A Shared Resource for Building Polymer-Based Microelectrode Arrays as Neural Interfaces

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***Abstract*— Chronic functionality of neural interfaces (NI) is hampered by the physiological response to foreign objects, in part due to the mismatch of mechanical properties between soft neural tissue and the rigid materials used in interface construction. Polymer-based NIs have emerged as a key new technology in the pursuit of chronically stable neural recording and stimulation, but most polymer NIs are bespoke devices developed as part of specific research missions; many researchers do not have access to polymer-based NIs technology and among those who do there is a severe lack of standardization in material, construction, packaging, and testing, leading to a lack of repeatability among datasets. Here we present the Polymer Implantable Electrode (PIE) Foundry, a shared-resource for fabricating and disseminating standardized polymer-based microelectrode arrays for use in NIs. The model is based on the successful shared prototyping concept developed for the field of semiconductor research. Professional staff, supported by the BRAIN Initiative funding and operating in cleanroom space provided by the University of Southern California, offer design, fabrication, packaging, and testing of polymer-based microelectrode arrays as a free service to academic and non-profit research groups. The core enabling technology is a standardized set of micromachining protocols applied to the biocompatible, thin-film polymer Parylene C. By leveraging this method, we produce microelectrode arrays of varied size, shape, channel count, and application, disseminating hundreds of arrays to 18+ research groups in our first three years of operation. By standardizing materials, fabrication, and packaging, we create repeatable and comparable devices and have built a library of shareable designs. Channel counts range from 2 to 64, electrode sizes range from 15 µm diameter to 1 mm, designs include penetrating neural probes, spinal paddle electrodes, surface arrays for electroencephalography, and peripheral nerve cuffs for recording and stimulation, animal models include songbird, mouse, rat, cat, and sheep. Here we present details of our organizational structure, fabrication and packaging methods, representative examples of *ex vivo* and *in vivo* electrode performance, and key results from the first three years of Foundry operation.**

Keywords—electrodes, polymer, neural recording, microelectrodes, flexible

I. Introduction

Chronically viable neuroelectronic interfaces are required for neuromodulation therapy and fundamental neuroscience research, but most available tools have short functional lifetimes due in part to the body's immune response [1], [2]. Soft, flexible microelectrode arrays (MEA) are an emerging technology that offer a means to mitigate the immune response by replacing silicon and metal-based electrodes with polymers as a softer alternative [3]–[8]. However, there are few polymer MEAs (pMEA) available to researchers, and fewer still which meet the range of needs of current neuroscience research.

PMEAs customized to different species and applications have been developed and demonstrated. These are commonly produced via sponsored research involving collaboration between neuroscientists and select academic laboratories with both microfabrication expertise and access to micro/nanofabrication facilities. Since such collaborations usually target a specific region in a specific species, this one-by-one approach produces few custom-designed devices suitable for initial demonstration purposes yet does not scale to support research studies requiring large numbers of devices. This is in part attributed to the use of research trainees to design, fabricate, and package devices as an intermediate step in their career development and the absence of affordable and convenient contract research services to rapidly develop and produce custom pMEAs. Highly trained research staff can support rapid prototyping, scale up of custom device production for specific neuroscience users, and disseminate generic designs to a wider user base. Therefore, to address the needs of the research community, a flexible process was devised, which could produce pMEA devices of arbitrary design, size, and channel count, and incorporate form-factors including surface arrays, penetrating probes, and peripheral nerve cuffs (Fig. 1).

We launched the Polymer Implantable Electrode (PIE) Foundry as a shared-resource center to develop and fabricate polymer MEAs for neuroscience researchers.

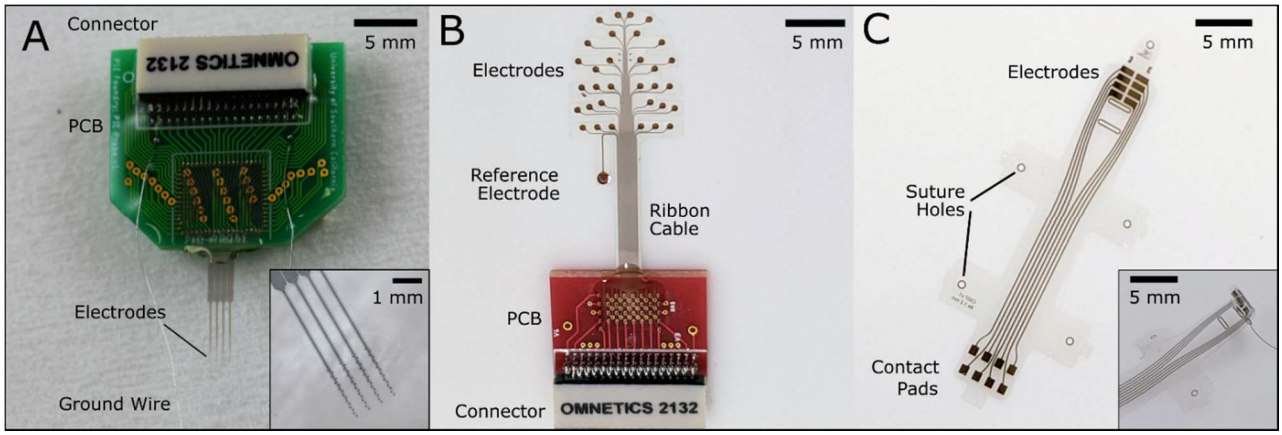

Fig. 1. Representative examples of polymer microelectrode arrays of different archetypes: (A) A 64 channel penetrating array for (sub)cortical recording with magnified view of electrodes in inset; (B) A 32 channel surface recording electrode array for electrocorticography; (C) An 8 channel extrafasicular peripheral nerve interface with inset showing the pMEA in a curled configuration.

II. Materials & Methods

A. Shared-Resource Model

The PIE Foundry is supported as a research resource grant through the National Institutions of Health under the BRAIN Initiative [9] and is based in the labs of Dong Song and Ellis Meng and core research facilities at the University of Southern California. The Foundry is operated by full-time professional staff who offer design, fabrication, and testing of pMEAs. Users can also access training services that include multielectrode array design, fabrication protocols, and implementation of devices in animal studies. PIE Foundry services are provided at no cost to research community for the duration of the award and at cost to commercial users.

The PIE Foundry offers fabrication of user-submitted designs using a multi-project wafer (MPW) model, in which designs adhering to a standard set of guidelines are processed simultaneously, with multiple user designs sharing space on the same carrier wafer. Users who require assistance designing their electrodes, or who require non-standard materials or design features as part of their project, can request custom fabrication services. Under this model PIE Foundry staff design, fabricate, package, and provide basic characterization of the users. Due to the added effort and cost, custom projects require the submission of a short proposal, which is reviewed by an external scientific steering group. In addition, genericized "off-the-shelf" electrode arrays are available for users who do not need custom solutions. This includes a 64 channel Parylene C 'standard' recording array (Fig. 1A) for use in rats and small mammals, described previously [20].

Users submit digital design files (.gds, .dxf, .cif) or a proposal through email or the online portal [10]. Microfabrication services typically take 1-2 months depending on the current workload, while custom projects can take 3-4 months following approval, depending on complexity of the project. Designs include brain-machine interfaces, peripheral nerve cuffs, spinal cord arrays, and retinal arrays among others.

B. Polymer Microelectrode Array Fabrication

Foundry pMEAs consist of a simple multi-layer design, comprising a base layer of Parylene C, a metal layer containing the electrodes, traces, and contact pads, and an insulating layer of Parylene, which is etched to uncover the electrodes and contacts. Parylene C was chosen due to its proven history in chronic biomedical implants, strong insulating properties, and thermoplastic nature, which allows planar arrays to be thermoformed into cuffs, coils, and other shapes. PMEAs are fabricated using a combination of photolithography, chemical and physical vapor deposition, and plasma etching, with all processing steps performed in a class 1000 (ISO 6) cleanroom.

The typical fabrication process is summarized here. First, 100 mm diameter silicon carrier wafers are conformally vapor-coated in approximately 10 µm of Parylene C to form the base of the pMEA. Next, a single thin-film metal layer, containing all traces, contact pads and electrodes, is fabricated using a combination of image-reversal photolithography, metal evaporation, and solvent lift-off. Wafers are treated with AZ5214 photoresist, 1.1 µm thick, and patterned in image reversal mode. Following a brief O_2 plasma treatment to clean the Parylene C surface, wafers are coated with a metal layer using e-beam evaporation. Typical processing entails either a single 200 nm Pt layer or a Ti/Au/Pt stack (20/155/25 nm). Lift-off is performed in a bath of N-methyl-2-pyrrolidone (NMP) at 60 °C; Pt coated wafers are treated with mild agitation while Ti/Au/Pt coated wafers require an ultrasonic bath.

A second Parylene C layer, also approximately 10 µm thick, is deposited, forming the insulation and top surface of the pMEA. Wafers are first treated with A174 silane, an adhesion promotor, then coated in Parylene C. Total thickness of the multi-layer stack is approximately 20 µm

To remove the insulation above the electrodes and contact pads, and to cut-out the shape of the polymer MEA, wafers are etched with O_2 plasma using two separate photoresist masks. Wafers are treated with P4620 photoresist, 15 µm thick, then patterned using contact UV lithography. Then Parylene C is etched to a depth of 10 µm using an O_2 reactive ion etch (RIE)

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process (150 mT, 150 W, 50 sccm O_2, Oxford RIE80), yielding an approximate etch rate of 0.21 µm/minute. A switched-chemistry Bosch-like process can also be used in a deep reactive ion etch tool, and details have been reported previously [11]. Following the first etch step, the photoresist mask is stripped, the second etch mask is applied in the same manner, and the etching process is repeated. The second etch mask is then stripped, and the devices are released by submerging the wafer in water and peeling devices off the wafer using tweezers.

To improve adhesion between the Parylene C layers pMEAs are annealed for 48 hours under vacuum at 200 °C, sandwiched between ceramic alumina plates (0.635 mm thick). Finally, electrodes are cleaned with a brief exposure to O_2 plasma (100 W, 100 mT, 300 seconds).

C. Packaging

The majority of devices manufactured by the Foundry are attached to printed circuit boards (PCBs) for connection to external electronics and headstages using a direct ultrasonic weld referred to as polymer-ultrasonic on bump (PUB) bond [14]. Contact pads on PCBs (200×350 µm, 50+ µm thick, soft gold finish) are first 'bumped' using a ball bonding tool (Hybond 626). A gold ball with an approximate diameter of 100 µm is ultrasonically bonded to the center of each pad, then flattened into a disk using a wire bonding tool fitted with a tape-automated bonding (TAB) attachment (7045-Ti, Smart Precision Tools). This step flattens and levels the gold bump, while imprinting a waffle pattern into the surface. Using the same tool, force and ultrasonic energy is applied to the back of the pMEA, welding the metal of the pMEA contact pad to the gold bump. The process typically takes 2 seconds per connection. Afterwards the bonded connection is underfilled with epoxy (301-3M, EpoTek) for mechanical support.

When required, PUB bonding can be replaced with alternative packaging scheme, including the use of a zero-insertion force (ZIF) connector. ZIF connectors offer reversible connection between flat flexible cables and PCBs using a mechanical clip. ZIF compatible contact pads are incorporated into the pMEA design, oversized by 2.5% to account for polymer shrinkage during annealing steps; pMEAs are then mounted onto PEEK films (25.4 µm thick) using epoxy (301-3M). The film provides the necessary thickness and mechanical support to mate with the ZIF connector.

D. Characterization

Representative electrodes are characterized with electrochemical impedance spectroscopy (EIS) and cyclic voltammetry (CV) using a Gamry Reference 600 potentiostat (Fig. 2). CV is performed in 0.05 M H_2SO_4 in the potential range of −0.2–1.2 V versus an Ag/AgCl reference and large Pt counter electrode. The solution is purged with N_2 prior to and during the CV. Scan rate was 250 mV/s for 30 cycles. EIS is performed in 1× phosphate-buffered saline (PBS) following CV cycling, also using Ag/AgCl and Pt as the reference and counter, respectively. Impedance is measured in the range of 1 Hz–1 MHz. To assess end-to-end continuity, single-point electrochemical impedance, at either 1 or 10 kHz in 1× PBS is performed on electrode sites. Full electrochemical characterization is typically performed only upon request, with results provided to the user.

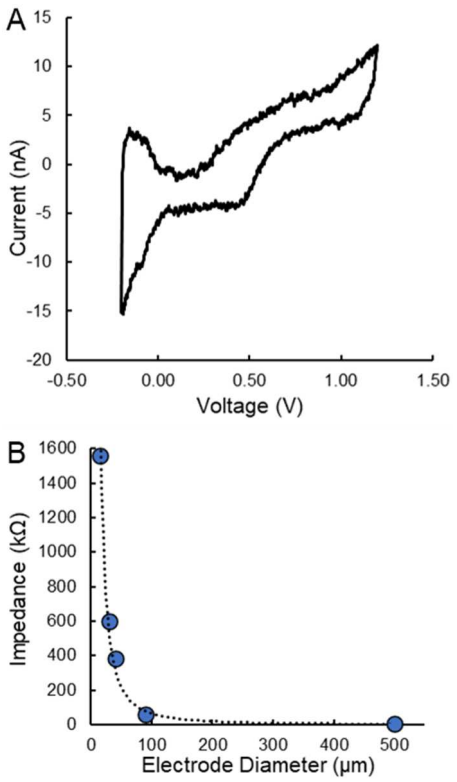

Fig. 2. (A) Cyclic voltammetry profile of a representative 30 µm Pt electrode on a PIE Foundry standard array. (B) Electrode impedance of Pt coated circular electrodes of different sizes in 1× PBS at 1 KHz against a Pt counter.

E. Implantation

Penetrating brain probes built from pMEAs require mechanical assistance to implant. PIE Foundry users have used a variety of methods, including metal wire shuttles, dissolvable braces, and temporary stiffening agents. The most common method, developed by Foundry staff, is to dip-coat arrays in molten polyethylene glycol (PEG) with 8 kDa molecular weight. Cortical and subcortical implantation entails removing both dura mater and pia mater before inserting arrays using a stereotaxic controller. PEG dissolves upon contact with physiological fluid. Stainless steel anchor screws are placed in the skull of the animal model, and dental cement is used to fix the pMEA interface-board to the skull, using the anchor screws as an attachment point. In-house testing of the 64-channel 'standard' array entailed implantation of Parylene C shanks 5 mm deep in adult rats, targeting either the somatosenory cortex or CA1/CA3 hippocampal layers. Both acute and chronic tests erre performed; typical chronic tests involved recording from free-moving rats over a period of 6-12 weeks. A more detailed account was published previously [12]. Surface and peripheral nerve pMEAs are typically implanted based on user developed surgical methods.

III. Results

Since launching in November of 2019, the PIE Foundry has delivered more than 400 individual pMEAs to 18 different research groups at 12 different institutions, totaling many thousands of individual electrode sites. Our fabrication methods have been successfully used to develop a wide range of devices,

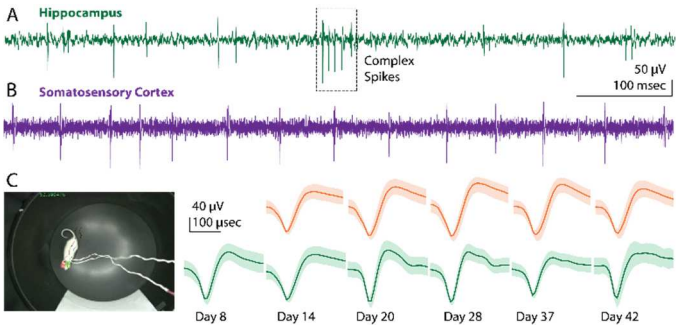

Fig. 3. In vivo recording obtained with the standard pMEA. (A) Unitary activities recorded from the hippocampus of an anesthetized rat. (B) Unitary activities recorded from the cortex of an anesthetized rat. (C) Units recorded by two different channels (orange and green) over a period of 34 days.

including surface arrays, peripheral nerve interfaces, and cortical and sub-cortical penetrating arrays for animal models including songbird, mouse, rat, cat, and sheep. Electrode counts range from as low as 2 per device to 64 per device, and constructed layouts include stereotrode, tetrode, linear arrays, and anatomically mapped custom arrays. pMEA size ranges from surface electrode arrays 25 mm^2 in area, to penetrating shanks just 100 µm wide. While these arrays are designed principally for recording, several users have reported using paddle and cuff designs for stimulation of peripheral nerves.

Our fabrication technique has proven flexible and robust; hundreds of pMEAs are now regularly produced in batch processing, with multiple user designs mixed into each MPW run. Penetrating arrays, surface arrays and peripheral nerve cuffs can all be fabricated on the same wafer as a result of the generalizable fabrication process, which enables fast turn-around times for users and reduces cost for the Foundry. The lithographic methods allow micromachines features, including metal traces, with critical size and pitch as small as 2 µm, minimizing implant size while maximizing the number of electrode sites. The PUB bonding method has proven the most effective packaging method, more scalable and more robust than the use of ZIF connectors, and faster and more reliable than manual alternatives such as conductive epoxy. A 64 channel pMEA can be PUB bonded to a PCB in just a few minutes, in a space 1/3 the size of the smallest available ZIF connector, and the technique easily scales to hundreds of channels, far more than the largest available ZIF. Across more than 100 tests, we have yet to observe a PUB bond fail after packaging. In contrast, ZIF connectors can damage the thin film metal contacts of pMEAs.

Fig. 2 presents representative datasets showing electrode CV response and electrochemical impedance. Electrode impedances scale inversely with electrode size. While the PIE Foundry does not offer electrochemical coatings, several users have used PIE Foundry devices with commercial or personally-developed systems for coating porous gold, PEDOT, and other surface finishes, and have achieved significant decreases in impedance.

In vivo testing of pMEAs have proven chronic stability of polymer interfaces in free-moving animals. In-house testing of the 64-channel standard array entails 5 mm deep implantations in male rats, targeting hippocampal layers, with unitary recording from both cortex and hippocampi with animals exploring an open field. Individual channels show stable recording over a period beyond a month (Fig. 3).

IV. Discussion

Use of pMEAs for brain-machine interfaces is likely to expand, as researchers increasingly adopt the technology for developing longer-lasting devices. As polymer microfabrication is in general much less mature than traditional semiconductor micromachining, and as there remain few commercial options for pMEAs, the shared-resource model may be the best available option for most neuroscientists to gain access to this important technology. Over the next few years, we expect to significantly expand the number of Foundry users, make key improvements in our pMEA technology, including increasing channel count, increasing the library of standardized devices, and incorporating multiplexing, and we expect to disseminate fabrication and packaging protocols to other institutions.

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