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Microfabricated Polymer-Based Neural Interface for Electrical Stimulation/Recording, Drug Delivery, and Chemical Sensing – Development

Angela Tooker, Teresa E. Madsen, Allison Yorita, Andrea Crowell, Kedar G. Shah, Sarah Felix, Helen S. Mayberg, Satinderpall Pannu, Donald G. Rainnie, Vanessa Tolosa

Abstract— **We present here a microfabricated, multi-functional neural interface with the ability to selectively apply electrical and chemical stimuli, while simultaneously monitoring both electrical and chemical activity in the brain. Such a comprehensive approach is required to understand and treat neuropsychiatric disorders, such as major depressive disorder (MDD), and to understand the mechanisms underlying treatments, such as pharmaceutical therapies and deep brain stimulation (DBS). The polymer-based, multi-functional neural interface is capable of electrical stimulation and recording, targeted drug delivery, and electrochemical sensing. A variety of different electrode and fluidic channel arrangements are possible with this fabrication process. Preliminary testing has shown the suitability of these neural interfaces for *in vivo* electrical stimulation and recording, as well as *in vitro* chemical sensing. Testing of the *in vitro* drug delivery and combined *in vivo* functionalities this neural interface are currently underway.**

I. Introduction

Recently, deep brain stimulation (DBS), a method of electrically stimulating specific brain regions using an implanted electrode, has been approved by the FDA for the treatment of symptoms of Parkinson's disease, essential tremor, and dystonia. More recently, DBS has also been applied to a variety of neuropsychiatric disorders, such as obsessive-compulsive disorder (OCD) and major depressive disorder (MDD) [1-4]. Ongoing studies of DBS targeting the subcallosal cingulate white matter have shown sustained, long-term, antidepressant response without appreciable side effects in otherwise treatment resistant patients [1, 3-4]. Despite these encouraging results, DBS mechanisms are unknown, slowing refinement of surgical targeting and stimulation parameters that might further optimize clinical outcomes.

To understand a subject as complex as brain function and to treat an illness as elusive as treatment-resistant depression, a comprehensive approach is required. We are developing a multifunctional neural interface to selectively apply electrical and pharmacological treatments to a behaving animal, while simultaneously monitoring electrical and neurochemical brain activity.

Some of the most common neural interfaces are thin-film micromachined probes, utilizing either silicon or polymer backbones [5-18]. In general, these devices have limited functionality, allowing for only electrical stimulation and/or recording [5-6, 11-15] or only chemical sensing [16]. Initial work has concentrated on incorporating fluidic channels for drug delivery into these neural interfaces [7-10, 17-18]. Recently, Frey et al. have demonstrated a silicon-based neural interface with electrical stimulation/recording, drug delivery, and chemical sensing [10]. However, there are concerns regarding the suitability of silicon-based neural interfaces for long-term *in vivo* studies [19]. Further, the continuous micro-motion of the neural tissue can induce strain between the neural tissue and the implanted interface, inducing chronic injury and glial scarring at the implant site. Unlike silicon-based, polymer-based neural interfaces are fully flexible. Thus, the strain between the neural tissue and the implanted probe is minimized, thereby minimizing injury and scarring at the implantation site [20].

We present here a microfabricated, multifunctional, polymer-based neural interface (Fig 1.). The multifunctional interface is capable of electrical stimulation/recording, targeted drug delivery, and electrochemical sensing. The fabrication process is extremely versatile, allowing a variety of different electrode and fluidic channel geometries to be produced.

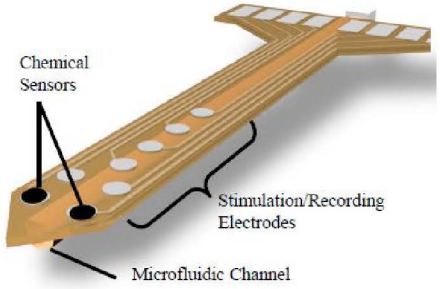

Figure 1. Model of the multifunctional neural interface presented here.

II. Multifunctional Neural Interface Fabrication

A. Neural Interface Fabrication

The fabrication process depicted here can be used for a variety of different electrode quantities (8 – 120), sizes (10 µm to 2 mm), and materials (e.g. platinum, iridium, iridium-oxide, gold). This process can also be used for a variety of different fluidic channel dimensions: height (1 µm – 100

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A. Tooker is with Lawrence Livermore National Laboratory, Livermore, CA 94550 USA (phone: 925-422-2326; fax: 925-422-2373; e-mail: tooker1@llnl.gov).

V. Tolosa, K.G. Shah, S. Felix, and S. Pannu are with Lawrence Livermore National Laboratory, Livermore, CA 94550 USA (e-mail: tolosa1@llnl.gov, shah22@llnl.gov, felix5@llnl.gov, pannu1@llnl.gov).

A. Yorita is with Chemical and Biomolecular Engineering Department, University of California, Los Angeles, CA (email: ayorita@ucla.edu)

T.E. Madsen, A. Crowell, and D.G. Rainnie are with Emory University School of Medicine, Atlanta, GA (email: tmadsen@emory.edu, andrea.crowell@emory.edu, drainni@emory.edu)

H.S. Mayberg is with Department of Psychiatry, Emory University, Atlanta, GA (email: hmayber@emory.edu)

μm), width (10 μm – 1mm), and length (5 mm – 100 mm). In addition, multiple fluidic channels can be included on a single neural interface.

A model of the multifunctional neural interface is shown in Fig. 1. This multifunctional device contains: (1) electrodes for both electrical stimulation and recording, (2) fluidic channels for targeted drug delivery, and (3) post-fabrication, surface-modified electrodes for electrochemical sensing. The fabrication process is versatile, allowing for a variety of different orientations of electrodes and fluidic channels (Fig. 2). The fabrication steps are as follows:

1. Etch pillars into the silicon at the electrode and electrical connector locations (Fig. 2A) using a standard Bosch process. These pillars allow the electrodes to be recessed from the surface of the parylene, which creates more uniform electric fields during electrical stimulation [21]. The height of the pillars defines the recess depth of the electrodes. The first layer of parylene is then deposited and O_2 plasma is used to remove the parylene at the pillar locations.
2. The electrode and trace metals are then deposited and patterned (Fig. 2B). A variety of electrode metals can be used (platinum, iridium, and iridium-oxide are the most common). The trace metal is typically gold. The metals can be patterned using either liftoff or etching (wet or dry) techniques.
3. The next layer of parylene is then deposited (Fig. 2C) and interconnection vias are etched through this parylene layer using O_2 plasma (Fig. 2D) at both the electrode and electrical connector locations. The second layer of trace metal is then deposited and patterned. The process is then repeated for a third layer of parylene and a third layer of trace metal (Fig. 2E).
4. The parylene is then through-etched using O_2 plasma to create the fluidic inlet (Fig. 2F). This places the fluidic inlet on the same side of the device as the electrodes and the electrical connector. Although not shown in the fabrication process depicted here, if the fluidic outlet is desired on the same side of the device as the electrodes, this would also be etched at this time. Similarly, if the fluidic inlet is desired on the opposite side of the device, this step can be omitted.
5. The sacrificial photoresist used to define the fluidic channel is patterned and the final layer of parylene is then deposited (Fig. 2G). The fluidic outlet is then etched through the parylene using O_2 plasma (Fig. 2H). The location of this fluidic outlet on either side of the neural interface (as opposed to the tip of the device) is crucial to prevent occlusion during insertion [22].
6. Finally, the sacrificial photoresist in the fluidic channel is removed and the devices are released from the silicon (Fig. 2I). Individual electrodes are then surface-modified to create the chemical sensors.

The process used here can be used with varying numbers of trace metal layers (up to 4 layers of trace metal have been demonstrated [23]) and varying orientations of electrodes and fluidic channels. With this process it is possible to put electrodes on both sides of the devices and/or inside the fluidic channels.

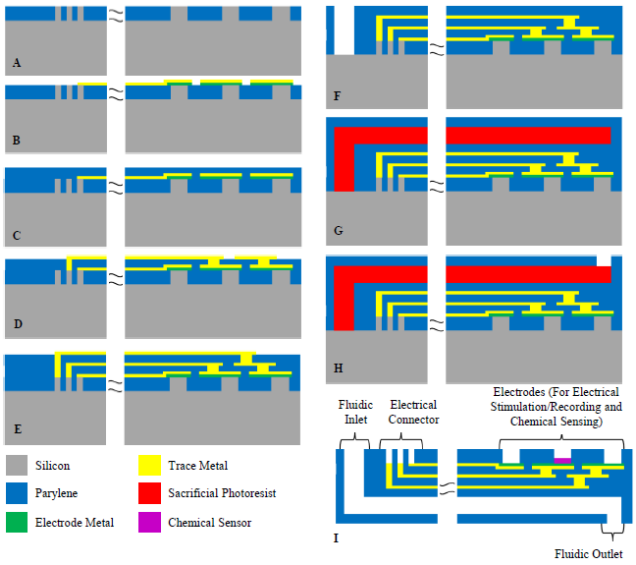

Figure 2. Fabrication process of the multifunctional neural interface.

B. *Electrochemical Sensor*

Post-fabrication chemical modifications are performed on individual electrodes. These electrodes can be selectively modified to detect multiple analytes. As a representative chemical sensor, an amperometric dopamine (DA) sensor was developed. Platinum electrodes were chemically modified with permselective polymers to allow for the detection of dopamine and rejection of interferents [24]. Fig. 3 shows the results of an *in vitro* calibration of a DA sensor. The sensor shows a step response to each injection of 10 μM of DA but no response to injections of 250 μM of ascorbic acid, a common interferent present in extracellular fluid. Additionally, the sensor responds strongly to 1 μM hydrogen peroxide, making the device suitable for use as an enzymatic sensor when modified with appropriate enzymes.

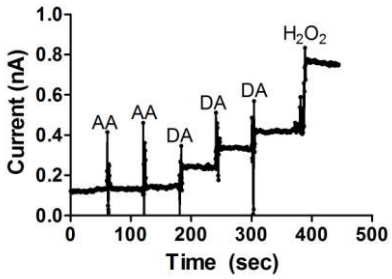

Figure 3. *In vitro* calibration showing a step response to 5 μM dopamine (DA) and 1 μM hydrogen peroxide (H_2O_2), but no response to the interferent ascorbic acid (AA) at 250 μM per injection.

C. *Electrical and Fluidic Connectors*

A variety of different electrical connectors can be used with this neural interface, depending upon the application. Most standardly used are the Omnetics (Omnetics Connector Co., Minneapolis, MN) and the zero-insertion-force (ZIF)

connectors. This neural interface can also be used with specially-designed, percutaneous connectors for long-term use, such as that designed by Shah et al. [25]. Alternately, specialized connectors, with on-board electronics and wireless telemetry, can also be used [15]. All of these methods allow for reliable and repeatable electrical connections.

The most commonly used fluidic connectors for drug delivery consist of tubing epoxied to the neural interface [8-9, 17]. The neural interface presented here can be used with this type of interface.

D. Polymer Neural Probe Insertion Stiffeners

A major challenge with these polymer-based neural interfaces is their flexibility as the probes tend to buckle upon insertion, thereby preventing successful penetration into neural tissue. We have developed a method for temporarily attaching the neural interface to a silicon stiffener with biodissolvable polyethylene glycol (PEG) [26]. The silicon can easily penetrate the neural tissue, and once inserted, the PEG dissolves, the silicon stiffener can be extracted, and the polymer probe regains its intended flexibility. The removable silicon stiffener has been tested with devices that have electrical stimulation and recording capabilities and no loss of functionality has been seen due to the PEG dissolution or the removal of the stiffener. Plans are underway to test the removal silicon stiffeners with the chemical sensing and delivery functionalities.

III. Neural Interface Characterization

Images of the multifunctional neural interfaces are shown in Fig. 4. The images show both multi-shank and single-shank interfaces, with both top (fluidic channel is on top) and bottom views (electrodes are on top). As can be seen, the fabrication process is compatible with a variety of different probe, fluidic channel, and electrode designs.

A. In Vitro *Electrical Characterization*

Both iridium and platinum electrodes were tested. For the iridium electrodes, activation was performed using biphasic potential pulsing in phosphate-buffered saline to form an activated iridium oxide film (AIROF). All electrodes were characterized to determine charge storage capacity (CSC) and impedance. Cyclic voltammetry (CV) and electrochemical impedance measurements were made 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. Potential cycling for the CVs was performed between -600 mV and +800 mV at a scan rate of 100 mV/s. The CSC for a typical 100 µm AIROF electrode is 21.8 mC/cm^2, with an impedance of 3.3 kΩ (at f = 1 kHz). Other electrode sizes exhibit similar results. The CSC for a typical 100 µm platinum electrode is 1.72 mC/cm^2, with an impedance of 42.2 kΩ (at f = 1 kHz).

B. Preliminary In Vivo *Testing*

Preliminary *in vivo* testing of these neural interfaces was performed to demonstrate their efficacy in both neural electrical stimulation and recording. For these experiments, two neural interfaces were used: one inserted into the basolateral amygdala (BLA) and the other inserted into the medial prefrontal cortex (mPFC).

Figure 4. Images of three different multifunctional neural interfaces. The top image shows a probe with 4 separate shanks, where each shank has a fluidic channel. The middle image shows a single-shank design. The bottom image shows a single-shank design with a tetrode array. The top and middle images show top-down views of the neural interfaces (i.e. the fluidic channel is on top). The bottom image shows a bottom-up view of the neural interface (i.e. the electrodes are on top).

1) Neural Recording

For this test, one of the neural interfaces presented here was implanted in the BLA and used as the recording array. A commercial monopolar electrode was implanted in the mPFC and used for stimulation. Fig. 5 shows the evoked response potentials (ERPs) recorded using the neural interface in the BLA.

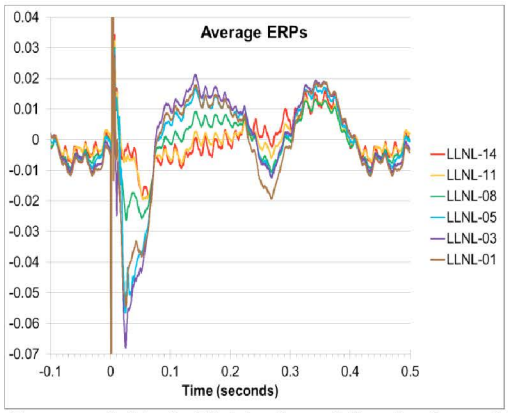

Figure 5. Data recorded in the BLA by the multifunctional neural interface (following stimulation in the mPFC).

2) Neural Stimulation

For this test, data was recorded from the BLA using a commercial microwire array during stimulation from the mPFC using a neural interface presented here. Fig. 6 shows the data recorded after stimulation.

IV. Conclusion

We present a complete microelectrode array designed for electrical stimulation and recording and chemical delivery

and sensing. We have demonstrated a versatile fabrication process for multifunctional neural interfaces. The neural interface was designed to be implanted in soft tissue using a removable stiffener. Preliminary testing has shown the suitability of these neural interfaces for *in vivo* electrical stimulation and recording and *in vitro* chemical sensing. *In vitro* testing of the fluidic channels for drug delivery is currently underway. Additional *in vivo* testing of the drug delivery and chemical sensing functions of this neural interface is also planned.

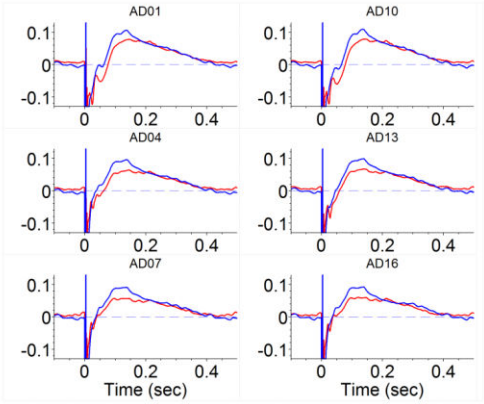

Figure 6. Data recorded in the BLA following stimulation in the mPFC by the multifunctional neural interface.

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