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STUDY ON DBS DEVICE FOR SMALL ANIMALS

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Abstract—**although deep brain stimulation (DBS) therapy has been achieved, fine tuning on the operational parameters and the equipment are needed in order to make the stimulation treatment more applicable. Thus, the purpose of this study is to design and produce a deep brain stimulation device for DBS experiments for small animals (e.g. rats). Physical size, durability, cost of device and convenience of operation are the major focuses in this study. The designed pulse generator can produce pulses with adjustable frequencies, pulse widths and amplitudes. Telemetry and remote control of the system reduced the physical size of the implant component. Battery voltage measurement and electrode impedance measurement justified the values of parameters applied for stimulation. Power consumption is low enough and test results show it is expected to work for more than three months when using typical pulse parameters. Finally, we use the device on the DBS experiment of rats. The results prove that the design of the device can fulfill the requirements for deep brain stimulation in animal experiments.**

I. INTRODUCTION

Deep brain stimulator, commonly known as "brain pacemaker", is a medical device which works in the human body for a long time and carries out deep brain stimulation (DBS) treatment. It integrates the research results of various fields, such as low-power circuit design, micro-manufacturing, biocompatible materials, high-performance batteries, wireless communication and so on. The deep brain stimulator is composed of the electrodes implanted in brain, the implanted pulse generator and the extended wire connecting the electrodes and pulse generator. Pulse generator is the core part of the system. The pulse generated is transferred to unilateral or bilateral electrode through the extended wire, inhibiting abnormal discharge of brain nuclei thus to achieve treatment effect. With the development on DBS in recent years, DBS has been widely used clinically. It is the preferred surgery not only for Parkinson's disease but also for epilepsy, dystonia, cluster headache and so on. Recently, it is also used for the treatment of mental diseases such as obsession, depression, Tourette syndrome and so on[1-6].

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Although the effectiveness of DBS therapy has been proven clinically, further exploration on the mechanism of brain function regulation by deep brain stimulation is necessary. Therefore, animal studies on DBS are needed. The stimulation parameters and the corresponding treatment outcomes have to been further investigated in order to produce a durable and easily implantable DBS device. The brain pacemaker for human is obviously too big and heavy for small animals. Also, production of a human DBS devices is too complicated and costly that it is not cost-effective for animal trials. Liu (2007) developed a small-size DBS device which met the requirements for animal trials[7]. However, the stimulation pulse of their device was adjustable only by 8 voltage steps, which does not meet clinical requirement. The DBS device for rats developed by Kyou (2010), was powered by external radio frequency electromagnetic waves, with lacked stability during the animal trials, because the rat would move freely[8]. To overcome these problems, this study aims to develop a cheap, durable and easily applicable deep brain stimulation device for small animals which meets clinical requirements.

II. OVERALL SCHEME AND DESIGN OF HARDWARE AND SOFTWARE

A. Overall scheme of the system

The deep brain stimulation system specialized for small animal consists of circuit modules of the pulse generator, a battery, a bipolar coaxial electrode and a programmer. Overall frame of the system is shown in Figure 1:

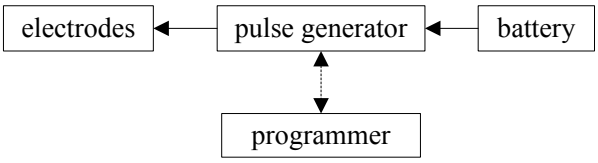


Figure 1 Overall frame of the system

The pulse generator is a programmable stimulator governed by a microprocessor. The device is powered by a button-type battery. The electrical pulses produced action in the deep brain region of rats via electrodes. The programmer can regulate the mode and parameters of the stimulation pulse and can receive work information from the pulse generator via wireless communication.

Table 1 shows the key design parameters of the system, similar to Medtronic's commercial stimulator[9]. They are consistent with the parameters of brain pacemaker for the human body, except for the range of pulse amplitude.

TABLE I
KEY DESIGN PARAMETERS OF THE SYSTEM

Parameters	Range
Pulse amplitude	0~2.5 V (in 0. 1 V or 0.05V steps)
Pulse frequency	2~250 Hz (62 steps): 2，5，10，15，20，25，30，35，40，45，50，55，60，65，70，75，80，85，90，95，100，105，110，115，120，125，130，132，135，137，140，142，145，147，150，152，155，157，160，162，165，167，170，172，175，177，180，182，185，190，195，200，205，210，215，220，225，230，235，240，245，250
Pulse width	60~450μs (in 30μs steps)
On-time	0.1 s~24 h: 0.1~1 s (in 0.1s steps), 1~60 s (in 1 s steps), 1~30 min (in 1 min steps), 0.5~24 h (in 0.5 h steps)
Off-time	0.1 s~24 h: 0.1~1 s (in 0.1s steps), 1~60 s (in 1 s steps), 1~30 min (in 1 min steps), 0.5~24 h (in 0.5 h steps)
Day-cycle on-time	00:00~23:30 (in 0.5 h steps)
Day-cycle off-time	00:00~23:30 (in 0.5 h steps)

B. Design and implementation of software and hardware

The main hardware component of the system includes a pulse generator and a programmer. The pulse generator consists of a control center, which is a highly integrated microcontroller (mixed-signal microcontroller), and other segments like pulse output module, communication module and so on. The programmer consists of transmitting and receiving parts, and the receiving / transmitting antenna are the common components of the two parts.

Figure 2 shows the overall circuit diagram of the pulse generator. It is powered by a button battery, whose type is CR2032 and capacity is 220mAh. MSP430F169 microcontroller is used as the system controlling center, which has a variety of low-power modes, and integrates FLASH, RAM, timer, DAC, ADC, and other peripheral modules[10]. An external low frequency crystal oscillator of 32768Hz is used to reduce system power consumption. Output circuit provides a constant stimulus pulse output. The charge balance circuitry provides a reverse current after the falling edge of the stimulation pulses to balance electric charges, ensuring that the net charge flowing though the nerve tissue throughout the cycle is zero. Wireless communication between components is carried out via the communication circuit[11].

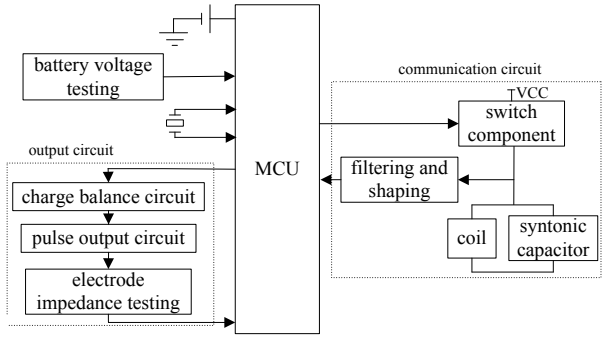


Figure 2: The overall circuit diagram of pulse generator

The main functions of the software in the pulse generator are application implementation and hardware management. The software is coded with C language. The software system of the pulse generator is summarized in Figure 3.

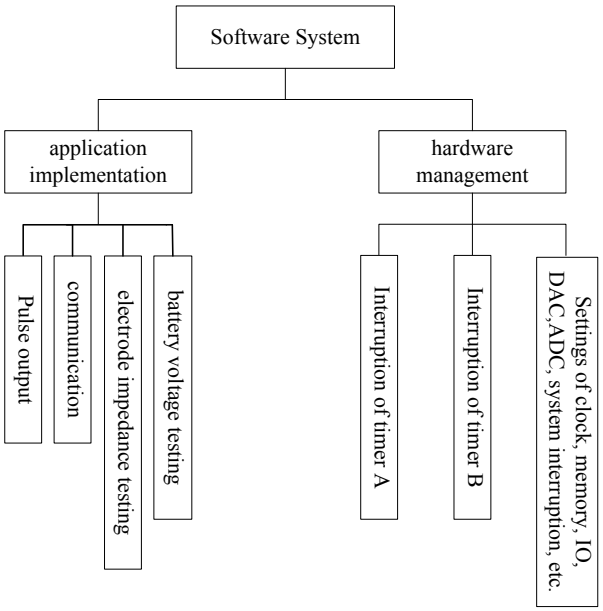


Figure 3: Pulse generator software system

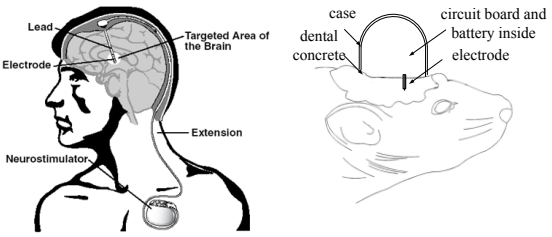
III. PROTOTYPE PRODUCTION, TESTING AND VALIDATION

A. Prototype production

In the current clinical DBS system, the pulse generator circuit module and battery are pre-packaged in a titanium case, which is connected to the extension with a sealed connector made of medical polymer. As showed in figure 4(a), in the operation, the lead will be implanted into brain tissue with caudal connector ostium outside the skull and below the scalp, and the pulse generator is implanted in the chest, which is connected with the lead via the extension subcutaneously[12]. In the device implantation for small animals, there are many difficulties in the package of the pulse generator, the production of electrode suit, the tightness between components and the reliability of the system. Therefore, we modified the structural design of the DBS device for small animals. Its main feature is that the pulse generator circuit module and battery are packaged in a plastic case instead of a titanium one and the electrode is connected with the circuit module though a pinhole under the plastic case with a lead. The root of the electrode is fixed by glue. As showed in figure 4(b), during surgery, only the electrode is put into the brain, and the pulse generator is fixed outside the skull with dental concrete. This design not only simplifies the production process, but also improves the reliability of the system connection and reduces the requirements of the sealing performance of the system.

The completed prototype of the DBS device is shown in Figure 5(a). In order to ensure a small contact area at the bottom of the device, vertical design of the circuit board and battery is adopted as shown in Figure 5(b). The positive and negative sides of the battery are connected to the circuit board with a soft wire. The wires are tightly packed in the space

within plastic case to reduce the physical size of the device.



a b

Figure 4: a. The current clinical DBS system of Medtronic;
b. The DBS device used for small animals

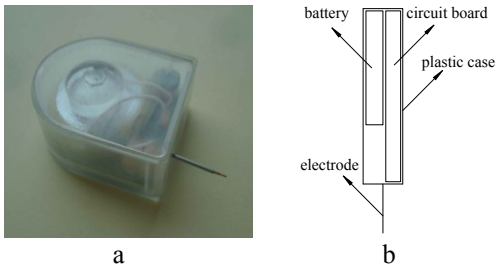


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Figure 5: a. The completed prototype of the DBS device;
b. Schematic diagram of structure of pulse generator

The shape and size of the circuit board are designed according to the specification of the battery. The type of battery used is CR2032. It is circular with a diameter of 20mm and a thickness of 3.2mm. The shapes of the plastic case and the circuit board are designed according to that of the battery. The width of the circuit board is 20mm and the length is 25mm. The total thickness of the device is 12mm. The functions of the outside plastic case are: 1) to contain the circuit board and battery, 2) to prevent the rat scratching the device and 3) to make the device more attractive.

With reference to literature[7], the coaxial electrode, or concentric electrode, is used (Figure 6(a)). Figure 6(b) shows the structure of the tip of electrode. The outer layer is a stainless steel tube, with outer diameter of 0.6mm and an inner diameter of 0.34mm, serving as the reference electrode of positive polarity. The core region is fitted with an enameled copper wire, whose diameter is 0.3mm (including the insulation), serving as the stimulating electrode of negative polarity by scraping the insulating layer on its tip. The lengths of insulating and conductive parts in tip region are both 1mm respectively while the total length of the electrode is about 10mm.

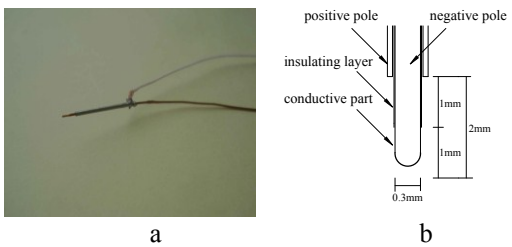

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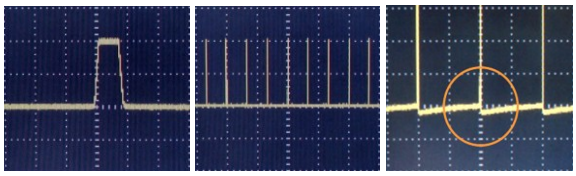
Figure 6: a. External appearance of the electrode ;
b. The structural drawing of the electrode tip

B. System function test

The pulse generator circuit board was tested based on established protocol. Firstly, the quality of the output pulse shape was tested. The default parameters of the pulse were 150Hz frequency, 90μs pulse width and 1V amplitude. The waveforms were shown in Figure 7 (TDS2002, Tektronix). The pulse parameters were consistent with the default values that the oscillation of the waveform baseline was very small, having no effect on the nerve. Also, the rising edge and falling edge of the pulse were steep enough. These met the application requirements of the device. When the waveform was magnified vertically, a reverse balance voltage after the falling edge of the pulse could be clearly observed. This provided information on prevention of damaging the nerves and electrode by the constant current during electrical stimulation.



a b c

Figure 7: a. single pulse; b. multiple pulse; c. charge-balancing

Then the output pulse parameters were tested. The results proved that errors in the pulse amplitude, pulse width, frequency and other parameters (Table 1) were small, within the permissible range.

Besides the basic parameters, we also set the stimulation mode of pulse generator, circularly or uninterruptedly, measured the electrode impedance and battery voltage. The results confirmed that the device responded to all the input commands correctly.

Finally, the power dissipation of the pulse generator was tested. When stimulation was off, the total current was only 4.73uA(17B, Fluke). When the output pulse was set into typical values of 2V, 90us, 150Hz, the total current was 61.3uA. While the capacitance of the CR2032 button battery is 220mAh, thus the system fulfilled the duration requirement of more than three months with the typical values of 2V, 90us, 150Hz.

C. Preliminary rat experiment

Animal trial was performed in order to verify the functions of the prototype device. Male Wistar rat weighted 250–300g was chosen for the research object and was housed in an environmentally controlled room (20–23˚C, 12-hour light/12-hour dark cycle, lights on at 7 h). The rat was anaesthetized with pentobarbital (40 mg/kg, i.p.), the action time of which is about 4 hours. Then head of the rat was fixed to the stereotaxic frame (Model 1430, David Kopf Instruments, Tujunga, CA), and fore and hind feet were tied to stable position. We incised the scalp and drilled holes through the skull in given positions for the electrode to go in. The device was fixed on the skull with dental acrylic cement as shown in figure 8.

According to the method introduced in [13], Kainic Acid (KA, Sigma) was dissolved in phosphate buffer solution (0.2

M, pH 7.4) at a concentration of 2μg/μl. 0.2 μl KA solution was administered into the left dorsal of hippocampus (AP, −4.2 mm; lateral, 2.6 mm; depth, −3.6 mm) for 3 minutes under the driving of MicroSyringe Pump (UMC4, World Precision Instruments Inc., U.S.A.), then the needle was withdrawn 1mm and sustained for another 3 minutes, with that prevented leakage of KA solution into the surrounding structures. Thus the rat was induced temporal lobe epilepsy status and secondarily generalize seizure status.

During the experiment, no error occurred in the communication between the DBS device and the programmer. We could modify the mode and parameters of the stimulation pulse and measure battery voltage or electrode impedance with the programmer. For the injection of KA, the rat presented a typical symptom of temporal lobe epilepsy, which included trembling like a wet dog, convulsion of fore legs, falling down, generalized tonic clonic seizure and so on. A significant remission of the rat's epilepsy symptoms can be observed when putting the electrical stimulation on the anterior thalamic nucleus(ANT)[14-15].

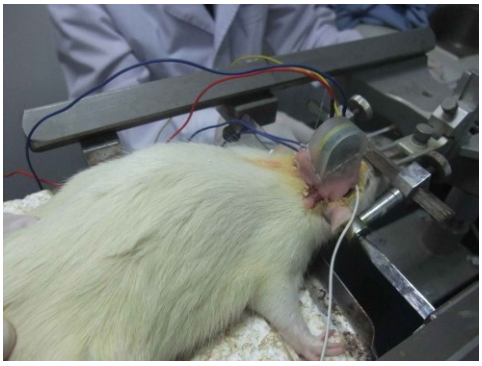


Figure 8: Rat installed with the DBS device

IV. Conclusions and discussion

In this study, a DBS device was developed according to clinical requirements and technical verification on the functions in terms of pulse output signal, different modes of stimulation as well as durability of the DBS device was performed. The results of animal experiment showed that the device developed in this study is stable and easily applicable. The design of the device can fulfill the requirements for deep brain stimulation in animal experiments. Also, telemetry and remote control design ensured convenient operation. Furthermore, low power consumption enhanced the durability of the device.

However, much further study should be done on the aspects below to improve the performance of the system:

1) the function of bilateral stimulation –The DBS device we designed for small animals has achieved one channel output of electrical stimulation pulses. But in some cases, bilateral stimulation may be necessary in animal experiments. We can modify the circuit suitably to realize it.

2) the diversification of the stimulation pulse modulation - The stimulation pulse needed in the different cases varies in waveform, frequency, pulse width and amplitude. The DBS device we designed for small animals has achieved stepwise adjustment of the pulse amplitude, frequency and width, but it can only output rectangular wave. We considered adding the function of waveform modulation to adapt to the needs in different cases.

3) further extension of the lifetime of the device - We used a non-rechargeable button type battery for the system power supply. The device stops working when the battery is used up. That is to say, the lifetime is limited no matter how low the power consumption is. If the RF technology is used to recharge some rechargeable battery, the lifetime of the device could be extended.

4) improvement of the telemetry function - In this study, we could only get the operational data of the stimulator itself. The effect of the therapy could not be reflected. The ideal therapy process is a closed loop, which means the device can sense the response of the curer during the treatment. This requires the stimulator to measure and process the electrical signal of the nerve tissue. If so, we can analyze the rationality of the therapy parameters by the received data.

Acknowledgements

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