Three-dimensional Tip Electrode Array Technology for High Resolution Neuro-Electronic System used in Electrophysiological Experiments *in-vitro*

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Abstract—**A three-dimensional tip electrode array technology for *in-vitro* electrophysiological experiments is presented. Based on simulation results obtained with a finite element model of the neuron-electrode interface, it has been shown that the electrical coupling between the neural cells and the three-dimensional tip electrode array is improved compared to standard planar electrodes. Consequently, three-dimensional microelectrode arrays (3D-MEAs) exhibiting a higher spatial resolution than classical integrated MEA systems have been manufactured using the proposed fabrication process. Three-dimensional tip electrode arrays with an electrode diameter of 3-4µm, a height of 1.75µm, and a pitch dimension of 5-6µm have been manufactured on silicon substrate. Future *in-vitro* electrophysiological experiments are expected to confirm the superiority of the three-dimensional electrodes over the planar electrodes.**

Background

The study of neural cellular function and response has been used for decades to better understand the operation of the brain. As technology has improved, neuroscientists have shown increased interest in *in-vitro* experimentation methodology to support advanced studies of the brain and the operation of its constituting neurons. Using MEAs, it is now possible for populations of neural cells to be examined simultaneously, thereby providing better insight into the functionality and interconnectivity of cellular networks [1]. However, due to micro-fabrication and electrical issues, it is still very difficult to fabricate electrode arrays with high spatial resolution [2]. Current MEAs have inter-electrode spacing of 18-200µm [3], [4]. These dimensions are much larger than the 10µm typical size of neuron cells used in electrophysiological experiments.

Here, we discuss a new approach based on 3D tip electrodes in order to increase the electrical coupling between the neural cells and the electrode array. Thus, MEAs with higher spatial resolution can be achieved. Herein we describe the modeling of the neuron-electronic interface and the manufacturing process of the 3D tip electrodes.

Current Results

Arrays of 3D tip electrodes with a base diameter of 2-5µm and a pitch dimension limited to 4-6µm have been considered in order to guarantee that every neuron in the cell culture are lying on the top of several electrodes. Neurons are expected to adapt to the surface topology in one of the two possible schemes depicted in Fig. 1. Cells may lie on the tips of the electrodes where the membrane rigidity prevents any adaptation, as described in Fig. 1(a). In this case, the distance between the electrode tips and the neuron membrane is expected to be reduced compared to planar electrodes, thus enabling an improved electrical coupling as proved in the cell-electrode interface simulations. Alternatively, the cell membrane may attach to the surface and follow its topology, as in Fig. 1(b). In this case, the electrical coupling between an electrode and a neuron is improved due to an increased cell-electrode contact area.

The current flow distribution of a cell with a typical size of 10µm, and adequately lying on top of an electrode has been simulated using COMSOL Multyphysics^{TM}, a finite element method simulation software. In these simulations, an intracellular potential equal to 100mV is applied in order to study the behavior of the dc current in the neuron-electrode environment.

The current flow simulation of a 10µm diameter neural cell with an intracellular potential equal to 100mV lying on top of a 4µm diameter planar electrode is depicted in Fig. 2(a) for a cell-electrode distance equal to 100nm, which corresponds to an average neuron-electrode distance. In Fig. 2(b), the same simulation has been performed using a 1.5µm high and 4µm diameter 3D tip electrode. The distance between the cell and the top of the 3D tip electrode is equal to 20nm, which is an estimation of how close will be the tip electrode from the cell membrane. As shown in Fig. 2(a), a significant amount of the current flowing out of the cell is collected by the planar electrode. However, for the 3D tip electrode, practically all the current is collected by the electrode. Therefore, sensing the membrane current from a neuron is expected to be improved using this type of 3D tip electrode.

The fabrication process for the 3D tip electrode array has also been established. First, a 1.75µm thick layer of SiO_2 is sputtered on top of Pt planar electrodes, as depicted in Fig. 3(a). The thickness of this layer will set the height of the 3D electrodes. Then, as depicted in Fig. 3(b), an isotropic etching in BHF is performed in order to create the 3D tips. The Si_3N_4 layer is used as an etching stop. Metallization of the tip electrodes is conducted in a further step by evaporating a 10nm thick Ti adhesion layer followed by a 100nm thick Pt layer. Finally, a 300nm thick SiO_2 passivation layer is sputtered on the surface of the chip. The final cross-section of the 3D electrode array is depicted in Fig. 3(c).

3D tip electrode arrays with an electrode diameter of 3-4µm, a height of 1.75µm, and a pitch dimension of 5-6µm have been manufactured on silicon substrate, as described in Fig. 4. The minimum tip diameter that has been obtained is around 0.5µm. Future electrophysiological experiments are expected to confirm the superiority of the 3D electrodes in terms of electrical coupling.

References

[1] S. Marom and G. Shahaf, “Development, learning and memory in large random networks of cortical neurons: lessons beyond anatomy,” in *Quartely Reviews of Biophysics*, vol. 35, no.1, pp. 63-87, May 2002.

[2] L. Berdondini *et al.*, “High-density electrode array for imaging in vitro electrophysiological activity,” in *Biosensors and Bioelectronics*, vol. 21, pp. 167-174, Jul. 2005.

[3] U. Frey et al., “An 11k-electrode 126-channel high-density microelectrode array to interact with electrogenic cells,” in *Proc. IEEE ISSCC 2007*, pp. 158-593.

[4] D. A. Wagenaar, R. Madhavan, J. Pine, and S. M. Potter, “Controlling bursting in cortical cultures with closed-loop multi-electrode stimulation,” *Journal of Neuroscience*, vol. 25, no.3, pp. 680-688, Jan. 2005.

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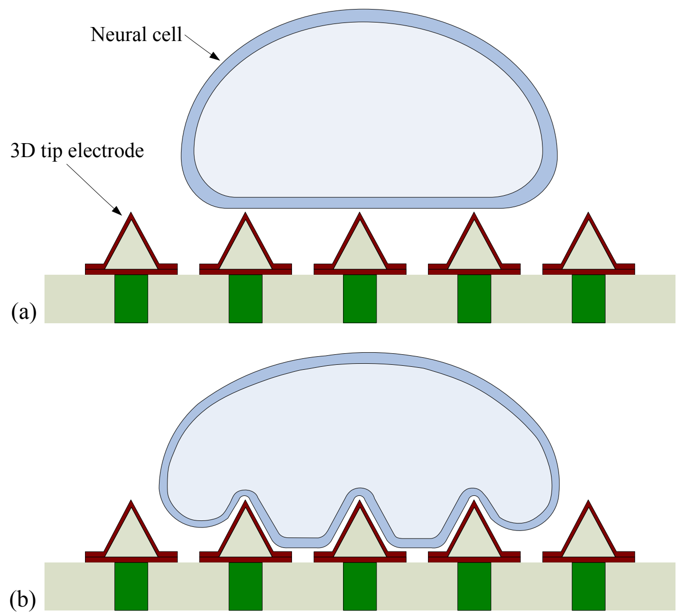

Fig. 1. Conceptual cross-section of a neural cell lying on the tips of a three-dimensional electrode array with (a) the cell lying on the top of the tips and with (b) the attached membrane having the same topology as the surface of the MEA.

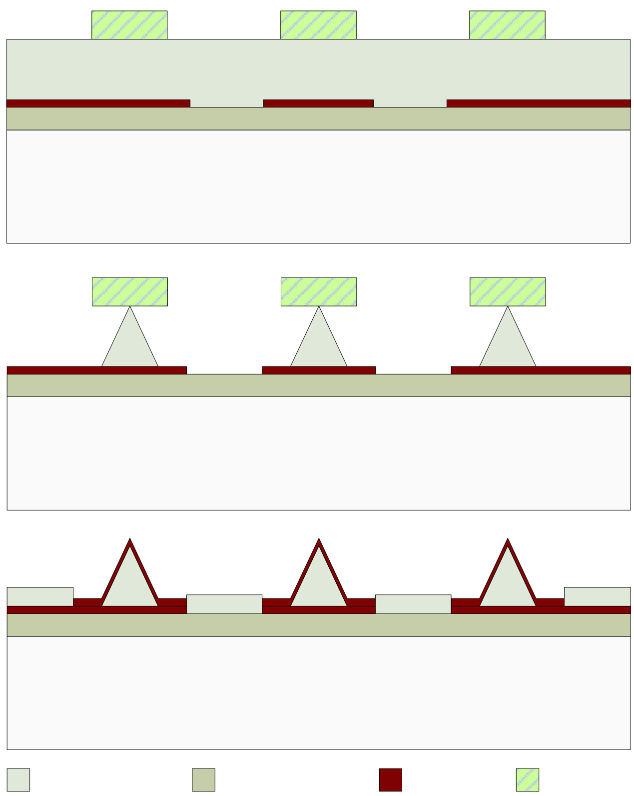

Fig. 3. Schematic view of the cross-section of selected steps of the three-dimensional tip electrodes fabrication process.

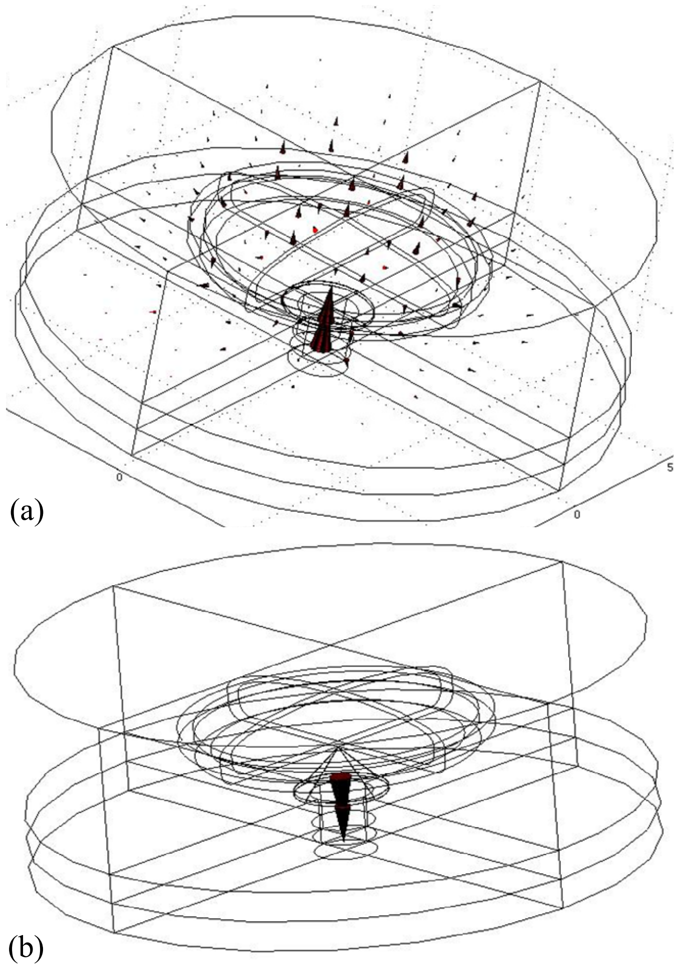

Fig. 2. Current flow simulation of a 10µm diameter neural cell with an intracellular potential equal to 100mV lying on top of (b) a 4µm diameter planar electrode at a cell-electrode distance equal to 100nm and (c) a 1.5µm high and 4mm diameter three-dimensional tip electrode at a cell-tip distance equal to 20nm.

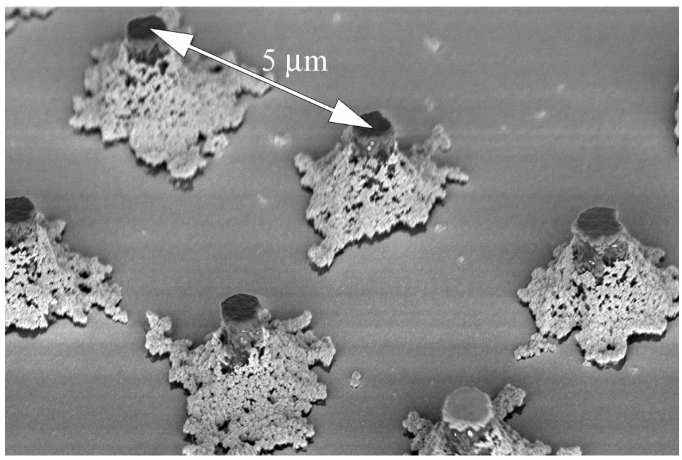

Fig. 4. SEM microphotograph of a three-dimensional tip electrode array with a tip height of 1.75µm, a pitch of 5µm, and a tip size of around 0.5µm.