A CMOS-based implantable imaging device for wide-area brain functional imaging

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1. Introduction
To explore neural activities which control animal behaviors, there is a strong demand for technology to observe neural activities on multiple domains in a brain. In particular, fluorescence imaging techniques are suitable for brain imaging because of their capability to observe neural activity of each neuron in the brain [1, 2]. The authors have been developing techniques to measure neural activity using CMOS-based implantable imaging devices [3, 4]. Since the devices are so small and implantable, they are very useful for fluorescence imaging of the brain. Thus, the CMOS-based imaging system is applicable for in vivo behavior experiment in freely-moving situations. However, since the observing area of the reported devices was narrow as 1-3 mm², we cannot simultaneously observe multiple domains in a brain. In this study, we developed a CMOS imaging device with hexagonal shape which is advantageous to realize a wide-area observation using multiple device configuration.

Fig. 1 Concept of wide-area brain functional imaging using hexagonal imaging devices.

2. Design and performance of CMOS imaging device with hexagonal shape
In order to realize wide-area brain imaging, we propose a system with multiple hexagonal sensors, as shown in Fig. 1. The hexagonal shape of the sensors is advantageous to be arranged on a spherical surface like a brain. Fig. 2 and Table I show layouts and specifications of the hexagonally shaped CMOS imaging device. The sensor was fabricated with a 0.35-µm 2-poly 4-metal standard CMOS technology. The size of the pixel was 30 µm × 30 µm, and fill factor of the pixel was 78%. We also improved pixel sensitivity and performance of functional brain imaging. In order to perform accurate brain functional imaging, higher sensitivity was required [5]. In this study, we designed a new pixel for a higher sensitivity. We employed a larger pixel area with which realizes a larger photocurrent / photodiode capacity ratio. The pixel sensitivity of the fabricated sensor was compared with the previous study. The result shows that the pixel sensitivity was improved by approximately 12 dB, as shown in Fig. 3.

Fig. 2 Layout of (a) the sensor chip, and (b) a pixel.

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<th>Table I Specifications of the CMOS imaging device</th>
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3. Fluorescence imaging using the hexagonally shaped CMOS imaging devices.

We fabricated a hexagonally shaped CMOS imaging device module and performed fluorescence imaging using the module. The sensing module consists of a CMOS imaging device, LEDs, and an absorptive light filter. A schematic of the module structure and a micrograph of the sensor module are shown in Fig. 4. The main target fluorophore of the present device is a voltage-sensitive dye. In this study, prior to experiments using voltage-sensitive dye, we characterized the performance of this sensor using fluorescent beads. We used red-orange fluorescent beads (F-21012, Carboxylate) injected into a brain of a mouse. The fluorescent beads have peak wavelength of 565 nm and 580 nm for absorption and emission, respectively. The result of fluorescence imaging on the brain is shown in Fig. 5. A hexagonal outlines in the figures indicate position of the CMOS imaging device. We observed some fluorescent beads in the hexagonal outline, as shown in Fig. 5(b). These beads were excited by LEDs mounted around the sensor and we performed fluorescence imaging. The fluorescent beads were successfully imaged with the hexagonally shaped CMOS imaging device, as shown in Fig. 5(c). We also carried out a preliminary trial of wide-area imaging using multiple hexagonal sensors on the brain, as shown in Fig. 6. Three sensors were arrayed on the brain surface of the mouse in this experiment. Currently, we are performing simultaneous operation of the three sensors, as shown in Fig. 6(b). Results of these trials will be reported in the conference, too.

Fig. 3 Sensitivities of the present and the previous [3] CMOS imaging devices for brain imaging.

Fig. 5 Micrographs of brain surfaces with injected fluorescent beads. (a) Conventional and (b) fluorescence images taken with an external microscope, and (c) fluorescence image captured with the present imaging device.

Fig. 6 (a),(b) Situation of wide-area brain imaging with multiple sensors.

4. Conclusions

We have developed a hexagonally shaped CMOS imaging device and implantable imaging device for wide-area brain imaging. The sensitivity of 30 µm square pixels was 12 dB higher in comparison with the 7.5 µm square pixel used in our previous works. We demonstrated fluorescence imaging with the hexagonally shaped CMOS imaging device on the brain of the living mouse. We also performed fluorescence imaging with multiple hexagonal sensors on the brain for wide-area brain imaging. The sensor is expected to be a useful tool for exploring multi-domain brain activities, because we can align the imaging devices closely and configure a spherical imaging surface that can fit to surface of the mouse’s brain.

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References