AN ULTRA-COMPLIANT, SCALABLE NEURAL PROBE WITH MOLDED BIODISSOLVABLE DELIVERY VEHICLE

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ABSTRACT

This paper describes an ultra-compliant parylene–platinum neural probe embedded in a biodissolvable delivery vehicle. High probe compliance is achieved using thin wires (width of 10.0 μm and thickness of 2.7 μm) and by meandering the probe. The insertion of the ultra-compliant probe is achieved by encasing it in a dissolvable delivery vehicle made from molded carboxy-methylcellulose. *In vivo* implantations of delivery vehicles with 1.5 mm long shanks, widths of 100 μm and 300 μm and a targeted thickness of 135 μm have been done through the dura in the cortex of Sprague-Dawley rats at a speed of 80 mm-s^{-1}. The delivery vehicle becomes a gel over a period of less than three minutes, after which the handling portions of the delivery vehicle are removed leaving the shanks embedded in the brain.

INTRODUCTION

Neural recording stability in high channel count arrays must be achieved by a neural probe technology before it can be translated into the clinical environment for long-term human implantation. However, robust signal stability over a span of decades is far from being realized with existing microfabricated intracortical electrode technologies.

The literature suggests neural tissue recovers from acute injury but has a chronic reactive response to the implanted electrode [1,2]. The chronic tissue response is characterized by neuronal cell death near the probe and glial encapsulation. In turn, this reduces the recorded signal magnitude and increases the electrode impedance. It is hypothesized that the reactive tissue response can be reduced, and possibly eliminated, by reducing relative motion between implanted probes and the neural tissue and by delivering therapeutic bioactive molecules to the tissue around the recording electrode.

State-of-the-Art

Intracortical probes are traditionally made from materials like Si, W and Pt that have elastic moduli of 100's of GPa, compared to brain tissue that has an elastic modulus on the order of 10's of kPa [3,4]. The mechanical mismatch between the neural probe and brain tissue is thought to be one of the causes of chronic reactive tissue response around the probe. More flexible materials such as parylene (Px) (0.25-1 GPa), an excellent biocompatible insulator, have been associated with reduced tissue reaction after implantation compared to traditional stiffer materials [3].

Si-based probes have effective diameters around 100 μm, and single implantable W and Pt microwires have dimensions > 75 μm. Reducing the size of the probe and making it from a more compliant material can attenuate the tissue response; however, this reduces the probe's strength for insertion. Seymour and Kipke [3] overcame this by using a Px "lattice" structure in which electrodes are located on a 4 μm x 5 μm arm placed 100 μm from a stiff shank that provides the mechanical strength for insertion. Chorover and DeLuca [5] dip-coated an 8-wire bundle of 25 μm Pt-Ir microwire electrodes in melted dextrose. The final wire-dextrose bundle was about 800 μm in diameter, which was stiff enough to implant. The dextrose dissolved after implantation, leaving only the fine wires in the brain. Lewitus et al. [6] revisited this method and dip-coated single 70 μm thick Pt-Ir wires in a tyrosine-derived polymer to a final insertion diameter of 200 μm.

Each of these innovations enable implantation of smaller more flexible probes, however they are still met with limitations. The microwires are not small enough to avoid the foreign body response (<20 μm) and result in very large volumes when scaled to hundreds of channels. Although the lattice concept achieves the dimensional goal and is scalable, the lattice is tethered by fixed beams to a large, stiff structure in the brain. Thus, considerable relative motion between electrode and tissue is expected.

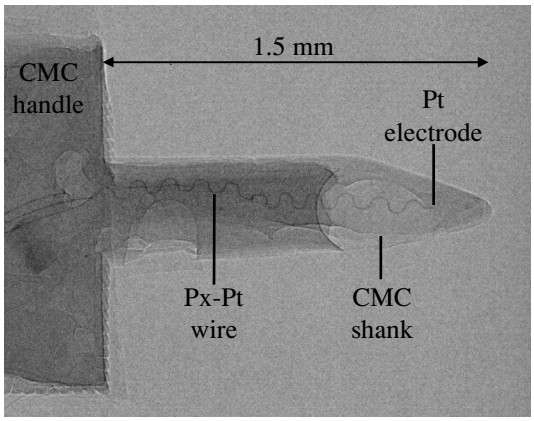

Figure 1: Micro coherence tomography image of a molded CMC delivery vehicle with embedded Px-Pt neural probe.

In contrast, this paper introduces an innovative device design (see Fig. 1) and a fabrication technology to increase neural probe compliance while retaining channel-count scalability. The high compliance is attained by shrinking the probe to the micron-scale (0.5 μm by 4 μm cross-section Pt wire that is insulated by a 1.1 μm thick conformal coating of Px for insulation) and by meandering the probe. To enable insertion of this low-stiffness probe into neural tissue, a stiff delivery vehicle that encases the probe is fabricated from biodissolvable carboxy-methylcellulose (CMC). After implantation, the delivery vehicle absorbs moisture from both the neural

tissue and an applied saline rinse to soften into a gel within a few minutes. Additionally, therapeutic agents can be added to the CMC delivery vehicle to further improve tissue recovery and long-term health [7].

IMPLANT DESIGN

Ultra-compliant Probe

The Px-Pt probe is a meander made of circular arcs of finite width (a two-period section is shown in Fig. 2) with an exposed Pt electrode at its tip. The meander is characterized by its amplitude a_m, the radius r_m of the center line of the arc, its width w_m and its period p_m. The circular arcs each subtend an angle θ_m. Finite element analysis shows the use of circular arcs results in the smoothest stress distribution. By modifying the characteristic parameters, meanders of different compliance are formed.

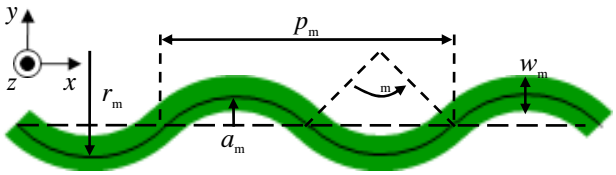

Figure 2: Plan view of a section of ultra-compliant probe with characteristic dimensions.

Delivery Vehicle

The shank of the CMC delivery vehicle shown in Fig. 3 is characterized by its length l_s, width w_s, tip radius r_{st}, tip angle θ_{st}, base angle θ_{sb} and the radius r_{sf} of the fillet at the base of the shank where it connects to the handle. The base angle can have a positive or negative value. In Fig. 3, θ_{sb} is shown in its negative sense. The handling tab dimensions are dependent on the application and the handling requirements of the surgical implantation. The thickness of the delivery vehicle is t_s.

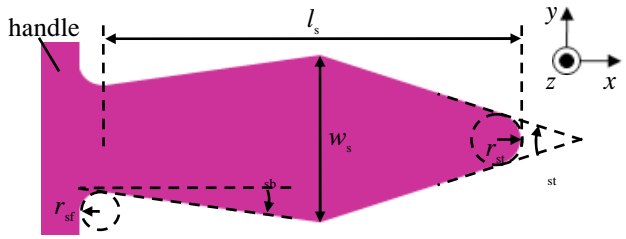

Figure 3: Plan view schematic of the shank of the CMC delivery vehicle with characteristic dimensions.

PROBE FABRICATION

The fabrication process flow to produce a delivery vehicle with 135 µm micron thickness is shown in schematic cross-section in Fig. 4. Some unit processes are omitted from the figure. The flow consists of three modules: (1) formation of the meandering probe wire suspended over a lower CMC mold etch pit (Fig. 4(a) - 4(c)); (2) fabrication of an open polyvinyl siloxane (PVS) CMC upper mold and its attachment to the lower mold (Fig. 4(d) - 4(f)); and (3) molding of the CMC delivery vehicle and removal of the completed device from the molds (Fig. 4(g) - 4(i)).

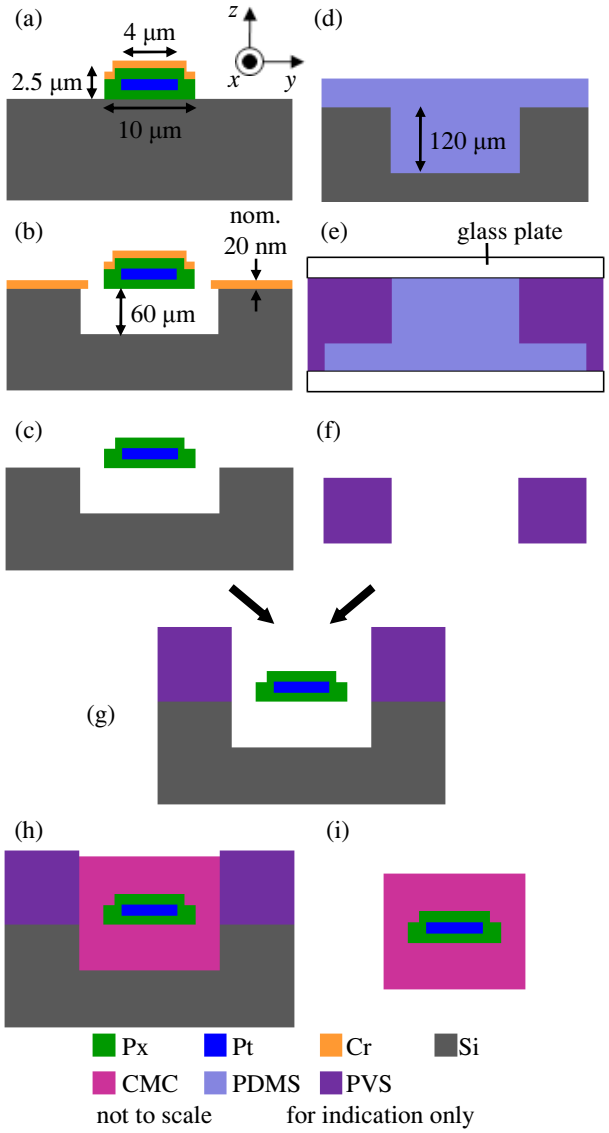

Figure 4: Cross-sectional schematics of the ultra-compliant neural probe and biodissolvable delivery vehicle fabrication process flow. (a) Px-Pt wire patterning using a Cr-resist etch mask. (b) Bottom CMC mold formation by combination Si-DRIE and isotropic etching with Cr-resist mask. (c) Px-Pt wire suspended over Si etch pit. (d) PDMS intermediate mold formation using Si mold master. (e) PVS top mold formation using sandwich technique. (f) Demolded and trimmed PVS top mold. (g) Mounting of PVS top mold on wired bottom Si mold. (h) CMC molding. (i) Demolding of CMC delivery vehicle with embedded meandering Px-Pt wire.

Wire Formation

The Px-Pt probe is made at the wafer level using standard batch microfabrication techniques. 1.1 µm of Px is deposited on a clean Si surface as the lower insulation layer of the probe. 0.5 µm Pt is deposited on top of the Px and patterned by ion milling with a photoresist mask. 1.1 µm of Px is deposited on top of the patterned Pt following photoresist strip and clean. An approximately 20 nm Cr film is deposited on the Px surface and the probe pattern is transferred into it. The Cr film prevents damage to the Px layer that was observed during Px

etching in a Trion Phantom II RIE O_2 plasma that is used to pattern the meandering probe and the output cable (Fig. 4(a)). The photoresist used to pattern the Cr remains on the wafer during Px etching.

Mold Formation

The mold is formed in two parts for wired delivery vehicles. Following probe patterning and mask removal, a second nominally 20 nm Cr film is deposited and the bottom mold pattern is transferred into it. Si DRIE on an STS-ASE ICP etcher is used to etch the exposed Si to a depth of 40 µm and an isotropic Si etch on the same equipment is used to etch the Si under the probe to a final depth of 60 µm and release the probe from the substrate (Fig. 4(b)). Residual organics are removed from the surface of the wafer and the Cr is removed (Fig. 4(c)). 6 µm wide tethers from the probe to the Si substrate suspend the probe over the etch pit. SEMs of the suspended meandering wire are shown in Fig. 5.

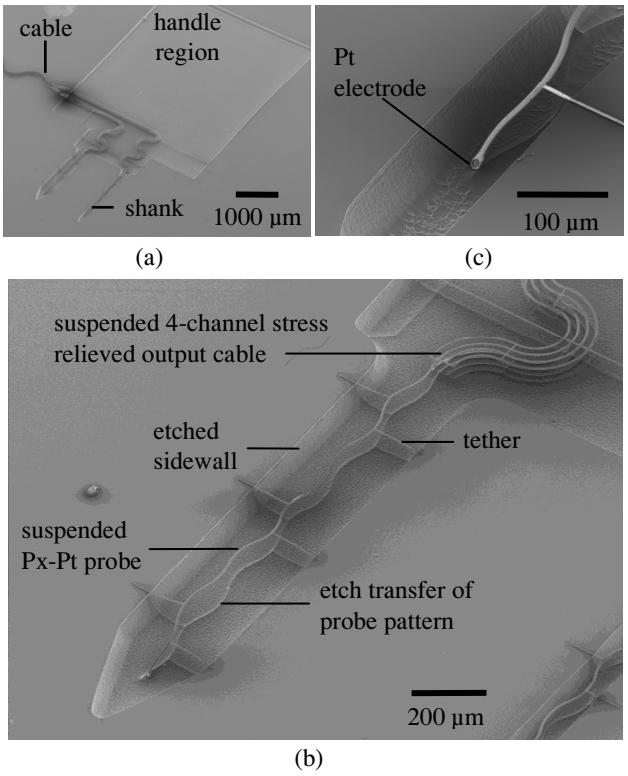

Figure 5: SEM images of the meandering Px-Pt probe suspended over the Si DRIE etch pit. (a) Low magnification view showing bottom molds for 300 µm and 100 µm wide shanks, the handle region and the cable. (b) Suspended meandering wire. (c) Exposed Pt electrode.

The top polyvinyl siloxane (PVS) mold is formed using what we refer to as the "sandwich" technique. Aspect ratio dependent etch modulated (ARDEM) Si processing with a photoresist mask [8] is used to create a Si mold master with a mirror image of the CMC bottom mold. The Si mold master is cleaned and coated with DRIE polymer as a release layer. Sylgard® 184 from Dow-Corning is used to make a compliant intermediate mold (Fig. 4(d)). The intermediate mold is sandwiched between two plates of glass and PVS is flowed into the space between the glass plate and the PDMS intermediate mold (Fig. 4(e)). After curing, the glass plates are removed and the PVS top mold is peeled from the PDMS and trimmed to shape (Fig. 4(f)).

For non-wired CMC delivery vehicles made for histological testing, a single Si mold is used. The bottom mold pattern is transferred to a Si wafer using ARDEM Si processing. The Si is etched to a depth of 180 µm. Following etch, DRIE polymers and residual photoresist are removed from the surface. The molds are then recoated with DRIE polymer as a release layer.

Probe Molding

The PVS top mold is mounted to the wired bottom mold using a Laurier M9A device bonder (Fig. 4(g)). A CMC gel is prepared by mixing CMC powder with water to obtain a 20 wt% solid-to-water ratio. The gel is applied to the assembled molds (Fig. 4(h)) and centrifuged for 6 hrs to completely dry the CMC gel into solid. For non-wired probes, CMC gel is applied directly to the Si mold. Probes are manually demolded after drying (Fig. 4(i)). Optical microscope images of a dual-shank non-wired CMC delivery vehicle are shown in Fig. 6. After demolding, each delivery vehicle is measured for shank length and total length.

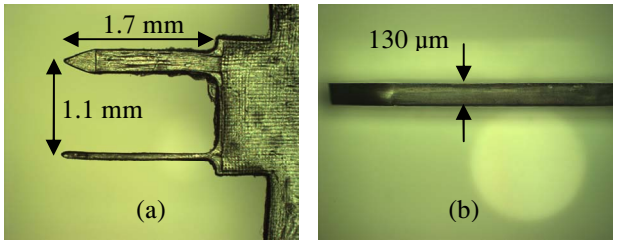

Figure 6: Optical microscope images showing (a) a plan view of a dual shank delivery vehicle and (b) a side view of a single shank.

IN VIVO IMPLANTATION

Implantation Preparation

After removal from the mold, CMC delivery vehicles exhibit stressed-induced curling which must be eliminated for successful implantation. The probes must also be sterilized to reduce the risk of infection in the test subject. To sterilize the delivery vehicles, they are heated to 120° C for 30 mins. By applying pressure to the delivery vehicles during sterilization, plastic changes are induced in the CMC so probe sterilization and flattening are achieved in parallel. A stainless steel "clam shell" jig was devised for this procedure. Delivery vehicles are placed in recesses in the jig and a lid is fastened on top of them. The jig is placed in an oven for sterilization and allowed to cool prior to releasing the pressure and removing the delivery vehicles for implantation.

Implantation Procedure

Adult male Sprague–Dawley rats (Charles River Laboratories) weighing 300–350 g were prepared for cortical implants using previously established methods [9] approved by the University of Pittsburgh, Division of Laboratory Animal Resources and Institutional Animal Care and Use Committee in accordance with the standards for humane animal care as set by the Animal Welfare Act

and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Animals are anesthetized with 5% isoflurane and oxygen. After induction, isoflurane is reduced to 2%. The animal is placed into a stereotaxic frame and a 2 mm by 2 mm craniotomy is made over the primary motor cortex.

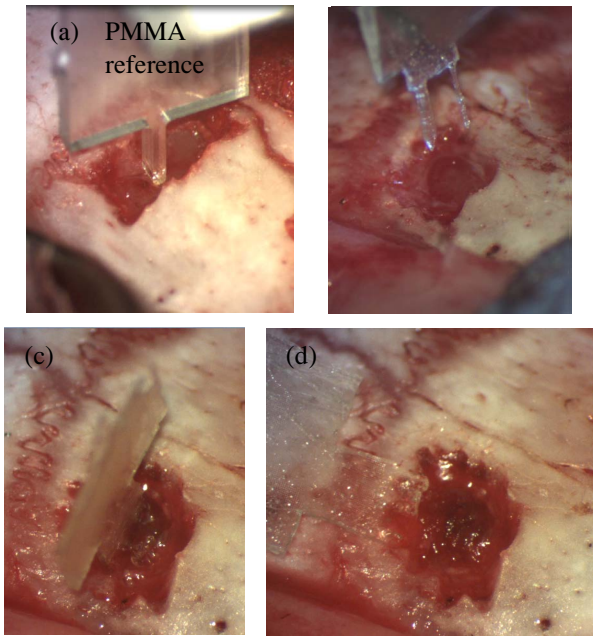

Figure 7: Frame grabs of delivery vehicle implantation. (a) Identification of the brain reference level. (b) Final targeting of CMC delivery vehicle implantation site. (c) Implanted CMC delivery vehicle. (d) Gelled CMC handling tab folded over onto the surface of the skull.

Using a stereotaxic manipulator the brain reference level is identified using a PMMA reference probe of known dimension. The dummy probe is held with a pneumatic clamp mounted on a M272piezomotor (Physik Instrumente, Germany) attached to the stereotaxic manipulator and is brought into contact with the dura on the surface of the brain (see Fig. 7 (a)). The CMC delivery vehicle is then mounted in the clamp, final targeting is performed (see Fig. 7(b)), and the delivery vehicle is implanted through the dura at 80 mm-s^{-1} (see Fig. 7 (c)). Following implantation, the CMC absorbs moisture from the brain tissue and turns to gel. Over time, the CMC handling tab folds over onto the surface of the skull (see Fig. 7 (d)). A saline rinse further softens the CMC so the handling regions of the delivery vehicle can be removed with forceps without disturbing the implanted shanks.

IMPACT AND OUTLOOK

The ultra-compliant neural probe with biodissolvable delivery vehicle presented in this paper provides control of the geometry of the delivery vehicle so it can be optimized for insertion and minimal tissue damage. The shape of the probe can be controlled so its compliance is better matched to neural tissue than existing intracortical probes. The shape of the probe allows multiple electrodes to be carried in a single shank of the delivery vehicle. These features offer the possibility of a scalable neural probe technology that would avoid chronic reactive tissue responses that degrade signal stability of current neural probe technologies. A histological study currently underway comparing the long-term tissue response of non-wired and wired delivery vehicles with the tissue response to control microwires will determine the ultimate fate of the delivery vehicle and verify whether these micron-scale, ultracompliant probes outperform the conventional devices in minimizing tissue reaction and improving recording quality and longevity.

ACKNOWLEDGEMENTS

We thank Chris Bowman and his staff in the Carnegie Mellon Nanofab for their equipment support and Xia Li and Kasey Catt of the U. Pitt Cui Lab for their support of the *in vivo* probe implantations. This material is based on work supported by SPAWAR and the DARPA RE-NET program under award N66001-11-1-4025. Any opinions, findings, and conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of SPAWAR or DARPA.

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