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A Multimodal CMOS Sensor Device with an On-Chip Mounted LED and Electrodes for Imaging of Fluorescence and Electrical Potential in a Mouse Deep Brain

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1. Introduction

Neural activities in deep brain are of current interest in medical and biological fields. Noninvasive imaging technologies such as functional magnetic resonance imaging (fMRI) have become powerful tools for bioimaging. Also various electrodes have been developed for electrophysiology [1, 2]. However, they have not enough temporal or spatial resolutions to image neural activities in deep brain of small animals. We have proposed and demonstrated CMOS sensor devices to realize real time imaging of neural activities in a mouse deep brain [3, 4]. In this study, we have developed a multimodal CMOS sensor device which has functions of fluorescent imaging and electrical potential recording.

2. Multimodal CMOS Sensor Device

Photographs of the multimodal CMOS sensor chip and the assembled device are shown in Fig. 1. The specifications are shown in Table I. The chip is designed to have a length of approximately 3.8 mm so that it can be used to image from shallow to deep area of a mouse brain. The sensor chip includes the electrodes on the pixel array for stimulating and measuring electrical potential in the brain tissue. The cross section of the unit pixel is shown in Fig. 2. The top layer acts as the electrode. Windows are opened over the photodiodes in the electrode so that fluorescence can transmit to the photodiode through the electrode. Each electrode has 12 × 12 windows and the perimeter of unit electrode is light-shielded as a marker in the experimental trials. There are 10 electrodes on the pixel array. Depositing layers of metals such as Au, Pt or Pt black would improve biocompatibility.

The sensor chip was shaped like a shank by deep reactive ion etching in order to facilitate smooth insertion into the brain tissue. For excitation of green fluorescent protein (GFP), A 300 μm × 300 μm blue LED was flip-chip bonded on the CMOS sensor chip using Au bumps. A 2-μm-thick green filter resist layer was spin coated onto only the pixel array to transmit green fluorescence selectively. The polyimide substrate was also cut in the shape of the shank. The entire device was coated with parylene for biocompatibility. The green filter resist and the parylene resin on the electrode were selectively removed by laser.

3. Functional Demonstrations for Real Time Imaging

3.1. Simultaneous Imaging of Fluorescence and Electrical Potential in Same Area of a Brain Phantom

In order to demonstrate the simultaneous imaging of fluorescence and electrical potential in the same region, we performed an experiment using a brain phantom and the green fluorescent beads (Fluoresbrite® YG Microspheres 10 μm, Polysciences, Inc.). The properties of the phantom are similar to those of brain tissue [3]. The pixel array was covered with the fluorescent beads and the brain phantom was placed over the sensor array. A sinusoidal wave signal with amplitude of 20 mV was applied to the brain phantom. Figure 3 (a) shows the captured image of the excited fluorescent beads on the pixel array. Figure 3 (b) shows a magnified view in the unit electrode. The result of the sensing of the electric potential of the brain phantom is shown in Fig. 3(c). We used three different settings for the frame rate of the image sensor—no imaging, 2 fps, and 4 fps. Although the output signal became noisy affected by the alternate current of image sensor, the simultaneous real-time imaging was successfully demonstrated.

3.2. *In Vivo* Imaging in Hippocampus of a Mouse Brain

We implanted the CMOS sensor device into the hippocampus of a mouse to demonstrate *in vivo* imaging. The *in vivo* experimental setup is shown in Fig. 4(a). All the experiments were carried out in accordance with the Institutional Guidelines of the Nara Institute of Science and Technology. A laboratory mouse was injected with a short-term anesthetic and the CMOS sensor device was implanted into the hippocampus. Figure 4 (b) shows the captured image during the insertion and after complete implantation in the brain. The surface of the brain was covered with a liquid so that the light was scattered on the pixel array. Therefore, a bright area appears at the center of the captured image. The edge of the device was at a depth of approximately 4.5 mm from the surface of the brain so that the pixel array was partially inserted in the hippocampus. In the captured image, the areas in the electrodes are bright, implying that the photodiodes in the electrode sensed the light intensity through the windows of the electrode. We have successfully demonstrated that the device can operate and the photodiodes under the electrode can sense the light intensity in the hippocampus of an anesthetized mouse. After the *in vivo* experiment, the device was observed to operate normally, and the mouse remained alive and acting normally.

4. Conclusion

We developed a multimodal CMOS sensor device. The fluorescent beads and the electrical potential in the brain phantom were successfully imaged simultaneously by the

device. Also *in vivo* imaging in the anesthetized mouse was demonstrated. Further *in vivo* experiments are underway and will be reported at the conference.

Acknowledgements

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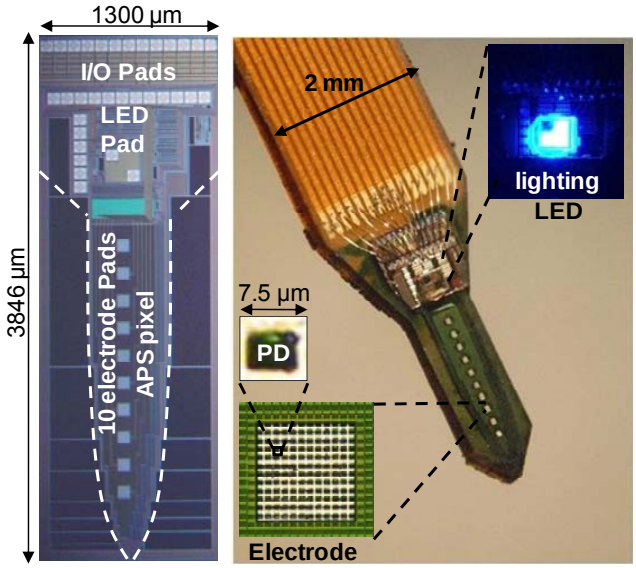

Fig. 1. Photographs of (a) sensor chip and (b) assembled device.

Table I: Specifications of the multimodal CMOS sensor

CMOS chip		Technology	0.35-µm 2-poly 4-metal Standard CMOS Process
		Operating voltage (V)	3.3
		Chip size (µm^2)	1300 × 3846 (max)
	Pixel	Array size (µm^2)	450 × 2310 (max)
		Type	3-transistor Active Pixel Sensor
		Photodiode	Nwell - Psub
		Pixel size (µm^2)	7.5 × 7.5
		Fill factor (%)	35
		Number	13852
	Electrode	Size (µm^2)	90 × 90
		Number	10

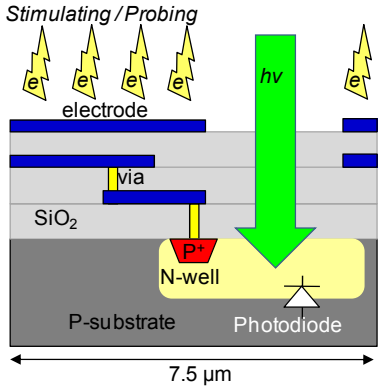

Fig. 2. Cross section of a unit pixel.

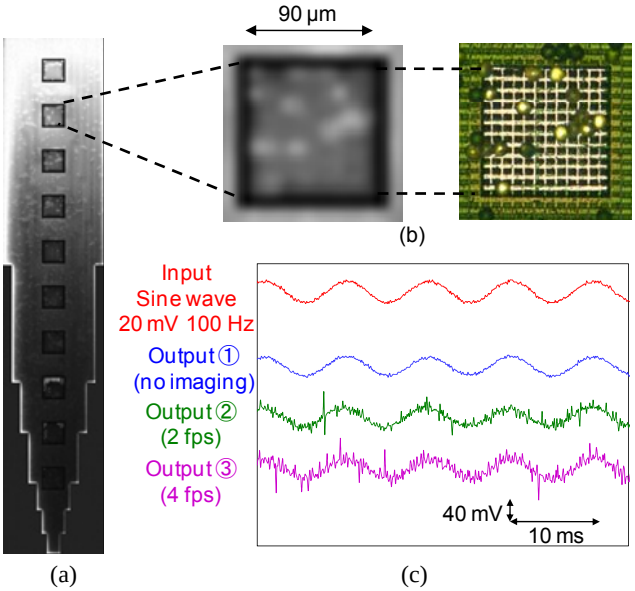

Fig. 3. The result of the dual imaging in brain phantom. (a) Captured image of the fluorescent beads. (b) Magnified image of the fluorescent beads in the unit electrode. (c) Measured electrical potential signal.

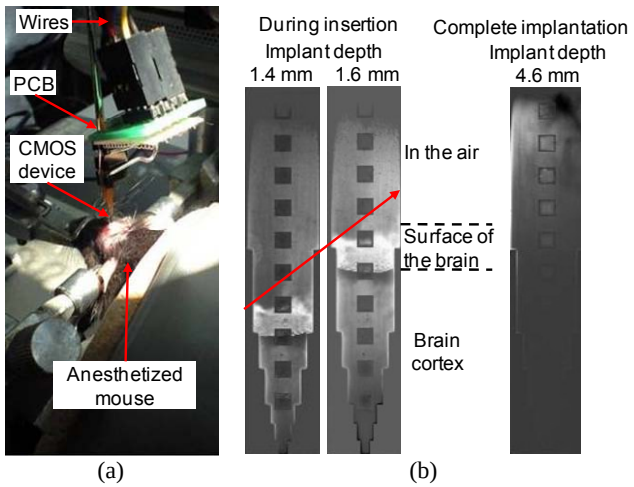

Fig. 4. (a) Experimental setup for *in vivo* imaging. (b) Captured image during insertion and after complete implantation in deep brain of the mouse.