Pulse Count Modulation Based Biphasic Current Stimulator for Retinal Prosthesis and *in vitro* Experiment Using rd1 Mouse

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***Abstract*— For a retinal prosthesis, retinal nerve cells are electrically stimulated by current pulses. Typically, the amplitude of the current pulses is modulated to control the amount of injected charges. However, a high spatial resolution can be difficult to achieve with this amplitude modulation method, because the neural response spreads more widely as the amplitude of the current pulses is increased. In this paper, a biphasic current stimulator integrated circuit (IC) using a new modulation method called, the pulse count modulation, is proposed. In the pulse count modulation method, the amplitude and the width of the current pulses are fixed, and the amount of injected charges is controlled by the number of applied current pulses in a base period. The proposed stimulator IC is fabricated by a 0.35 μm bipolar-CMOS-DMOS (BCDMOS) technology. The operation and performance of the stimulator IC are evaluated in an *in vitro* experiment environment with rd 1 mice. It is shown that a higher spatial resolution can be achieved compared with the amplitude modulation method.**

I. Introduction

A retinal prosthesis is a visual rehabilitation method for people blinded from age-related macular degeneration (ARMD) and retinitis pigmentosa (RP). These medically incurable diseases lead to visual loss in more than 15 million people [1, 2]. In previous studies, some of retinal nerve cells can conduct normal neural functions for many years, despite of the retinal remodeling and the degeneration of photoreceptors [3, 4]. These findings lead to the development for retinal prostheses [5].

In microelectrode type retinal prostheses, current pulses are used to electrically stimulate the retinal nerve cells, and the amplitude of the current pulses is modulated to control the amount of injected charges [6, 7]. Exact numbers vary by a specific implementation, but a stimulation duration of 1 ~ 4 ms with a maximum current of 100 μA at a base interval of 50 ~ 100 ms is representative in the amplitude modulation method [8, 9]. However, it is hard to achieve a high spatial resolution with the amplitude-modulated current pulses, because the neural response spreads more widely as the amplitude of the current pulses is increased [10]. Thus, the maximum amplitude should be limited to prevent overlapping stimulations from adjacent electrodes [11].

In this paper, a biphasic current stimulator integrated circuit (IC) using a new modulation method called, the pulse count modulation, is proposed to overcome this drawback. In the pulse count modulation method, the amount of injected charges is adjusted by changing the number of current pulses with a low amplitude of 20 μA and a short pulse width of 250 μs. A conceptual comparison between the amplitude modulation method and the pulse count modulation method is shown in Fig. 1.

The proposed stimulator IC is fabricated by a 0.35 μm bipolar-CMOS-DMOS (BCDMOS) technology. In each stimulator pixel circuit, the number of biphasic current pulses generated in a base period is controlled by input signals. An *in vitro* experiment with rd1 mice is conducted to evaluate performance of the stimulator IC. From the experimental results, neural responses and spatial resolutions depending on the modulation methods are analyzed and compared.

II. Design

A. System Architecture

A system architecture of the stimulator IC based on the pulse count modulation is shown in Fig. 2. The stimulator IC consists of a 4 × 4 pixel array. The stimulator pixel circuits in a selected row operate at the same time. A total of 8 different stimulation time signals are used to determine the number of biphasic current pulses in a base period. In order to select a stimulation time signal, 3-bit data generated by a 3-bit analog to digital converter (ADC) is applied on the stimulator pixel

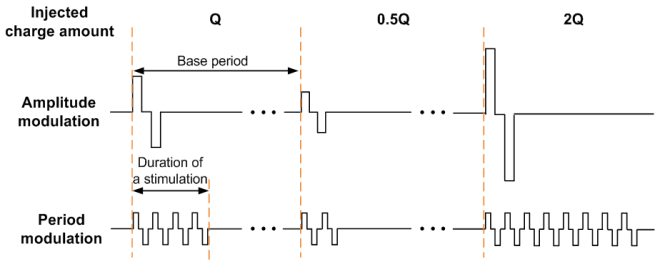

Figure 1. A conceptual comparison between the amplitude modulation and the pulse count modulation. (Q is an arbitrary nominal quantity)

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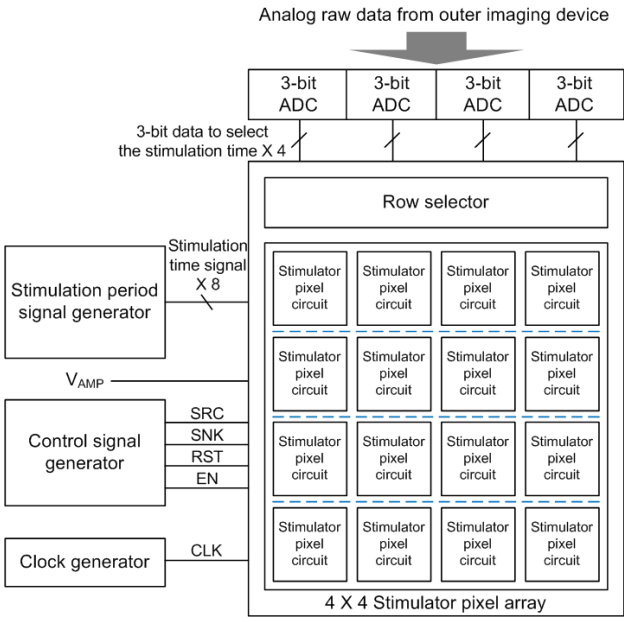

Figure 2. The system architecture of the proposed stimulator IC.

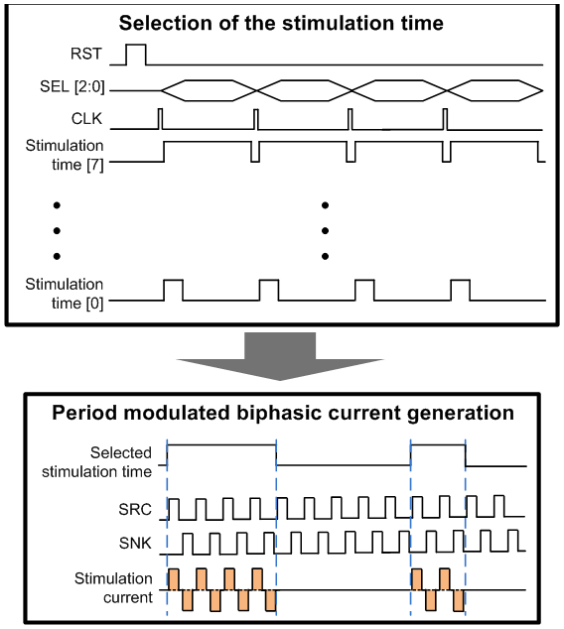

Figure 4. The timing diagram of the control signals and generated biphasic current pulses.

circuit. The amplitude of the current pulses is determined by the V_{AMP} signal. The source (SRC) and sink (SNK) signals determine directions of the current stimulations.

B. *Schematic of the Stimulator Pixel*

A schematic of the stimulator pixel is described in Fig. 3. The pixel circuit consists of a 3-bit D flip-flop memory, an 8-to-1 multiplexer (MUX), a SRC/SNK signal generator, a biphasic current generator, and a voltage controlled current source (VCCS). The biphasic current generator and the VCCS are designed to operate with a high supply voltage of 12 V to reduce the size of electrodes because there is an inversely proportional relationship between the electrode size and its impedance [12]. Other blocks are designed to operate with a supply voltage of 5 V.

In the pixel circuit, the pulse count modulated current pulses are generated in the following manner. At first, the applied 3-bit data are stored in the 3-bit D flip-flop memory. The stored data are used as the select signals in the 8-to-1 MUX. In the SRC/SNK signal generator, the SRC and SNK signals with a duration of 250 μs are generated within the the selected stimulation time. After the levels of the SRC and SNK signals are changed from 5 V to 12 V in level shifters, these signals are applied on the biphasic current generator. The biphasic current generator makes bidirectional stimulation current pulses according to the SRC and SNK signals. The VCCS is connected under the biphasic current generator. The amplitude of the current pulses is determined by a level of the V_{AMP} as shown in our previous study [13]. The level of the V_{AMP} is fixed as 1 V to generate current pulses with the low amplitude of 20 μA. A timing diagram of the stimulator pixel circuit is depicted in Fig. 4.

III. Experiment

In order to evaluate the operation and performance of the proposed stimulator IC, an *in vitro* experiment with the rd 1 mice is conducted using the fabricated stimulator chip shown

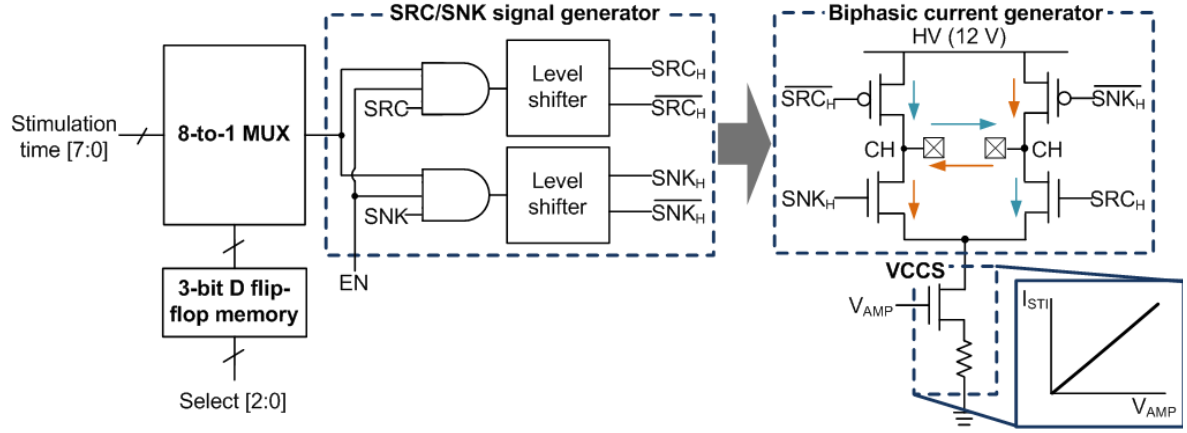

Figure 3. The schematic of the pixel circuit. The pixel circuit consists of the 3-bit D flip-flop memory, the 8-to-1 multiplexer (MUX), the SRC/SNK signal generator, the biphasic current generator, and the voltage controlled current source (VCCS).

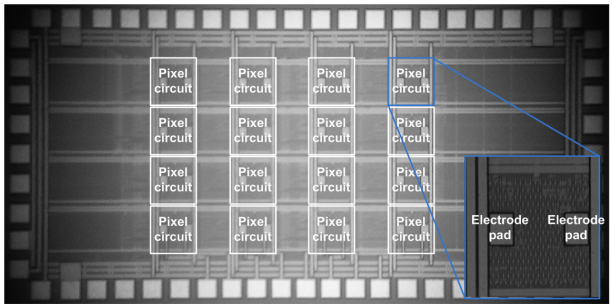

Figure 5. The fabricated stimulator IC with the 4 x 4 pixel array. The size of the chip is 2.4 mm x 1.2 mm. Each pixel occupies 175 μm × 185 μm.

in Fig. 5. The stimulator chip is fabricated in a 0.35 μm 2-poly/4-metal bipolar-CMOS-DMOS (BCDMOS) technology of Dongbu Hi-Tek, Bucheon, Korea. In multi project wafer (MPW) runs, the die size is limited to 2.4 mm × 1.2 mm. Each stimulator pixel circuit occupies an area of 175 μm × 185 μm.

A. *in vitro Experiment*

Degenerated retinal tissues of the rd1 mice are prepared for *in vitro* experiments. A total of 3 different retinas are used in the experiments. A 2D circle-shaped Au microelectrode array (MEA) is fabricated for the experiment (Fig. 6). All animal use protocols are approved by the Institutional Animal Care Committee of Chungbuk National University (permit number: CA-25). A diameter of each stimulating electrode is 150 μm. Other small electrodes with the diameter of 50 μm are used as recording electrodes. Especially, the 16 recording electrodes located at the center of the MEA represent the intensively stimulated area (Fig. 6 (c)). The recording electrodes are connected to the MEA 60 recording system (Multi Channel Systems, GmbH, Germany) to electrically record neural spikes.

In the experiments, the biphasic current pulses are injected to the retinal ganglion cells (RGCs) as bipolar stimulation, according to two types of the modulation methods. First, the amplitude modulated current pulses are applied on the RGCs. The duration of the SRC and SNK current pulses is fixed at 1 ms. In addition, there is an interphase delay of 1 ms between the SRC and SNK current pulses. The amplitude of the current pulses is changed as 10 μA, 20 μA, and 40 μA. Second, the pulse count modulated current pulses are injected to the RGCs. The duration of the SRC and SNK current pulses and the interphase delay are fixed at 250 μs. The amplitude of the current pulses is fixed at a level of 20 μA. The number of generated current pulses is changed as 2, 4, and 8 depending on the applied stimulation time signals. In the experiments, each stimulation is repeated 50 times with a base interval of 1 sec to reduce possible interferences by previous stimulations.

B. *Results*

Recorded neural spikes at the intensively stimulated area are analyzed to observe the evoked neural responses. The spike sorting software, Offline Sorter™ (Plexon Inc., USA), is used to analyze the evoked neural spikes. The artifact signals, which are generated by the stimulation current, are invalidated by removing the waveforms whose amplitude is larger than 1 mV. The difference between the average number of neural spikes before and after the stimulation is calculated to measure the neural spikes evoked by the current stimulation. The average number of evoked spikes, recorded in the intensively stimulated area, is plotted as a function of the amount of injected charges in Fig. 7. In both modulation methods, more neural spikes are evoked as the amount of injected charges is increased.

The spatial resolution is calculated using the resolution factor which is defined as the ratio of the average number of evoked spikes at the intensively stimulated area to that number at the rest of the area. The resolution factor is a term devised in this paper to compare the two stimulation methods. The resolution factor as a function of the amount of injected charges is plotted in Fig. 8. In the amplitude modulation method, the resolution factor is decreased as the amount of injected charges increases. Whereas, in the pulse count modulation method, the resolution factor is increased as the amount of injected charges increases.

IV. Discussion

In Fig. 7, the average number of evoked spikes increases as more charges are injected in both modulation methods. The average number of evoked spikes per stimulation in the pulse count modulation method is slightly lower than that in the

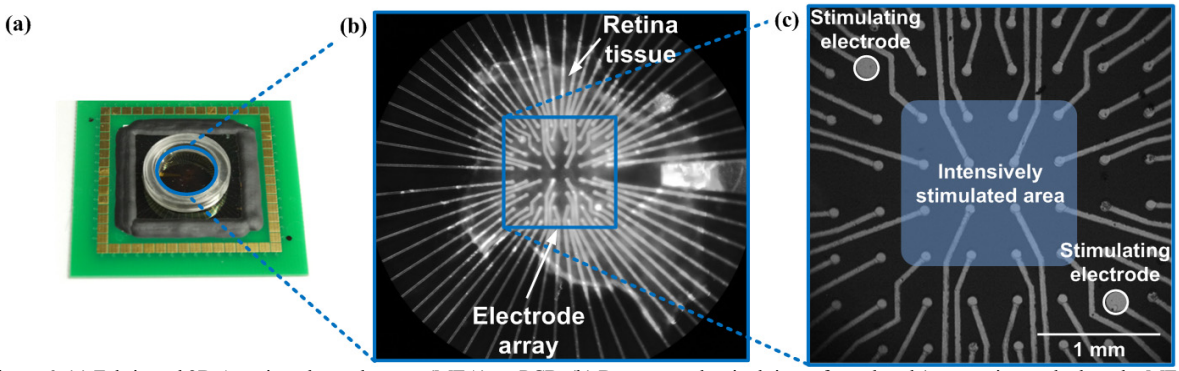

Figure 6. (a) Fabricated 2D Au microelectrode array (MEA) on PCB. (b) Degenerated retinal tissue from the rd 1 mouse is attached on the MEA. (c) MEA consists of 2 stimulating electrodes (150 μm diameter) and 57 recording electrodes (50 μm diameter). The 16 recording electrodes located at the center are intensively stimulated.

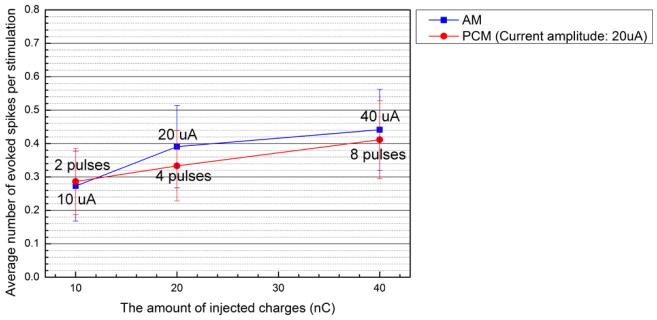

Figure 7. Average number of evoked spikes as a function of injected charges in 50 repetitions (n = 3).

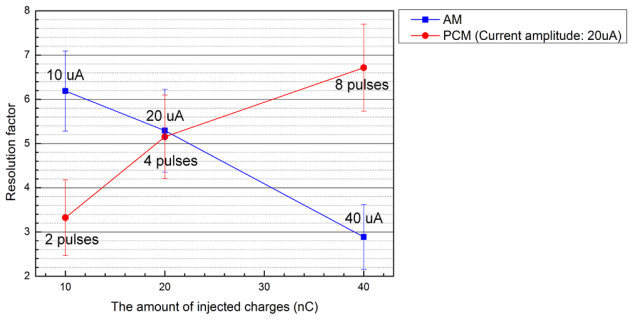

Figure 8. Resolution factors as a function of the amount of injected charges in 50 repetitions (n = 3).

amplitude modulation method, which is consistent with the purpose of the pulse count modulation method.

In the pulse count modulation method, the spatial resolution is increased as the amount of injected charges increases, in contrast with the amplitude modulation method where the spatial resolution decreases with increasing charges. The obtained results are consistent with the hypothesis that the neural response spreads more widely as the amplitude of the current pulses is increased.

According to the results in [14], the frequency modulation method can be also used to obtain a higher spatial resolution, when compared to the amplitude modulation method. However, the size of elicited phosphenes is gradually enlarged as the stimulation frequency is increased [14]. In other words, it can be postulated that, in the frequency modulation method, the spatial resolution is decreased as the amount of injected charges increases. Therefore, the developed pulse count modulation method is more advantageous and suitable for achieving a high spatial resolution.

V. Conclusion

In this paper, an integrated circuit chip for retinal stimulator IC using a new modulation method called, the pulse count modulation, is proposed. In the pulse count modulation method, the amount of injected charges is determined by the number of current pulses generated in a base period. The proposed IC is fabricated using a 0.35 μm BCDMOS process, and experiments are performed using the retinal neurons from rd1 mice *in vitro*. The experimental results indicate that a higher spatial resolution can be achieved by the proposed pulse count modulation method, when compared to the conventional amplitude modulation or frequency modulation method. In order to optimize the pulse count modulation method, additional research is required to optimize the pulse width and the base period.

Acknowledgment

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