Mechanical Machining-based Three-Dimensional Electrode Array for Chronic Neural Stimulation

YASUO TERASAWA,*,***, HIROYUKI TASHIRO,**,*** YUKARI NAKANO,* TAKASHI TOKUDA,*** JUN OHTA***

Abstract
Implantable neural stimulators have recently attracted attention because of their potential applicability to the treatment of sensory neural disorders such as hereditary hearing loss and retinitis pigmentosa. However, the requirements for stimulation electrodes tend to be contradictory in some applications that require transmission of complex information to the nervous system, such as cochlear implants and retinal prostheses. They have to be sufficiently small to realize fine interfacing with the nervous system while remaining sufficiently large to inject enough charge to stimulate neurons without causing an irreversible electrochemical reaction. One solution to these requirements is to employ three-dimensional (3D) instead of planar electrodes. However, in conventional photolithography, the available material and size for fabricating electrodes are greatly limited. To overcome these limitations, we propose a novel fabrication process for stimulation electrodes, using mechanical micromachining. Using 3D bullet-shaped electrode increased the surface area by 3.6 times compared to conventional planar electrode with the same diameter. The proposed electrode, which was developed for retinal prostheses, showed sufficient charge injection capacity (CIC) to evoke light perception (phosphenes) for blind patients. Furthermore, the CIC and electrode surface morphology remained stable during a six-month period of current pulsing in phosphate-buffered saline, which suggests suitability for chronic neural stimulation. The cause of the variance in the measured CIC and future applications of the proposed 3D electrodes were also considered.

Keywords: mechanical machining, electrode, charge injection capacity, 3D, surface area.


1. Introduction
Recently, research on neuromodulation devices that artificially modulate neural systems is expanding rapidly. Most of the devices employ electrical stimulation to intervene neural functions. Therefore, the performance of the stimulation electrode is a critical factor for neuromodulation devices. Especially for sensory neuromodulation devices such as cochlear implants [1] and retinal prostheses [2], a large number of electrodes are required to interface with neural tissue in a spatially confined area. For example, in a subretinal prosthesis, 1600 electrodes are arranged in an area of approximately 3.2 × 3.2 mm² [3]. In such applications, the stimulation electrode needs to be minute in size. However, the stimulation electrode also needs to be able to safely inject an electrical charge to excite the target neural tissue. One method to improve the performance is to coat the electrode surface with high-performance materials such as titanium nitride and iridium oxide [4], but such surface coating may delaminate in some cases owing to charge injection [5]. Another method is to employ three-dimensional (3D) instead of planar electrodes. However, in conventional photolithography, the available material and size for fabricating electrodes are greatly limited. Recently, remarkable advances in mechanical machining have been made. Fabricating structures smaller than 100 µm with a precision of less than 1 µm is now easy. The aim of this study was to overcome the limitations of conventional photolithography-based fabrication by developing a novel fabrication process for stimulation electrodes, using mechanical micromachining.

2. Methods
First, bullet-shaped platinum electrodes (Fig. 1[a]) were fabricated from a 1-mm-diameter platinum bar using a turning machine (B007, Tsugami). The diameter and height were 0.5 and 0.5 mm, respectively. An array of 7 × 7 holes was then formed on the surface of an acrylic plate using a machining center (MultiPro, Takashima). The diameter, height, and spacing of these holes were 0.5, 0.5, and 0.2 mm, respectively. Then, Pt–Ir conductive lines were welded to the bullet-shaped electrodes (Fig. 1[b]). The electrodes were then inserted into the holes of the acrylic plate (Fig. 1[c]). After deposition of a 50-µm-thick parylene C [poly(1-monochloro-para-xylylene)] substrate, the acrylic plate was dissolved in an organic solvent.

The electrode performance was evaluated by measuring the charge injection capacity (CIC), which is the maximum injectable charge that does not cause an irreversible electrochemical reaction. The CIC was measured by monitoring the electrode potential during current pulsing using an Ag/AgCl reference electrode, a custom-made stimulator, and an oscilloscope (DL750, Yokogawa). The maximum charge at which the electrode potential exceeded the water window (−0.6 to +0.8 V vs. Ag/AgCl) was recorded. The CIC was then calculated by dividing the maximum...
charge by the surface area of the electrode. The CICs of nine electrodes were evaluated in phosphate-buffered saline (PBS, P4417, Sigma-Aldrich, buffer concentration 0.01 M) at room temperature.

The functionality and long-term stability of the 3D electrode were evaluated by continuously applying current pulses (1.0-mA amplitude, 0.5-ms duration, and 50-Hz cathodic-first charge-balanced biphasic pulses) to two electrodes in PBS at room temperature for six months. The CIC measurement and scanning electron microscopy were performed once a month during the pulsing period.

3. Results

3.1 Fabrication

A 7 × 7 electrode array was successfully fabricated (Fig. 2). The tip and sidewalls of the electrodes were completely exposed by the proposed simple process described in Fig. 1. We found that close matching between the electrode and hole diameters was essential to avoid parylene C from infiltrating the sidewalls of the electrodes during the deposition process. Keeping close contact between the Pt–Ir insulated wires and acrylic plate during parylene C deposition was necessary to integrate the wires and parylene C substrate. The position and number of the electrodes can be modified very easily by reprogramming the machining center to fabricate the required acrylic plate.

3.2 Charge injection capacity (CIC)

The CICs of the nine bullet-shaped electrodes were measured in PBS at room temperature. The mean CIC was 101.2 [µC/cm²] (Table 1), which corresponds to a ~1.5-mA amplitude and 0.5-ms duration current pulse. The measured CIC was consistent with those in previous studies [6, 7].

3.3 Long-term stability

The CIC measurement and scanning electron microscopy were performed once a month during the six-month pulsing period. The measured CIC ranged from 88 to 148 µC/cm². No apparent trend in variation of the CIC was observed during chronic stimulation over the six-month period (Fig. 3). Moreover, no apparent morphological changes both in the platinum electrodes and parylene C substrates were observed under scanning electron microscopy (Fig. 4).

4. Discussion

Semiconductor technologies such as photolithography are conventionally employed to fabricate high-density electrodes [8, 9]. Although this technology allows the fabrication of very fine struc-

![Fig. 1 Fabrication stages of the proposed electrode array. (a) Electrodes were fabricated from a platinum bar using a turning machine. (b) Pt–Ir insulated wires were welded to the electrodes. (c) Electrodes were inserted into the holes of an acrylic plate. (d) After parylene C deposition, the acrylic plate was dissolved in an organic solvent.](image)

![Table 1 Summary of the charge injection capacity (CIC) of the proposed electrodes.](image)

<table>
<thead>
<tr>
<th>Number of electrodes</th>
<th>Mean CIC [µC/cm²]</th>
<th>S.D.</th>
</tr>
</thead>
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<tr>
<td>9</td>
<td>101.2</td>
<td>33.7</td>
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</table>

![Fig. 2 3D 7 × 7 electrode array.](image)

![Fig. 3 Stability of the CIC during chronic pulsing in PBS. The CICs of two electrodes (no. 2 and no. 9) were examined monthly for six months.](image)
During the six-month pulsing period (Fig. 3), this can be par-tially explained by the fact that there were differences in surface area among individual electrodes caused by the fabrication process. In addition, the CIC is affected by the electrode potential before onset of the current pulse (interpulse potential, IPP), which is governed by the oxidation state of platinum, dissolved oxygen level in PBS, and the buffer type and concentration. Controlling these parameters would help lower the variations in the measured CIC. Leung et al. [12] reported a smaller variation in IPP compared to our results. The discrepancy may be explained by several differences between the two studies. One difference is that they measured the CIC only once, while we repeated the measurement once a month for half a year. Another difference is that they used 0.1 M phosphate-buffered saline (PBS) while we used 0.01 M PBS because the 0.1 M buffer seems to have too strong buffer capacity to mimic the physiological environment. A strong buffer would stabilize the pH of PBS, and stable pH results in stable electrode potential according to the Nernst equation [4].

The CIC and the surface morphology exhibited excellent sta-bility for the six-month pulsing period. Although a six-month pe-riod is the standard duration to estimate the long-term perfor-mance of neural prostheses [13], testing over longer periods such as several years is necessary to confirm the long-term perfor-mance.

In this paper, we described the measurement of CIC in phys-iological saline. However, animal studies to assess chronic electric-stimulation is also important to prove the safety of the elec-trical stimulation. We have developed an automated system for chronic stimulation and impedance acquisition [14] and proved the safety of one-month chronic electrical stimulation with 3D porous electrodes [15]. In that chronic stimulation study, we used a single-channel electrode for measuring the electrically evoked potentials (EEP) to confirm the functional preservation of retinal tissue. However, a chronically implantable nine-channel record-ing electrode is being developed in our group [16]. Future study using this electrode would provide more in-depth knowledge on the spatial properties of cortical activation evoked by chronic electrical stimulation to the retina.

Current distribution is important for realizing effective elec-trical stimulation. In our application to retinal prosthesis, the 3D electrodes are implanted in a scleral pocket. Therefore, only the tip of the electrode touches the sclera, and the residual part of the electrode is surrounded by interstitial fluid when the electrode is implanted. It is possible that the majority of the stimulation current dissipates into the interstitial fluid because the impedance of the fluid is lower than that of the sclera. However, a histological evaluation after one-month of implantation showed that the side-wall of the electrode was surrounded by fibrous tissue rather than interstitial fluid [15]. Therefore, the stimulation current is expect-ed to be distributed isotropically in the tissue. Furthermore, we recently added porosity to the tip area of the stimulation elec-trode [15, 17]. This would lower the relative impedance of the electrode tip compared to the sidewall of the electrode. The ma-jority of the electrical current is expected to be distributed near the tip of the electrode.

We developed the 3D electrode for retinal prostheses, but the high performance of the electrode would also improve the device performance of other applications such as spinal cord stimulation [18] and cortical stimulation [19]. Especially in cortical stimulation using non-penetrating electrodes, our 3D electrode would
help realize a higher spatial density.

5. Conclusion

A 3D electrode array was successfully fabricated without employing photolithography. The surface area of the proposed 3D electrode was 3.6 times greater than that of conventional planar electrode with the same diameter. Therefore, we successfully injected a larger charge without enlarging the electrode diameter. Furthermore, the electrodes were stable for at least six months in PBS. In subsequent stage of development, we will evaluate the long-term stability of electrodes with different sizes and surface morphologies.

Conflicts of interest (COI)

Yasuo Terasawa and Yukari Nakano are employees of Nidek Co., Ltd. Hiroyuki Tashiro, Takashi Tokuda, and Jun Ohta received a research grant from Nidek Co., Ltd.

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