging field that relies on electrical signals to modulate complex neuronal circuits, particularly in the peripheral nervous system, as an alternative to drug-enabled therapeutics. Small autonomic nerves are one of the targets in this field, however, interfacing peripheral nerves smaller than 300 □m remains a challenge. Here we report the development of a Microchannel Electrode Array (□CEA) capable of interfacing nerve fascicles as small as 50-300□m. The current μCEA records and stimulates from 28 channels and is designed for easy implantation and removal, bearing promise to enable neural interfacing in BM.**

I. INTRODUCTION

Neural interfaces form a connection between the nervous system and medical devices such as deep brain stimulators [1], cochlear and retinal implants [2, 3], neuromuscular stimulators [4, 5], brain/machine interfaces [6, 7] and peripheral nerve/machine interfaces [8, 9]. Such interfaces are implanted at the target nerves to provide precisely controlled electrical stimuli with tailored intensities, duration and frequencies, to restore or supplement lost function due to disease or injury (e.g., hearing, vision). Some peripheral nerve interfaces are also designed to record neuronal activities related to intended movement and used to control advanced robotic limbs [8, 10].

Bioelectronic medicine is a fast emerging field that relies on applying electrical functional patterns to nerve tissue through neural interfacing to modulate neuronal circuits to achieve better clinically relevant outcomes compared to drug-enabled therapeutics [11]. Recent reports have demonstrated that Rheumatoid arthritis, an autoimmune disease causing chronic painful inflammation of the joints, can be potentially treated by vagus nerve stimulation [12]. Further, nerve stimulation has also been shown to reduce the production of tumor necrosis factors from the spleen, leading to the significant decrease of joint inflammation and pain [13].

Several types of peripheral nerve electrode arrays have been proposed including: extra-neural (cuff/FINE), inter-fascicular (TIME), intra-neural (USEA), and regenerative (sieve, REMI). While all of them can effectively stimulate and record from peripheral nerves, most were designed for and tested in relatively large nerves such as the vagus (e.g., 500 μm in the rat). Often, these large nerves innervate many different targets, resulting in broad systemic stimulation, leading to unwanted side effects. To obviate these limitations, the electrodes should be implanted into small nerve fascicles, preferentially closer to the target organ. This has been demonstrated in studies reporting effective modulation of the spleen via stimulation of the splenic fascicle of the vagus nerve; however, most organ-modulating fascicles are relatively small in the animal models currently used (50-300μm) and electrode designs are not suitable for targeting them.

Here we report the development of a novel Microchannel Electrode Array (μCEA) designed specifically to interface small diameter somatic/autonomic nerves (e.g., 50-300μm). The μCEA was developed to facilitate the placement of a target nerve into a microchannel with multiple electrodes. Upon placing a nerve, a cap is placed over the micro channel securing the nerve in place and forming a closed micro channel (Fig. 1). This design allows for both acute and chronic placement of the μCEA as needed, avoiding nerve damage by placement or removal of the interface.

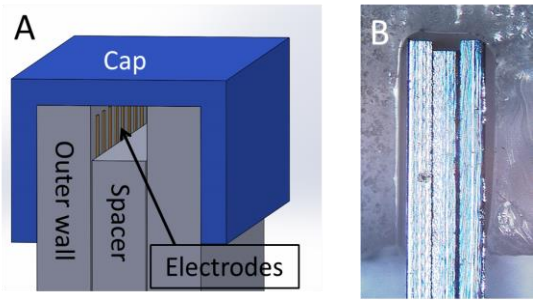

Figure 1. A) Schematic representation of the μCEA for neural modulation of small diameter (50-300μm) nerves. B) Fabricated μCEA with a U-Shaped cap attached for forming of the closed microchannel.

II. MATERIAL AND METHODS

A. Design concept:

Interfacing small peripheral nerves with multi-electrode arrays is challenging due to the diameter of the nerves along with the number of electrodes needed for selectivity and special resolution. The μCEA design offers customizable high-density electrode arrays placed bilaterally along nerve fibers of various sizes (Fig. 1). The open architecture is

This work was supported by the TxMRC and UTARI grants (MIR).
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designed for easy placement of the target nerve into the µCEA channel while the cap secures the nerve in place creating the closed microchannel environment that limits ion diffusion and increases signal amplification. The proposed design not only amplifies the low amplitude extracellular signals associated with peripheral nerve interfacing, but also provides multiple electrode locations for selectivity. Further, the customizable microchannel with cap design can be tailored for minimally invasive interfacing of small nerves of various diameters with minimal disturbance.

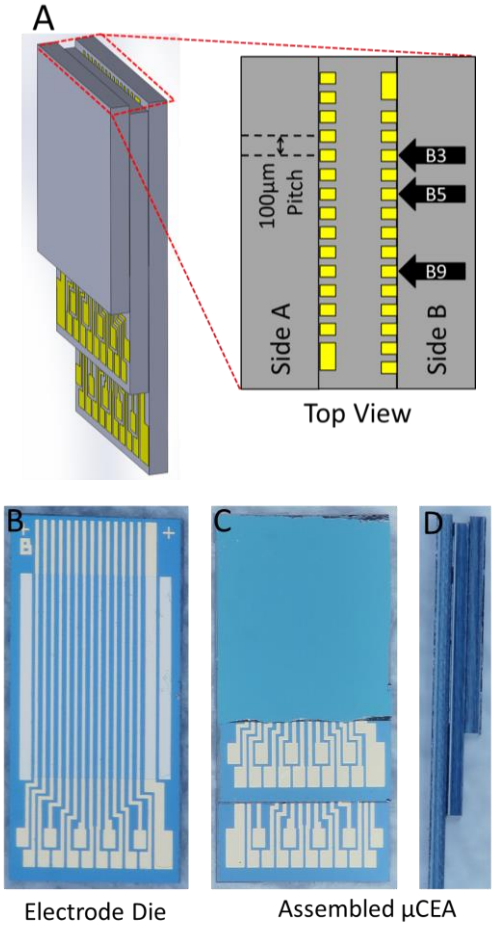

Figure 2. A) Schematic of the assembled µCEA (inset shows top view of electrode layout with recording electrodes used in Fig.5C). B) Photograph of single die. C) Photograph of the assembled µCEA. D) Side view of the assembled µCEA.

B. Fabrication of µCEA

The µCEA is a stacked die structure with three layers that form a microchannel along their edge as shown in Fig.2A. The inset for Fig. 2A shows the top view of the assembled die structure with 28 individual electrodes placed at a 100 µm distance. Each wall of the microchannel contains 14 recording/stimulating electrodes and 1 ground site. The exposed gold contacts have an estimated area of 2000 μm^2 with individual electrodes of 40 µm wide by 50 µm tall at a 100 µm pitch. In total, the 30 contact points were routed to wirebond pads for connecting to recording and stimulating electronics (Fig. 2A). The µCEA is fabricated using a four-inch silicon wafer, 200 µm thick, with a silicon dioxide insulating layer. Upon metal deposition and patterning, the wafer was singulated and bonded to form the die stack structure that formed the microchannel. The spacer layer of 200µm thick separates the two walls of the channel and serves as both a bonding and electrical routing layer (Fig. 2C). The U-shaped microchannel measures 200 µm wide, with 100 µm-tall walls (Fig. 2). These dimensions were designed for reading the neural output of a small diameter nerve in the rat, of less than 200µm. However, by changing the thickness of the spacer, the µCEA can be tailored for various nerve diameters, and the number and size of electrodes can be easily adjusted. This structure design also allows the use of other substrate materials such as glass, polyimide, or Kapton. Upon forming the die stack structure the µCEA was coupled to an Omnetics connector using 5 cm long, 25µm diameter, Parylene-C insulated gold wires. After wire bonding, the connector and the gold contacts were further insulated with epoxy (Fig. 3A).

Measurements at 1kHz (Plexon stimulator) confirmed that 90% of the electrodes have impedance values lower than 100kOhms. Using a dissected segment of the cutaneous branch of a rat's sciatic nerve (approximately 200µm in diameter), we confirmed the ability to accommodate small diameter nerves inside the µCEA (Fig. 3).

C. Implantation of µCEA into the cutaneous branch of the sciatic nerve

Five Adult Sprague Dawley rats (300-350g) were used. The animals were anaesthetized with an intraperitoneal injection of a mixture of Ketamine and Xylazine (90 mg/kg Katamine and 10 mg/kg Xylazine). The surgical area was shaved and the incision site cleansed with a chlorohexaderm scrub. After a skin incision along the femoral axis, the thigh muscles were separated with a blunt-tip scissors and the

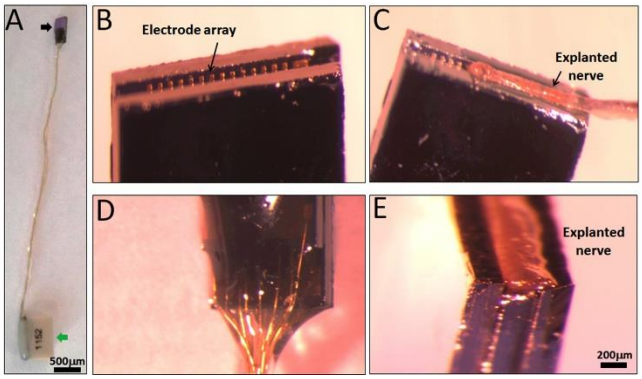

Figure 3. Fabricated µCEA. A) Parylene-C insulated 25µm gold wires are sonically bonded on the gold contact on the silicon pad (black arrow) and on the Omnetics connector (green arrow). B) Photographs showing the gold electrode array (15 electrodes) on the side of the microchannel. (C and E) Explanted cutaneous branch of sciatic nerve (~200µm diameter) was placed on the U-shape microchannel of µCEA. D) Sonically bonded gold wires on the silicon pad and insulated with epoxy.

cutaneous branch of the sciatic nerve was exposed. The cutaneous branch of sciatic nerve was inserted into the

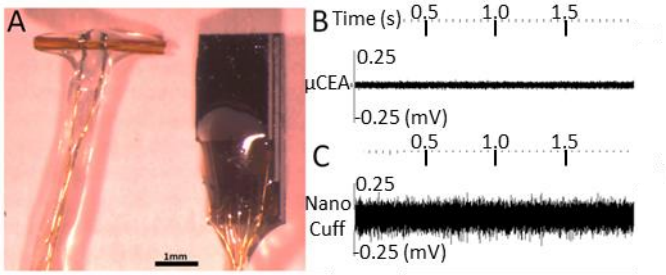

Figure 4. Comparison of µCEA and Nanocuff electrodes. (A) Pictures of the Nanocuff and the µCEA electrodes. Noise baseline recorded from the cutaneous branch of the sciatic nerve with (B) µCEA and (C) Nanocuff electrodes. Scale bar = 1mm

microchannel of µCEA and secured. The Omnetics connector was then connected to the multi-channel electrophysiology acquisition system (Plexon) for recording neural activities. In a separate control group, rats were implanted with the commercially available Nanocuff (160µm inner diameter, Microprobes Inc). The Nanocuff has two contacts of 25µm Pt/Ir wire separated by 0.5mm. The Pt/Ir wires are coiled 10mm from the cuff and then micro welded to Teflon insulated stranded stainless steel wires (Fig. 4A). All procedures were conducted according to UTA Institutional Animal Care and Use Committee (IACUC). The quality of recording signals was compared between the cuff and the µCEA electrodes (Fig. 4).

D. *In vivo Electrophysiology*

Recording: A bipolar hook electrode was placed on the proximal side of the sciatic nerve while the µCEA was placed on the cutaneous nerve branch for measuring the evoked neural activities (Fig. 5A). Two electromyography (EMG) needle electrodes were inserted into the lateral tibialis anterior muscle for recording. Evoked compound

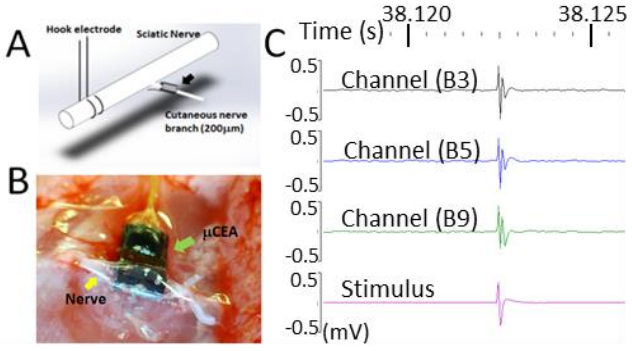

Figure 5. Evoked neural activity recording. A) Experimental setup. A bipolar hook electrode placed on the sciatic nerve was used for stimulation. The µCEA was placed on the distal cutaneous branch for recording. (B) Picture showing the implanted µCEA (green arrow) and the nerve (yellow arrow) placed on the microchannel of µCEA. C) Representative recordings of the evoked compound action potentials from 3 of the electrode contacts in the µCEA.

action potentials were recorded using the µCEA in anesthetized animals at 40kHz using an Omniplex® Neural Data Acquisition System. The recorded neural activities were further processed using Neuroexplorer and a custom MATLAB program to evaluate the signal characteristics.

Stimulation: For nerve stimulation, the µCEA was placed on a fascicle of the sciatic nerve, and was connected to a constant current Plexon Stimulator. Cathodic leading biphasic pulses were used to stimulate through individual and groups of the electrodes in the µCEA to illicit muscle activity. EMG recordings were done using needle electrodes inserted into the hindlimb muscles via a four channel Biopac MP36 acquisition system. The recorded data was analyzed with Biopac software.

III. RESULTS AND DISCUSSION

A. *Control over electrode design.*

The µCEA electrode was designed to achieve precise control over the microchannel dimensions, number of electrodes, pitch between electrodes, and surface area of each electrode. Microchannel dimensions such as width and depth can be fabricated to fit a specific target nerve diameter. The width and depth of the channel can be precisely controlled by the thickness of the silicon spacer die and the relative distance between the spacer's edge and the top edges of the outer walls, respectively. The number of electrodes, pitch between electrodes, and surface area of each electrode can be changed based on recording and stimulation needs. In addition, the µCEA fabrication is based on reliable silicon fabrication techniques.

B. *Neuromodulation*

Noise baseline: Figure 4 shows the commercially available Nanocuff with a 160µm inner diameter and the µCEA with a microchannel width of 200µm. The noise baseline recorded in cutaneous branch of the sciatic nerve with the µCEA was calculated to be approximately ten times less compared to that recorded with the Nanocuff.

Evoked compound action potential measurement: A hook electrode was placed on the proximal side of the sciatic nerve and the µCEA was placed on the cutaneous nerve branch for measuring the evoked compound action potential. Upon electrical stimulation of the proximal sciatic nerve, compound action potentials were recorded by all electrodes placed on both sides of microchannel. Figure 5C shows the representative compound action potentials recorded from three different gold electrodes in the µCEA (see Fig. 2A for electrode locations) along with a constant current pulse shown on a time/voltage scale with current to voltage scaling.

Stimulating evoked neural activity: Electrical stimulation via the µCEA elicits physiological effects. Constant current stimulation was performed through an individual electrode as well as through a group of electrodes in the array while EMG from the lateral tibialis anterior was recorded to evaluate the efficacy of the stimulation. The sample shown

in Fig. 6 depicts the compound muscle activity recorded in response to a cathodic leading biphasic pulse with a 12µA,

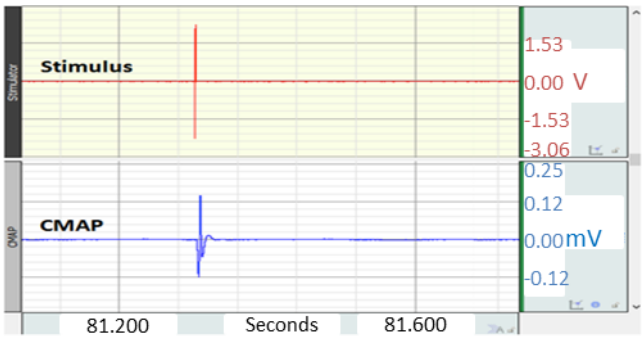

Figure 6. Nerve stimulation using µCEA. The cutaneous branch of sciatic nerve was electrically stimulated by the µCEA and evoked compound muscle activity recorded in the lateral tibialis anterior muscle.

30µs pulse duration at 2 Hz. This stimulation also resulted in a visible hind limb movement, and robust muscle contractions were observed with currents as low as 1µA when all of the electrodes were simultaneously stimulated. This shows the effective stimulation with low amplitudes using multiple contacts in the µCEA interfaced fascicle. The electrical stimulation by the µCEA through both individual and combined electrodes underlies its potential application towards bioelectronic medicine applications.

C. Potential clinical applications of the µCEA

Electro-acupuncture treatments have reportedly beneficial effects for the treatment of inflammatory conditions (e.g., asthma, Bell's palsy, rheumatoid arthritis, and inflammatory bowel disease) and cardiovascular diseases such as hypertension, stroke, and arrhythmia. [14-17]. While the exact mechanism responsible for the reported clinical effect remains unknown, increasing evidence suggests that neuromodulation of the peripheral nervous system, both somatic and autonomic, maybe implicated. This has been suggested as stimulation of somatic afferent neuronal activities such as electroacupuncture of common peroneal nerves, can significantly reduce blood pressure [18]. Neural interfacing of small nerve fascicles can avoid several caveats inherent to electroacupuncture such as variability in: needle insertion, depth of insertion, angle of needle insertion, the placement and number of needles needed to achieve maximum clinical benefit. The reported µCEA can be used to test the clinical effect of small nerve fascicles.

Summary

We have developed a µCEA that interfaces small nerves with diameters less than 300µm with relative ease, compared to current technology. Validation experiments demonstrate stimulation/recording through individual contacts of small nerve fascicles. The small size, multiple contacts, micro-channel signal amplification, and easy deployment, are characteristics that support the use of the µCEA electrode for bio-electronic applications.

ACKNOWLEDGMENT

The authors thank Taesu You for graphical assistance using SolidWorks.

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