Towards a Large-Scale Recording System: Demonstration of Polymer-Based Penetrating Array for Chronic Neural Recording

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Abstract— **The brain is a massively interconnected network of specialized circuits. Even primary sensory areas, once thought to support relatively simple, feed-forward processing, are now known to be parts of complex feedback circuits. All brain functions depend on millisecond timescale interactions across these brain networks. Current approaches cannot measure or manipulate such large-scale interactions. Here we demonstrate that polymer-based, penetrating, micro-electrode arrays can provide high quality neural recordings from awake, behaving animals over periods of months. Our results indicate that polymer electrodes are a viable substrate for the development of systems that can record from thousands of channels across months to years. This is our first step towards developing a 1000+ electrode system capable of providing high-quality, long-term neural recordings.**

I. Introduction

The brain is a massively interconnected network of specialized circuits. Even primary sensory areas, once thought to support relatively simple, feed-forward processing are now known to be parts of complex feedback networks. Current approaches for *in vivo* electrophysiological recordings are limited in both the number of recording channels and their distribution across regions; therefore, they cannot hope to measure or manipulate the sheer volume and complexity of these neural circuits. In order to identify and control such large-scale interactions, thousands of recording channels are required.

To develop a system that can effectively record from thousands of channels, several technological challenges for the electrode arrays must be addressed. First, the electrode arrays must be capable of penetrating brain tissue to gain access to more components of the feedback circuits. Second, the arrays must have both a high number and a high-density of electrodes. This will enable large-scale recordings with small spatial resolutions. Third, the arrays must have a very small footprint. To record from thousands of channels it is highly probably in order to minimize the overall damage caused by the arrays and to ensure minimal disruption of the neural circuitry under study. Finally, the electrode arrays must be able to record for long periods of time: months to years.

Current approaches for developing these arrays with thousands of channels can generally be divided into two categories: micro-wire arrays and micro-fabricated arrays [1-16]. While very suitable for deep-brain penetration, micro-wire arrays have drawbacks that limit their utility for expansion into a 1000+ channel recording system. First, the electrodes are often limited to a single insertion plane. This limits their ability to target the complex and variable neural architectures found in many brain areas. Second, only a limited number of electrodes are permissible to ensure a small device footprint is maintained. In general, increasing the number of electrodes increases the number of wires, thereby increase the overall size of the array. Further, these micro-wire arrays are often hand-made; the introduction of additional electrodes can drastically increase the fabrication time and cost, and in some cases is simply not practical. This also limits the reproducibility of these arrays

Micro-fabricated electrode arrays are a more viable option for developing a 1000+ channel recording system [5-16]. They utilize traditional micro-fabrication techniques that allow for large numbers of electrodes, in a high-density, small-footprint array, to be fabricated on a single device, with no significant increase in fabrication cost or time. This allows for high spatial resolution and minimal disruption of the neural circuitry during implantation. These micro-fabricated arrays have electrodes along the entire insertion length enabling recordings from different layers of neurons with a single array. Further, micro-fabrication enables relatively easy integration of multiple, individually implantable, arrays into a single device. This allows these micro-fabricated arrays to simultaneously measure and manipulate large regions of the brain.

Traditionally, these micro-fabricated electrode arrays have been fabricated out of either silicon [5-7] or polymers [8-16], such as polyimide or parylene, since these materials are compatible with the MEMS-based fabrication processes needed to create the arrays. Both silicon-based and polymer-based arrays have been used for penetrating, multi-electrode, neural recordings [5-16]. However, when looking to develop

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an electrode array that can record from thousands of channels across months to years, the polymer-based arrays have several advantages. First, the mechanical properties of the polymer-based arrays are more closely matched to the neural tissue than the silicon-based arrays [17-20]. Thus, the silicon-based arrays are more likely to cause chronic injury of the neural tissue at the implantation site, especially over the long-term, due to continuous micro-motion of the tissue [17-20]. Second, integration of flex cables/wires to the silicon arrays can be extremely difficult and complicated, especially for chronic, large-scale applications [21]. Also, the connection the point between the external wires and the silicon arrays is a common mechanical and/or electrical failure point. With polymer arrays, though, the flex cables/wires are integrated into the device during fabrication; no additional, complex attachment of external wires is needed.

Given these advantages, we selected micro-fabricated, polymer-based arrays as our substrate of choice as a starting point for our efforts to develop a 1000+ electrode system capable of year-long recording. The first step towards this goal was to develop an expandable electrode array capable of providing high-quality, long-term neural recordings.

II. Penetrating Electrode Array

A. Electrode Array Design

The penetrating, multi-electrode device is a 2-shank, 36-electrode, polymer array (Figure 1). The electrodes are divided evenly between the two shanks. The shanks are both 6 mm long and 100 µm wide; they are separated by 2 mm. Each electrode is 20 µm in diameter with a center-to-center spacing of 110 µm. On each shank, the electrodes are arranged in a single-line on the outside edge of the device. The electrodes are placed off-center so they are located closer to the non-damaged tissue. The electrode distribution was specially designed to record local field potentials.

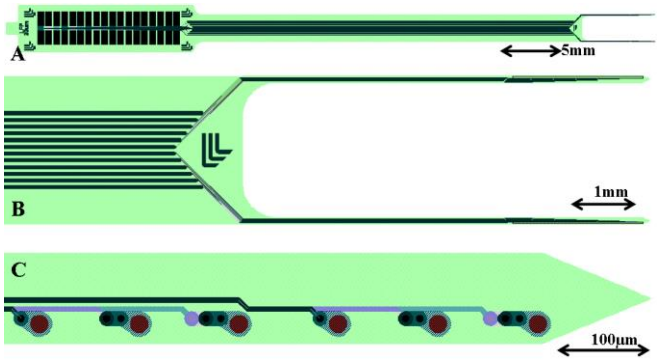

Figure 1. Top-down schematic view of the 2-shank, penetrating, multi-electrode device (A). The device utilizes a standard 36-pin Omnetics Connector (Omnetics Connector Co., Minneapolis, MN). The middle image (B) shows an enlarged view of the implanted region of the device showing the two individual shanks. The bottom image (C) shows an enlarged view of the tip of the bottom shank. The six electrodes shown (in red) are located at the outside edge. Although not shown, there are 18 electrodes on each shank.

B. Electrode Array Fabrication

The devices are fabricated using interleaved layers of polyimide and metal [15-16]. A cross-section of the device is shown in Figure 2. There are 4 layers of metal total: 1 layer of metal for the electrodes and 3 layers of metal for the conducting traces. The electrodes are platinum. Each layer of metal is separated by a layer of polyimide. The total device thickness is 14 µm.

The devices are fabricated "upside" down; in other words, the electrodes are built first and the traces are added on top. Traditional fabrication utilizes a "right-side" up order, in which the electrodes are added on top of the traces. The primary advantage of this "upside" down fabrication is that the electrodes are flush with the outer polyimide layers; this decreases the physical distance between electrodes and the neural tissue [16]. ("Right-side" up fabrication yields electrodes that are recessed from the outer polyimide layers.)

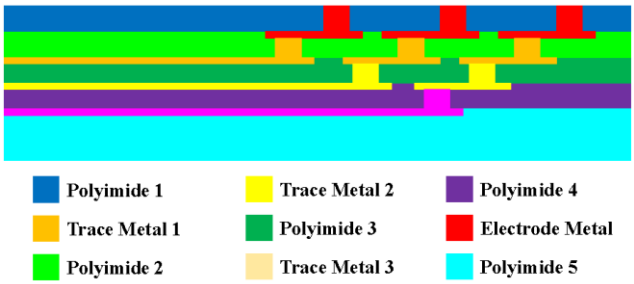

Figure 2. Cross-section of the fabricated devices (not drawn to scale). Although shown with the electrodes on top, the devices are fabricated with the electrodes on the bottom to allow the electrodes to be flush with the outer polyimide layers.

C. Insertion Stiffeners

Specially-designed insertion stiffeners are also fabricated. Details on the design and fabrication of these stiffeners can be found in Ref. 22. The polymer electrode arrays are temporarily attached to the stiffener using bio-dissolvable polyethylene-glycol (PEG) [22]. These insertion stiffeners are required as the flexibility of the polymer arrays results in buckling and folding of the arrays upon insertion, thereby preventing successful insertion. The stiffener, on the other hand, easily penetrates the neural tissue. Once the stiffened array is inserted, the PEG dissolves allowing the stiffener to be extracted. The polymer array thus regains its flexibility. In vitro tests have shown no loss of electrical functionality is caused by the PEG dissolution. For this preliminary demonstration, the stiffeners were fabricated from a silicon substrate. They were specifically designed for this electrode array; they are 50 µm thick with 2 shanks and an insertion depth of up to 6 mm (Figure 3).

D. In Vitro Electrical Characterization

Electrochemical impedance measurements were made on the electrodes with a Princeton Applied Research (PAR) potentiostat using vendor-supplied software. All measurements were made in a three-electrode cell using a Pt counter electrode, an Ag/AgCl reference electrode, and phosphate-buffered saline (pH 7.4) as the electrolyte. The impedance of the electrodes is approximately 950 kΩ at 1 kHz.

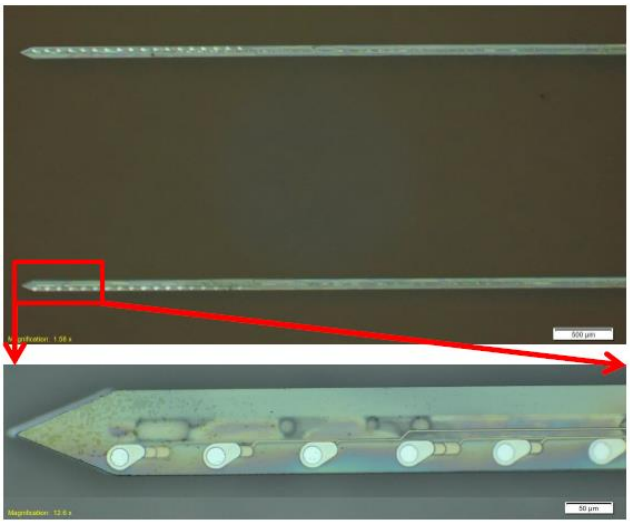

Figure 3. Image of the penetrating electrode array attached to the insertion stiffener. The top image shows both shanks which have been attached simultaneously to a single insertion stiffener. The bottom image shows an enlargement of the tip of one of the shanks. The shank is attached on top of the insertion stiffener with PEG. The six tip-most electrodes are visible.

III. *In Vivo* Experiments

A. Animal Surgery

All surgical procedures and animal care conform to guidelines set by the University of California, San Francisco, and the National Institutes of Health. The devices were surgically implanted into the hippocampus of one wild-type and four transgenic ChAT-Cre Long Evans rats [23]. The first shank was targeted 3.7 mm posterior and 2.0 mm lateral of Bregma and the second shank was targeted at 2.29 mm posterior and 3.41 mm lateral of Bregma. The insertion stiffener of the electrode array assembly was attached to a Kopf Model 2660 direct drive micropositioner and lowered into position. The PEG was given 30 minutes to dissolve in saline before the stiffener was retracted, leaving the polymer array in the neural tissue. The array was then secured to the skull surface using dental acrylic.

B. Electrophysiological Recordings

The arrays electrode distribution was designed to record local field potentials (LFPs) along the rostrocaudal axis of the hippocampal structure. This allows for the measurement of the electroanatomy of the hippocampal cortical layers [24]. Following implantation, electrophysiological data were collected using the NSpike Data Acquisition System (L.M. Frank, J. MacArthur, Harvard University, Cambridge, MA). Data were collected at 30 kHz and digitally filtered from 1 Hz – 11 kHz before being saved to disk.

Data from the rats were collected for up to 3 months post-implantation, after which the experiment was terminated. In each animal, the electrode arrays continued to provide high-quality LFP data for the entire duration of the experiment. An example of this can be seen in Figure 4, which shows raw data taken from eight consecutive channels recorded at three weeks and at three months following implantation. The traces in the figure are centered on a sharp-wave ripple event, a characteristic electrophysiological signature of hippocampal activity. In some cases, we were also able to obtain well-isolated single units, although we noted that there was some small variation from day to day that could be a result of electrode movement relative to the tissue. Nonetheless, the long duration of the recordings demonstrates the utility of these polymer-based electrode arrays.

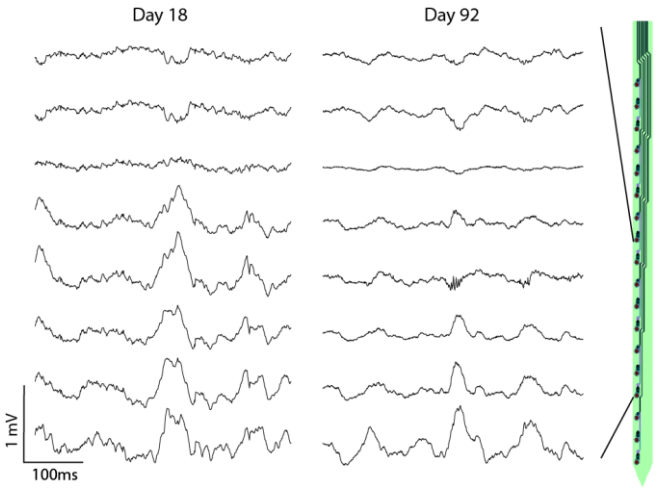

Figure 4. LFP signals recorded from one shank of a polymer electrode array three weeks (left) and three months (right) after implantation. The traces show the measured signals from eight adjacent channels of one shank. The signals are centered on a sharp-wave ripple event from the hippocampus, which includes a high frequency ripple oscillation that is most prominent on the 5th channel (front the top) on the right.

IV. Conclusion and Future Work

Our results demonstrate that polymer-based electrode arrays can be successfully inserted into deep-brain structures and that they can provide high-quality recordings for long periods of time. These results lay the groundwork for future studies that will optimize polymer electrode arrays for long-term, stable, single-neuron recordings.

Towards our ultimate goal of developing a 1000+ electrode recording system, we are focusing on four important areas.

1. Smaller devices have the potential to yield more stable recordings, which would allow recordings from the same sets of neurons across many days. Micro-fabrication techniques will allow further miniaturization of these devices, while maintaining the high channel counts and increasing the electrode density. We are therefore exploring devices that measure as small as 60 μm by 20 μm, with greater than 20 electrodes.
2. We are investigating new insertion tools that will allow easy implantation of many electrode arrays in various regions of the brain. This will enable us to target the specialized circuitry and the complex and variable neural architectures found in many different areas of the brain.
3. We are continuing to test the electrode arrays, both *in vitro* and *in vivo,* to further quantify the long-term recording characteristics. We are also carrying out

longer-term recordings in which we are isolating large numbers of single neurons. Although we have demonstrated high-quality recordings over a 3 month time period and other polymer-based electrode arrays have demonstrated multi-year use [25] it remains to be seen, however, whether the further miniaturization of these devices will limit the effective lifetime.

4. We are working on integrated probe-headstage assemblies that will eliminate the need for bulky connectors. If the devices are directly coupled to chips that preamplify, multiplex, and digitize the signals, very high-density and high channel count recordings become possible.

5. We are working on a new data acquisition system capable of capturing data from 1000+ channels. Our approach uses gigabit Ethernet to provide high bandwidth, low latency data transmissions and allows for real-time feedback on the basis of ongoing brain activity.

Together, these technology development efforts have the potential to yield tools that can be used to measure the activity of thousands of neurons in awake, behaving animals. Further, as previous polymer devices we have created have been approved for use in humans [25], this technology provides a path forward to large-scale recordings from the human brain.

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