IEICE TRANS. COMMUN., VOL.E94–B, NO.9 SEPTEMBER 2011

INVITED PAPER *Special Section on Information Communication Technology for Highly Reliable Human Health Care Services*

CMOS Imaging Devices for Biomedical Applications

Jun OHTA[†,††a)], ***Member***, **Takuma KOBAYASHI**[†,††], **Toshihiko NODA**[†,††], ***Nonmembers***, **Kiyotaka SASAGAWA**[†,††], ***and*** **Takashi TOKUDA**[†,††], ***Members***

SUMMARY We review recently obtained results for CMOS (Complementary Metal Oxide Semiconductor) imaging devices used in biomedical applications. The topics include dish type image sensors, deep-brain implantation devices for small animals, and retinal prosthesis devices. Fundamental device structures and their characteristics are described, and the results of *in vivo* experiments are presented.

key words: *CMOS image sensors, biomedical applications, retinal prosthesis, deep-brain implantation, multi-electrode array*

1. Introduction

The rapid growth of CMOS (Complementary Metal Oxide Semiconductor) image sensors has led to a wide variety of applications in, for example, automobiles, security/surveillance, communications, biotechnology, and medicine [1]. In addition, biomedical applications have recently emerged and continue to develop. For applications in biotechnology, fluorescence is widely used in markers for the detection of target molecules using conventional dyes, quantum dots (QDs), green protein fluorescence (GFP), and voltage sensitive dyes (VSDs). Previously, fluorescence was measured using an optical microscope in conjunction with an image sensor. Recently, another configuration has emerged, in which bio-materials or living tissues containing fluorophores are in direct contact with the surface of an image sensor, which allows more compact measurement systems to be realized [2]. Such a compact system can also be implanted into a living body. The implantation of an imaging system also enables new applications of clinical devices. A typical example of such clinical applications using imaging devices is a retinal prosthesis [3], an imaging device that is implanted into the eye.

Biomedical devices using image sensors can be classified as having three types of configurations. The first type is a conventional configuration, such as in an optical microscope, where an image sensor is attached to the optics of the microscope. Conventional sensors can be used in this configuration. The second type of device is a hermetic device, in which an image sensor is installed in an enclosure. A capsule endoscope [4] is a typical example of this type of device, as illustrated in Fig. 1. In this configuration, the image sensor is required to be small enough to fit into small enclosures, such as a capsule that can be swallowed. The third type of device is configured such that the image sensor comes into contact with a bio-material or living tissue. For example, cells can be cultured on the conditioned surface of an image sensor. Another example is a retinal prosthesis, which is an image sensing device that is implanted into the retina [5]. The configurations of these imaging devices are shown in Fig. 1.

In developing such biomedical devices, we face several challenges, as shown in Fig. 2 [2]. The surface of the device can affect living tissues or cells, and these effects can include cytotoxicity. For example, in order to culture cells on a chip, the surface must be treated, for example, by coating it with poly-L-lysine [6]. Packaging materials and/or electrode materials may be dissolved into the affected tissues

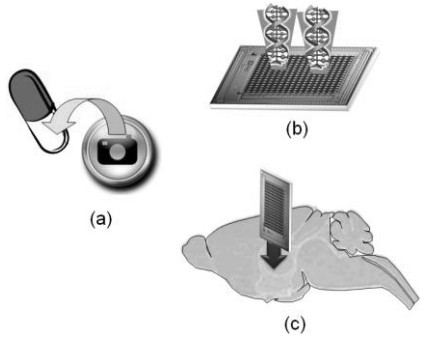

Fig. 1 Configurations of biomedical imaging devices. (a) Hermetic, (b) "dish," and (c) implanted imaging devices.

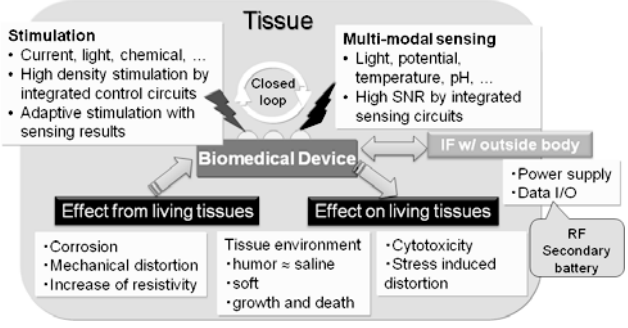

Fig. 2 Advantages and disadvantages associated with biomedical devices (adapted from [2]).

Manuscript received April 19, 2011.
Manuscript revised April 30, 2011.

[†]The authors are with Nara Institute of Science and Technology, Ikoma-shi, 630-0101 Japan.
[††]The authors are with JST, CREST, Kawaguchi-shi, 332-0012 Japan.
a) E-mail: ohta@ms.naist.jp

DOI: 10.1587/transcom.E94.B.2454

and cells. In addition, during stimulation, electrochemical reactions can occur when the stimulation voltage exceeds the voltage window, and pH changes and/or bubbling can have harmful effects on neural cells [7]. Moreover, devices that come into contact with living materials are also affected by the living environment. The living environment is composed primarily of saline solution, so that a CMOS chip with no coating may be damaged. Therefore, a highly water-tight packaging, such as parylene, is necessary. Of course, this material must be biocompatible. An implanted device is stressed by living tissues and, as such, the device may be deformed or broken. For example, although a thin CMOS chip can be easily implanted, such a chip may be broken by stress from tissues because thin Si is fragile. Living tissues may grow and die, so that the configuration between the device and the tissues may change gradually. This may cause impedance changes between an electrode and living cells. The implanted devices must be designed while recognizing that the configuration of the device may change.

The power supply is also an important issue. Some devices are used a wireless transmission of power electromagnetically and/or optically, while some are installed a battery inside a body [8]. In any cases, total amount of power supply is very limited. Biofuel cell technology is promising to alleviate this issue [9], although it is still early stage for implantation.

The present paper focuses on implanted imaging devices by reviewing recent results obtained using CMOS imaging devices in biomedical applications. Two bio-imaging devices are considered, namely, a dish-type imaging device for *in vitro* measurement [6] and a brain-implantable imaging device for *in vivo* measurement [10], [11]. A retinal prosthetic device is then introduced for medical applications [5], [14]. In the following sections, we describe and demonstrate these devices and then discuss future issues.

2. Dish Imaging Device

2.1 Multi-Site Measurement of Neural Activities

Multi-site measurement of neural potential is important in clarifying how neural networks are organized and represented. Currently, multi-electrode arrays (MEAs) and multi-electrode dishes (MEDs) are used as compact analytical instruments to enable the simultaneous analysis of the potential status of several neurons [15]. However, potentiometric analysis using metal electrodes has a physiological limitation due to the trade-off between the size of the electrode providing the effective charges and the density of electrodes, as well as the problem of metal corrosion. In order to realize higher-density and wider-range measurement, optical imaging is effective. Among optical imaging methods, voltage-sensitive dye (VSD) imaging, an optical method of measuring the membrane potential, is a powerful tool for studying neural activity [16]. Since VSD molecules bind to cell membranes, the change in membrane potential can be evaluated based on the change in the absorbance or fluorescence spectra of these molecules. Usually, an optical microscope is used to measure fluorescence from a specimen.

2.2 Multi-Site Measurement Using the Dish Image Sensor

Although a measurement system using VSD enables high-density and wide-range measurement of neural activities, such a system is bulky due to the use of an optical microscope, as compared with MED or MEA systems. In order to address this problem, we have developed a measurement system in which an imaging device is used as a specimen dish and can directly detect the fluorescence pattern from the specimen, which is dyed by VSD. This dish imaging device enables the realization of a novel potential multi-site measurement system [6].

The dish device is based on a newly developed implantable CMOS image sensing device, which we refer to as a biomedical photonic LSI (bmp-LSI) device, as shown in Fig. 3(a). Such on-chip imaging realizes simultaneous real-time analysis with a high density and a wide range, as compared to existing measurement systems. The bmp-LSI is described in detail in the following section.

By coating the bmp-LSI surface with poly-L-lysine and placing the surface into a cultural medium, as shown in Fig. 4, we succeeded in realizing an on-chip cell culture

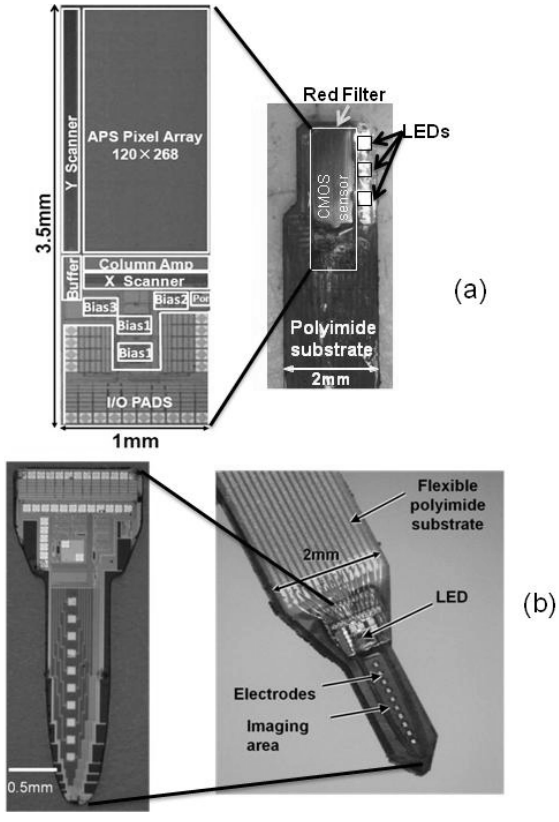

Fig. 3 Bmp-LSIs. (a) Rectangular bmp-LSI for both implantation and contact measurement. (b) Shank bmp-LSI for implantation. Electrodes are integrated on the imaging area. Adapted from [6] and [13].

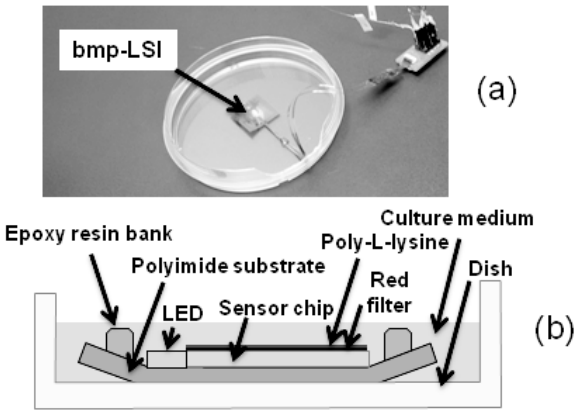

Fig. 4 Bmp-LSI for dish application (adapted from [6]). (a) Experimental setup. (b) Conceptual illustration of the system.

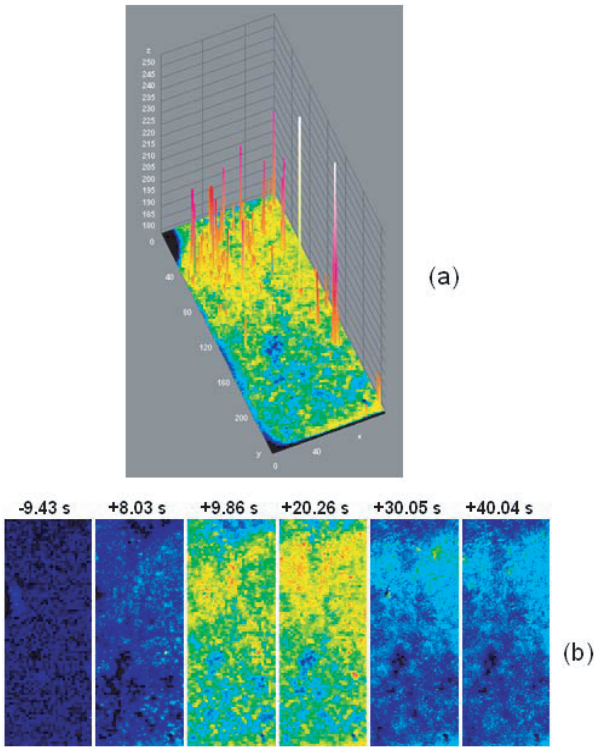

Fig. 5 Potentiometric imaging of cortical neurons using the dish bmp-LSI (adapted from [6]). (a) Three-dimensional representation of a potentiometric image shown in pseudo-color after baseline signal subtraction. (b) Sequential images obtained by time-lapse imaging.

for over one month and detected the fluorescence signals of on-chip-cultured cells with cellular resolution, which means that the resting membrane potential of cells was visualized. Using this device, we succeeded in potentiometric imaging of the depolarizing process on pheochromocytoma cells (PC12 cells) and mouse cerebral cortical neurons in a primary culture. After high- K^+ stimulation, the fluorescence intensities of neurons rapidly decreased on almost all of the pixels, indicating that several thousand neurons were activated, as shown in Fig. 5. We demonstrated that the proposed application realizes simultaneous multi-measurement of the potential status of several thousand neurons with a high density over a wide range using a compact analytical instrument with sufficiently high spatiotemporal resolution to analyze the process of depolarization.

We are currently developing a dish type imaging device that incorporates on-chip stimulation/recording electrodes [17]. Recently, a CMOS-based multi-electrode array was developed and commercialized, whereas the proposed device has an advantage by virtue of an on-chip imaging function. Other dish-type imaging devices have been reported, including a pH imaging device [18] based on the ISFET (Ion-Sensitive Filed Effect Transistor) structure.

3. Brain Implantable Imaging Device

3.1 Brain Imaging Measurement

Neural activities in the deep brain are important for learning and memory. Investigating the neural activities of small animals, such as a mouse, without tethering, is difficult using currently available measurement tools such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and functional near infrared spectrometer (fNIRS)/optical tomography. In order to address this problem, several devices have been developed [1], [2]. However, the observation of neural activities in the deep mouse brain using these devices remains difficult.

We have developed a CMOS-based bmp-LSI imaging device with a sub-millimeter/sub-second spatiotemporal resolution and have successfully demonstrated monitoring of the time course of serine protease activities inside the mouse hippocampus [10]–[13].

3.2 The Bmp-LSI and Deep Brain Imaging

The bmp-LSI is based on a CMOS image sensor fabricated using standard 0.35-μm CMOS technology. The pixel structure is a three-transistor type active pixel sensor (APS) with a parasitic photodiode composed of n-wells and p-substrate junctions. The number of input/outputs is limited to four in order to minimize the constraint of the implanted animals by the external wires [13]. The pixel size was designed to be $7.5 \times 7.5\,\mu m^2$, which is sufficient to image neural cells with sizes of approximately 10 to 50 μm, because spatial resolution is directly related to pixel size. In this setup, only the object in the vicinity of the sensor can be clearly observed because the device has no imaging optics. The frame rate of the bmp-LSI can be as high as 13.5 fps, as calculated based on a temporal resolution of approximately 75 ms. Since nerve kinetics change in periods of approximately 100 ms, the temporal resolution of the bmp-LSI is used to image neural activities. The bmp-LSI is sufficiently thin and long to observe the corpus striatum in a basal ganglion with minimal invasion. In addition, the dimensions of the bmp-LSI are expected to allow implantation into deeper regions in the brain and to enable stable imaging in the deep

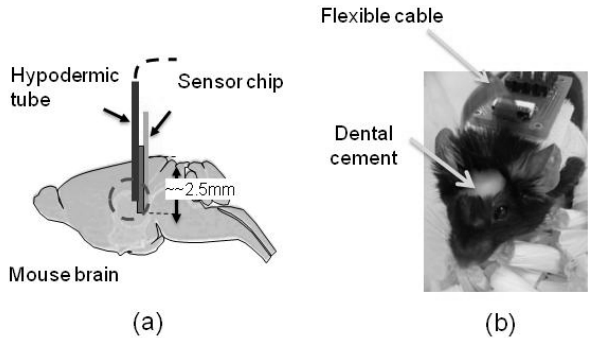

Fig. 6 Implantable imaging device. (a) Implantation into the mouse deep brain. (b) Freely-moving mouse implanted with the device.

brain of a freely moving mouse.

The bmp-LSI is compactly packaged in a polyimide substrate with light-emitting diodes (LEDs) and an excitation light filter for fluorescent imaging and improved biocompatibility. The polyimide substrate is fully flexible and has been shown to be biocompatible for the surgical insertion of implanted devices into the living body. The color filter blocks the excitation light, allowing only fluorescent emission to reach the image sensor. LEDs are also implemented on the polyimide substrate. In order to protect the chip during the experiment, the chip is sealed in an optically transparent and waterproof epoxy resin. The thickness of the assembled CMOS imaging device is approximately 350 μm. Figure 3 shows two examples of bmp-LSIs. One bmp-LSI is used for implantation as well as for culturing cells, whereas the other bmp-LSI is used for implantation with on-chip electrical measurement. These bmp-LSIs have different shapes.

In this experiment, a bmp-LSI was implanted into the basal ganglion of the mouse brain. The bmp-LSI was fixed to the skull with dental cement and was connected to a wiring harness through a slip-ring connector, as shown in Fig. 6. As a fluorophore, a chemical substance was introduced into the mouse brain through a hypodermic tube. The substance changes from a non-fluorophore into a fluorophore when neural activities occur in hippocampus, which means that the sensor can detect a specified molecular activity.

We have confirmed that the device implanted into the deep mouse brain could be successfully operated, and the mouse implanted with the device was alive and able to move freely one week after implantation. Based on a previous experiment, we confirmed that the mouse brain was intact, except for the region in which the device was inserted, and that the brain tissues were not severely damaged. No foreign-body reaction was observed. Figure 7 shows typical experimental measurement results for deep brain neural activities obtained using a bmp-LSI implanted in a mouse hippocampus. Spatio-temporal neural activities have been measured successfully.

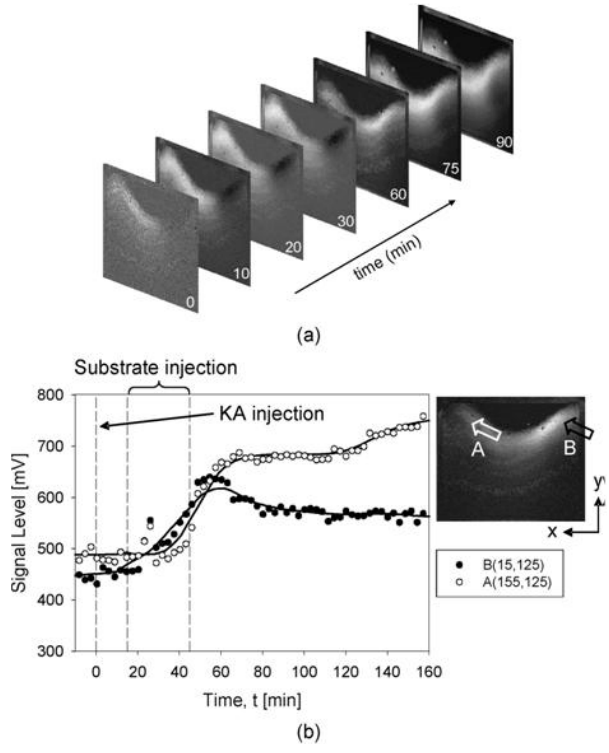

Fig. 7 Experimental results for neural activity in the mouse hippocampus obtained using the implanted CMOS imaging device (adapted from [11]). (a) Time course of the obtained images. (b) Signal level as a function of time. ©2008 IEEE.

4. Retinal Prosthetic Device

4.1 Principle of the Retinal Prosthesis

This section describes a retinal prosthetic device for use as an implantable image sensing device. In some diseases of the eye, the photoreceptor cells are dysfunctional, whereas most of the other retinal cells, such as ganglion cells, remain healthy, unless the disease is in the terminal stage [19]. Consequently, by stimulating the remaining retinal cells, visual sensation or phosphene can be evoked. This is the principle of the retinal prosthesis, or artificial vision. Based on this principle, a retinal prosthesis device stimulates retinal cells with a patterned electrical signal so that a blind patient may sense a patterned phosphene, or something like an image. The retinal prosthesis system is shown in Fig. 8, where power/data is sent by wireless transmission through a coil system [14], [20].

A retinal prosthesis requires an imaging device. Two types of imaging systems have been developed: the extraocular imaging system and the intraocular imaging system. In the extraocular imaging system, a CMOS camera is installed outside the body, for example, in a pair of eyeglasses. In the intraocular imaging system, a photo-sensor is integrated with a stimulus electrode, which acts as a photoreceptor cell.

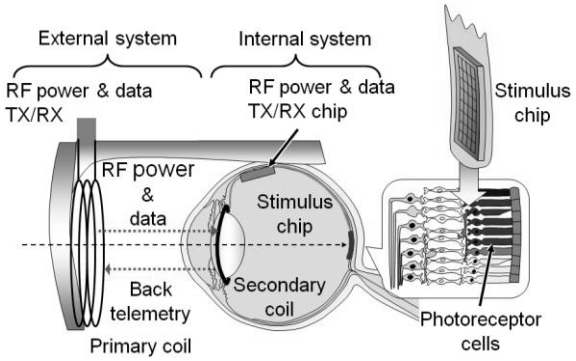

Fig. 8 Retinal prosthesis system.

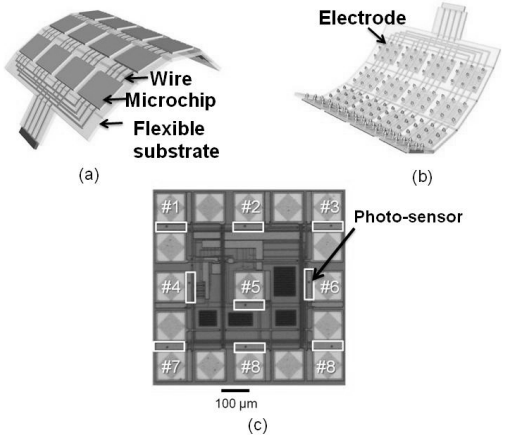

Fig. 9 Distributed microchip retinal stimulator (adapted from [23]). (a) Back of the stimulator. (b) Front of the stimulator. (c) Photograph of the microchip. ©2009 IEEE.

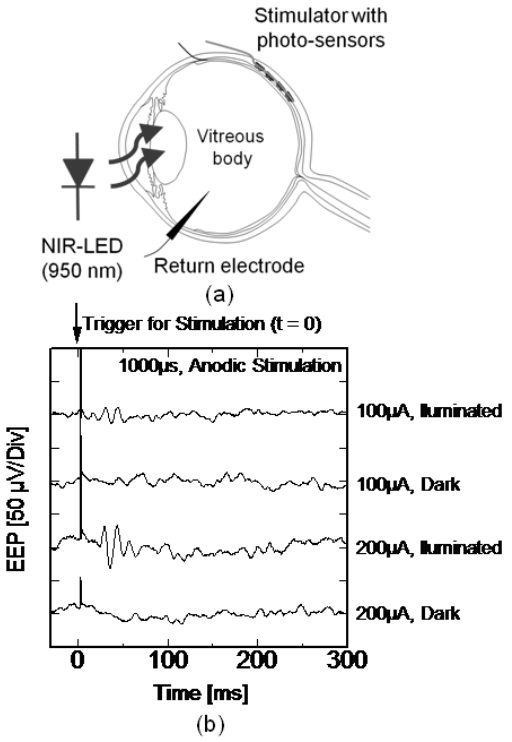

Fig. 10 (a) Experimental setup of retinal stimulation, and (b) EEP signals of the implanted stimulator. A NIR-LED emitting at approximately 950 nm is used as the illumination source. The current value indicates the input current to the microchip. The stimulus current can flow only if the NIR light illuminates the chip. Note that EEP signals were obtained only when the chip was illuminated. Adapted from [23]. ©2009 IEEE.

4.2 Retinal Prosthetic Device Based on CMOS Technology

In order to realize better vision through a retinal prosthesis, the incorporation of over 1,000 electrodes is preferable. When increasing the number of electrodes, we are faced with problems associated with the interconnection of electrodes and external lead wires with good mechanical flexibility. Specifically, the stimulator must be bent to match the curvature of the eyeball.

In order to solve this problem, we have developed a new type of smart stimulator that consists of a number of CMOS-based microchips distributed on a flexible substrate, as shown in Fig. 9 [14], [21]–[23]. As shown in Fig. 8, each microchip incorporates several stimulus electrodes, which can be externally controlled such that the electrodes can be turned on and off through an external control circuit. In addition to solving the interconnections issue, CMOS-based stimulators offer several advantages, such as signal processing. In order to allow flexibility, we place several microchips on a substrate in a distributed manner.

A microchip has a light-sensing function, as shown in Fig. 9 [23]. The stimulus current is controlled by the light impinging on the microchip. When the light intensity reaches a threshold value in the chip, the stimulus current control switch is turned on, and the stimulus current flows into the retinal cells. After the chip fabrication, as stimulus electrodes, nine Pt bumps were formed on the Al pads of the chip. The four microchips were assembled on a flexible polyimide substrate using a flip-chip bonding technology specially developed for this distributed architecture.

The fabricated stimulator was implanted into a pocket formed in the sclera of a rabbit eye. A near infrared (NIR) LED array illuminated the eye at the location at which the stimulator was implanted. Note that NIR light cannot evoke photoreceptors and can penetrate the epithelium and the sclera of the rabbit eye to some distance. The electrical evoked potential (EEP) signal was measured through screw electrodes set in the visual cortex. After implanting the stimulator, we confirmed that a visual evoked potential (VEP) signal was not produced by the NIR light used in this experiment before the measurement of the EEP signal. When NIR light is incident on the eye, a clear EEP signal was obtained, as shown in Fig. 10, and thus the stimulation of retinal cells was successfully demonstrated [23].

5. Conclusion

Although implantable CMOS devices are very useful for

biomedical applications, there are several issues to be considered. In this review, we discussed three examples of implantable CMOS devices for biomedical applications: *in vitro* neural activity imaging, an *in vivo* brain implantable CMOS imaging device, and a retinal prosthesis.

The implantable CMOS image sensing device is introduced for monitoring the neural activity both on cultured cells on the chip and in the deep brain of a mouse. These applications demonstrate the effectiveness of the proposed device for use in biological science. The dish imaging device can be applied to optogenetics. We are currently developing a blue LED array for attachment to the dish imaging device in order to evoke neural cells, which are genetically modified with ChR2 [24].

The next step in improving the implantable CMOS imaging device is to improve the resolution of the sensor. Unlike bulky optics, micro-optics are suitable for use in implantable devices. We have demonstrated that a light guide array structure is effective for use in the developed device. The other requirement is to construct a wireless system for a complete implantable device. In addition, we must reduce tissue damage when inserting the device. By reducing the chip size, we can address this problem [25].

The next step in improving the retinal prosthesis device is to ensure durability and biocompatibility in long-term operation inside living tissue. One of the most difficult problems is obtaining a suitable package for a Si microchip. Although palyrene is a good candidate for this package, the long-term water-resistant characteristics of parylene are unknown. Although a ceramic hermetic case is effective for providing water resistance, this case has a large volume for a microchip. A deposited metal film is another candidate, but depositing a metal film that has no pinholes is difficult, and if pinholes exist, water can penetrate into the chip.

Although there are several problems to be solved in terms of biocompatibility and durability in order to realize long-term operation, biomedical imaging CMOS devices will play an important role in future biomedical applications.

Acknowledgments

We would like to thank Prof. T. Fujikado of Osaka University and Dr. Y. Terasawa of Nidek Co. Ltd. for their valuable discussions and conducting animal experiments involving retinal prosthesis, and Profs. S. Shiosaka and H. Tamura for their valuable discussions and conducting animal experiments involving implantable image sensing devices.

References

[1] J. Ohta, Smart CMOS Image Sensors and Applications, CRC Press, Boca Raton, FL, 2001.

[2] J. Ohta, T. Tokuda, K. Sasagawa, and T. Noda, "Implantable CMOS biomedical devices," Sensors, vol.9, pp.9073–9093, 2009.

[3] M.S. Humayun, J.D. Weiland, G. Chader, and E. Greenbaum, eds., Artificial Sight, Springer, New York, NY, 2007.

[4] G. Iddan, G. Meron, A. Glukhovsky, and P. Swain, "Wireless capsule endoscopy," Nature, vol.405, p.417, 2000.

[5] T. Tokuda, K. Hiyama, S. Sawamura, K. Sasagawa, Y. Terasawa, K. Nishida, Y. Kitaguchi, T. Fujikado, Y. Tano, and J. Ohta, "CMOS-based multichip networked flexible retinal stimulator designed for image-based retinal prosthesis," IEEE Trans. Electron Devices, vol.56, no.11, pp.2577–2585, 2009.

[6] T. Kobayashi, A. Tagawa, T. Noda, K. Sasagawa, T. Tokuda, Y. Hatanaka, H. Tamura, Y. Ishikawa, S. Shiosaka, and J. Ohta, "Potentiometric dye imaging for pheochromocytoma and cortical neurons with a novel measurement system using an integrated complementary metal-oxide semiconductor imaging device," Jpn. J. Appl. Phys., vol.49, 117001, 2010.

[7] W.F. Agnew and D.B. McCreery, eds., Neural Prostheses, Prentice Hall, Englewood, Cliffs, NJ, 1990.

[8] R. Puers and J. Thoné, "Short Distance Wireless Communications," in Bio-Medical CMOS ICs, ed. H.-J. Yoo and C. van Hoof, Springer, New York, NY, 2011.

[9] T. Miyake, M. Oike, S. Yoshino, Y. Yatagawa, K. Haneda, H. Kaji, and M. Nishizawa, "Biofuel cell anode: NAD^+/glucose dehydrogenase-coimmobilized ketjenblack electrode," Chem. Phys. Lett., vol.480, no.1-3, pp.123–126, 2009.

[10] D.C. Ng, H. Tamura, T. Tokuda, A. Yamamoto, M. Matsuo, M. Nunoshita, Y. Ishikawa, S. Shiosaka, and J. Ohta, "Real time in vivo imaging and measurement of serine protease activity in the mouse hippocampus using a dedicated CMOS imaging device," J. Neurosci. Method, vol.156, no.1-2, pp.23–30, 2006.

[11] D.C. Ng, T. Nakagawa, T. Mizuno, T. Tokuda, M. Nunoshita, H. Tamura, Y. Ishikawa, S. Shiosaka, and J. Ohta, "Integrated in vivo neural imaging and interface CMOS devices: Design; packaging; and implementation," IEEE Sens. J., vol.8, pp.121–130, 2008.

[12] H. Tamura, D.C. Ng, T. Tokuda, H. Naoki, T. Nakagawa, T. Mizuno, Y. Hatanakaa, Y. Ishikawaa, J. Ohta, and S. Shiosaka, "One-chip sensing device (biomedical photonic LSI) enabled to assess hippocampal steep and gradual up-regulated proteolytic activities," J. Neurosci. Methods, vol.173, no.1, pp.114–120, 2008.

[13] A. Tagawa, H. Minami, M. Mitani, T. Noda, K. Sasagawa, T. Tokuda, H. Tamura, Y. Hatanaka, Y. Ishikawa, S. Shiosaka, and J. Ohta, "Multimodal complementary metal-oxide-semiconductor sensor device for imaging of fluorescence and electrical potential in deep brain of mouse," Jpn. J. Appl. Phys., vol.49, 01AG02, 2010.

[14] J. Ohta, T. Tokuda, K. Kagawa, T. Furumiya, A. Uehara, Y. Terasawa, M. Ozawa, T. Fujikado, and Y. Tano, "Silicon LSI-based smart stimulators for retinal prosthesis," IEEE Eng. Med. Biol. Mag., vol.25, no.5, pp.47–59, 2006.

[15] H. Oka, K. Shimono, R. Ogawa, H. Sugihara, and M. Taketani, "A new planar multielectrode array for extracellular recording: Application to hippocampal acute slice," J. Neurosci. Methods, vol.93, p.61, 1999.

[16] L.B. Cohen and B.M. Salzberg, "Optical measurement of membrane potential," Rev. Physiol. Biochem. Pharmacol., vol.83, p.35, 1978.

[17] A. Nakajima, T. Noda, K. Sasagawa, T. Tokuda, Y. Ishikawa, S. Shiosaka, and J. Ohta, "Planar multi electrode array coupled CMOS image sensor for *in vitro* electrophysiology," Extended Abstract 2011 Int'l Solid-State Devices and Materials, pp.1170–1171, Tokyo, 2010.

[18] H. Nakazawa, M. Ishida, and K. Sawada, "Progressive-type fused pH and optical image sensor," Jpn. J. Appl. Phy., vol.49, no.4, 04DL04, 2010.

[19] M.S. Humayun, M. Prince, E. de Juan, Y. Barron, M. Moskowitz, I.B. Klock, and A.H. Milam, "Morphometric analysis of the extramacular retina from ostmortem eyes with retinitis pigmentosa," Invest. Ophthalmol Vis. Sci., vol.40, pp.143–148, 1999.

[20] J. Ohta, "Artificial retina IC," in Bio-Medical CMOS ICs, ed. H.-J. Yoo and C. van Hoof, Springer, New York, NY, 2011.

[21] T. Tokuda, Y.-L. Pan, A. Uehara, K. Kagawa, M. Nunoshita, and J. Ohta, "Flexible and extendible neural interface device based on cooperative multi-chip CMOS LSI architecture," Sensors & Actuators

A, vol.122, no.1, pp.88–98, 2005.
[22] J. Ohta, T. Tokuda, K. Kagawa, S. Sugitani, M. Taniyama, A. Uehara, Y. Terasawa, K. Nakauchi, T. Fujikado, and Y. Tano, "Laboratory investigation of microelectronics-based stimulators for large-scale suprachroidal transretinal stimulation (STS)," J. Neural Eng., vol.4, no.1, pp.S85–S91, 2007.
[23] T. Tokuda, K. Hiyama, S. Sawamura, K. Sasagawa,Y. Terasawa, K. Nishida, Y. Kitaguchi, T. Fujikado, Y. Tano, and J. Ohta, "CMOS-based multichip networked flexible retinal stimulator designed for image-based retinal prosthesis," IEEE Trans. Electron Devices, vol.56, no.11, pp.2577–2585, 2009.
[24] T. Tokuda, T. Noda, K. Sasagawa, and J. Ohta, "Optical and electric multifunctional CMOS image sensors for on-chip biosensing applications," Materials, vol.4, pp.84–102, 2011.
[25] J. Ohta, A. Tagawa, T. Kobayashi, T. Noda, K. Sasagawa, and T. Tokuda, "Implantable distributed biomedical photonic devices," to appear in Sensors and Materials.

Jun Ohta received B.E., M.E., and Dr. Eng. degrees in applied physics, all from the University of Tokyo, Japan, in 1981, 1983, and 1992, respectively. In 1983, he joined Mitsubishi Electric Corporation, Hyogo, Japan. From 1992 to 1993, he was a visiting researcher at the Optoelectronics Computing Systems Center, University of Colorado at Boulder. In 1998, he joined the Graduate School of Materials Science, Nara Institute of Science and Technology (NAIST), Nara, Japan as Associate Professor. He was appointed as Professor in 2004. His current research interests are smart CMOS image sensors, retinal prosthesis, and biomedical-photonic LSIs. He is a member of JSAP, ITE, IEEE, and OSA, and serves as a Far East Regional Committee and an International Technical Program Committee of ISSCC.

Takuma Kobayashi received a B.S. degree from Shinshu University, Nagano, Japan, in 2004. He received M.S. and Ph.D. degrees from Nara Institute of Science and Technology (NAIST), Nara, Japan, in 2006 and 2009, respectively. Since 2009, he has been a Postdoctoral Researcher at NAIST. Dr. Kobayashi is a member of the Molecular Biology Society of Japan, the Japanese Society of Developmental Biologists, the International Society of Developmental Biologists, the Japan Neuroscience Society, and JSAP.

Toshihiko Noda received B.E. and M.E. degrees in electrical and electronic engineering and a Ph.D. degree in engineering from the Toyohashi University of Technology (TUT), Aichi, Japan, in 2001, 2003, and 2006, respectively. He was a Postdoctoral Researcher of the Venture Business Laboratory at TUT from 2006 to 2007. He joined the faculty of the Intelligent Sensing System Research Center at TUT in 2008 as Assistant Professor. Since 2009, he has been an Assistant Professor at the Nara Institute of Science and Technology (NAIST), Nara, Japan. His current research interests focus on retinal prosthesis devices and bioimaging with CMOS image sensors.

Kiyotaka Sasagawa received a B.S. degree from Kyoto University, Kyoto, Japan, in 1999, and the M.E. and Ph.D. degrees in materials science from the Nara Institute of Science and Technology, Nara, Japan, in 2001 and 2004, respectively. From 2004 to 2008, he was a Researcher at the National Institute of Information and Communications Technology (NICT), Tokyo, Japan. In 2008, he joined the Nara Institute of Science and Technology (NAIST), Nara, Japan, where he is currently an Assistant Professor. His research interests include bioimaging, biosensing, and electromagnetic-field measurement.

Takashi Tokuda received B.E. and M.E. degrees in electronic engineering and a Dr. Eng. degree in materials engineering from Kyoto University, Kyoto, Japan, in 1993, 1995, and 1998, respectively. He has been an Assistant Professor since 1999 and an Associate Professor since 2008 in the Graduate School of Materials Science, Nara Institute of Science and Technology (NAIST). Since 1999, he has been working on photonic materials science and photonic device engineering. His research interests include CMOS image sensors, retinal prosthesis devices, bio-imaging sensors, and biosensing devices.