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Anisotropic etching in (311) Si to fabricate sharp resorbable polymer microneedles carrying neural electrode arrays

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Abstract. Polymer microneedles that get resorbed after insertion in the body have several interesting applications, for example in the insertion of ultra-flexible electrode arrays in neural tissue. In this work, we explore the use of molds created by etching in (311) silicon as a basis for the fabrication of such microneedles. Such molds can be etched anisotropically to much sharper angles compared to standard (100) silicon. It is demonstrated that sharp PLGA microneedles can be fabricated using the molds. It is also shown that by simple thermal bonding the fabricated PLGA microneedles can be combined with a ultra-flexible polyimide-based thin-film electrode array.

1. Introduction

Communicating directly with the nervous system by applying and measuring electric pulses is a topic that has inspired scientists ever since the discovery of bioelectricity by Alessandro Galvani in 1791. As progress grew, miniaturized electronics and fine wire electrodes became commonplace in experimental neuroscience. A major step in increasing the resolution of the recordings was the advent of micromachined electrode arrays, often in needle shape, to allow insertion in the brain to areas close to the neuron cell bodies [1]. Currently, neural electrode arrays with integrated electronics are becoming commercially available, but are not widely employed yet in neuroscience.

When the goal of the research is long term (chronic) interfacing, such as for example to steer an advanced prosthetic device, the in vivo lifetime of the implant becomes an important issue. The lifetime is determined by factors such as the degradation of the insulation resistance and the evolution of the electrode impedance [2]. Another factor is the encapsulation of the implant by scar tissue, which increases the distance to the nearest viable neurons and thus limits the available resolution in recording while also hampering stimulation. Minimisation of scar tissue, allowing neural recording implants that last a lifetime, is the main long-term goal of the work presented here.

The formation of the so-called glial scar around a foreign object in the brain is relatively well documented [3][4][5]. Damaged cells and pro-inflammatory factors from damaged blood vessels attract immunoactive cells such as microglia that try to remove the source of the inflammation. The release of pro-inflammatory factors attracts more immune cells and opens the blood-brain barrier, a process of positive feedback. If the source of the inflammation persists nevertheless, astrocyte cells start to form a dense layer around the object, shielding it from the brain. Turner et al. [6] have shown that this process leaves a permanent cavity if the object is removed after 4 weeks or more.

At this point, substantial evidence has been gathered that reducing the mechanical damage exerted by the implant during insertion and during its operation is very important to reduce scar formation. To avoid chronic mechanical irritation caused by movement of the brain parenchyma relatively to the implant, several measures can be taken. Firmly anchoring the implant to the skull should be avoided [7]. Also, the implant should be made compliant enough to move along with the brain by reducing its cross section and using compliant materials [8]. Using ultra-compliant, sub-micrometer thick SU-8 based implants, Lieber et al. have shown recently that it is possible to interweave electrodes and neural tissue without the formation of any scar tissue [9].

However, these results were achieved by injecting these thin, mesh-shaped electrodes in the brain using a fine glass syringe. Another method would be to use a resorbable carrier, which could allow a more precise control of the electrode positions. Several resorbable materials have been reported in literature, including maltose [10], PEG [11], silk [11][12], chitosan[13] and extracellular matrix proteins [14]. In this work, we will investigate the use of short-chained PLGA (Poly Lactic-co-Glycolic Acid), which is a well established material in medical applications such as drug delivery. However, no application related to the delivery of neural electrodes was reported yet.

Moreover, in the field of neural implants, the resorbable materials have been mainly applied using simple dip coating techniques. In other fields, such as microneedles for drug delivery, more advanced approaches based on e.g. microfabricated silicon molds have been investigated already [15][16][17][18][19][20].

In this work, we will use such molds as well, but furthermore improve their sharpness drastically by introducing (311) oriented silicon to the process instead of the common (100) variant. A micromachining process that allows combining lithographically fabricated thin film electrode arrays with needles micromolded in (311) silicon is presented, together with preliminary in vitro measurement results.

2. Fabrication process

2.1. Nonresorbable backbone fabrication

The nonresorbable backbone, containing the electrodes, metal connections and an upper and lower polyimide isolation layer is fabricated using a micromachining processes published earlier [22]. A design was used that features four 12 μm diameter electrodes in a tetrode configuration, in line with two 32 μm diameter electrodes that can serve as reference or as stimulation electrode (Figure 1, upper right).

Four inch silicon wafers are cleaned and a 150 nm thick aluminium layer is deposited as a sacrificial layer (Figure 1, steps 1-2). Then, a polyimide (PI) layer is deposited by spin coating (PI2611, diluted with NMP in a weight ratio of 1:1.6, 3000 rpm), (step3). The layer is partially cured at 200 °C according to our protocol designed to improve insulation lifetime [22]. In a next step, a patterned platinum layer is deposited using lift-off processing and sputter coating (step 4). A second PI layer is then spun on and cured at 350 °C (step 5). After spin coating and patterning a positive photoresist, reactive ion etching (RIE) is then used to pattern the polyimide, defining the outline of the electrode array (step 6). As the RIE stops on the platinum as well as on the aluminium layer, the electrodes and bondpads can be opened in the same etch step. Bonding and release (steps 7 and 8) are discussed in paragraph 2.4.

Figure 1: Steps 1-8: fabrication sequence of non-resorbable backbone and assembly of connector and PLGA microneedle. Top right: electrode layout. Note that needle will get larger than drawn due to underetching of the vertical lines defining the shaft.

2.2. Etching in (311) silicon

It is well known that it is possible to create pyramidal pits in (100) silicon by anisotropic wet etching, which reveals the non-etching (111) planes. However, as the angle between the (111) planes and the surface is 54.7°, if used to create molds for the fabrication of needles this yields rather blunt devices. We therefore decided to investigate anisotropic etching in (311) silicon for this purpose [23][24]. (311) silicon is rarely used, but is still available commercially (Sil'Tronix, France).

The orientation of the intersections of the (111) planes and the (311) wafer surface was calculated to be at an angle of $\pm 16.78^\circ$ from the (110) wafer flat, as well as $\pm 16.78^\circ$ from the line perpendicular to the flat. This is displayed graphically on the top part of figure 2. It can be seen that it is possible to etch cavities with a sharp point oriented towards the right side of the wafer.

The calculated angles were verified in the etch experiment described below. In this experiment, molds were fabricated that were thereafter employed for the fabrication of sharp PLGA microneedles. For this experiment, the mask layout shown on the bottom part of figure 2 was used.

Figure 2, top: (311) wafer with three non-etching (111) planes revealed. $\alpha=16.78^\circ$. $\beta=27.1^\circ$. A fourth non-etching plane exists, at an angle of $-\alpha$ from the line perpendicular to the (110) flat. Bottom: Mask layout for (311) Si etch and mold experiment. Another version with a vertical edge to the left was also included. Note that the horizontal lines will be underetched, resulting in wider needles shafts than designed.

(311) Silicon wafers were cleaned in an ultrasonic bath in DI water, and then in piranha and in 1% HF. To etch the mold in (311) silicon, first a 2 micron thick wet thermal oxide was grown at 1200°C for 6.5 hours.

The results of the anisotropic etch experiments is shown in figure 3. In the first etch experiments, etching was done in 30% KOH at 60°C . KOH was preferred over TMAH as it has reduced toxicity [25], though nevertheless in both cases appropriate safety measures need to be taken to allow handling the chemicals safely. However, this comes at the price of reduced selectivity towards the oxide mask [26]. The non-etching planes were as expected on figure 2. Downward etching proceeded at $0.41\ \mu\text{m}/\text{min}$. Horizontal lines (i.e. parallel with the flat) underetched at a rate of $0.21 - 0.24\ \mu\text{m}/\text{min}$, but in a somewhat rough pattern as is clear from the underetch variation. The sidewalls thus are under a 58.8° angle with the wafer surface. Vertical lines (i.e. perpendicular to the flat) created a profile with a 32.7° angle with the wafer surface. The bottom surface was also quite rough, having a Ra of 100 nm.

In further experiments, a switch was made to 42.5% KOH in order to reduce roughness. This reduced bottom surface roughness to a Ra of 60 nm (figure 3, middle). The downwards etching rate was measured to be 0.31 $\mu\text{m}/\text{min}$ at that concentration.

After stripping the oxide mask, a thin silicon overhang was still visible at the upper edge of the etched pits. This would clearly hinder demolding, and is therefore removed with a short reactive ion etch step (3 minutes at 100W, 90 sccm SF_6 , 10 sccm O_2 , 80 mTorr pressure, 6 inch platen diameter).

Figure 3: Results from etching in (311) silicon. Top left: sharp tipped trench formed out of intersecting (111) planes. Top right: PLGA needle molded by of the trench tip (see section 2.3). Middle: showing the decrease in shank roughness when switching to a higher KOH concentration. Bottom left: showing the undercut of convex right corners (A) and the small angle plane showing near a vertical line (B). Bottom right: needle base defined only using (111) planes, to eliminate underetch and roughness. Note that in these pictures, the wafer flat is located horizontally, above the field of view.

2.3 Molding of microneedles in (311) silicon

Our molding process to fabricate sharp microneedles is summarized in figure 4. Wafers etched in 42.5% KOH as described in section 2.2 were used as molds. To form a sacrificial layer to release the supporting needles, a Ti / Al stack was deposited by sputter coating. (3' Ti sputtering at 300W, 35' Al sputtering at 200W for a layer thickness of 2.2 μm , 3" targets).

PLGA (Purasorb PDLG 5002A) was then melted on the wafer at 130°C and spread using a scraper while the wafer was cooling down on the hotplate. After filling the mold cavities, the assembly was

heated up tot 130 °C once more and a fresh scraper was used to remove excess PLGA. Then, the wafer was mounted on a carrier wafer using wax, and polished from the front side over a series of rotating wet polishing mats, ranging from grid 80 to 1000. This removed all PLGA from the surface, leaving only PLGA in the mold cavities.

In a final step, the needles were released from the mold by submerging in 7.5% HCl overnight. An acidic release step was preferred as the decomposition of PLGA is a reaction that releases lactic acid, and is thus expected to be slowed down in a low pH environment as per Le Chatelier's principle. This was verified experimentally as well: PLGA beads were bathed in HCl for one week and seemed undamaged, while the same beads did dissolve in a 0.1 NaOH solution.

It was possible to use an ultrasonic bath to remove the needles that did not dislodge spontaneously. The wafer could be cleaned with piranha for re-use.

Figure 4: micromolding process. (1) (311) Si wafer. (2) Etching a needle shaped recess. (3) Ti/Al sacrificial layer. (4) PLGA casting and spreading. (5) Polishing (6) Release from mold.

2.4 Assembly of PLGA needle and non-resorbable backbone

The needles were put on the wafer that contained the non-resorbable backbone structures and aligned using a pick-and-placer. They were bonded to the wafer simply by heating the assembly to 70°C for a few minutes. In case of bending up or down by built-in stress, the needles were first put on an aluminium block at 45°C, which caused them to relax and to straighten out. The assembly of the PLGA needles and the non-resorbable backbone was then released from the wafer by immersion in 6% HCl overnight. Figure 5 shows an assembled device, ready for testing.

Figure 5: Result of assembly of PLGA needle and non-resorbable backbone with Pt electrodes and connections

3. Measurements

While the molding process had a very high yield, the bonding process was yield-limiting, reducing the total fabrication process yield to about 25%. As a preliminary in vitro test, two of the fabricated needles were inserted in a fresh rat cadaver brain (figure 6). The insertion was done at a speed of 10 μm/min to a depth of 2 mm, while insertion force was monitored. The needles were 390 μm wide at the bottom, and 190 μm wide at the top. Two silicon needles of similar size were inserted to serve as a reference. The insertion procedure consisted of four phases: a run-up phase in which the needle does not contact any tissue, followed by an insertion phase in which the force increases linearly with time as the needle enters the tissue. The insertion force needed was about 2 times higher for the PLGA needles than for the silicon needles. After the maximum depth was reached, we waited about two minutes during which the built up tension was seen to relax. During retraction of the needles, a considerable difference between the silicon and the PLGA needles was observed: while retracting silicon needles required less or about equal force than required to insert them, retracting the PLGA required 1.5x to 2x more force. A possible explanation is the fact that films of PLGA tend to take up water and swell with a time constant in the range of a few minutes [27].

Figure 6: Force measurements during and after insertion of two PLGA microneedles in rat cadaver brain (green, blue), compared with the insertion of two silicon microneedles (red, black). Insertion speed was $10 \mu\text{m}/\text{sec}$. The insertion phase is marked with A. In phase B, relaxation takes place. During needle retraction (phase C), the PLGA needles seem to stick to the tissue more than the silicon needles.

4. Discussion and conclusion

We have shown that (311) silicon is a suitable material to fabricate molds out for the casting of sharp-tipped microneedles. To our knowledge the prior art closest to this is [28], in which razor-blade shaped molds but no pointy needle shapes are fabricated out of (113) Si. No needle shapes were made, though. The molds were utilized to fabricate sharp resorbable microneedles out of low molecular weight PLGA. It was shown to be possible to release the PLGA needles in good shape using an aluminium sacrificial layer and an acidic etching bath. We have also shown that it is possible to bond the fabricated PLGA needles to electrode arrays that are still attached to a wafer, and to release the assembly without adhesion loss.

The assemblies hold promise to be a suitable insertion vehicle for inserting submicrometer-thick electrode arrays in the brain, of which an in vitro insertion test on a cadaver is a first indication. The insertion speed of PLGA microneedles in the brain can be much slower than when using fast dissolving organic materials such as saccharose. The lower dissolution and slower water absorption makes handling in real-life situations more practical. Still, when retracting the needles after 7-8 minutes, already higher forces are needed which indicates interaction with the tissue is already taking place.

It is likely that other applications may benefit as well from the presented process for molding in (311) Si, an obvious example being drug delivery.

Further fabrication optimisation work should entail the optimisation of the thermal bonding step, which is a bottleneck for the yield of the process. A series of temperatures and pressures could be tested. Larger temperatures and pressures will most probably improve the bonding yield, but could induce more deformation of the PLGA structures. A solution could be to selectively apply pressure to the shafts, but not to the needle tips.

Further characterisation work should also involve electrical characterisation of the electrodes, though standard materials were used that are already well understood. To test the use for the intended application, relatively long term in vivo tests are needed. Only this can lead to a firm conclusion of the suitability of the devices presented here for long term neural recording without substantial scar tissue formation.

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