A Neurostimulator Design for Long-term Animal Experiments

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Abstract

This article reports on a neural prosthesis stimulation system for long-term use in animal electrical stimulation experiments. The presented system consists of an implantable stimulator which provides continuous electrical stimulation, and an external component which provides preset stimulation parameters and power to the implanted stimulator via a paired RF (radio frequency) coil. A rechargeable internal battery and a parameter memory component were introduced to the implanted neural stimulator. As a result, the external component was not necessary during the stimulation cycles. The implantable stimulator was implemented with IC chips and the electronics, except for the stimulation electrodes, were hermetically packaged in a biocompatible metal case. A polyimide-based gold electrode array was used for realization of the animal implantation test using retinal prosthesis approach.

1. Introduction

In the neural prosthesis research, long-term preclinical animal experiments are needed to evaluate the efficacy, safety and durability of the devices or to demonstrate the feasibility of the newly suggested stimulation strategies. The neural prosthetics, such as cochlear implant or retinal prosthesis, needed a wired or a wireless external component to provide stimulation parameters and power to the internal electrodes [1, 2]. When those systems were used for long-term electrical stimulation in animals [3, 4], there were many problems that needed to be solved. Systems with a percutaneous connection to the external portion restricted the animals' movement and posed an infection risk. In systems having transcutaneous connections to an external controller worn by the animals, the external part usually separated from the animals or was damaged.

In this article, an implantable neural prosthesis system is proposed for a chronic electrical stimulation test in an animal model. For this purpose, a small rechargeable battery and a parameter memory were introduced into the implanted stimulator so the external power supply and control part could be removed during a chronic stimulation experiment. The external unit is needed for two purposes only: passing the parameter and charging the battery. Animal experiments were done using retinal prosthesis approach to show the feasibility of the implantation of this newly suggested stimulation system. To check whether the implanted electrode could induce appropriate cortical response upon electrical stimulation, we measured the electrically evoked cortical potentials (EECPs) from rabbits in which electrodes were implanted.

2. Methods

Neural prosthesis system design

The implantable neural prosthesis system for a chronic animal experiment consists of an internal unit for neural stimulation and an external unit for stimulation control and battery charging (Figure 1). A paired RF coil links these two units for the transmission of data and power.

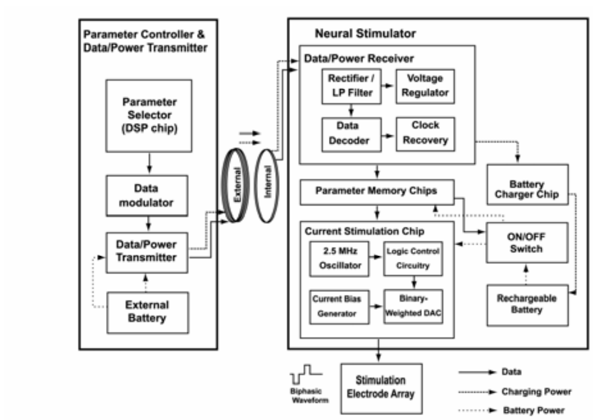

Figure 1. Block diagram

The external unit has a stimulation waveform parameter selector used to control the channel selection, amplitude, duration and rate of stimulation. This parameter selector generates a parameter data frame and was implemented using a commercially available digital signal processing chip (TMS320VC5509, Texas Instruments, Dallas, Texas, USA). The control codes were implemented in-house using the C programming language, and the parameter data frame consists of 22-bit as shown in Figure 2. The same stimulation waveform is simultaneously delivered to all selected channels. To transmit this parameter data into the internal stimulator, the pulse width modulation (PWM) encoding method is used (Figure 2). Logic ‘1’ and ‘0’ are encoded to have a duty cycle of 75% and 25%, respectively, and the ‘end-of-frame (EOF)’ bit has a 50% duty cycle. Such an encoding method enables easier synchronization and decoding because each bit has a uniform rising edge at its beginning [1]. The transmission data rate is 125 kbps. For transmission of PWM encoded data, a class-E tuned power amplifier (data/power transmitter) is used with amplitude shifted keying (ASK) modulation. The carrier frequency is 2.5 MHz.

The transmitted data are received by the internal coil and then the envelope is extracted through a half-wave rectifier and a low-pass filter. Using this envelope signal, a data decoder in the data/power receiver chip recovers the parameter data and saves it to the parameter memory chip. Using the same envelope signal, a voltage regulator generates power to be consumed by the data/power receiver chip (Figure 1).

The internal unit was implemented with a rechargeable battery and IC (integrated circuit) chips including the data/power receiver chip, current stimulation chip, parameter memory chips, and battery charging chip. The data/power receiver chip has data decoding and voltage regulation function blocks. Both the data/power receiver chip and the current stimulation chip are custom IC’s designed by our laboratory (0.8 μm CMOS (complementary metal-oxide semiconductor) technology, Austria Microsystems, Austria). The parameter memory chips and battery charging chip are off-the-shelf commercial chips (Figure 1). Except for the data/power receiver chip, the other chips in the stimulator are powered by a rechargeable battery. Therefore, once the parameters are passed to the parameter memory, the external unit can be removed from the animal during the electrical stimulation test. The retinal stimulator has two modes of function: a stimulation mode and a battery recharging mode.

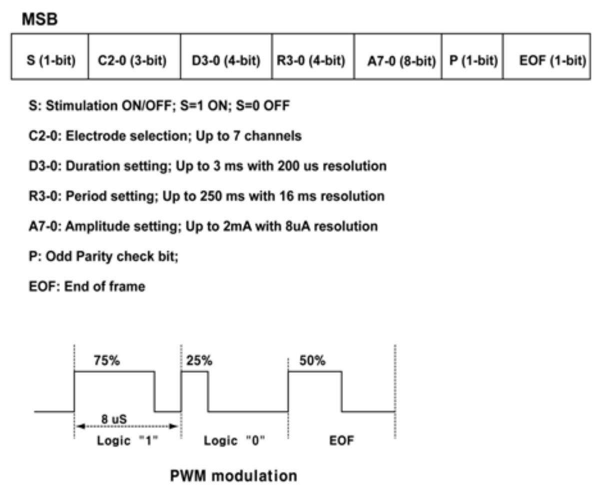

Figure 2. Data Format and PWM modulation

In stimulation mode, the saved parameter data in the parameter memory component are provided to the current stimulation chip. The parameter memory component was composed of three 8-bit shift registers (SN54AHC595, Texas Instruments, Dallas, Texas, USA) for 22-bit data storing. The parameter data do not change unless a new parameter is transmitted from the external component. The current stimulation chip consists of current generator circuitry and timing logic circuitry. The current generator circuitry has current bias circuitry (8 μA) and an 8-bit binary current-weighted DAC (digital-to-analog converter). The timing logic circuitry has a 2.5

㎒ oscillator and switch control logic circuitry for controlling the current stimulation waveform.

In the battery recharging mode, 2.5 ㎒ sinusoidal waves were transmitted with no data. A rechargeable coin-type lithium ion battery (PD2320, Korea Power cell, INC. Daejeon, Korea) is used as the power source for the internal implant. A charging chip (LTC4054L, Linear Technology Corporation, Milpitas, CA, USA) is used to control the battery recharging.

In this work, only one inductive coupling was used for data transmission and battery charging. Simultaneous transmission of the stimulation parameter and charging power is difficult because the battery charger circuit affects the precisely designed load value of the data/power receiving circuit and can induce the failure in data reception. To separate the stimulation mode and battery charging mode, a switch circuit was positioned between the voltage regulator in the data/power receiver chip and the battery charge chip to control the recharging of the battery.

To protect the ICs from body fluids and mechanical forces, the electronics of the stimulator were hermetically housed in a metal package which consists of biocompatible titanium housing, platinum feedthroughs, and a ceramic plate. The feedthroughs connect the electrode array and receiver coil to the retinal stimulator. A ceramic sintering process is used to fix the feedthroughs in the ceramic plate that provides electrical isolation. Brazing and laser welding techniques were employed to achieve hermetic sealing of the titanium housing [1].

A polyimide-based seven-channel, strip-shaped (750 x 300 μm) gold electrode array was used for realization of the animal experiment using retinal prosthesis approach. The stimulating sites were constructed in a 4 ㎜ x 4 ㎜ area. One side of this array was lengthened and connected to the stimulator via feedthroughs.

Implantation of the prosthesis system into rabbits

A New Zealand White rabbit weighing 2.0~2.5 ㎏ was used to evaluate the proposed system. All procedures of animal experimentation were approved by the Institutional Review Board of Seoul National University Hospital Clinical Research Institute and followed the Association for Research in Vision and Ophthalmology (ARVO) Statement on Use of Animals in Ophthalmic and Vision Research. Implantation of the entire system was performed under general anesthesia achieved by repetitive intramuscular injection of 25 ㎎ ketamine and 6 ㎎ xylazine per kilogram of body weight.

The skin was prepared and a longitudinal incision was made at the right auscultation triangle of the back. Meticulous dissection was done between the subcutaneous and muscular layers. A subcutaneous tunnel was made by an elevator from the medial angle of the scapula to the inferior conjunctival fornix. The forniceal opening was created with a blade and the tip of the elevator was extruded from the forniceal opening thereby completing the subcutaneous tunnel. The internal stimulator was inserted into the subcutaneous tunnel from the opening of the back. The connection part and the polyimide electrode array were protected by a soft polyethylene tube and passed through the tunnel. After being introduced through the conjuctival forniceal opening, the connection wire was turned around the eyeball under the extraocular muscles and temporarily anchored onto the sclera with two 6-0 Prolene sutures, which is a process similar to Humayun's method [5].

A 5 mm sized Scleral tunnel incision parallel to the limbus was made with a blade and scissors about 5 mm away from the limbus in the upper lateral quadrant of the eyeball. To prevent vitreous prolapse and to lower the intraocular pressure, 0.1 – 0.2 ml of aqueous humor was drained from the anterior chamber before the scleral opening was created. The polyimide electrode array was inserted through the scleral opening and slided into the suprachoroidal space to reach the visual streak. The scleral opening was closed with 8-0 Vicryl sutures and the connection wire was permanently anchored onto the sclera with sutures. The reference electrode was left outside the eyeball to contact the sclera without fixation. The conjunctival incisions were repaired with 8-0 Vicryl sutures and the skin incision was repaired with 6-0 Catgut sutures. After the operation, the entire system was inside the body and was not exposed.

Recording of electrically evoked cortical potentials

Stainless needle electrodes were used as recording electrodes. An active recording electrode was placed into the primary visual cortex 6mm lateral and 6mm anterior to lamda, which is the same location as in Okuno's method [6]. A reference recording electrode was placed into the cortex 20mm anterior to lamda. The animal was grounded by an electrode on the ipsilateral ear. The electrically evoked cortical potentials (EECPs) elicited by stimulating one eye were recorded from the active recording electrode placed on the contralateral side.

An integrated hardware/software platform (TDT System 3, Tucker-Davis Technologies, Alachua, FL, USA) was used for amplifying, acquisition, and storage of EECP signals. Signals are digitized at 25 kHz on the preamplifier and sent over a fiber optic link to a DSP device where they are filtered (0.5-300 Hz) and processed in real-time. Ordinarily, 30 consecutive responses were summed and averaged on one EECP record.

For recording the EECPs, a cathodic-first biphasic constant current stimulus waveform was simultaneously applied to all selected active channels. Both pulse duration and interpulse delay were 1ms and amplitudes were varied as noted. The repetition frequency was 4 Hz.

3. Results

Neural prosthesis system

A current mode, charge-balanced, cathodic-first biphasic stimulation waveform was generated in the stimulation mode and provided to a stimulation electrode array. The current stimulation chip can simultaneously deliver a stable current from 8 ㎂ to 2 ㎃ to all channels. The pulse width and the interphase delay can be changed up to 3 ㎳. The interphase delay was designed to have the same time duration as the pulse width.

The stimulator consumed around 2 ㎽ when delivering 520-㎂ biphasic current pulsed with 1-ms pulse width at a stimulation rate of 10 Hz.

The capacity of the battery was 75 ㎃h (4.2 V) and the battery could supply the power to the internal circuitries for over 30 hours under the 520-㎂ amplitude, 1ms stimulation duration. The battery was fully recharged within three hours with 25 ㎃ charging current through the RF inductive link when in the battery recharging mode.

Postoperative state of rabbits

Implantation of the stimulation system into the rabbit was successfully achieved. The internal portions were harbored safely and post-operatively remained *in situ*, as verified with fundus photography. There were no limitations in eye movements or shoulder movements on the implanted side and the entire stimulation system could be safely protected under the skin during the follow-up period. There was no need to anesthetize the rabbit while changing the stimulation parameters by attaching the external RF coil onto the skin overlaying the internal RF coil.

EECPs

Figure 3 shows a typical record for a single rabbit with varying stimulus current.

The EECP waves are shown in Figure 3. The EECPs were well recorded upon electrical stimulation from the implanted electrodes. There is a correlation between the amplitude of EECP waves and the electrical stimulation currents. The EECPs were disappeared after the optic nerves were severed.

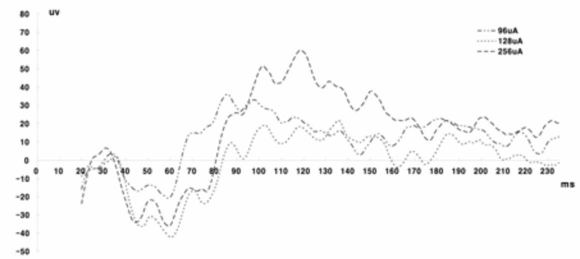

Figure 3. Electrically evoked cortical response following retinal stimulation with a suprachroidal electrode.

4. Discussion

The stimulation system presented in this article is intended to provide a useful tool for long-term animal experiments on neural prostheses. To remove the external connection or the external unit from the animal during electrical stimulation, we used a small rechargeable battery in the implantable stimulator. This battery can be simply recharged using an RF inductive link while the system is idle. This system makes it possible to conduct chronic electrical stimulation tests in such a way that the animal can move and act freely without any external unit restriction during the stimulation test. Therefore, there is no need to anesthetize the animal frequently and the stimulation system is also protected from the animal's claws and teeth.

The implantable retinal stimulator was built using IC chips and discrete elements for this proof-of-concept. An integrated IC chip can be developed to reduce power consumption and further miniaturize the implanted component of the device.

Acknowledgements

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