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CMOS-Based Optoelectronic On-Chip Neural Interface Device

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SUMMARY On-chip neural interface devices based on CMOS image sensor technology are proposed and demonstrated. The devices were designed with target applications to optogenetics in bioscience. Multifunctional CMOS image sensors equipped with an addressable on-chip electrode array were integrated with a functional interface chip that contained embedded GaInN light emitting diodes (LEDs) and electrodes to create a neural interface. Detailed design information regarding the CMOS sensor chip and the functional interface chip including the packaging structure and fabrication processes are presented in this paper. The on-chip optical stimulation functionality was demonstrated in an *in vitro* experiment using neuron-like cells cultured on the proposed device.

key words: *CMOS image sensor, optogenetics, on-chip bioimaging, optical stimulation, GaInN LED, implantable electronics*

1. Introduction

Neuroscience, including brain science, has been one of the most important research fields in the history of science. Electrophysiology is a methodology within neuroscience in which neural cells' activities are probed using electrical devices. For a long time, electrophysiology was one of only a few localized stimulation schemes for neural cells in both *in vitro* (out of body) and *in vivo* (in a living body) experimental conditions. However, this situation drastically changed owing to the development of optogenetics at the beginning of the 21st century. Optogenetics is a technology that gives mammal cells light-detecting capabilities by changing their genetics [1]–[3]. A membrane protein such as channelrhodopsin-2 (ChR2) is introduced into the target cells; it then acts as a light-detecting ion channel.

For example, cells with ChR2 fire when they are illuminated by blue light [1]–[3]. This phenomenon was an epoch-making breakthrough because various precisely localized, cell-selective stimulation techniques based on the concept of optogenetics were proposed and demonstrated.

Within the framework of optogenetics, optical stimulation systems to illuminate the target cells also play an important role. There are several approaches to the design of optical stimulation systems, as shown in Fig. 1. In Fig. 1, the CMOS-based on-chip neural interface device presented in this paper is also shown. Optical-fiber-based light delivery is the simplest method for optical stimulation [3]–[5]. In this approach, the light source and the delivery method can be designed separately; thus, users can take advantage of various light sources with different wavelengths and emission powers. The drawback of the optical-fiber-based approach is the difficulty of localized stimulation. Furthermore, it is not easy to use optical fiber-based light delivery in *in vivo* experiments in freely moving situations.

For optogenetic experiments under a microscope, including *in vitro* experiments with detached neural tissues (e.g., brain slices), or *in vivo* experiments in which an animal is anesthetized and fixed under the microscope, localized stimulation can be achieved using projection-type light delivery systems [6]–[8]. From the viewpoint of localization, the microscope-based approach is particularly advantageous. However, it cannot be applied in freely moving situations.

The LED array device is another promising candidate for optical stimulation in optogenetics. The emission wavelength region of GaInN LEDs matches the typical channelrhodopsin-based proteins used in optogenetics. Huber *et al.* introduced single-LED devices mounted on the skull of a mouse as an alternative to optical fibers, and successfully demonstrated optical stimulation [9]. LED-based devices can be applied for stimulating not only the surface of

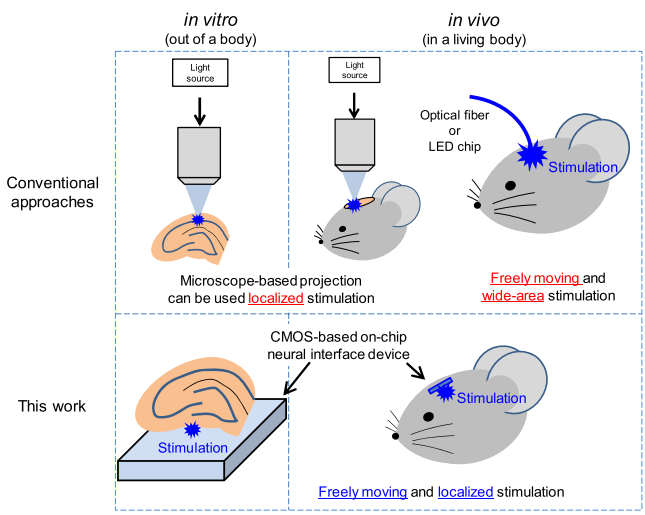

Fig. 1 Optical stimulation systems for optogenetics.

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the brain, but also the inside of the brain. Kim *et al.* demonstrated an opto-electric probe (optorode) for cortical stimulation and measurement [10]; they integrated small-sized (50 μm × 50 μm) GaInN LED chips on a shank neural probe.

Furthermore, LED array devices are expected to provide promising solutions for two-dimensional patterned stimulation. Some GaInN LED array devices designed for both on-chip and projection-type optical stimulation have been reported [11], [12].

To realize an LED array device for localized optical stimulation in optogenetics, addressing capabilities must be implemented on the device. *x*-*y*-matrix-type addressing was widely used in the preceding studies [11], [12]. On the other hand, we have proposed and demonstrated CMOS-based random-access capabilities [13]. We designed a multifunctional CMOS image sensor that has addressable surface electrodes. We integrated a GaInN LED array on the multifunctional CMOS image sensor for on-chip optical neural stimulation. Compared to conventional (simple) GaInN LED array devices, this architecture is advantageous for not only its flexible LED accessibility but also its functional expandability. With the proposed CMOS-based approach, we can realize multifunctional neural interface devices using both optical and electrical accessibility to neural systems.

In this paper, we present the design of multifunctional CMOS image sensors, structures of the LED and electrode array chips which are mentioned as "functional interface chips", device packaging, and functional demonstrations of the CMOS-based on-chip neural interface devices.

2. Building Blocks of the CMOS-Based On-Chip Neural Interface Device

2.1 Structure of the On-Chip Neural Interface Device

Figure 2 shows the concept of the CMOS-based on-chip neural interface device system. The device consists of two semiconductor chips: a multifunctional CMOS image sensor and a functional interface chip. These two chips are bonded using a flip-chip bonding technique, as described in Sect. 3.

In this work, we present two types of on-chip neural interface devices. Figure 3 shows structures and functionalities of two types of CMOS-based on-chip neural interface device in the present work. The first one is for optical stimulation and imaging without electrical accessibility for on-chip cells or tissues (i.e., the optical-only device, Fig. 3 (a)), and the other is a device with both optical and electrical accessibility to the targets (i.e., the optoelectronic-type device, Fig. 3 (b)). We designed several types of the multifunctional CMOS image sensors and functional interface chips for these two devices. As the base functionality, the multifunctional CMOS image sensors are capable of capturing optical images. In addition, the sensors are equipped with on-chip electrode array over the optical imaging pixel array. We can electrically access the surface through an addressing function integrated on the CMOS sensor. As the functionality of the multifunctional CMOS image sensor, we can use the electrodes for bidirectional electric interfacing, thus, sensing and voltage application/current injection, depending on the device design.

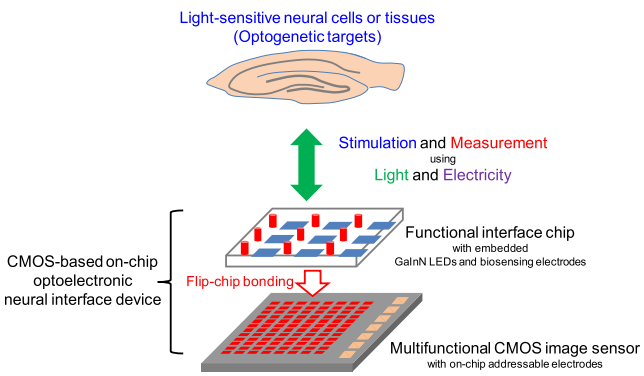


Fig. 2 Concept of the CMOS-based on-chip neural interface device.

As shown in Fig. 3 (a), for optical-only devices, a commercially available GaInN array chip was used as the functional interface chip. The GaInN LEDs, with a size of approximately 200 μm × 200 μm, were formed on a double-side-polished sapphire substrate. All LEDs have individual anode and cathode electrodes on the top surface. We bonded the GaInN array chip to the multifunctional CMOS image sensor in a face-to-face manner using a flip-chip bonding process. In this packaging structure, the surface of the device is the bottom of the sapphire substrate; thus, the CMOS sensor surface is electrically insulated from the biological targets. Therefore, it is impossible to perform electric stimulation or measurement.

As shown in an inset of Fig. 3 (a), all *n*-type regions of the GaInN LEDs are monolithically connected. Therefore, we operate a selected LED by injecting current from p-type regions of the LEDs.

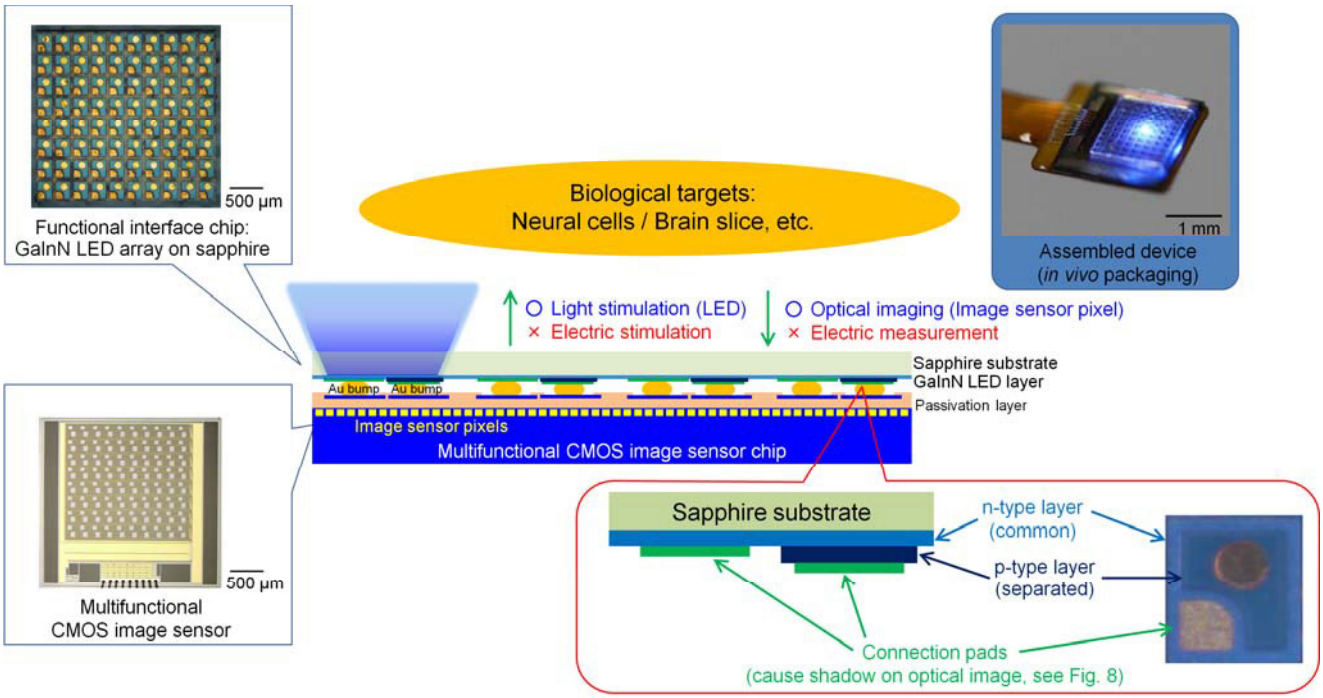
For optoelectronic-type devices, we fabricated another type of functional interface chip (Fig. 3 (b)). We prepared a Si chip with an embedded through-Si-via (TSV) array and cavities for LEDs. On the top surface of the TSV, Pt electrodes for neural stimulation/measurement were formed. We integrated diced GaInN LEDs on the TSV wafer creating an optoelectronic-type functional interface chip. The LEDs can be used for optical stimulation. The Pt electrodes can be used for electrical stimulation or measurement.

2.2 Multifunctional CMOS Image Sensor

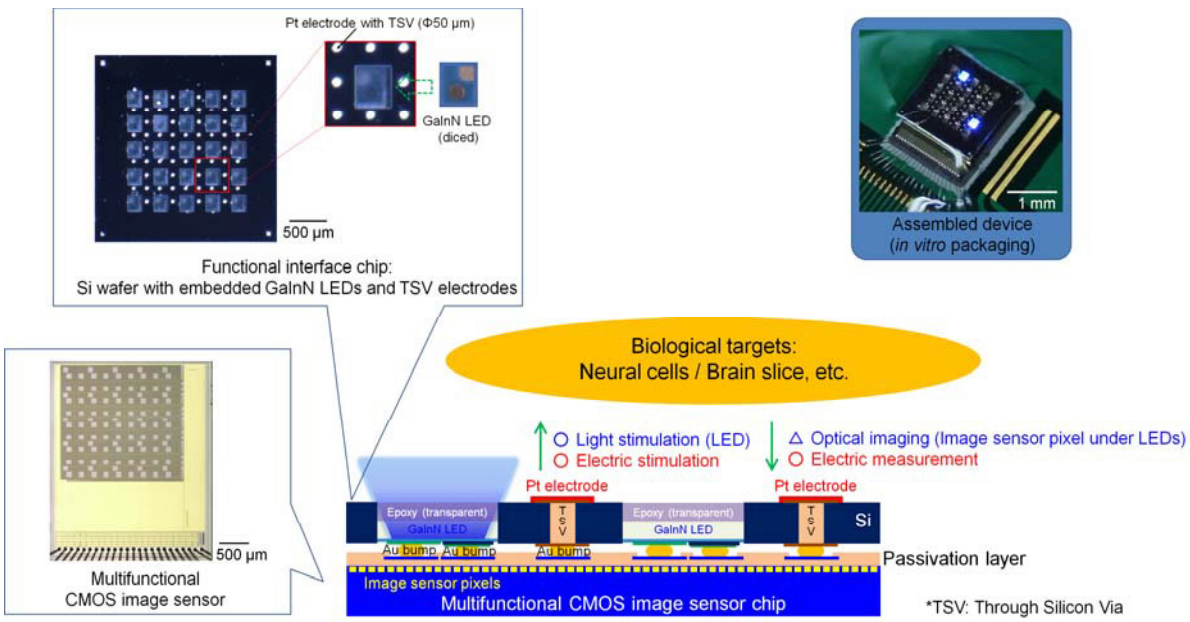
Multifunctional CMOS image sensors have been designed using 0.35-μm standard CMOS technology. Figure 4 shows block diagrams of the multifunctional CMOS image sensors. Table 1 shows the specifications of the multifunctional CMOS image sensors. The multifunctional CMOS image sensors consist of two parts: an (optical) image sensor part and an addressable electrode part.

[CMOS image sensor part]

The image sensor part in the two multifunctional CMOS im-



(a) Optical-only device



(b) Optoelectronic-type device

Fig. 3 Structures of the CMOS-based on-chip neural interface devices.

age sensors is identical in circuit design; it was designed with 3.3 V transistors. The image sensor part is equipped with a 260×244 pixel array. The pixel circuitry is a conventional 3-transistor active pixel sensor (3-Tr APS) with a size of $7.5\,\mu\text{m} \times 7.5\,\mu\text{m}$. The detailed pixel circuitry and signal pathway is presented in a previous publication [14]. As the minimum configuration, the image sensor part can be operated with four I/O connections: VDD and GND for the power supply, CLK_O for timing control, and Vout for the output. Bias voltages for the inner circuits are generated by a bias generator implemented on the sensor chip. The signal offset caused by the mismatch of bias voltages are canceled in image capturing software, by subtracting the pixel signal taken in completely dark situation.

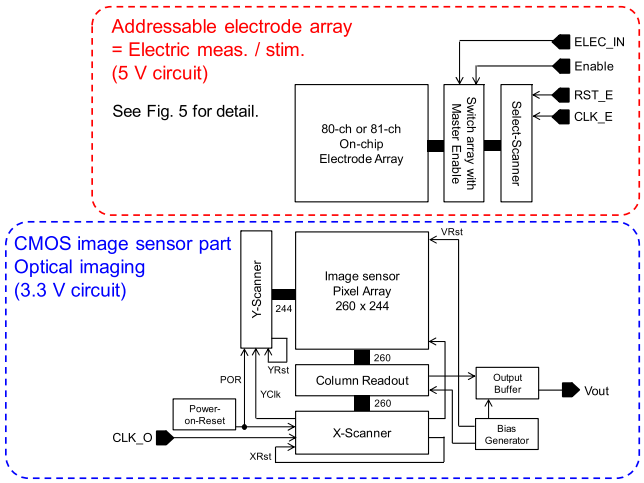


Fig. 4 Block diagram of the multifunctional CMOS image sensors.

Table 1 Specifications of the multifunctional CMOS image sensors.

	Optical-only	Optoelectronic-type
Technology	0.35 μm 2-poly 4-metal standard CMOS process	
Chip size	2200 μm × 2500 μm	2403 μm × 3508 μm
Imaging pixel size	7.5 μm × 7.5 μm	
Pixel circuitry	3-Tr active pixel sensor	
Photodiode type	*n*-well/*p*-sub	
Image sensor array	260 × 244	
Operating voltage	Image sensor part: 3.3 V Addressable electrode part: 5 V	
Active electrodes	80	81
Number of I/O pads	9	24 (including test lines)

An optical imaging function can be used to observe the shape of the measurement target placed directly on the sensor surface. Although no optics such as lenses are integrated with the sensor's surface, we can obtain optical images of the target cells or tissues [15]–[17].

[Circuit for electrode addressing]

As shown in Fig. 4, addressable electrode array part was designed as 5V circuit. In the current CMOS process, 5V-torelant MOS and I/Os are also provided as a part of standard design library. We used them to design the circuit for electrode addressing. The active channel number is 80 for the optical-only device and 81 for optoelectronic-type device. Figure 5 shows (a) schematic and (b) timing diagram of the addressable electrode array part. One of the electrodes can be selected by an electrode selector to perform current injection into an LED or electrical stimulation/measurement device. A scanner circuit configured with serially connected D flip-flops was used as the electrode selector.

We can choose any of the electrodes by incrementing the scanner circuit by applying pulses to the CLK_E input. The selected electrode is connected to a common connection line. Then, the common connection line is connected to an external I/O pad of the CMOS sensor chip (ELEC_IN in Figs. 4 and 5 (a)). Because no current generator is implemented on the CMOS sensor chip, we use an external

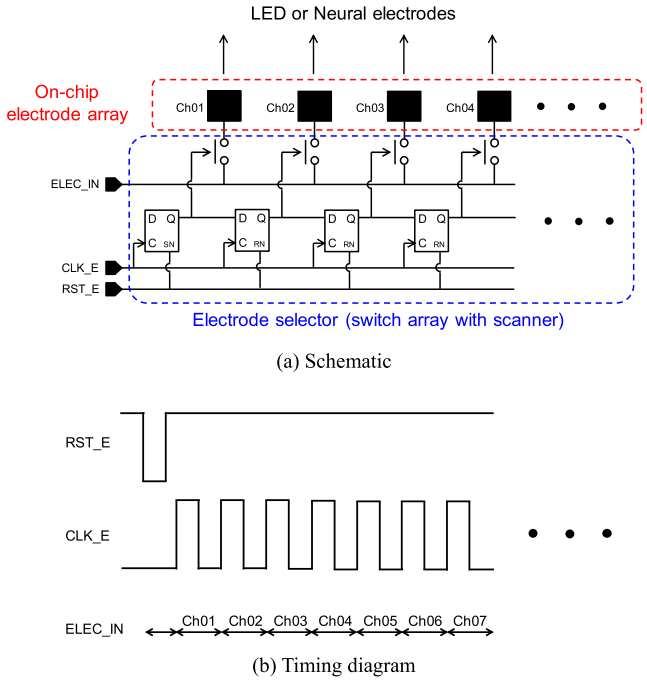


Fig. 5 (a) Schematic and (b) timing diagram of the addressable electrode array part.

current source to operate the LED array for optical stimulation. This selectable electrode array can be used not only for current injection to operate an LED but also for electric neural stimulation and measurement of neural activity. For electric neural stimulation or measurement, we connect the on-chip electrode to a TSV/Pt electrode (see Fig. 3 (b)).

[Electrode array]

Both multifunctional CMOS image sensors are equipped with 8 × 10 functional electrode arrays over the image sensor pixel arrays. These electrodes can be selected and accessed via the addressing circuit. The electrodes have a size of 95 μm × 95 μm. The positions of the electrodes are designed to match those of the corresponding functional interface chip, namely, the GaInN array chip or the TSV array chip with embedded LEDs. For the optical-only device, the functional interface chip is a simple GaInN LED array formed on a sapphire substrate (Fig. 3 (a)). To operate an LED, both the anode and cathode electrodes must be connected to the CMOS chip. Each functional electrode is accompanied by another electrode to form the cathode terminal of the LEDs. However, in the actual packaging, as mentioned in Sect. 2.1, we need to connect only one or limited number of cathode electrodes on the LED array, because the *n*-type region of the LEDs are shorted on the LED array chip. For the optoelectronic-type device, the positions of the electrodes on the CMOS chip are designed to match either the LEDs or the TSV electrodes of the functional interface chip (the TSV chip). In this device structure, because the LEDs are separately embedded in the TSV chip, we must connect all anode and cathode electrodes of the LEDs.

3. Packaging of the CMOS-Based On-Chip Neural Interface Device

3.1 Preparation of the Functional Interface Chips

For the optical-only device, we prepared a GaInN LED wafer that was divided into 8×10 arrays. As previously mentioned, the sapphire substrate is double-side-polished. The thickness of the GaInN array chip was approximately 90 μm. Because GaInN layers and sapphire substrates are nearly transparent to visible light, we can perform optical imaging through the GaInN LED array chip. However, as shown in the inset of Fig. 3 (a), the anode and cathode electrodes of the LEDs are not transparent, which causes shadows in the captured images [13].

The structure of the TSV chip with integrated GaInN LEDs, which is used as the functional interface chip in the optoelectronic-type device was shown in Fig. 3 (b). The thickness of the chip was 200 μm. For neural stimulation and measurement, Pt electrodes with a diameter of 50 μm were deposited on the top side of the TSVs. The Si chip with TSV-Pt electrodes were manufactured by Shinko Electric Industries Co., Ltd. We integrated separate GaInN LED chips on the cavities. The surfaces of LED chips were aligned flat with the surface of the TSV chip. The LEDs were molded with transparent epoxy resin.

3.2 Flip-Chip Bonding and Packaging

We used a flip-chip bonding process to integrate the multifunctional CMOS image sensor and the functional interface chip. Au bumps were formed on one of the bonding surfaces. Then, the two surfaces were put in contact and fixed using anisotropic conducting paste (ACP, TAP0401C, Kyocera Chemical).

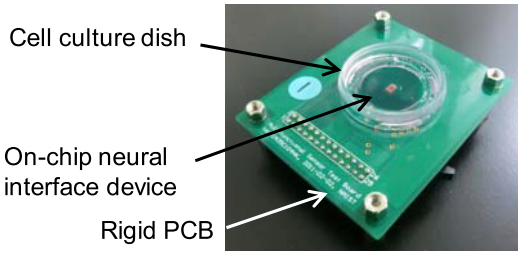
We used two types of device packaging for *in vitro* and *in vivo* applications. The bonded chips were mounted on a rigid printed circuit board (rigid PCB, for *in vitro* applications) or a flexible PCB (for *in vivo* applications). Aluminum wires were bonded between the connection pads of the multifunctional CMOS image sensor and the rigid or flexible PCB. The wires and sidewalls of the integrated chips were molded with epoxy resin.

For the packaging for *in vitro* applications, a cell-culture dish with a removed bottom was attached to the rigid PCB. The assembled devices are shown in Fig. 6. In this paper, we present a functional demonstration using the *in vitro* package.

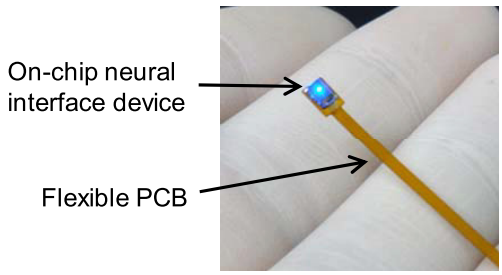
4. *In Vitro* Demonstration of On-Chip Optical Neural Stimulation

We performed an *in vitro* experiment to confirm the optical stimulation functionality when using the integrated LED and the on-chip imaging function. We used the optical-only device for this experiment. As the on-chip biological target, ChR2-expressed Neuro-2A cells were cultured on the device. Neuro-2A cells are neuron-like cells that originate from neuroblastomas in mice. Prior to cell culturing, the surface of the device was treated with poly-L-lysine for 24 hours to enhance cell attachment [18]. Then, Neuro-2A cells were seeded in the culture dish structure of the device. After the cells were stably cultured, ChR2 DNA was introduced into the cells. After the introduction process, ChR2 was expressed in a part of the Neuro-2A cells. Because the ChR2 DNA was coupled with DNA for mCherry fluorescence protein, the expression can be confirmed using fluorescent microscopy, as shown in Fig. 7.

Figure 8 shows (a) the experimental setup, (b) an image taken by an external microscope, and (c) an image taken by the imaging function of the proposed neural interface device. In the experiment, optical stimulation of a ChR2-expressed Neuro-2A cell was performed using an LED. The response of the cell was observed using the conventional patch-clamp technique with a glass capillary electrode. We expect a change in membrane current, caused by the optical



(a) For *in vitro* applications



(b) For *in vivo* applications

Fig. 6 Device packages for optogenetic applications.

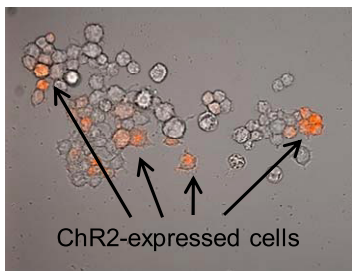
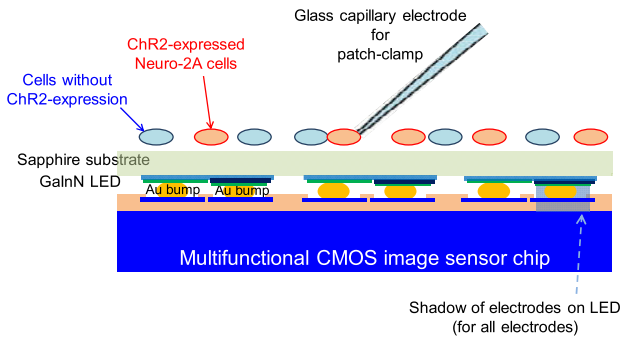
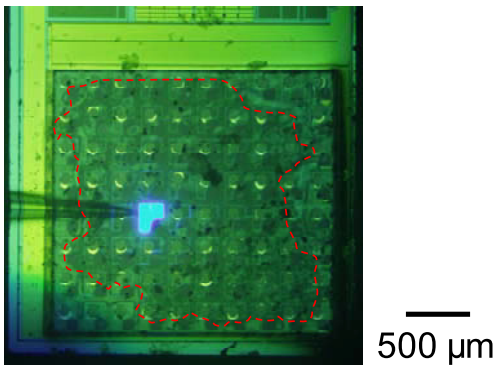


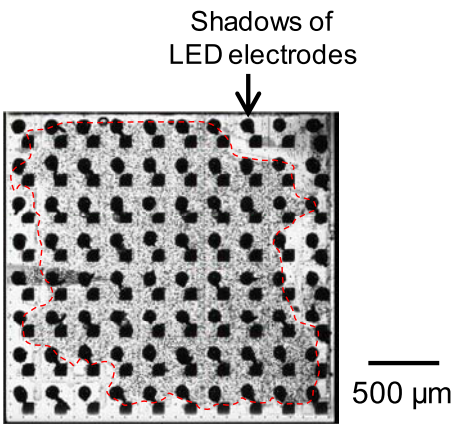
Fig. 7 ChR2-expressed Neuro-2A cells cultured on the optical-only device with *in vitro* package. The expression of ChR2 can be observed with red fluorescence from mCherry.



(a) Experimental setup



(b) Image captured by an external microscope



(c) Image taken by the proposed device

Fig. 8 (a) Experimental setup, (b) images taken by an external microscope, and (c) images taken by the imaging function of the multi-chip CMOS image sensor.

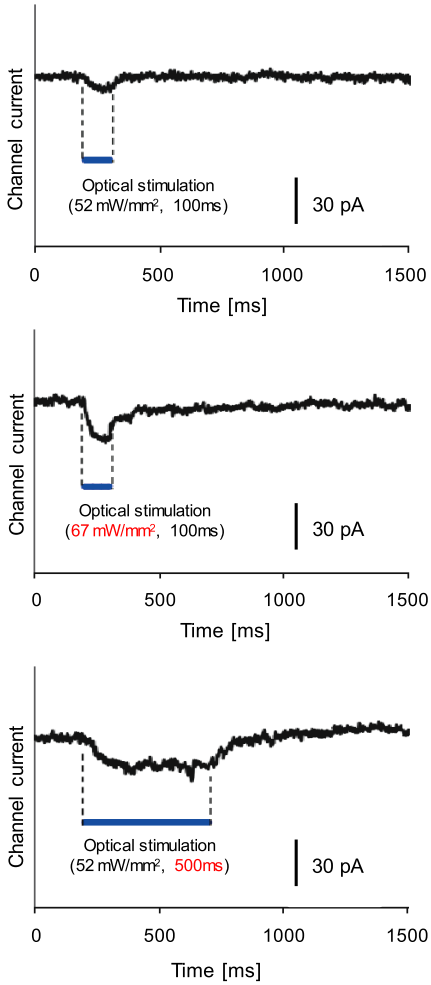


Fig. 9 Response (in membrane current) resulting from optical stimulation from the CMOS-based on-chip neural interface device. The response of the cell was observed with the conventional patch-clamp technique (voltage clamp) with a glass capillary electrode.

stimulation of the cell.

Prior to the optical stimulation trial, we chose a ChR2-expressed cell and "patched" the glass capillary electrode onto the cell membrane. In the image captured by the imaging function of the multifunctional CMOS image sensor, we can see the cultured cells only as a region of contrast difference (areas surrounded by red dashed lines in Figs. 8 (b) and 8 (c)). Because of the distance between the cells and the imaging pixels on the CMOS sensor chip, cells cannot be observed clearly. However, we can know the two-dimensional distribution of the cells and the position of the glass capillary electrode.

After we have established an appropriately contacted (patched) condition on the cell membrane, we performed optical stimulations using the integrated LED. We selected an LED below the cell and illuminated the LED.

Figure 9 shows the time courses of membrane current measured when using the glass capillary electrode. A decrease in the membrane current, which indicates an increase in the current flow via ChR2, was clearly observed, coincident with the optical stimulation. As shown in Fig. 10, peak channel current increased when either the illumination intensity or the illumination duration was increased.

The intensity required to obtain the response in the membrane current was nearly one order larger than the typically reported intensity required to activate ChR2 [1]; this phenomenon is considered to be caused by a non-optimized transfection procedure for ChR2 introduction. However, the experimental results suggest that the present approach of using a GaInN LED array is applicable not only for well-prepared optogenetic experiments but also for exper-

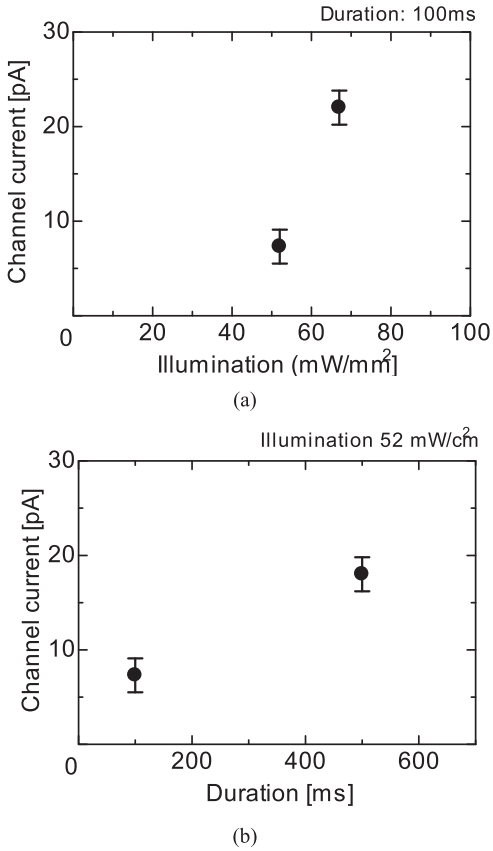


Fig. 10 Peak channel current as functions of (a) illumination intensity, and (b) illumination duration.

iments with low-efficiency genetic introduction and other non-ideal factors. The illumination intensity of more than 50 mW/mm^2 is one of the promising features of the device when used as an optical stimulator for optogenetics. Furthermore, taking advantage of the on-chip optical imaging, we can observe the operation of the optical stimulation function based on the position of the activated LED or the intensity of the LED emission [13]. In *in vivo* applications, this functionality is considerably advantageous when the device is fully implanted in the animal's body. Generally, in the fully implanted situations, we cannot know the illumination intensity of the LED in the animal body. However, using the present CMOS-based optoelectronic neural interface device, we can monitor the illumination intensity using the imaging function of the CMOS sensor chip.

5. Conclusions

We developed a CMOS-based on-chip neural interface device with optical stimulation functionality for use in optogenetics. The proposed devices consist of a multifunctional CMOS image sensor integrated with a functional interface chip. Two versions of the device structure, optical-only and optoelectronic-type, were presented. An *in vitro* experiment using a neuron-like cultured cell was performed and the ability to perform on-chip optical stimulation was demonstrated.

Our results confirmed both that sufficient emission intensity is available and that optical stimulation can be achieved, even with low-efficiency ChR2 expression. This device architecture is promising because of the high emission intensity (because of the good performance of GaInN LEDs) and the high functional flexibility and extendibility of the CMOS image sensor-based architecture.

Acknowledgments

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References

[1] E.S. Boyden, F. Zhang, E. Bamberg, G. Nagel, and K. Deisseroth, "Millisecond-timescale, genetically targeted optical control of neural activity," Nat. Neurosci., vol.8, no.9, pp.1263–1268, Sept. 2005.
[2] T. Ishizuka, M. Kakuda, R. Araki, and H. Yawo, "Kinetic evaluation of photosensitivity in genetically engineered neurons expressing green algae light-gated channels," Neurosci. Res., vol.54, no.2, pp.85–94, Feb. 2006.
[3] K. Deisseroth, "Optogenetics," Nat. Methods, vol.8, no.1, pp.26–29, Jan. 2011.
[4] V. Gradinaru, K.R. Thompson, F. Zhang, M. Mogri, K. Kay, M.B. Schneider, and K. Deisseroth, "Targeting and readout strategies for fast optical neural control in vitro and in vivo," J. Neurosci., vol.27, no.52, pp.14231–14238, Dec. 2007.
[5] A.M. Aravanis, L.-P. Wang, F. Zhang, L.A. Meltzer, M.Z. Mogri, M.B. Schneider, and K. Deisseroth, "An optical neural interface: In vivo control of rodent motor cortex with integrated fiberoptic and optogenetic technology," J. Neural Eng., vol.4, no.3, pp.S143–S156, Sept. 2007.
[6] O.G.S. Ayling, T.C. Harrison, J.D. Boyd, A. Goroshkov, and T.H. Murphy, "Automated light-based mapping of motor cortex by photoactivation of channelrhodopsin-2 transgenic mice," Nat. Methods, vol.6, no.3, pp.219–224, March 2009.
[7] A.M. Leifer, C. Fang-Yen, M. Gershow, M.J. Alkema, and A.D.T. Samuel, "Optogenetic manipulation of neural activity in freely moving Caenorhabditis elegans," Nat. Methods, vol.8, no.2, pp.147–152, March 2011.
[8] S. Sakai, K. Ueno, T. Ishizuka, and H. Yawo, "Parallel and patterned optogenetic manipulation of neurons in the brain slice using a DMD-based projector," Neurosci. Res., vol.75, no.1, pp.59–64, Jan. 2013.
[9] D. Huber, L. Petreanu, N. Ghitani, S. Ranade, T. Hromádka, Z. Mainen, and K. Svoboda, "Sparse optical microstimulation in barrel cortex drives learned behaviour in freely moving mice," Nature, vol.451, no.7174, pp.61–64, Jan. 2008.
[10] T.-I. Kim, J.G. McCall, Y.H. Jung, X. Huang, E.R. Siuda, Y. Li, J. Song, Y.M. Song, H.A. Pao, R.-H. Kim, C. Lu, S.D. Lee, I.-S. Song, G. Shin, R. Al-Hasani, S. Kim, M.P. Tan, Y. Huang, F.G. Omenetto, J.A. Rogers, and M.R. Bruchas, "Injectable, cellular-scale optoelectronics with applications for wireless optogenetics,"

Science, vol.340, no.6129, pp.211–216, April 2013.
[11] N. Grossman, V. Poher, M.S. Grubb, G.T. Kennedy, K. Nikolic, B. McGovern, R.B. Palmini, Z. Gong, E.M. Drakakis, M.A.A. Neil, M.D. Dawson, J. Burrone, and P. Degenaar, "Multi-site optical excitation using ChR2 and micro-LED array," J. Neural Eng., vol.7, no.1, 016004, Feb. 2010.
[12] B. McGovern, R.B. Palmini, N. Grossman, E.M. Drakakis, V. Poher, M.A.A. Neil, and P. Degenaar, "A new individually addressable micro-LED array for photogenetic neural stimulation," IEEE Trans. Biomed. Circuits Syst., vol.4, no.6, pp.469–476, Dec. 2010.
[13] T. Tokuda, H. Kimura, T. Miyatani, Y. Maezawa, T. Kobayashi, T. Noda, K. Sasagawa, and J. Ohta, "CMOS on-chip bio-imaging sensor with integrated micro light source array for optogenetics," Electron. Lett., vol.48, no.6, pp.312–314, 2012.
[14] T. Tokuda, M. Takahashi, K. Uejima, K. Masuda, T. Kawamura, Y. Ohta, M. Motoyama, T. Noda, K. Sasagawa, T. Okitsu, S. Takeuchi, and J. Ohta, "CMOS image sensor-based implantable glucose sensor using glucose-responsive fluorescent hydrogel," Biomed. Opt. Express, vol.5, no.11, pp.3859–3870, Oct. 2014.
[15] T. Kobayashi, M. Motoyama, H. Masuda, Y. Ohta, M. Haruta, T. Noda, K. Sasagawa, T. Tokuda, H. Tamura, Y. Ishikawa, S. Shiosaka, and J. Ohta, "Novel implantable imaging system for enabling simultaneous multiplanar and multipoint analysis for fluorescence potentiometry in the visual cortex," Biosens. Bioelectron., vol.38, no.1, pp.321–330, Oct. 2012.
[16] M. Haruta, C. Kitsumoto, Y. Sunaga, H. Takehara, T. Noda, K. Sasagawa, T. Tokuda, and J. Ohta, "An implantable CMOS device for blood-flow imaging during experiments on freely moving rats," Jpn. J. Appl. Phys., vol.53, no.4S, 04EL05, Jan. 2014.
[17] T. Kobayashi, H. Masuda, C. Kitsumoto, M. Haruta, M. Motoyama, Y. Ohta, T. Noda, K. Sasagawa, T. Tokuda, S. Shiosaka, and J. Ohta, "Functional brain fluorescence plurimetry in rat by implantable concatenated CMOS imaging system," Biosens. Bioelectron., vol.53, pp.31–36, March 2014.
[18] R. Weis, B. Müller, and P. Fromherz, "Neuron adhesion on a silicon chip probed by an array of field-effect transistors," Phys. Rev. Lett., vol.76, no.2, pp.327–330, 1996.

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