3D NEURAL PROBES WITH COMBINED ELECTRICAL AND CHEMICAL INTERFACES

Y. Li¹, J. John^{1,2}, X. Zhang³, J. Zhang^{3,4}, J. A. Loeb² and Y. Xu^{1*}

¹Electrical & Computer Engineering, Wayne State University, Detroit, MI

²Neurology and the Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI

³Department of Otolaryngology, Wayne State University, Detroit, MI

⁴Department of Communication Sciences & Disorders, Wayne State University, Detroit, MI

ABSTRACT

This paper reports a novel neural probe technology that enables the manufacture of 3D arrays of electrodes and the integration of microchannels simultaneously. This new technology is based on a silicon island structure and a simple folding procedure. This method simplifies the assembly or packaging process of 3D neural probes, leading to higher yield and lower cost. Prototypes with 3D arrays of electrodes have been successfully developed. Preliminary animal tests have been carried out to verify the recording capability of the developed neural probes. Microchannels have been successfully integrated into 3D neural probes as well and the flow characteristic has been preliminarily measured.

INTRODUCTION

Neural probes have played critical roles in developing an understanding of the function of neural networks within the brain, and have been implanted in different regions of the brain to study and treat many neural diseases and disorders. A variety of MEMS neural probes have been developed, including the well known Michigan probes and Utah electrodes [1-3].

There is an increasing need for 3D arrays of high-density electrodes because of the 3D nature of the nervous system. The 3D versions of Michigan probes were realized by microassembling multiple planar chips on a silicon platform with the help of vertical and horizontal spacers [4]. 3D neural probes were also constructed by stacking discrete 2D devices [5-6]. Polymer 3D electrode arrays were developed by bending the polymer shanks out of the plane [7-8]. The NeuroProbes consortium of the European Union reported a 3D technology by slotting planar 2D devices into cavities on a silicon backbone [9]. The electrical contact was made using gold clips hanging over the edge of the cavities.

Currently, electrical stimulation is the most common way of activating neurons. However, neural action potentials are more naturally triggered by the neurotransmitters released from presynaptic neurons. Neurotransmitters may be excitatory or inhibitory in postsynaptic neurons. On the contrary, electrical stimulation only excites the neurons it directly stimulates. There are also other problems associated with pure electrical stimulation. For example, electrical stimulation usually has wide spatial spread, leading to poor spatial resolution. The currents required to depolarize neurons are fairly large, which may cause degradation of metal electrodes and dissociation of water. These electrochemical reactions pose a serious risk of device failure and neuron damage. Many of these limitations could be overcome or circumvented by using more naturalistic chemical stimulation based on neurotransmitters.

Furthermore, it is widely recognized that tissue inflammation, biofouling, encapsulation, or death of neuron cells caused by the implanted neural probes are major obstacles for successful chronic implantation. One potential approach to address this problem is to deliver drugs to implantation sites using integrated microchannels [10-11]. Therefore, it is highly desirable to integrate microfluidic

channels with neural probes to deliver substances that reduce and even prevent the inflammation and biofouling associated with probe implantation.

There have been many efforts to integrate microchannels with electrodes. Solid state channels have been integrated with neural probes using anisotropic silicon etching, boron etch stop, and thermal oxidation/Low pressure chemical vapor deposition (LPCVD) sealing [12]. The integration of microfluidic channels with electrodes using wafer-bonding method has been reported [9]. K.I. Koo *et al.* presented single-unit neural probe containing in-plane shanks with buried microchannels [13]. A method of fabricating multielectrode arrays with integrated fluidic channels using silicon-on-insulator (SOI) wafers has also been developed [14]. However, it is very challenging to integrate channels into 3D arrays of electrodes.

In this paper, we demonstrated a novel technology of developing 3D neural probes based on a silicon island structure and a simple folding procedure. This technology brings several highly desirable features. First, it provides a simple and reliable method to fabricate and assemble high-density 3D arrays of electrodes. Second, this technology enables the integration of microchannels for chemical stimulation or local drug delivery to reduce tissue response. In addition, this technology allows the easy incorporation of a flexible cable between probe shanks and the interfacing die, which leads to very low-profile implants and helps to reduce the movement between brain tissue and probes [15]. These important features will make the developed devices a valuable tool for various neural prostheses and neural disorder studies/treatments.

DESIGN

The new neural probe technology is schematically illustrated in Fig.1. First, planar devices consisting of multiple silicon islands are fabricated on a Si wafer using conventional MEMS technology and a flexible skin process [16]. In Fig. 1, the top two silicon islands are actually 2D neural probe devices, each of which carries a 2D electrode array and drug delivery ports. The electrodes and microchannels on different islands can be accessed by the bonding pads and inlet ports on the bottom silicon island. These silicon islands are connected by a parylene C layer, in which metal interconnects and microchannels are embedded. Parylene C is widely used for implantable devices due to its good biocompatibility. The planar devices are assembled into 3D probes by folding the two islands on top of each other. A spacer is inserted between these two silicon islands to adjust the distance between two rows of probes, as shown in Fig.1 (b). Compared with the stacking method utilizing discrete electrode arrays, the major difference here is the built-in interconnects between the 2D devices. Here we just show the folding of two silicon islands (which results in a 2×3×2 3D array of electrodes) for simplicity. More islands or denser electrodes can be integrated to make 3D arrays with larger dimensions. It is also worth noting that drug

reservoirs and micropumps can be integrated for on-chip drug delivery or chemical stimulation.

Figure 1: (a) Schematic of the planar device consisting of multiple silicon islands before folding. (b) the assembled 3D neural probe with a $2 \times 3 \times 2$ array of electrodes (2 silicon islands, 3 shanks per island and 2 electrodes per shank) and integrated microchannels.

FABRICATION PROCESS

The fabrication of the neural probe started with one double-side polished silicon wafer. First, a 200 nm SiO_2 layer was grown using thermal oxidation, and then a 20 nm Cr thin film and a 200 nm Au thin films were sequentially deposited using E-beam evaporation. These two metal layers were then patterned to form electrical recording/stimulating sites, interconnects and bonding pads. The exposed SiO_2 was subsequently removed by buffered HF (BHF). A 2 μm thick parylene layer was deposited and patterned to open the access areas for the microchannels (including inlet ports and outlet ports). XeF_2 , an isotropic gas phase silicon etchant, was then used to form trenches with semi-sphere cross sections in the silicon substrate. The parylene microchannels were formed and sealed in the next step by depositing another layer of parylene with a thickness greater than the half width of the opening. The parylene deposition is a very conformal process. Therefore, this parylene layer was able to deposit on the inside surfaces of the trench, forming the bottom and side walls of the parylene channels (Fig.2(c)). This parylene layer, together with the first one, was then patterned with a thick photoresist (AZ4620) mask. Next, DRIE was carried out from the front side of the Si wafer without stripping the photoresist mask. This etching was carried out to shape the outline of the probes and stops after the etching depth was about 150 μm (Fig.2(d)). Next, DRIE etching was carried out on the backside of the wafer to release the silicon

islands and probe shanks. Due to the different etching depths of silicon islands and probe shanks, this DRIE etching was carried out using two masks. Note that the probes with only electrodes were fabricated by simply eliminating the microchannel processes, i.e., XeF_2 etching and parylene refilling.

Figure 2: Simplified fabrication process of neural probes with integrated microchannels: (a) grow a thermal oxide layer; evaporate/pattern Au/Cr; (b) deposit and pattern a 2 μm thick parylene C layer; etch with XeF_2 ; (c) deposit the 2nd parylene C layer to seal the channel; (d) pattern parylene and continue with DRIE; (e) DRIE from back side to release the silicon islands and shanks. Left column: cross sectional view of silicon islands. Right column: cross sectional view of one probe shank.

RESULTS AND TEST

Neural probes with different parameters have been designed and fabricated. Fig. 3(a) shows a photograph of one fabricated planar device with two shank islands and one interfacing island (with bonding pads). The fabricated probe shanks are 2800 μm long, 100 μm wide and 150 μm thick. The open electrode area is $40 \times 40 \mu\text{m}^2$. The interfacing die is connected to the shank island with a flexible parylene cable, which leads to low-profile implants and reduction of micro-motion between probes and brain tissues. The assembled 3D neural probe with $2 \times 3 \times 2$ array of electrodes is shown in Fig. 3(b). The folded parylene C layer connecting the Si islands can be clearly observed.

Figure 3: (a) Planar silicon islands structure before folding; (b) One assembled neural probe with $2 \times 3 \times 2$ electrode array (2 silicon islands, 3 shanks per island, and 2 electrodes per shank).

3D neural probes with integrated microchannels have been demonstrated as well. A prototype with a $2 \times 3 \times 2$ 3D array of electrodes and four microchannels is shown in Fig. 4(a). The four

beams on the interfacing die are used to couple external tubing to on-chip microchannels. Figure 4(b) shows an SEM picture of a shank with two electrodes and two microchannel outlet ports. Note that both metal traces and microchannels are embedded in the flexible parylene cables. The SEM image of the backside of a bent parylene cable is shown in Fig. 4(c). The embedded microchannels and metal traces can be observed. No breaks or cracks were observed on the folded microchannels. The cross section of a microchannel is shown in Fig. 4(d). It is clearly seen that the microchannels are sealed completely by the thick parylene.

Figure 4: (a) Photograph of a neural probe device with a $2 \times 3 \times 2$ 3D array of electrodes (2 silicon islands, 3 shanks per island and 2 electrode per shank) and 4 integrated microchannels; (b) SEM image of a probe shank with 2 electrodes and 2 microchannels outlet ports (the inset shows a $5 \mu\text{m} \times 5 \mu\text{m}$ outlet port); (c) SEM image of the backside of a bent parylene cable between two islands; (d) SEM image of the cross section of a parylene microchannel.

The electrode impedance was measured in diluted Phosphate Buffered Saline solution (PBS) with an HP 4284A Precision LCR meter. Pt wire was used as the counter electrode. The results for one electrode with a recording area of $40 \times 40 \mu\text{m}^2$ are plotted in Fig. 5.

The microchannel flow rate was also measured using DI water. A flexible Microbore tubing (with an inner diameter of 620 microns) was coupled to the microchannel and then sealed using epoxy. A programmable syringe pump and digital pressure gauge were used for dispensing liquid and measuring pressure. No leaks were observed on the surface of the microchannels when DI water was pumped into the channel. The flow rate as a function of pressure applied was measured preliminarily and plotted in Fig. 6.

To preliminarily test the functionality of the developed arrays, one prototype has been acutely implanted in the primary auditory cortex of the rat. Figure 7 (a) shows clearly differentiated spikes from two neurons. Using unit sorter software, we were able to separate the spike activity from both neurons (Fig. 7 (b)).

The device was also acutely implanted into the somatosensory cortex of an adult rat. The rat was placed under general anesthesia using pentobarbital after which a craniotomy

was performed to expose the somatosensory cortex. The packaged neural probe device was then placed into the cortex of the animal via a stereotactic frame and the package was fixed in place with methyl methacrylate (dental cement). With the rat still under general anesthesia, the connector of the device package was joined with the connector of our Stellate EEG/ECOG recording system. As shown in Fig. 8, burst suppression-like neural signals associated with pentobarbital anesthesia were identified across all of the working channels, thereby verifying proper placement of the electrodes.

Figure 5: Impedance of one electrode ($40 \times 40 \mu\text{m}^2$) on an assembled 3D neural probe

Figure 6: The measured relationship between flow rate and pressure. The inset picture shows a liquid droplet emerged from the outlet port of the microchannel at the probe tip.

Figure 7: (a) Spikes from two neurons recorded from the primary auditory cortex of a rat. Note the difference in amplitude and spike rate between the two neurons. (b) The spikes from the two neurons were well differentiated using a unit sorter program.

Figure 8: Acute field potential recordings of somatosensory cortex demonstrating burst suppression response associated with pentobarbital anesthesia.

CONCLUSION

A novel neural probe technology based on a silicon island structure and a simple folding process is proposed and successfully demonstrated. This technology simplifies the fabrication and assembly process, leading to high density 3D arrays of electrodes with integrated micro-channels. These microchannels, together with electrodes, enable combined electrical and chemical stimulation, or local drug delivery, opening the door to many new applications. In addition, a flexible cable structure can be readily integrated to make low-profile implants and reduce micro-motion between the implant and tissues, improving the reliability. 3D neural probes with $2 \times 3 \times 2$ electrode arrays and integrated microchannels have been fabricated and characterized. The electrical recording capability of the 3D neural probes has been preliminarily demonstrated by acute animal tests. The flow rate of the microchannel as a function of the pressure has been preliminarily characterized. The proposed neural probes are expected to make significant impacts in various neuroscience research and clinical applications.

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CONTACT

*Y. Xu, tel: +1-313-577-3850; yxu@ece.eng.wayne.edu