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Planer Multi Electrode Array Coupled CMOS Image Sensor for *in vitro* Electrophysiology

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1. Introduction

In neuroscience, little is known about the dynamics of micro-circuitry in brain regions such as cerebral cortex and hippocampus. To elucidate those mechanisms, several techniques have been developed such as fluorescent imaging, multi-electrode array (MEA) systems and so on[1, 2]. Since MEA probe is transparent and compatible with optical microscopy, combination of those two greatly enhances the visibility of the circuit dynamics with molecular and electrophysiological tools. However, optical systems tend to be large-sized and costly equipments, which minimize the benefit of multimodal recordings by prohibiting large scale monitoring or downsizing the possible recording points.

To solve those problems, we propose a multi-functional recording device for *in vitro* electrophysiology and designed Multi-electrode Array Coupled CMOS image (MARC) sensor. The novel recording device was designed based on Complementary Metal Oxide Semiconductor (CMOS) image sensor, and micro electrode arrays were fabricated using the top-metal layer of analog Large Scale Integrated circuits (LSI) platform. In this paper, we report design of MARC sensor and fabrication of Pt black microelectrode on Al metal layer in our MEA system. We also report a preliminary result from functional validations by imaging mouse brain slice.

2. Multi-electrode Array Coupled CMOS Image Sensor

Concept

Fig. 1. shows schematic representation of Multi electrode Array Coupled CMOS image (MARC) sensor. This sensor chip was designed for the simultaneous data acquisition from biological samples by using electrical recording/stimulation and fluorescence/transmitted light imaging. To implement such functions, the sensor has photodiode (PD) array, preamplifier, read-out scanner, and microelectrode array. The electrode array was fabricated on the same plane with PD array, so that both light and ionic current can be obtained on the same contact surface with biological samples. The surface of the sensor chip is chemically modified with biocompatible material.

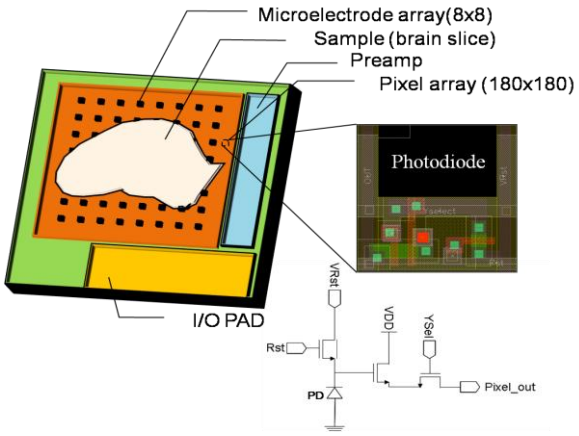

Fig. 1. Schematic representation of Multi-electrode Array Coupled CMOS image sensor (MARC sensor) for *in vitro* electrophysiology.

Design of MARC sensor

Fig. 2 shows microscopic image of MARC sensor. The inset shows magnified single microelectrode. Table 1. shows specification of the sensor chip. The sensor was fabricated on 2-poly 4-metal, 0.35 μm standard CMOS process. The effective recording field on MARC sensor is 1.4 mm x 1.4 mm, which has 180 x 180 pixels. The pixel array is composed of 7.5 μm x 7.5 μm, 3-transistor Active Pixel Sensors (APSs). For the electrical interface with biological substrate, 8 x 8 microelectrode array was fabricated using the top metal wiring layer of Al. As shown in Fig. 2, the microelectrode has two dimensional lattice structures. The square shaped hole among lattice is light receptive field of photodiode. The layout of top metal layer assigned for the electrode is overlapped with underlying shied layer of APS. In this way, multi electrode array is nicely woven into pixel array without drastically changing the fill factor of a single pixel. This layout design potentially enables simultaneous electrical recording or stimulation and imaging at the same recording sites.

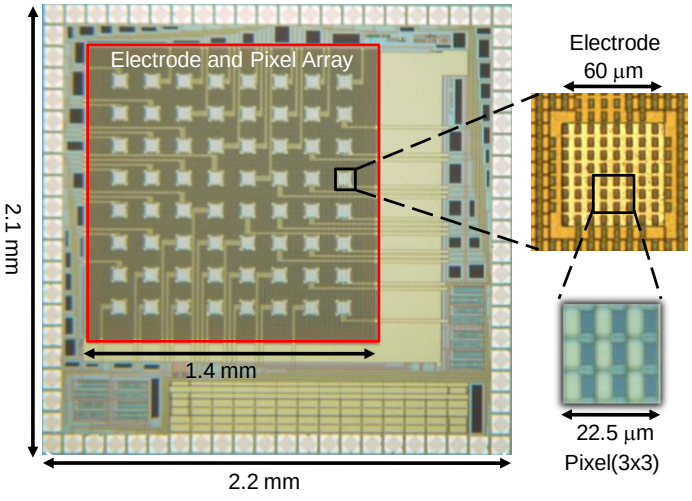

Fig. 2. Microscopic image of MARC sensor, magnified images of single electrode and 3 x 3 pixel array. Multi-electrode array and pixel array were fabricated on the same plane on the sensor chip.

Table 1. Specification of MARC sensor

Technology	CMP 0.35 μm 2Poly4Metal
Pixel array	180 x 180
Pixel size	7.5 μm x 7.5 μm
Photodiode	nwell-psub
Electrode size	60 μm x 60 μm
Electrode distance	90 μm
Pixel read-out	Active Pixel Sensor
Chip size	2.1 mm x 2.2 mm
I/O PADs	82
VDD	3.3 V

Fabrication of Pt Black Electrode on MARC sensor

The standard CMOS fabrication process employs Al for the wiring metal layer. Exposure to electrolyte that contains chloride ion such as saline solution and artificial cerebrospinal fluid (ACSF) causes corrosion of thin Al electrode. Furthermore, current injection capacity and voltage window for the neuronal stimulation electrode heavily depend on the employed metals and its surface roughness. Recent studies report Pt black, TiN and IrOx as the prominent electrode materials, in terms of biocompatibility, corrosion resistance and charge injection capacity[3]. We fabricated Pt black microelectrodes on our sensor chip based on the electrolyte plating process shown in Fig. 3. In this process, Pt was deposited by sputtering on Al metal layer to form electrode array scaffolds using photo lithography and lift-off. After this process, 10 μm of parylene was vapor deposited and electrode region was opened with O_2 plasma etching. Finally, the sensor chip was dipped into H_2PtCl_6 plating solution and Pt particles were deposited on Pt substrate with 30 mA/cm^2 DC.

Fig. 4(a) and (b) show microscopic images of Pt and Pt black electrode. Fig. 4(c) shows SEM image of sample electrode of Pt black formed with identical process described above. The cyclic voltammogram of Pt black sample electrode was obtained and shown to have approximately 25 times larger voltage window than Pt electrode in Fig. 4(d).

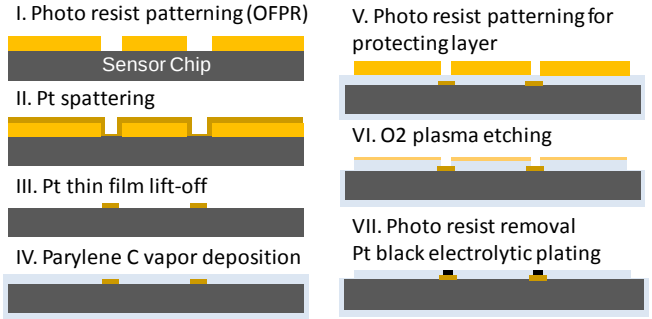

Fig. 3. Schematic representation of Pt black electrode fabrication process

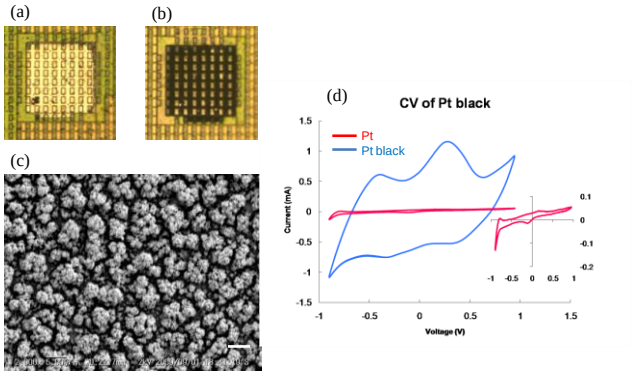

Fig. 4. Evaluation on Pt black electrode. (a) Pt layer on MARC sensor's on-chip electrode. (b) Pt black on MARC sensor's on-chip electrode. (c) SEM observation of Pt black sample electrode (bar = 5 μm). (d) Cyclic voltammgram of Pt black and Pt (inset) sample electrodes.

3. Imaging Results

We first qualitatively evaluated spatial resolution of our novel image sensor by capturing 20 μm fluorescent beads dispersion. The result of captured image is shown in Fig.5(a) with red circles. Then the brain slice was mounted on PD array as shown in Fig. 5(b), and image was captured with transmission light. Fig. 5(c) shows the result of captured image. Microelectrodes were successfully assigned on the mouse hippocampus slice.

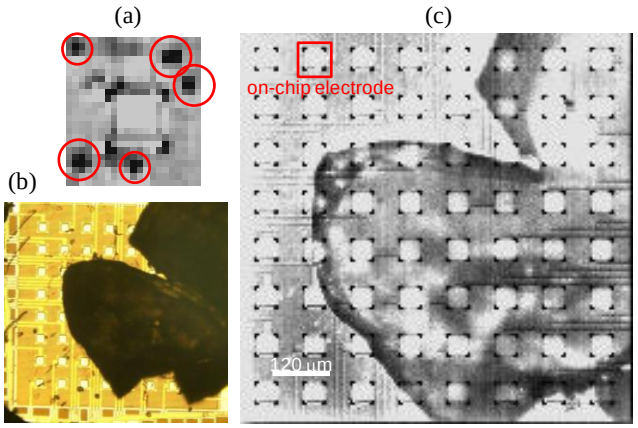

Fig. 5. Functional validation of MARC sensor by imaging biological sample. (a) Captured image of micro beads; the center of the image is on-chip electrode and the diameter of micro bead is 20 μm. (b) Microscopic image of mouse brain slice mounted on MARC sensor. (c) Captured image of mouse hippocampus slice, the on-chip electrode size is 60 μm. (bar = 120 mm)

4. Conclusions

We designed novel multi-electrode array coupled image sensor for *in vitro* electrophysiology and demonstrated its imaging function with mouse brain slice. Also, Pt black was fabricated on Al electrode array on the imaging device to increase the charge injection capacity of the electrodes.

Acknowledgements

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