31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

Light-controlled retinal stimulation on rabbit using CMOS-based flexible multi-chip stimulator

T. Tokuda, Y. Takeuchi, T. Noda, K. Sasagawa, K. Nishida, Y. Kitaguchi, T. Fujikado, Y. Tano, and J. Ohta

***Abstract*—We implemented a light-sensing function on CMOS-based multi-chip stimulator for retinal prosthesis. Using the light-sensing circuitry attached to each stimulation electrode, the flexible multi-chip stimulator is capable of image-based patterned stimulation. We verified the function of the light-controlled decision based on the light intensity measured just beside the stimulation site. We also experimentally demonstrated *in vivo* retinal stimulation on rabbit's retina with light-controlled decision. The result of the present work is a simplified demonstration for the concept of retinal prosthesis with on-site imaging.**

I. Introduction

LSI -based neural prosthesis / rehabilitation technology is attracting a lot of interest as the new therapeutic platform for various neural disabilities [1-8]. Retinal prosthesis is the neural prosthesis in which LSI-based device will play an essential role [3-8]

We have proposed multi-chip architecture to realize a CMOS-based flexible retinal stimulator [9-12]. Fig. 1 shows (a) concept and (b) photographs of the multi-chip flexible stimulator. A small-sized multi-electrode CMOS stimulators "unit chips" are arrayed on a flexible substrate to realize both high-resolution stimulation and flexibility. We have successfully fabricated and demonstrated the functionality of the multi-chip retinal stimulators in 3x4 and 1x4 configurations [9-12].

Concerning about image reconstruction in retinal prosthesis technology, image-based stimulation in which the stimulation pattern is generated based on the light intensity at the stimulation site is one of the promising option.

In this work, we designed a new CMOS chip for flexible retinal stimulator with capabilities of on-site light sensing and light-controlled stimulation. We characterized the functionality of the light-sensing and light-controlled stimulation. We also performed the light-controlled stimulation *in vivo* retinal stimulation trial on rabbit's retina.

Manuscript received April 23, 2009. This work was supported in part by Strategic Research Program for Brain Science, The Asahi Glass Foundation.

T. Tokuda, Y. Takeuchi, T. Noda, K. Sasagawa, and J. Ohta are with Nara Institute Science and Technology, Takayama-cho 8916-5, Ikoma, Nara, 630-0192, JAPAN (phone: +81-743-72-6054; fax: +81-743-72-6052; e-mail: tokuda@ms.naist.jp).

K. Nishida, Y. Kitaguchi, T. Fujikado, and the late Y. Tano are with Graduate School of Medicine, Osaka University, 2-15 Yamadaoka, Suita, Osaka 565-0871, JAPAN

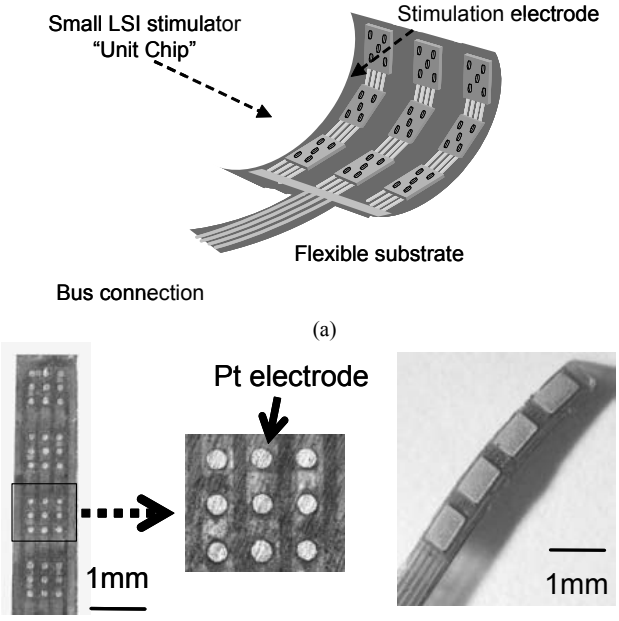


Fig. 1: (a) Concept and (b) photographs of multi-chip flexile retinal stimulator.

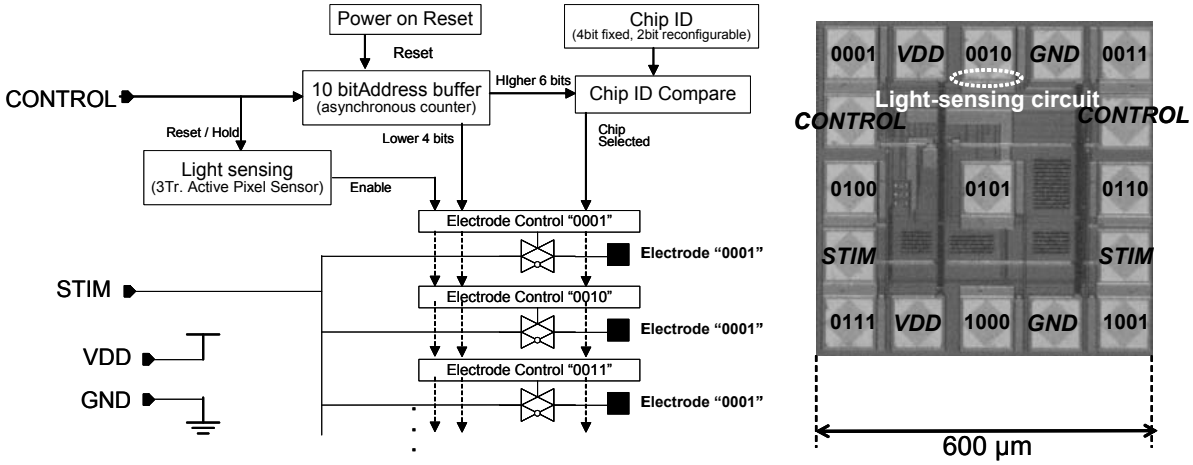
II. Design of the Flexible Multi-Chip Retinal Stimulator with Light Controlled Stimulation

Fig. 2 shows (a) block diagram and (b) layout of the unit chip, the core device of the multi-chip flexible retinal stimulator. In this work, we implemented the functionality of light-controlled stimulation without changing the basic design (area, number and layout of the I/O pads, and operation sequence) from the previous unit chip [10, 12].

The unit chip has four input lines; VDD, GND, CONTROL, and STIM, and nine stimulation outputs with addresses of "0001" - "1001". The device has a 10-bit asynchronous counter as an address buffer. Each unit chip counts the number of digital pulses applied on the CONTROL line and interpret it as an address of the stimulation electrode for stimulation. The lower 4 bits in the address buffer are used to identify the electrodes, and the higher 6 bits are used to code the unit chip to be used (Each unit chip has its unique ID.).

Fig. 3 shows typical control sequence of the multi-chip stimulator. After we turn on the chip by applying 5V between VDD and GND lines, we apply pulse train on CONTROL line. The number of the pulses was interpreted as the electrode address (6-bit chip ID + 4-bit electrode ID). Only the selected electrode on the selected unit chip is connected to the STIM line. Using an external stimulator, we can perform retinal stimulation with the selected electrode.

978-1-4244-3296-7/09/$25.00 ©2009 IEEE



(a) Block diagram (b) Layout

Fig. 2. (a) Block diagram and (b) layout of the unit chip.

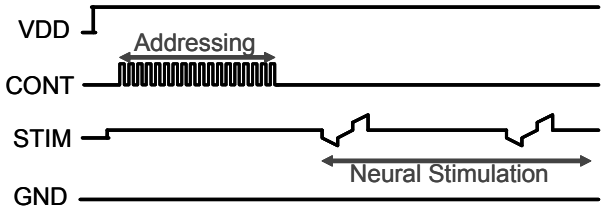


Fig. 3. Operating sequences of the multi-chip stimulator

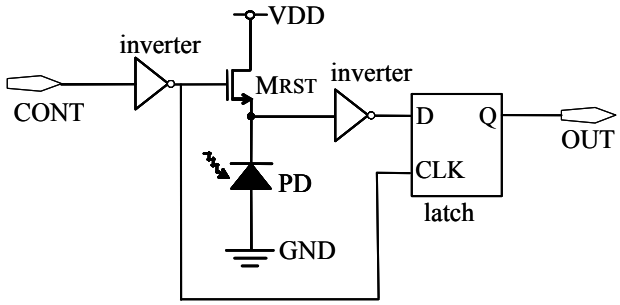


Fig. 4. Schematic of the light-sensing circuitry

Fig. 4 shows schematic of the light-sensing circuitry implemented on each stimulation output. To realize the light-controlled decision, we implemented an active pixel sensor (APS) circuitry with binary output. In contrast to conventional APS circuitry for CMOS image sensor pixels, VDD was used as the reset voltage. Owing to this simplification, we can implement the light-controlled functionality without any additional input. A comparator directly connected to the photodiode node transforms the photodiode level into binary output. The photodiode is reset and the comparator is latched when CONT is low. The photodiode starts to discharge at the Low to High transition for each pulse on CONT, and the decision at the High to Low transition of the pulse is latched until next pulse is applied. We used this binary output to enable / disable the stimulation output from each stimulation electrode. Thus, the final decision for stimulation can be controlled using the light intensity measured at the stimulation site. The threshold light intensity for light-controlled decisions can be adjusted with the length of the last pulse in addressing.

We assembled the unit chips on a polyimide flexible substrate using flip-chip bonding technology, and formed Pt/Au bump electrodes on the device. The detailed structure and packaging process are compatible with the previous versions of the flexible retinal stimulator [9-12].

III. Functional Characterization of the Light-Sensing Circuitry

Prior to assemble into the flexible retinal stimulator, we performed the functional verification of the unit chip circuitry in the dry situations. To verify the addressing function, we alternatively applied 5V digital pulses on the CONTROL and STIM lines with and without light illumination. Since each pulse on CONTROL line increments the address of the selected electrode, each pulse on STIM is transferred to different stimulation electrode.

We observed the potential of electrodes with addresses of "0000000111" and "0000001001". Fig. 5 shows experimentally obtained traces of the trials. Fig. 5(a) and 5(b) are the results in the situation with and without illumination, respectively. We can see the pulse applied on STIM line was transferred to electrode "0000000111" after the 7th CONTROL pulse and to "0000001001" after the 9th CONTROL pulse, only in the case the chip was illuminated. The results suggest that the functions of addressing and light-controlled decision are correctly working.

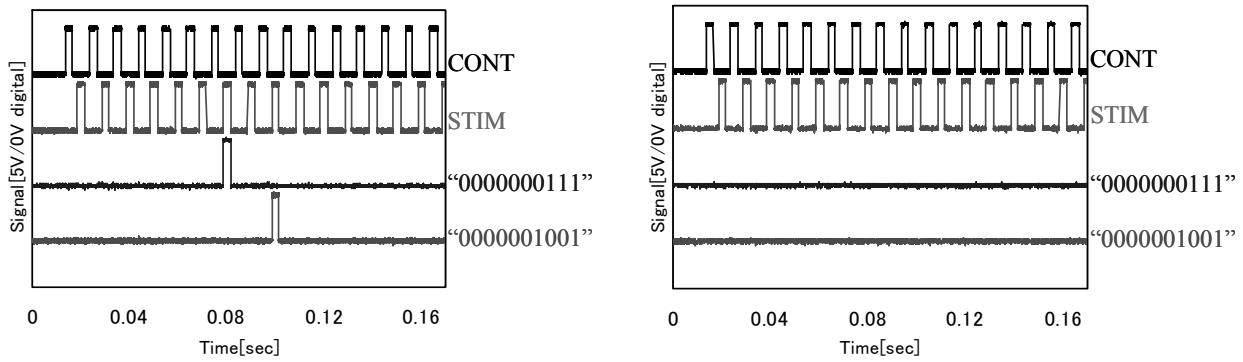


Fig. 5. Demonstration traces showing addressing and light-sensing functions (a) with and (b) without illumination.

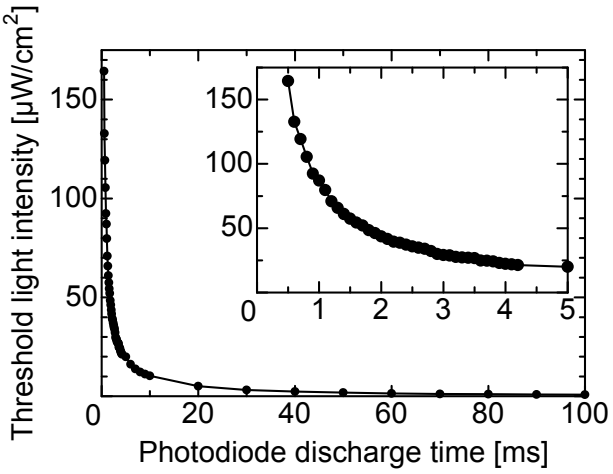


Fig. 6. Depencence of the threshold light intensity on the pulse length for APS discharge (measurement time).

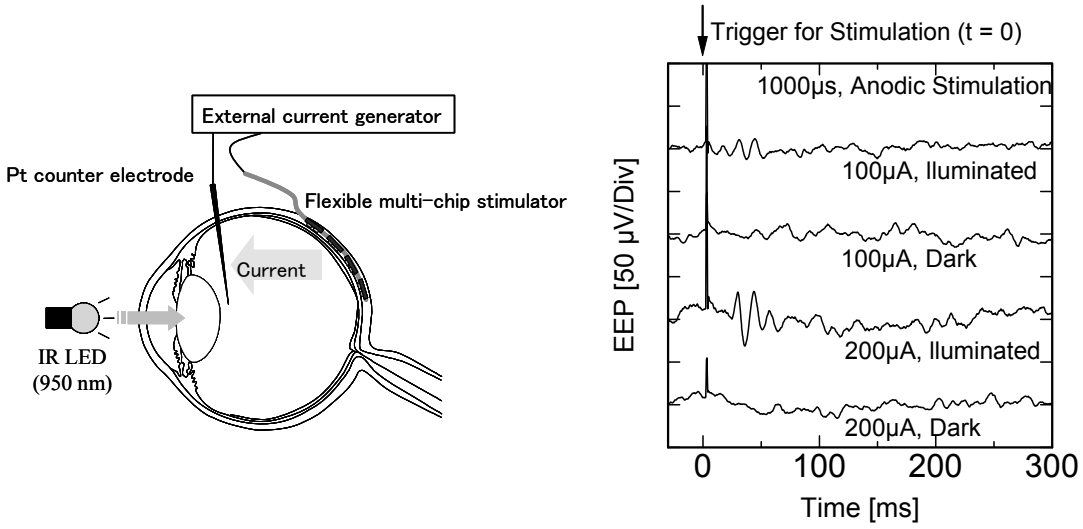
IV. *IN VIVO* EXPERIMENTAL DEMONSTRATION OF THE LIGHT-CONTROLLED STIMULATION ON RABBIT'S RETINA

We performed an *in vivo* experimental demonstration of light-controlled retinal stimulation. The retinal stimulation was performed with suprachoroidal transretinal stimulation (STS) configuration [13, 14]. We assembled the 4 x 1 unit chips into a flexible retinal stimulator. In the present work, we used the same device packaging and experimental procedure as our previous report [12] except that we illuminated the stimulator with infrared (IR) light through the rabbit's retina. Since the rabbit (Dutch black belted rabbit) was wild type and its retina had not degenerated, the wavelength chosen for the control light must be insensible by the rabbit's retina. We prepared an LED light source with a peak wavelength of 950 nm. A 3 × 3 array of IR LED (OSRAM, LD271H) was placed in front of the rabbit's eye. The distance between the implanted stimulator chip and LED light source was approximately 50 mm. We confirmed that no visually evoked potential (VEP) was observed by the IR illumination on the rabbit retina.

Fig. 7(a) schematically shows the situation of the retinal stimulation on the rabbit retina using the implanted multi-chip flexible stimulator. After the surgical operation to implant the stimulator, we confirmed that a clear VEP response in the visual cortex of the animal's brain was observed when we used visible light. We can confirm that the rabbit was appropriately anesthetized and the visual nerve system was ready for experiments.

In the *in vivo* experimental demonstration, we stimulated the rabbit's retina with an anodic constant-current injection. The pulse height was chosen to be between 50 and 300 μA, and the pulse duration was 1000 μs. The stimulation was performed 100 times with an interval of 2 s and the signal on the visual cortex of the brain was averaged and recorded.

Fig. 7(b) shows the results of the *in vivo* retinal stimulation experiment. In Fig. 7(b), the EEP traces show that the stimulation was successfully controlled by the IR light and caused differences in the response in the visual cortex of the rabbit's brain. For both conditions of 100 and 200 μA, clear responses were observed at 20 - 60 ms after stimulation. The duration and waveform observed on the EEP traces suggest that the stimulation on the retina was enabled by only illumination. Therefore, we can conclude that the rabbit's perception was controlled by light which was insensible to the rabbit's retina. This is a quite simple but direct demonstration of the concept for light-controlled (and image-based) retinal prosthesis.



(a) (b)

Fig. 7. (a) Set up and (b) results (EEP traces) of *in vivo* retinal stimulation experiment on rabbit's retina.

V. Conclusions

We designed a CMOS-based flexible multi-chip retinal stimulator for retinal prosthesis technology. To realize light-controlled stimulation, we implemented a light-sensing circuit. We verified the function of the light-controlled decision based on the light intensity measured just beside the stimulation site.

We also experimentally demonstrated *in vivo* retinal stimulation on rabbit's retina with light-controlled decision. The result of the present work is a simplified demonstration for the concept of retinal prosthesis with on-site imaging.

Acknowledgements

This work was supported by VLSI Design and Education Center (VDEC), the University of Tokyo in collaboration with Cadence Design Systems, Inc.

References

[1] K. Najafi, K.D. Wise, "An implantable multielectrode array with onchip signal processing," IEEE J. Solid-State Circuits, vol. sc-21, pp. 1035–1986 ,1986.

[2] C. Kim, K.D. Wise, "A 64-site multishank CMOS low-profile neural stimulating probe," IEEE J. Solid-State Circuits, vol. 31, pp. 1230–1238, 1996.

[3] M. S. Humayun, E. Jr. de Juan, J. D. Weiland, G. Dagnelie, S. Katona, R. Greenberg, and S. Suzuki, "Pattern electrical stimulation of the human retina," Vision Researchm vol. 39, pp. 2569-2576, 1999.

[4] S. C. DeMarco, W. Liu, P. R. Singh, G. Lazzi, M. S. Humayun, and J. D. Weiland, "An arbitrary waveform stimulus circuit for visual prostheses using a low-area multibias DAC," IEEE J. Solid-State Circuits, vol. 38, pp.1679-1690, 2003.

[5] E. Zrenner, A. Stett, S. Weiss, R. B. Aramant, E. Guenther, K. Kohler, K. D. Miliczek, M. J. Seiler, and H. Haemmerle, "Can subretinal microphotodiodes successfully replace degenerated photoreceptors?," Vision Res., vol. 39 pp. 2555-2567, 1999.

[6] T. Watanabe, R. Kobayashi, K. Komiya, T. Fukushima, H. Tomita, E. Sugano, H. Kurino, T. Tanaka, M. Tamai, and M. Koyanagi, "Evaluation of Platinum-Black Stimulus Electrode Array for Electrical Stimulation of Retinal Cells in Retinal Prosthesis System," Jpn. J. Appl. Phys, vol. 46, pp. 2785-2791, 2007.

[7] J. F. Rizzo III, J. Wyatt, J. Loewenstein, S. Kelly, and D. Shire, "Methods and Perceptual Thresholds for Short-Term Electrical Stimulation of Human Retina with Microelectrode Arrays," Invest. Ophthalmol. Vis. Sci., vol. 44, pp. 5355-5361, 2003.

[8] J. Ohta, N. Yoshida, K. Kagawa and M. Nunoshita, "Proposal of application of pulsed vision chip for retinal prosthesis," J. Jpn. Appl. Phys., vol. 41 pp. 2322-2325, 2002.

[9] T. Tokuda, Yi-Li Pan, A. Uehara, K. Kagawa, M. Nunoshita, J.Ohta, "Flexible and extendible neural interface device based on cooperative multi-chip CMOS LSI architecture," Sensors & Actuators: A, vol. 122, pp. 88-98, 2005.

[10] J. Ohta, T. Tokuda, K. Kagawa, T. Furumiya, A. Uehara, Y. Terasawa, M. Ozawa, T. Fujikado, and Y. Tano: IEEE Engineering in Medicine and Biology Magazine, vol. 25, pp. 47-59, 2006.

[11] T. Tokuda, S. Sugitani, M. Taniyama, A. Uehara, Y. Terasawa, K. Kagawa, M. Nunoshita, Y. Tano, and J. Ohta, "Fabrication and validation of a multi-chip neural stimulator for *in vivo* experiments toward retinal prosthesis", Jpn. J. Appl. Phys, vol. 46, pp. 2792-2798, 2007.

[12] T. Tokuda; R. Asano; S. Sugitani; M. Taniyama; Y. Terasawa; M. Nunoshita; K. Nakauchi; T. Fujikado; Y. Tano; J. Ohta, "Retinal stimulation on rabbit using CMOS-based multi-chip flexible stimulator toward retinal prosthesis," Jpn. J. Appl. Phys. 47 (4B), pp. 3220-3225, 2008

[13] K. Nakauchi, T. Fujikado, H. Kanda, T. Morimoto, J. S. Choi, Y. Ikuno, H. Sakaguchi, M. Kamei, M. Ohji, T. Yagi, S. Nishimura, H. Sawai, Y. Fukuda and Y. Tano, "Transretinal electrical stimulation by an intrascleral multichannel electrode array in rabbit eyes," Graefe's Archive for Clinical and Experimental Ophthalmology, Vol. 243, pp. 169-174, Feb. 2005.

[14] M. Kamei, T. Fujikado, H. Kanda, T. Morimoto, K. Nakauchi, H. Sakaguchi, Y. Ikuno, M. Ozawa, S. Kusaka, and Y. Tano, "Suprachoroidal Transretinal Stimulation (STS) Artifical Vision System for Patients with Retinits Pigmentosa," Invest. Ophthalmol. Vis. Sci, Vol. 47, E-Abstract 1537, 2006.