6th Annual International IEEE EMBS Conference on Neural Engineering
San Diego, California, 6 - 8 November, 2013

Perforated 2×2 Parylene Sheath Electrode Array for Chronic Intracortical Recording*

Seth A. Hara, *Student Member, IEEE,* Brian J. Kim, Jonathan T.W. Kuo, Curtis D. Lee, Christian A. Gutierrez, *Member, IEEE,* Tuan Hoang, Victor Pikov, and Ellis Meng, *Senior Member, IEEE*

Abstract— **We present the development of a perforated 2×2 Parylene sheath electrode array (PSEA). Parylene C is surface micromachined to create conical sheath structures with electrode sites on the interior and exterior. Individual probes can be configured into a 2×2 array. Building upon previous designs, the sheath geometry was redesigned to have sharper taper and incorporate perforations in order to minimize insertion trauma and facilitate cell-cell signaling, respectively, with the aim of improving long-term recording reliability. Bioactive coatings were applied to the PSEA to encourage dendritic growth and control the immune response. Benchtop electrochemical results confirmed that electrode sites possess appropriate impedance values for neural recording. A custom-made insertion shuttle was fashioned to deliver the PSEA to the target location in the cortical tissue and then retract, leaving only the flexible PSEA in the tissue. This system successfully implanted multiple PSEAs into the rat M1 motor cortex and a 6 month *in vivo* study is currently underway.**

I. Introduction

Chronic intracortical recording continues to be a challenge as current probe technologies experience the attenuation or loss of neural signaling over time. The causes of these failures can be attributed both to abiotic issues, such as compromised insulation, corrosion, or breakage, as well as biotic responses, including the formation of a glial sheath, activation of microglia, and neurodegeneration in the region surrounding the probe. These biotic responses have been attributed to insertion trauma, the chronic presence of a foreign body, and the mechanical mismatch between the probe and brain tissue [1-3].

The Parylene sheath electrode (PSE) was designed to address this biological response in three ways: (1) use of a three-dimensional (3D) geometry that allows for tissue growth into the open-lumen, thereby securing the probe in the tissue, (2) improved mechanical matching to tissue, and (3) bioactive coatings to manage the immune response and encourage dendritic growth. This approach is similar to that of the neurotrophic electrode [4]. Instead of using a rigid glass sheath to house wire electrodes, the PSE consists of a conical polymer sheath with eight thin film Pt electrode sites, four on the interior of the sheath and four on the lateral exterior. Like the neurotrophic electrode, it utilizes neurotrophic factors and anti-inflammatory coatings to encourage dendritic growth towards the electrode sites and manage the immune response, respectively. Fabricated from low Young's modulus Parylene C polymer [5], however, it more closely matches the mechanical properties of neural tissue than the glass cone of the neurotrophic electrode or conventional metal and silicon neural probes.

We previously reported in detail on the fabrication of the PSE [6] as well as preliminary data demonstrating the use of this technology to record neuronal activity *in vivo* [7]. In this work, we present the use of our Parylene C sheath neural probe technology to develop a novel perforated 2×2 PSEA. Each probe in the PSEA has eight electrodes for a total of 32 electrode sites. Utilizing lessons learned in a previous 28-day *in vivo* study with un-perforated probes, the sheath tips of the PSEA were redesigned with a sharp taper to minimize insertion trauma as well as perforated throughout the sheath to promote cell-cell signaling and waste/nutrient exchange for a reduced immune response and improved signal fidelity.

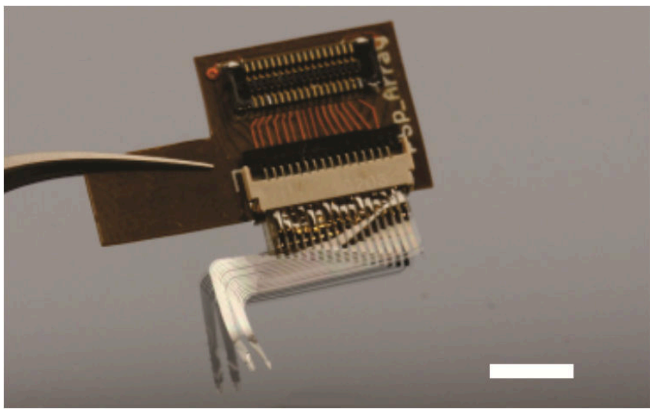

Figure 1. Optical micrograph of the fully packaged 2×2 Parylene sheath electrode array. Scale bar = 500 µm.

Benchtop electrochemical testing was conducted to evaluate electrode functionality and a coating process was developed to completely cover the hydrophobic Parylene C sheath surfaces with the bioactive coatings.

A custom-made insertion shuttle was developed to deliver the flexible PSEA to the desired depth in the cortical tissue. The shuttle is then retracted from the tissue, leaving the PSEA in place. This technique was first demonstrated in an agarose brain model and was subsequently successfully implemented in the rat M1 motor cortex to enable a chronic *in vivo* study.

* This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) MTO under the auspices of Dr. Jack Judy through the Space and Naval Warfare Systems Center, Pacific Grant/Contract No. N66001-11-1-4207.

S. A. Hara, B.J. Kim, J.T.W. Kuo, C. Lee, T. Hoang, and E. Meng are with the Department of Biomedical Engineering at the University of Southern California, Los Angeles, CA 90089 USA (corresponding author: 213-821-3949; e-mail: ellis.meng@usc.edu).

C. A. Gutierrez is an independent engineering consultant in Los Angeles, CA 90089.

V. Pikov is with the Huntington Medical Research Institutes (HMRI), Pasadena, CA 91105.

II. Materials and Methods

A. Probe Design

Parylene C, a USP Class VI polymer was selected as the substrate and insulating material. Parylene C can be surface micromachined, allowing for repeatable, high-throughput batch fabrication of the PSEA. Electrode sites and leads are patterned from thin film Pt, a biocompatible, inert metal often used in neural interfaces [8].

A previous *in vivo* study indicated that the use of a narrow, sharply-tapered sheath geometry is preferred as it minimizes damage to the surrounding tissue. Using this data, we designed a sheath with a taper from 50 to 300 µm. Additionally, in an effort to minimize inhibition of cell-cell chemical signaling, perforations were etched through both the top and bottom of the sheath structure. PSEAs were fabricated in 1×2 arrays on wafer with individual sheaths positioned 1 mm apart. Two 1×2 arrays are packaged back-to-back to create a 2×2 array with the four sheaths correctly spaced to target the rat M1 motor cortex.

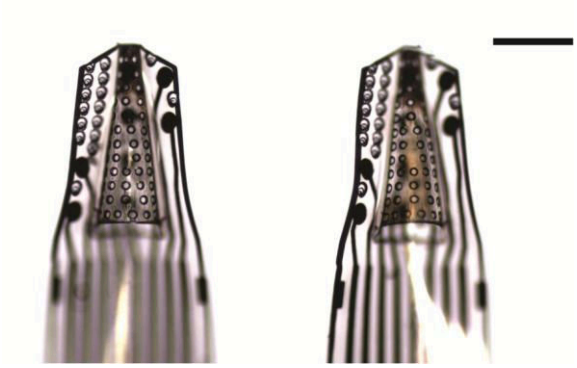

Figure 2. Optical micrograph of the tips of a 1×2 perforated Parylene sheath electrode array. Scale bar = 200 µm.

B. Fabrication and Thermoforming

A comprehensive description of the fabrication of the PSE was previously presented [6]. Briefly, thin film Pt electrodes and leads were e-beam evaporated and patterned via a lift-off process onto a Parylene C substrate on top of a Si carrier wafer (Fig. 3a). Additional Parylene C was deposited via vapor deposition to insulate the leads, followed by an oxygen plasma etch to expose electrode sites and etch perforations through the substrate (Fig. 3b). A third layer of Parylene C formed a trapezoidal microchannel through the use of a sacrificial photoresist mold (Fig. 3c). Electrode sites, perforations, and both sides of the microchannel were etched open with oxygen plasma (Fig. 3d). Finally, the final outline of the arrays was etched out, the arrays were released from the wafer, and the sacrificial photoresist was removed through an acetone soak (Fig. 3e). The probe was then thermoformed to its final shape using a microwire mold (Fig. 3f).

To create the 3D sheath structure from the initially flat surface micromachined channel (Fig. 4a), a custom-tapered microwire mold was inserted into each microchannel to mechanically open the sheath (Fig. 4b). With the microwire mold in place, the entire array was annealed at 200°C for 48 hrs. The microwires were then removed and the sheaths maintain their 3D shape (Fig. 4c).

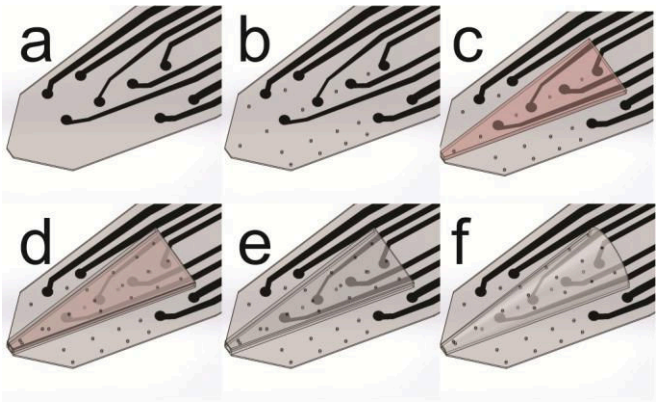

Figure 3. Abbreviated fabrication process for the perforated PSEA. Note: only the final outline of a single sheath is depicted for clarity.

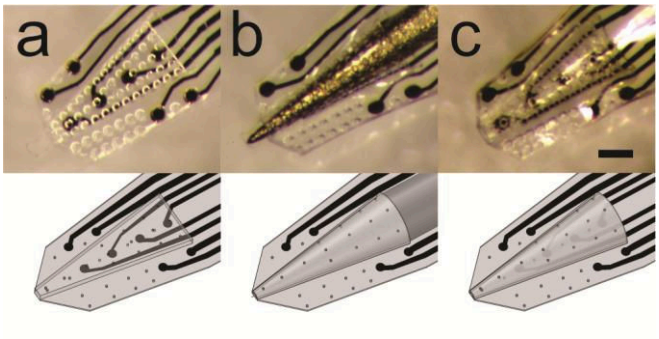

Figure 4. Photographs (top row) and illustrations (bottom row) showing the thermoforming process used to obtain the 3D sheath. Scale bar = 100 µm.

C. Packaging

A zero-insertion-force (ZIF) socket was used to reversibly attach the PSEA without the use of wirebonding, conductive epoxy, or soldering to a flexible PCB used to interface with the recording system. To create the 2×2 array, two 1×2 arrays were each inserted into back-to-back ZIF sockets on the same double-sided PCB (Fig. 5).

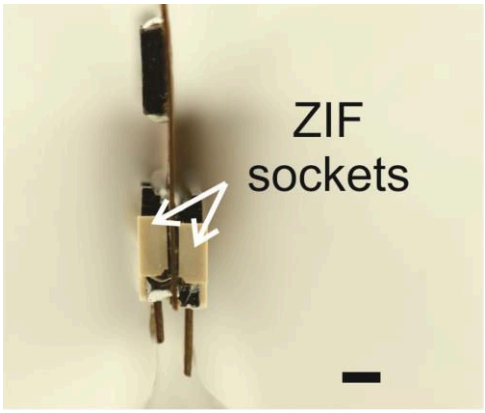

Figure 5. Side view of the packaged PSEA, showing the back-to-back placement of ZIF sockets. Scale bar = 1 mm.

D. Electrochemical Testing

Cyclic voltammetry (CV) was performed prior to testing to remove contaminants from the electrode surface (electrochemical cleaning) [9]. CVs were conducted in 0.05M H_2SO_4 from -0.2V to 1.2V at 250 mV/s for 30 cycles.

Electrochemical impedance spectroscopy (EIS) measurements were taken in 1× PBS with a 10 mV perturbation signal in a frequency range of 1-100,000 Hz. An Ag/AgCl reference electrode and 1 cm^2 Pt plate counter electrode were used for both tests.

E. Insertion Shuttle

Although the flexible substrate of the PSEA is desirable *in vivo,* the lack of rigidity inhibits the insertion of the array into the cortical tissue. Therefore, a custom-made insertion shuttle using stiff metal microwires was fashioned to provide the necessary temporary stiffness to deliver the PSEA to the desired depth in the cortex. The acrylic shuttle has laser-etched grooves to position four tungsten microwires (300 µm diameter) 1 mm apart laterally as well as in depth. To affix the array to the insertion shuttle, polyethylene glycol (PEG) was used as a biodegradable adhesive to mount the sheaths to the sides of the microwires and also to provide some strain relief by attaching the flexible PCB to the acrylic shuttle. This method along with the physical arrangement of the wires allows the four probes of the array to be positioned within a 1×1 mm area, appropriate spacing for the rat M1 motor cortex. A fifth microwire (150 µm diameter) aids in positioning the insertion shuttle for the proper insertion depth.

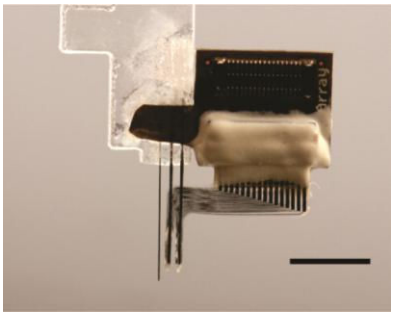

Figure 6. PSEA affixed to insertion shuttle with PEG. Scale bar = 6 mm.

III. Results and Discussion

A. Electrochemical Testing

Following electrochemical cleaning with CV, EIS was performed on all electrodes in the array. Across the electrodes, the EIS curves were very consistent, indicating a very reliable fabrication process (Fig. 7). At the physiologically relevant frequency of 1 kHz, the impedance magnitude was 148.6 ± 9.3 kΩ for 32 electrodes in an array (mean ± SE).

B. Insertion Shuttle

For *in vitro* insertion tests, a 0.5% agarose gel brain phantom was created to imitate the mechanical properties of cortical tissue. The PSEA, affixed to the insertion shuttle with PEG as described earlier, was implanted using a motorized inserter at 0.8 mm/s and the insertion site was flushed with saline. After 5 min, the PEG was completely dissolved and the insertion shuttle was retracted, leaving the PSEA in place (Fig. 8). Using the same protocol, the PSEA was also successfully implanted into the rat M1 motor cortex with the insertion shuttle and stereotactic mount (Fig. 9). Prior to implantation, the PSEA-insertion shuttle assembly was sterilized in ethylene oxide gas for 24 hr at room temperature. All procedures for the animal experiments were in accordance with the animal protocol approved by the Huntington Medical Research Institutes Institutional Animal Care and Use Committee (HMRI IACUC) and in compliance with the Animal Welfare Act.

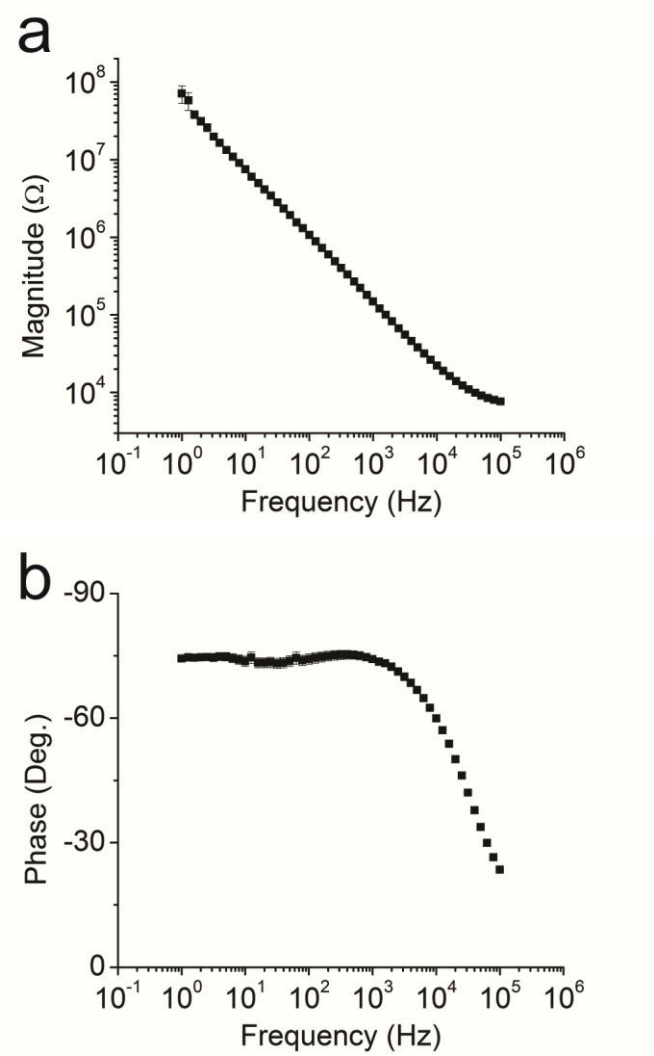

Figure 7. Magnitude (a) and phase (b) of EIS measurements. Mean ± SE, n = 32 electrodes.

IV. Conclusion

A 2×2 array configuration of the PSE was developed, thereby successfully demonstrating the scalability of the PSE technology and paving the way to electrode densities comparable to those in the Utah Electrode Array and the Michigan Electrode Array. With this increase in electrode density and thus access to neuronal populations, we hope to establish a more robust, reliable neural interface. Employing data collected in a 28-day *in vivo* study, the sheath structures of the PSEA were redesigned to minimize insertion trauma and promote cell-cell signaling by introducing perforations throughout the sheath structure. Along with the use of bioactive coatings, it is expected that these design considerations will better mitigate the brain's immune response [10] and therefore improve long-term signal

reliability. Benchtop electrochemical testing indicates that the electrode impedance values are suitable for neural recording. A customized insertion shuttle demonstrated successful delivery of the flexible PSEA both in an agarose gel brain phantom model as well as in the rat M1 motor cortex. *In vivo* electrophysiological data is currently being collected and the performance of the PSEA will be analyzed. This work represents a vital step in the exploration of the implementation and scalability of Parylene C technology to fabricate flexible neural probes for chronic recording. Furthermore, it demonstrates the versatility of the PSE technology to respond to developments in the neural interface field that call for novel probe shapes or surface topologies.

ACKNOWLEDGMENT

The authors would like to thank Dr. Saiyun Hou at Huntington Medical Research Institutes (HMRI, Pasadena, CA 91105) for performing the chronic animal implantations and the members of the Biomedical Microsystems Laboratory for their support.

REFERENCES

[1] V. S. Polikov, *et al.*, "Response of brain tissue to chronically implanted neural electrodes," *Journal of Neuroscience Methods,* vol. 148, pp. 1-18, Oct 2005.

[2] G. C. McConnell, *et al.*, "Implanted neural electrodes cause chronic, local inflammation that is correlated with local neurodegeneration," *Journal of Neural Engineering,* vol. 6, p. 056003 (12 pp.), 2009.

[3] R. Biran, *et al.*, "The brain tissue response to implanted silicon microelectrode arrays is increased when the device is tethered to the skull," *Journal of Biomedical Materials Research - Part A,* vol. 82, pp. 169-178, 2007.

[4] J. Bartels, *et al.*, "Neurotrophic electrode: Method of assembly and implantation into human motor speech cortex," *Journal of Neuroscience Methods,* vol. 174, pp. 168-176, Sep 2008.

[5] T. A. Harder, *et al.*, "Residual stress in thin-film parylene-c," in *Micro Electro Mechanical Systems, 2002. The Fifteenth IEEE International Conference on*, 2002, pp. 435-438.

[6] J. T. W. Kuo, *et al.*, "Novel flexible Parylene neural probe with 3D sheath structure for enhancing tissue integration," *Lab on a Chip,* vol. 13, pp. 554-561, 2013.

[7] B. J. Kim, *et al.*, "3D Parylene sheath neural probe for chronic recordings," *Journal of Neural Engineering,* vol. 10, p. 045002, 2013.

[8] E. Meng, *Biomedical Microsystems*, 1 ed.: CRC Press, 2010.

[9] S. A. Hara, *et al.*, "Pre-implantation electrochemical characterization of a Parylene C sheath microelectrode array probe," in *Engineering in Medicine and Biology Society (EMBC), 2012 Annual International Conference of the IEEE*, 2012, pp. 5126-5129.

[10] F. Johansson, *et al.*, "Porous silicon as a potential electrode material in a nerve repair setting: Tissue reactions," *Acta Biomaterialia,* vol. 5, pp. 2230-2237, Jul 2009.

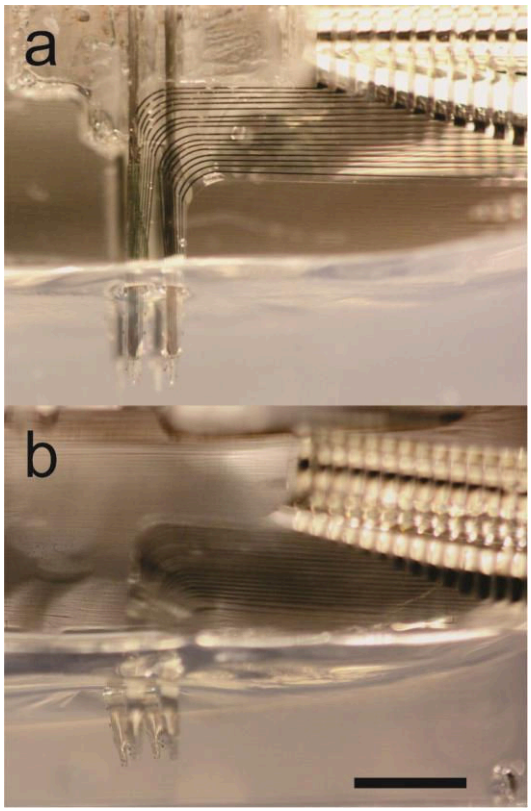

Figure 8. PSEA insertion (a) and shuttle retraction (b) in an agarose gel brain phantom model. Scale bar = 3 mm.

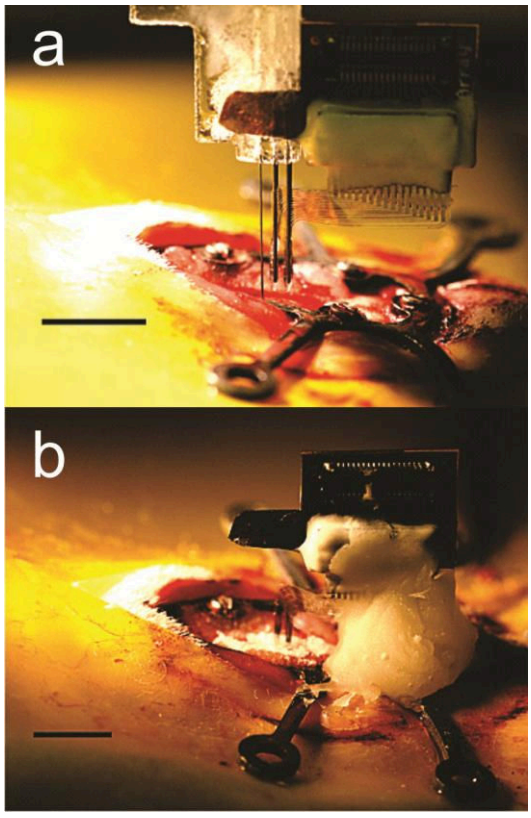

Figure 9. PSEA insertion (a) and shuttle retraction (b) in the rat M1 motor cortex. Scale bars = 6 mm.