Fabrication of drug delivery system with piezoelectric micropump for neural probe

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Abstract: This paper describes a microelectromechanical systems (MEMS) micromachined drug delivery system with micropump and microchannel for neural probe capable of selectively delivering chemicals as well as electrically recording. The neural probe is developed to support research in neurophysiology. For the realization of chemical stimulating at controlled release rate, the micropump and fluidic microchannel are integrated. The micropump is a peristaltic type with diffuser/nozzle elements actuated by the piezoelectric force. The process for the neural probe are performed with one silicon wafer. The structure of neural probe, microchannel and chamber of micropump are defined by silicon deep etch process. The membrane of micropump and dielectric passivation layer is fabricated by polydimethylsiloxane (PDMS).

1. Introduction

The research using electrode for recording neural activities and neural electrical stimulation is important to understand nervous system. The importance of electrode is exemplified by the fact that electrode find application in almost every aspect of biomedical and neuroscientific instrumentation. Formerly, glass micropipettes and wire electrodes were widely used for recording, but provided relatively little information. The microelectromechanical systems (MEMS) micromachined microelectrode for use in the neurosciences and neural prostheses provides both recording and stimulation from intact neurons.

The microsystem technologies facilitate device miniaturization, thus microelectrodes allow precise control of the location and minimize the damage at the penetration site. The MEMS microelectrode is capable of having integrated metal electrodes with high density and customized design and being batch fabricated reproducibly. Therefore micromachined neural probes have recently emerged for recording and stimulation at nervous system.

However, in order to obtain a better understanding of neural activities, it is necessary to deliver drugs to neural tissue in precise quantities while recording the neural signals. Adding microfluidic channels to microelectrode opens new fields in neuroscience, and it enables local delivery of small amounts of drugs to the tissue and to find out the drug's influence on the electrophysiological activity by neural recording simultaneously. The neural probe, which is able to chemically stimulate as well as electrically stimulate and record, is useful in neurosciences, neural prostheses and drug development. The integration of a fluidic channel into the neural probe permits highly localized injection of neurotransmitters or other drugs. This added functionality allows many applications.

Therefore MEMS neural probe with microelectrode which is able to electrically record and stimulate needs integration of drug delivery system with microchannel and micropump. This embedded drug delivery system extends the functionality of neural probe. The neural probes with microelectrode and microchannel were presented by some researchers [1-4], but a neural probe with drug delivery system including micropump has not been developed.

This paper describes the development of a MEMS micromachined neural probe with drug delivery system including piezoelectric micropump, which is able to experiment of chemical stimulation, electrical stimulation and recording on animal conveniently without external syringe pump.

2. Design

2. 1 Device Structure

The neural probe is designed to deliver a drug into the targeted region of an animal brain and to record neural activities induced by the drug stimulus. The neural probe includes a thick body part and a thin shank part. Figure 1 shows the structure of the neural probe. There are metal microelectrode sites for recording and electrical stimulation, microchannel and fluid outlets for chemical stimulation in a shank part. And there are a reservoir, metal pads and micropump for precise chemical delivery in a body part.

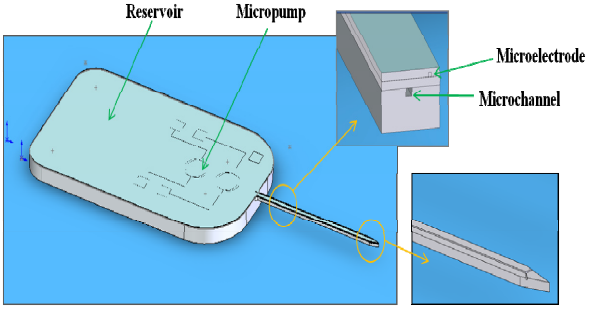


Fig.1. Neural probe with micropump and microchannel

The shape of the shank is straight, sharp and rigid for easy penetrating the cortex tissue without any fracture of the shank. The length, the thickness, and the width at the shank are 6 mm, 100 μm, and 200 μm, respectively. And the body is 500 μm thick.

2. 2 Device Description

Figure 2 shows the schematic of the neural probe with drug delivery system including micropump.

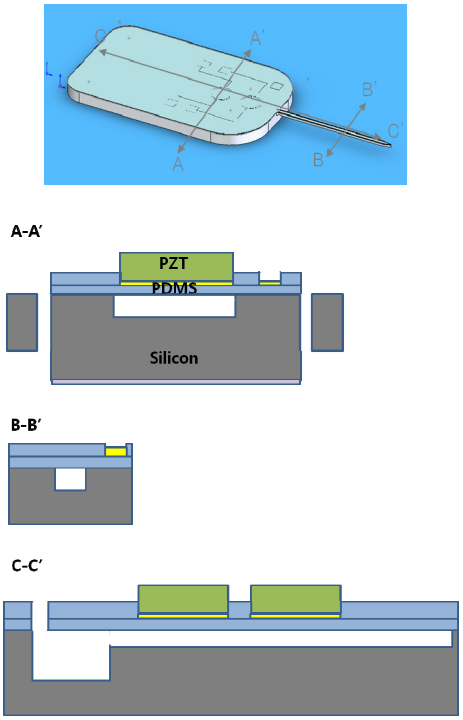


Fig.2. The schematic of the proposed neural probe (not to scale)

The micropump is an important component for desired flow rate and pressure. A bulk PZT actuated, peristaltic micropump is designed for low voltage actuation, fast response, high pressure and precise flow rate control. And diffuser/nozzle geometry is adopted for bidirectional characteristic. Various micropumps have been presented in the last decade. Different actuation methods have been introduced to develop micropumps such as piezoelectrics, shape memory alloys, electrostatics, magnetic, pneumatic, and thermal actuation. Nevertheless, piezoelectric actuation is promising because of simple structure and high actuation strength at low actuation voltage [5]. The peristaltic micropump is based on the peristaltic motion of the pump chambers connected in series, which squeeze the fluid into the desired direction. The efficiency of the micropump with two chambers driven by 2-phase actuation sequence can be increased better than that with single chamber. The valveless micropump had been presented to overcome problems induced by valves, sensitivity to the bubbles or small particles and the pressure drop at the valves. The diffuser/nozzle system has no moving part, and efficient bidirectional characteristic [6].

3. Fabrication

3. 1 Material

The neural probe is bulk-micromachined using one silicon wafer, and compatible to integrated circuit process. A thickness of the shank and a depth of the microchannel and micropump chamber are defined by silicon deep etch process.

The processes for the neural probe are performed with only one double-polished silicon wafer. The microchannel and the chamber of micropump in the neural probe are fabricated using deep silicon dry etching process. The polydimethylsiloxane (PDMS, Dow Corning Sylgard 184 silicone) is used as dielectric passivation material and membrane of micropump. A fluid reservoir, a handling body, and a shank of the neural probe structure is defined and released by the process of deep silicon dry etch on both side of the wafer. Detailed processes are described in figure 3, in which left figures show the process flow for the cross section A-A' in figure 2, and right figures show the process flow for the cross section B-B' in figure 2.

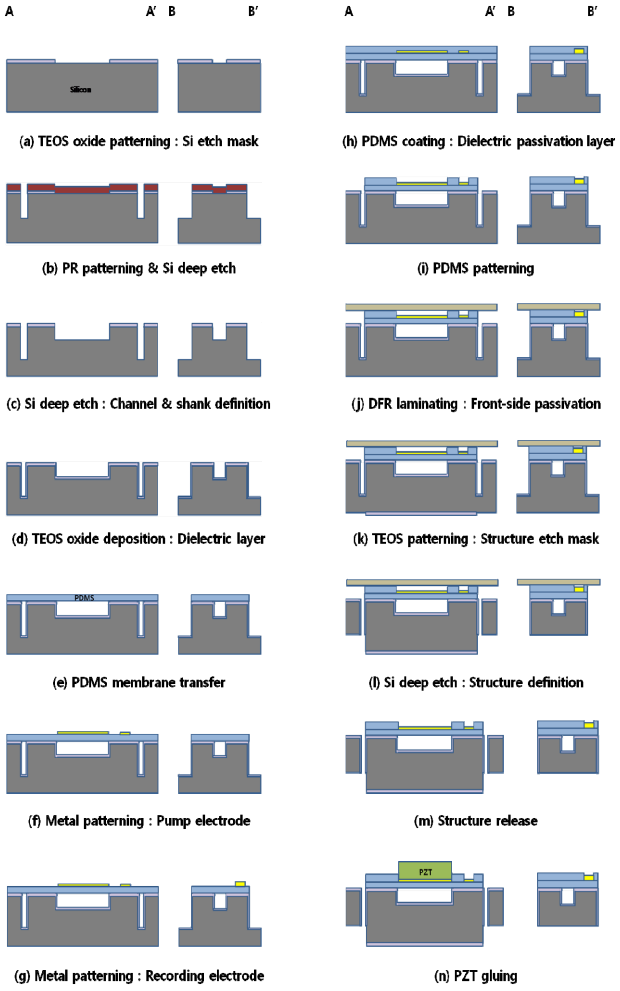


Fig.3. Fabrication process of neural probe

The usage of polymer materials in MEMS devices has increased considerably because polymers are more flexible, resistant, biocompatible, cheaper, and easier to process [4]. The membrane of micropump is made of PDMS elastomer, since it is flexible and robust. The micropump with PDMS membrane has larger deflection than that with silicon or glass membrane. Since the neural probe can be used as neural interfaces between biological organs, biocompatible polymer materials are often employed for the materials of neural probes.

3. 2 Fabrication process

The depth of microchannel and thickness of shank is defined by dry etch using TEOS (Tetra Ethyl Ortho Silicate) silicon dioxide film etch mask. The depth of the microchannel is 20 μm, and the thickness of the shank is 100 μm. TEOS with 0.5 μm and AZ4620 photoresist with 6 μm are used as etch mask, and removed using photoresist stripper, asher and 10:1 HF solution.

The PDMS membrane is fabricated using transfer method. The PDMS membrane is formed on another dummy silicon wafer and transferred onto the main silicon wafer. Liquid PDMS base and curing agent are mixed together with 10:1 weight ratio and pumped in an evacuated chamber for 30 minutes to remove air bubbles. Then the liquid PDMS mixture is spin-coated with 10 μm thickness and cured on hotplate at 75 ℃ for 30 minutes. To peel off PDMS membrane easily, the dummy wafer is coated by trichlorosilane using evaporation method in advance. The PDMS membrane is transferred by PDMS-silicon bonding using oxygen plasma treatment.

The metal layers are deposited with a thermal evaporator and patterned by wet etch. The titanium film is deposited after the oxygen plasma treatment of PDMS membrane for the adhesion. The evaporation process is at the temperature with 30℃ for thermal coefficient of expansion. The gold film is an electrode material for recording sites, bonding pads, and interconnection lines. The metal layers are patterned by AZ1512 photoresist and etched in wet etch solutions.

The metal lines and the microelectrodes are passivated with PDMS layer. The PDMS film is spin-coated with 10 μm thickness and cured. Triple-layer dielectric films with silicon dioxide/silicon nitride/silicon dioxide are used by some researchers, but biocompatible polymer films are better when considering chronic applications. The PDMS film is patterned by reactive ion etching with 3:1 CF_4/O_2 gas [7], power of 200 W, and pressure of 50 mTorr.

The neural probes are tethered to the silicon substrate in order to prevent the neural probes from floating away. A final structure of neural probe is defined and released from silicon substrate by silicon deep etch on back side of the wafer. The thickness of the handling body is 500 μm with the same thickness as the silicon wafer. The silicon dioxide hard mask on the back side is used as etch mask. The front side of the wafer is passivated by dry film resist during deep etch process.

PZT disks are then attached to the membrane using epoxy.

4. Results and Discussion

Figure 4 is a photograph of the silicon wafer in progress, and shows the neural probes. A neural probe is 16 mm long and 7 mm wide. The length of a shank is 6 mm.

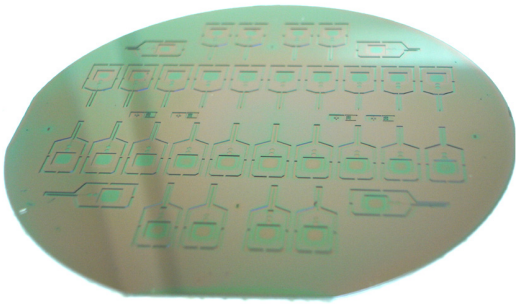


Fig.4. Photograph of the wafer in progress

The diameter of the actuation chamber is 1 mm, and the divergence angle of diffuser/nozzle geometry is 7°. The microchannel starts from the reservoir, and ends at the both sides of the neural probe shank. Figure 5 shows photograph of fabricated chamber of micropump. The microchannel is branched out in two directions as shown in figure 6.

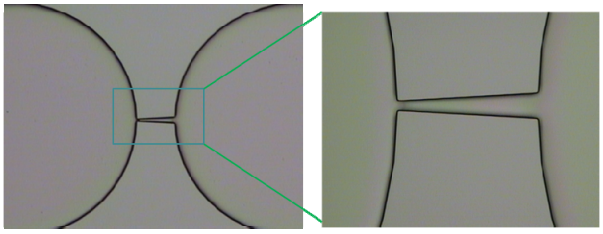


Fig.5. Photographs of fabricated micropump

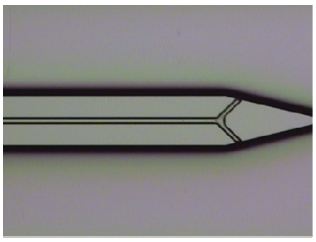
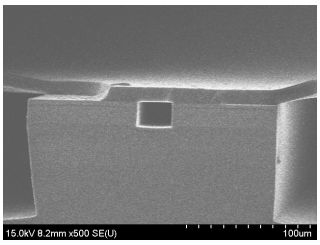
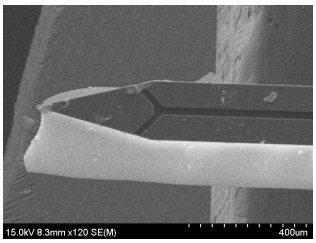


Fig.6. Photographs of fabricated microchannel

Figure 7 shows SEM images of fabricated neural probe. The cross section of shank is shown in figure 7 (a). The depth of microchannel and the thickness of shank are about 20 μm, and 100 μm, respectively as shown. The top view of shank is shown in figure 7 (b). The microchannel is patterned well, but the PDMS layer is disappeared as shown.



(a)



(b)

Fig.7. SEM images of fabricated neural probe
(a) cross-section of shank (b) top view of shank

Figure 8 shows a finally fabricated neural probe with drug delivery system including micropump, microchannel and reservoir. The PDMS films used as the actuation membrane and the passivation layer are damaged. After the transfer process of the PDMS membrane, the thin PDMS layer is damaged during following processes. The transfer process of PDMS membrane with thickness of several tens micrometers is difficult to have good quality, uniformity and throughput. Moreover the dry etch process of PDMS is difficult to get a uniform and good enough etch rate. The processes using PDMS has to be modified.

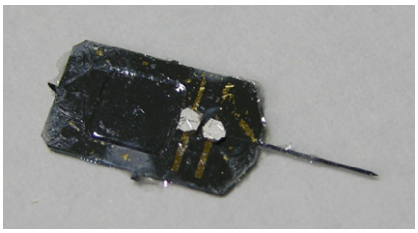


Fig.8. Photograph of fabricated neural probe

5. Conclusions

The addition of drug delivery component for the control of fluid flow within micromachined neural probe has been proposed. The neural probe with piezoelectrically actuated drug delivery system can be useful tool in neuroscience research.

Acknowledgement

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