INVITED PAPER Special Section on Analog Circuits and Their Application Technologies

Stimulator Design of Retinal Prosthesis

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SUMMARY This study focuses on the design of electrical stimulator for retinal prosthesis. The stimulator must be designed such that the occurrence of electrolysis or any irreversible process in the electrodes and flexible lead is prevented in order to achieve safe stimulation over long periods using the large number of electrodes. Some types of biphasic current pulse circuits, charge balance circuits, and AC power delivery circuits were developed to address this issue. Electronic circuitry must be introduced in the stimulator to achieve the large number of electrodes required to obtain high quality of vision. The concept of a smart electrode, in which a microchip is embedded inside an electrode, is presented for future retinal prostheses with over 1000 electrodes.

key words: *retinal prosthesis, neuro-stimulation, implantable devices, electrical stimulation, AC power delivery*

1. Introduction

Neuro-stimulation is a technology that cures diseases caused by loss of neurons in sensory organs by stimulating residual neuronal cells in the organs. Although magnetic or optical stimulation was recently developed for neuro-stimulation, we use only electrical stimulation for neuro-stimulation because of its wide use in medical devices at present. An artificial cochlear is a typical example of successful neuro-stimulation, where residual auditory ganglion cells are electrically stimulated and evoked in order to restore auditory sensation in a deaf patient.

Figure 1 illustrates the signal flow of a neuro-stimulator such as an artificial cochlear (cochlear implant) [1] and artificial retina (retinal prosthesis) [2]. It consists of two parts outside and inside the body electromagnetically coupled with a pair of coils located both inside and outside the body. The power and data are transmitted into the body and finally converted into the signal to stimulate neuronal cells.

In the cochlear implant, sound is one dimensional signal, therefore the stimulus electrodes are placed in one direction. The number of electrodes is typically less than 20. The stimulus electrode array is directly connected to the stimulus current generator as shown in Fig. 1.

On the contrary, in retinal prostheses, the input data is an image, therefore the stimulator must deal with two dimensional data. We must take special care of the design of the stimulator for retinal prosthesis. For example, the number of over 100 electrodes makes a direct interconnection difficult and requires electronic circuitry in the stimulator. It is noted that cochlear implants were commercialized in the 1980s and were successful, while two types of retinal prostheses were recently commercialized [3], [4] but they require improvements. Studies on two dimensional retinal stimulators are strongly demanded to develop durable high-performance retinal prostheses that are safe for prolonged use.

In this study, we discuss the stimulator design of retinal prosthesis from the perspective of electronic circuits and systems. First, the basic concept of a retinal prosthesis is introduced. Next, we focus on the stimulator design. This section includes four topics, three of which pertain to the safe operation of a retinal stimulator over long period, biphasic stimulation pulse, charge balance, and AC power delivery, while the fourth topic pertains to the large number of electrodes, i.e., how to achieve interconnection between an electrode and the flexible lead. Finally, we summarize the paper.

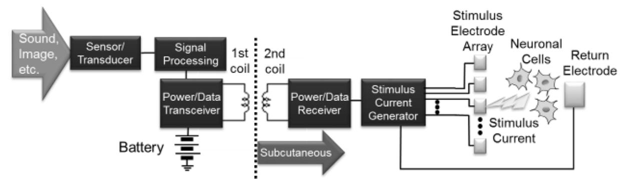

Fig. 1 Signal flow of a neuro-stimulator. Adapted from [2] with permission.

2. Retinal Prosthesis

The retina plays an important role in visual information collection and processing, therefore its dysfunction may result in blindness. Among blindness diseases, retinitis pigmentosa (RP) and age-related macular degeneration (AMD) have no effective remedies at present. In both cases, the photoreceptors gradually become dysfunctional, so that the patient eventually becomes blind. However, the some portion of the ganglion cells is still alive [5]. Consequently, by stimulating the remaining retinal cells, visual sensation or phosphenes can be evoked. This is the principle of the retinal prosthesis. Based on this principle, a retinal prosthetic device stimulates retinal cells with a patterned electrical signal so that a blind patient can sense a phosphene pattern, or something resembling an image.

Manuscript received February 23, 2017.
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DOI: 10.1587/transele.E100.C.523

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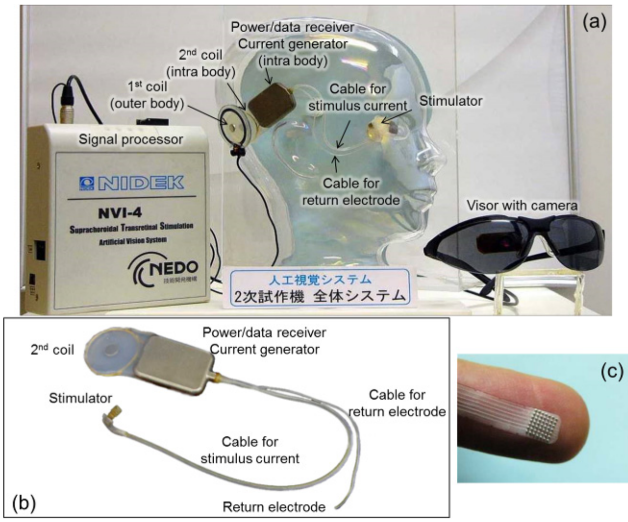

Fig. 2 Retinal prosthesis system. (a) Total system, (b) implant parts, and (c) electrode array.

Retinal prosthesis systems generally consist of three parts: the image acquisition part, a stimulus current generator, and a stimulator. Figure 2 shows the demonstration system of a retinal prosthesis, where power/data is transmitted wirelessly through a coupling coil system. The primary coil (1st coil) is placed behind the ear and the secondary coil (2nd coil) is implanted underneath the primary coil. The transmitted power and data are received and processed in the receiver circuitry, which is subcutaneously implanted. According to the acquired image data, a stimulus pulse pattern is generated and transmitted to a stimulus electrode array. CMOS technology is used in image acquisition, power/data transmission/receiving circuitry, and stimulus current generation circuitry, as shown in Fig. 1.

3. Stimulator Design

In this section, the design of a retinal stimulator is described in detail. First, we describe the environment of an implanted retinal stimulator. It is noted that the electrode and retinal cells are not in direct contact but electrically connected through the body fluid or electrolyte. The impedance between the electrode and the cells may change if the distance between the electrode and the cells changes. Thus, constant current stimulation is generally used because stimulation in retinal prosthesis is achieved by extra-cellular stimulation in which the stimulus current affects the neuron's activities flowing through the body fluid or electrolyte. The mobile ions in the body fluid produce an electric double layer on the surface of the electrode.

3.1 Biphasic Stimulation Pulse

The amplitude of the applied voltage must be lower than the value of the voltage window to prevent the occurrence of electrolysis in a stimulus electrode. In addition, a biphasic pulse current is usually used as shown in Fig. 3 in order to

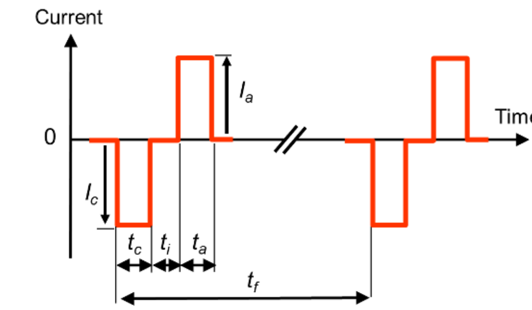

Fig. 3 Pulse parameters of stimulus biphasic current. The anodic current I_a and the cathodic current I_c are generated in current sources and injected into the electrolyte as a biphasic pulse. Adapted from [2] with permission.

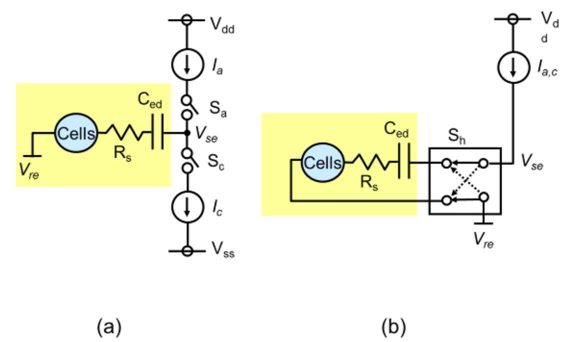

Fig. 4 Biphasic current circuits for stimulating neural cells. (a) two current generators for cathodic and anodic currents, and (b) one current generator with switching circuits [6]. Adapted from [2] with permission.

cancel out charges that are stored in the electric double layer capacitance. Without the cancellation, the stored charges increase, thus increasing the voltage in the electrode. Finally, it becomes equal to the voltage window, which causes electrolysis.

Figure 4 shows the circuits used to obtain a biphasic current. The circuits in Fig. 4(a) are simple but do not maintain charge balance if current mismatch appears in the two current generators, whereas the circuits in Fig. 4(b) can ideally maintain the charge balance because both cathodic and anodic currents are produced by the same current generator. In this method, some circuits are required on the return electrode side, thus complicating the total system.

3.2 Charge Balance

Figure 5 shows passive and active methods to maintain charge balance in retinal stimulation. Figure 5(a) is a passive charge balance circuit where a capacitance C_{dc} is inserted in front of a stimulus electrode to block the DC current [6]. In the first cathodic pulse phase, the current generator sinks current I_c from the neural cells. After some interval time t_i, the blocking capacitor C_{dc}, including neural cells, is electrically shorted by switching on S_d. This shorting process discharges the stored charge in the electric double layer capacitor, resulting in charge balancing in this stimulator.

In the passive method, the anodic phase is not a rectan-

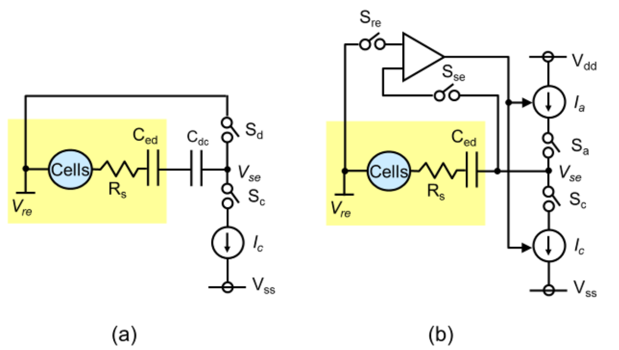

Fig. 5 Charge balance circuits. (a) Passive type [6], (b) active type. Adapted from [7] with permission.

gular pulse but a decay curve. It is noted that the blocking capacitor generally requires a large value of ~0.1 μF. For example, when $I_c = 500\,\mu$A and $t_c = 500\,\mu$s, and the voltage drop of $C_{dc} = 1$ V, the capacitance of C_{dc} is 0.25 μF. This means that I_a requires about 2.5 msec when $R_s \sim 1$ kΩ.

An active charge balancing method shown in Fig. 5(b) is proposed to avoid this [7]. In the circuits, the voltage at the electrode V_{se} is monitored and if $|V_{se}|$ exceeds some value V_{th}, a small amount of anodic or cathodic current pulse is added repeatedly according to the polarity at V_{se} until $|V_{se}| < V_{th}$.

3.3 Interconnection

In order to obtain better vision through a retinal prosthesis, over 1,000 electrodes would be preferable [8]. When increasing the number of electrodes, we are faced with problems associated with the interconnection between electrodes and external lead wires with good mechanical flexibility. Specifically, it is preferable to bend the stimulator to match the curvature of the eyeball.

Figure 6 shows the methods used to achieve a stimulus electrode array [2]. A direct connecting method, which is commonly used in retinal prosthesis devices, is shown in Fig. 6(a), where each electrode is directly connected by a lead wire. Figure 7 shows an implant system of a retinal prosthesis where only nine electrodes are directly connected to the main unit with flexible lead [9]. In this type, when the number of electrodes is increased, the flexible lead is too thick and rigid to implant.

A larger number of electrodes can be achieved by introducing a switching array or a multiplexer (MUX) as shown in Fig. 6(b) [10], [11]. A small number of lead wires can control the large number of electrodes. CMOS integrated circuits easily achieve such a MUX. Figure 8 shows a photograph of the implant part of a retinal prosthesis, which comprises the main unit, multiplexer (MUX), and a 49-channel electrode array. The main unit is implanted behind the ear of the patient. The MUX and electrode array are implanted on the eye. The main unit and MUX are connected by a subdermally-implanted flexible lead. The main unit receives both image information and electrical power, generates cur-

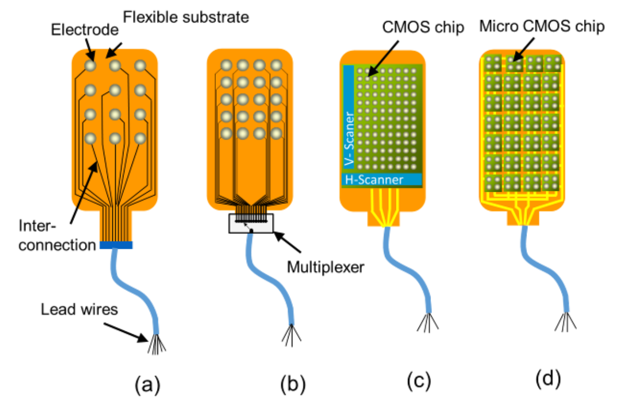

Fig. 6 Stimulator types. (a) Direct interconnection type, (b) MUX type, (c) CMOS chip type, and (d) Smart electrode type. Adapted from [2] with permission.

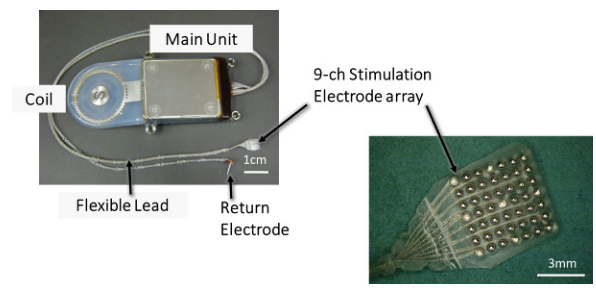

Fig. 7 Direct interconnection type.

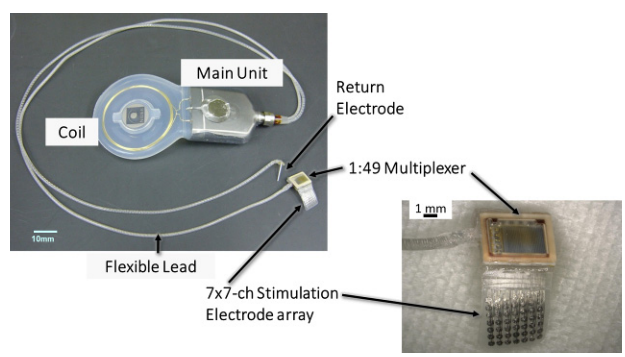

Fig. 8 MUX type. Adapted from [11] with permission.

rent pulses, and transmits the pulses to the MUX. The MUX connects one of the 49 electrodes to the current source of the main unit. The photographs and specifications of the main and MUX chips are shown in Fig. 9 and Table 1, respectively [11].

It is difficult to achieve 1000 electrodes using the previous configuration because all of the 1000 interconnection wires are needed to connect to a scanner, and the limited area of the substrate cannot accommodate such a large number of wiring.

It is a good idea to introduce a CMOS-based chip in the stimulator because scanning circuits (scanner) can be integrated in order to reduce the amount of wiring, as shown in Fig. 6(c). The thin and flexible CMOS-based stimulator is

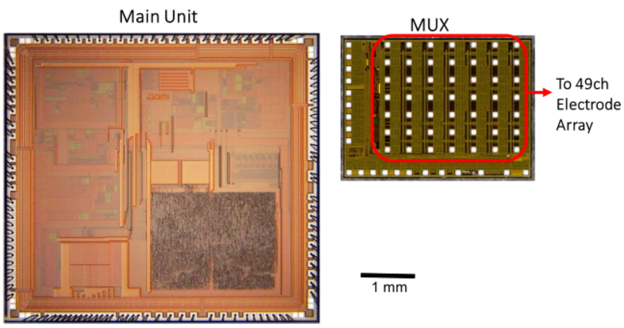

Fig. 9 Photographs of main unit chip and MUX chip. Adapted from [11] with permission.

Table 1 Specification of main chip and MUX chip.

	Main Unit	MUX
Technology	0.35μm HV CMOS	0.35μm HV CMOS
V_{DD}	12 V	6 V/ 15 V (boosted)
Die size	5 mm x 5 mm	3.4 mm x 2.5 mm
Power consumption	62 mW	0.3 mW
Data rate	93 kbps	1 Mbps

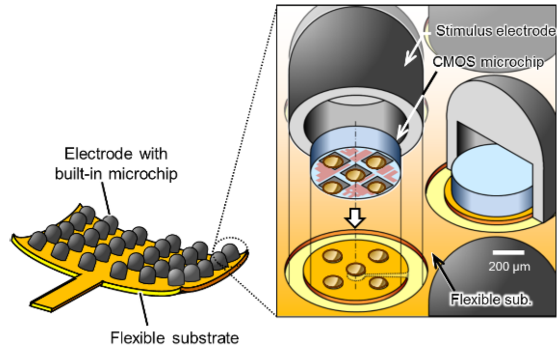

Fig. 10 Concept of a smart electrode. Adapted from [13] with permission.

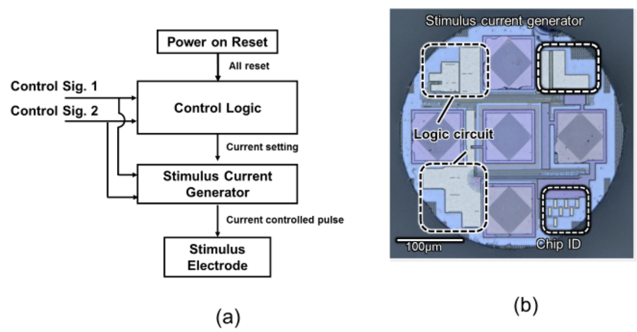

Fig. 11 Microchip for a smart electrode. (a) Block diagram, and (b) chip photograph. Adapted from [13] with permission.

preferable for implantation in order to fit the eye and avoid damaging tissue. However, silicon is rigid, and thinning of the CMOS chip increases the risk of breakage.

A smart stimulator that consists of a number of CMOS based microchips distributed on a flexible substrate, as shown in Fig. 6(d) is proposed and demonstrated [12], [13] to solve this problem. Each microchip incorporates one or a few stimulus electrodes, which can be externally controlled to turn on and off through an external control circuit. In addition to solving the interconnection issue, CMOS-based stimulators offer several advantages, such as signal processing. Microchips are placed on a flexible substrate in a distributed manner to allow flexibility. However, this does not ensure water-tight or hermetic property. Covering a CMOS chip with a polymer film such as parylene C is one of the solutions, but it does not guarantee durability over long periods over ten years.

We developed a smart electrode where a microchip is embedded in an electrode to address the issue. In this configuration, the metal electrode acts as a hermetic case of the microchip. Figure 10 shows the conceptual image of an array of smart electrodes with built-in CMOS microchips. Stimulus electrodes are mounted on the flexible substrate [13]. Each electrode has a microcavity on the bottom. The CMOS microchip is completely embedded into the microcavity. The boundary between the flexible substrate and electrodes is sealed hermetically. Hermetic sealing is one of the most important properties of chronic implantation. Stimulus electrodes act as a metal casing that protects the CMOS microchip from mechanical stress and interstitial fluid.

Figure 11 shows the block diagram and photograph of the microchip. The microchip has a control logic circuit and intrinsic chip identification (ID) number, which can be defined by laser processing after chip fabrication. While operating the device, a target electrode can be selected from among the stimulus electrodes by using the chip ID number. The stimulus current generator, which can deliver a maximum pulse current of 1 mA, was also integrated with the microchip. A stimulus pulse parameter can be programmed by externally wiring the control signal. The designed microchip was fabricated by using a 0.35-μm standard CMOS process.

The outside of the microchip was etched to shape the microchip into a circle of diameter 400 μm as shown in Fig. 11(b) in order to embed the microchip into the stimulus electrode. The rounded microchip is mounted on a flexible substrate with flip-chip bonding. The scanning electron microscope images of an electrode with a microcavity for an embedded microchip and the microchip after flip-chip bonding are shown in Fig. 12. The specifications of the microchip are shown in Table 2.

3.4 AC Power Delivery

It is difficult to completely avoid water infiltration into non-hermetically sealed parts in the human body for long periods. Conventionally, implantable medical devices are required to operate safely over five years. Applying a DC voltage to parts such as the flexible lead in Fig. 8 is potentially dangerous because water infiltration may cause metal corrosion and an irreversible electrochemical reaction. Therefore, power is supplied in the form of AC voltage instead of DC voltage through non-hermetically sealed parts.

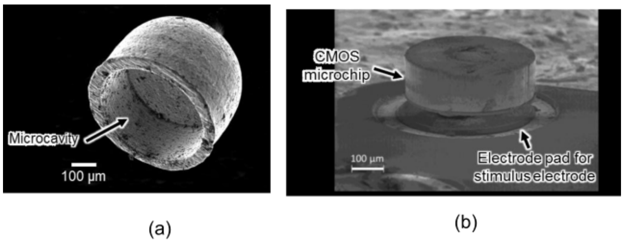

Fig. 12 SEM photograph of an electrode with microcavity (a) and a microchip after flip-chip bonding. Adapted from [13] with permission.

Table 2 Specification of microchip.

Technology	0.35μm 2P 4M CMOS
V_{DD}	5 V
Number of IO wiring	Power source:2, Control signal: 2
Die size	0.4 mm × 0.4 mm
Stimulus output	50 μA – 1 mA
Pulse mode	Monophasic, Biphasic

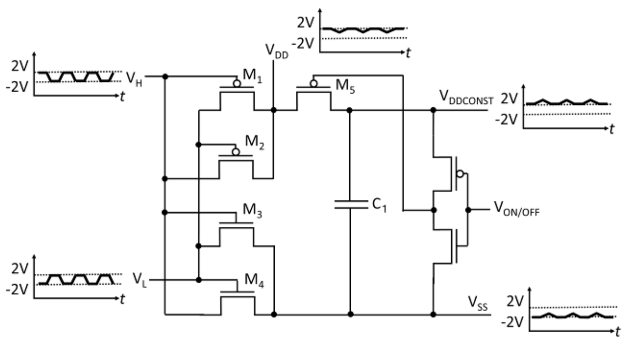

Fig. 13 AC power delivery system. (a) Pulse timing and (b) rectifier circuits. Adapted from [14] with permission

Figure 13 shows an example of AC power delivery [14]. In this case, the AC power is delivered in a flexible lead from the main unit to a stimulator CMOS chip as shown in Fig. 6(c). The AC power is delivered by complementary pulses of V_L and V_H as shown in Fig. 13(a). The AC signal is rectified in the circuits of Fig. 13(b). In this case, data/control signals are also AC pulses and delivered to the chip separately.

We developed AC power delivery with data signals [11]. The AC power is delivered through the flexible lead in Fig. 8, which is a non-hermetic sealed part. The electrode selection signal is superimposed onto the AC power supply voltage waves from the main unit to MUX. While high frequency is preferable for achieving high-speed communication, low frequency is better for lowering the noise emission. We proposed to implement communication between the main unit and MUX by pulse period sift keying (PPSK) as shown in Fig. 14. In the PPSK, whether the period difference is detected or not, bit 0 or 1 is established, respectively. The advantage of utilizing the PPSK is high-speed communication is attainable with simple configuration. In addition, the modulation method allows us to simplify the MUX receiver circuit because the detection is asynchronous, which makes the reconstruction of reference carrier redundant.

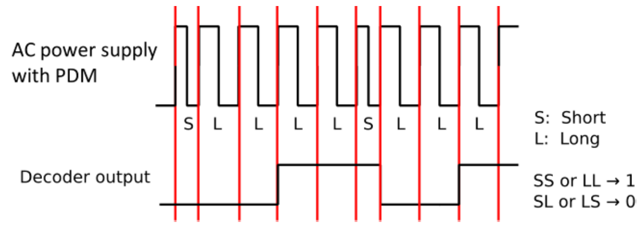

Fig. 14 Pulse period shift keying. Adapted from [11] with permission.

4. Conclusions

This study focuses on the electrical stimulator design of retinal prostheses. The stimulator must be designed to avoid electrolysis or any irreversible process in the electrodes and flexible lead in order to achieve safe stimulation over long periods using a large number of electrodes. Therefore, some types of biphasic current pulse circuits, charge balance circuits, and AC power delivery circuits were developed. Electronic circuitry must be introduced in the stimulator to achieve the large number of electrodes required to obtain high quality vision. The concept of smart electrode, in which a microchip is embedded inside an electrode, is presented for future retinal prostheses with 1000+ electrodes. A wide range of studies pertaining to materials and systems are required to achieve this.

Acknowledgments

We would like to thank Prof. T. Fujikado and Prof. H. Kanda of Osaka University of Medical School for their continuous supports.

References

[1] J.K. Niparko, ed. Cochlear Implants, Lippincott Williams & Wilkins, 2009.
[2] J. Ohta, "Artificial Retina IC" in Bio-Medical CMOS ICs, Eds. H.-J. Yoon and C.v. Hoof, Springer, 2010.
[3] M.S. Humayun, J.D. Dorn, L.D. Cruz, G. Dagnelie, J.-A. Sahel, P.E. Stanga, A.V. Cideciyan, J.L. Duncan, D. Eliott, E. Filley, A.C. Ho, A. Santos, A.B. Safran, A. Arditi, L.V.D. Priore, and R.J. Greenberg, "Interim results from the international trial of Second Sight's visual prosthesis," Ophthalmology, vol.119, no.4, pp.779-788, 2012.
[4] K. Stingl, K.-U. Bartz-Schmidt, F. Gekeler, A. Kusnyerik, H. Sachs, and E. Zrenner, "Functional outcome in subretinal electronic implants depends on foveal eccentricity," Invest. Ophthalmol. Vis. Sci., vol.54, pp.7658–7665, 2013.
[5] 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 postmorten eyes with retinitis pigmentosa," Invest. Ophthalmology & Visual Sci., vol.40, pp.143–148, 1999.
[6] A. Demosthenous, I.F. Triantis, and X. Liu, Circuits for Implantable Neural Recording and Stimulation, chapter 11. Artech House, Norwood, MA, 2008.
[7] M. Ortmanns, A. Rocke, M. Gehrke, and H.-J. Tiedtke, "A 232-Channel Epiretinal Stimulator ASIC," IEEE J. Solid-State Circuits, vol.42, no.12, pp.2946–2959, Dec. 2007.
[8] K. Cha, K.W. Horch, and R.A. Normann, "Mobility performance

with a pixelized vision system," Vision Research, vol.32, no.7, pp.1367–1372, 1988.
[9] T. Fujikado, M. Kamei, H. Sakaguchi, H. Kanda, T. Morimoto, Y. Ikuno, K. Nishida, H. Kishima, T. Maruo, K. Konoma, M. Ozawa, and K. Nishida, "Testing of semichronically implanted retinal prosthesis by suprachoroidal-transretinal stimulation in patients with retinitis pigmentosa," Invest. Ophthalmol. Vis. Sci., vol.52, pp.4726–4733, 2011.
[10] T. Fujikado, M. Kamei, H. Sakaguchi, H. Kanda, T. Morimoto, Y. Ikuno, K. Nishida, H. Kishima, T. Maruo, K. Konoma, M. Ozawa, and K. Nishida, "Testing of Chronically Implanted 49-Channel Retinal Prosthesis by Suprachoroidal-Transretinal Stimulation (STS) in Patients with Advanced Retinitis Pigmentosa," Invest. Ophthalmol. Vis. Sci., 56, E-Abstract 3816, 2015.
[11] Y. Terasawa K. Shodo, K. Osawa, and J. Ohta, "Features of retinal prosthesis using suprachoroidal transretinal stimulation from an electrical circuit perspective," VLSI Symposium, 2016.
[12] 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, S85–S91, 2007.
[13] T. Noda, T. Fujisawa, R. Kawasaki, H. Tashiro, H. Takehara, K. Sasagawa, T. Tokuda, and J. Ohta, "Fabrication and Functional Demonstration of a Smart Electrode with a Built-in CMOS Microchip for Neural Stimulation of a Retinal Prosthesis," EMBC 2015.
[14] A. Rothermel, L. Liu, N.P. Aryan, M. Fischer, J. Wuenschmann, S. Kibbel, and A. Harscher, "A CMOS Chip With Active Pixel Array and Specific Test Features for Subretinal Implantation," IEEE J. Solid-State Circuits, vol.44, no.1, pp.290–300, 2009.

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