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Microelectronics-embedded channel bridging and signal regeneration of injured spinal cords

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Abstract

Due to the difficulty in spinal cord regeneration with biological methods, the microelectronic neural bridge, a new concept based on microelectronic technology, is presented. The microelectronic system has been realized in the forms of hybrid and integrated circuits. The integrated circuits for neural signal detection, stimulation, and regeneration are realized in a CMOS process. In animal experiments with 100 toads, 48 rats, and 3 rabbits, nerve signals have been successfully detected from spinal cords and sciatic nerves, and functional electrical stimulation has been carried out for spinal cords and sciatic nerves. When the microelectronic system is bridged between the controlling and stimulated nerve, the relevant motion of legs and nerve signal waveforms, which are stimulated by the evoked or spontaneous nerve signal through such a system, have been observed. Therefore, the feasibility of the presented method was demonstrated.

Keywords: Nerve injury; Microelectrode arrays; Neural recordings; Neurostimulation; Functional recovery

1. Introduction

Spinal cord injury (SCI) is one of the most severe traumas for human beings. In accordance with the statistics of the *Fact Sheet* published by the National Spinal Cord Injury Statistical Center of the USA, approximately 11,000 new cases of SCI occur annually in the USA, and the total number of SCI patients has been estimated to be about 253,000 as of June 2006. According to the statistics of the Chinese State Administration of Work Safety, the annual incidence of SCI in China is 130,000 new cases or so and the total number of SCI patients is estimated to be more than 2 million. All these patients suffer from loss of perception and motor functions.

Substantial function regeneration of an injured spinal cord should include three aspects: (1) the proliferation of neurons to replace the lost or dead ones, (2) the regrowth of interrupted nerve fibres (dendrites and axons) of surviving neurons to rebuild the original signal transmission channels, and (3) the reconnection of the regrowing dendrites and axons with the destined neurons. On the first aspect, it was believed that the regeneration of the neurons in the central nervous system of an adult mammalian is impossible [1]. Therefore, further hope of neuronal regeneration was pinned on the second and third aspects. One idea was to regenerate the axons of surviving neurons from the

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proximal stump to the distal one of the injured spinal cord. To demonstrate the possibility, a segment of sciatic nerve grafts was used to form a biological "bridge" over an injured section [2] or between the medulla oblongata and the spinal cord [3]. Those experiments, however, demonstrated that there is a limitation in such cases that axons regrow from the peripheral nervous system into the central nervous system. This means that axon regrowth in a spinal cord is difficult.

In recent years, pioneering neuroscientists introduced stem cell technology to establish the desired neural function regeneration. Such research has shown that transplants of olfactory ensheathing cells into the injured spinal cords of laboratory rats had a remarkable capacity to repair damaged tissue and lay a 'bridge' across a gap in the injured nerve fibres [4]. Anderson and his colleagues [5] have used adult human neural stem cells to regenerate damaged spinal cord tissue and improve mobility in mice. These methods can be understood as the formation of biological "bridges" between proximal and distal stumps of injured spinal cord by means of newly introduced and differentiable neurons, instead of the proliferated original ones. However, much more basic and preclinical research must be completed before attempting human trials using stem cell therapies to repair injured spinal cords. Therefore, it is worth exploring alternative methods for repairing injured spinal cord.

In more than 100 years, different electric or electronic devices and systems have been introduced into the application of neural signal recoding and stimulation. With the continuous rapid progress of microelectronics, integrated circuits have reached the level of the so-called SOC (System on Chip). Moreover, by using micro-electro-mechanical-system technology, micro-electrode-arrays (MEA) can be manufactured in different structures for implanted neural interfaces. Up to now, a lot of microelectrodes such as microwire or cuff electrodes have been used to study the activity of the cerebral cortex and spinal cord [6–8]. Furthermore, researchers have attempted to use such microelectrodes incorporated with the SOC to restore the motor function of the upper limb of human beings [9]. Obviously, the chip implanted in an injured spinal cord is more pertinent, and therefore, more efficient for SCI patients.

Based upon SOC and MEA technology, we introduced the concept of microelectronics-embedded channel bridging and signal regeneration of an injured spinal cord [10] in 2004 and have realized the prototypes of the so-called microelectronic neural bridge in the forms of hybrid and integrated circuits [11]. The animal experiments with 100 toads, 48 rats, and 3 rabbits demonstrated that the nerve signal from a sciatic nerve or a spinal cord can be regenerated to an interrupted sciatic nerve in a toad or rat and an interrupted spinal cord can be connected bi-directionally in a rabbit, when the microelectronic system is bridged between the controlling and the stimulated nerve. Both bridge formations can regenerate both evoked and spontaneous neural signals.

In this paper, we report at first the system design and approaches of the microelectronics-embedded channel bridging and signal regeneration of the nervous system, which are aimed at recovering the function of injured spinal cords. Then, we show the results of the animal experiments and give discussions.

2. System design and approaches

The proposed concept on microelectronics-embedded channel bridging and signal regeneration for injured spinal cords is illustrated in Fig. 1(a), and the block diagram of the microelectronic module is proposed as shown in Fig. 1(b).

The microelectronics system consists of two MEAs and two multi-channel neural signal regenerators (NSR). MEA1 and MEA2 are interfaced with the proximal and distal stumps of an injured spinal cord, respectively. Part of the electrodes of MEA1 on the proximal stump is connected to the first multi-channel neural signal regenerator, NSR1, and used to detect signals from the axons of the neurons in the cortical centre. The output signals from NSR1 are supplied to part of the electrodes in MEA2 on the distal stump and used to stimulate the desired motor neurons. The downward channels in NSR1 are responsible for the regeneration of motor signals. Conversely, the rest of the electrodes of MEA2 on the distal stump are connected to the second multi-channel neural signal regenerator, NSR2, and used to detect signals on the axons from the sensory neurons in the dorsal root ganglia. The output signals from NSR2 are supplied to the rest of the electrodes of MEA1 on the proximal stump and are used to stimulate the desired axons that join the thalamus. The upward channels in NSR2 are responsible for the regeneration of sensory signals.

The block diagram of the microelectronic module along with two MEAs is illustrated in Fig. 1(b). The core part is the NSR array, which consists of a line-up of downward and upward channels. Between the NSR array and the MEAs, two channel switching fabrics are inserted. Their function is to switch the downward and upward channels, so that the neural signals can be regenerated along the intended channels even after implanting. The controlling unit carries out the switching function etc. The monitoring unit is used to monitor different parameters and functions of the system.

The signal processing unit includes detecting and stimulating modules, which detects and excites the neural signal propagating along the given neuron in the spinal cord, respectively [10]. The detecting circuit includes an RC network, a pre-amplifier, an active band-filtering stage, a notch network, and a shield-guarding circuit [12]. The stimulating module consists of a pre-amplifier and a post-amplifier. The former amplifier is to amplify the input signal to sufficient amplitude, and the latter one consisting of

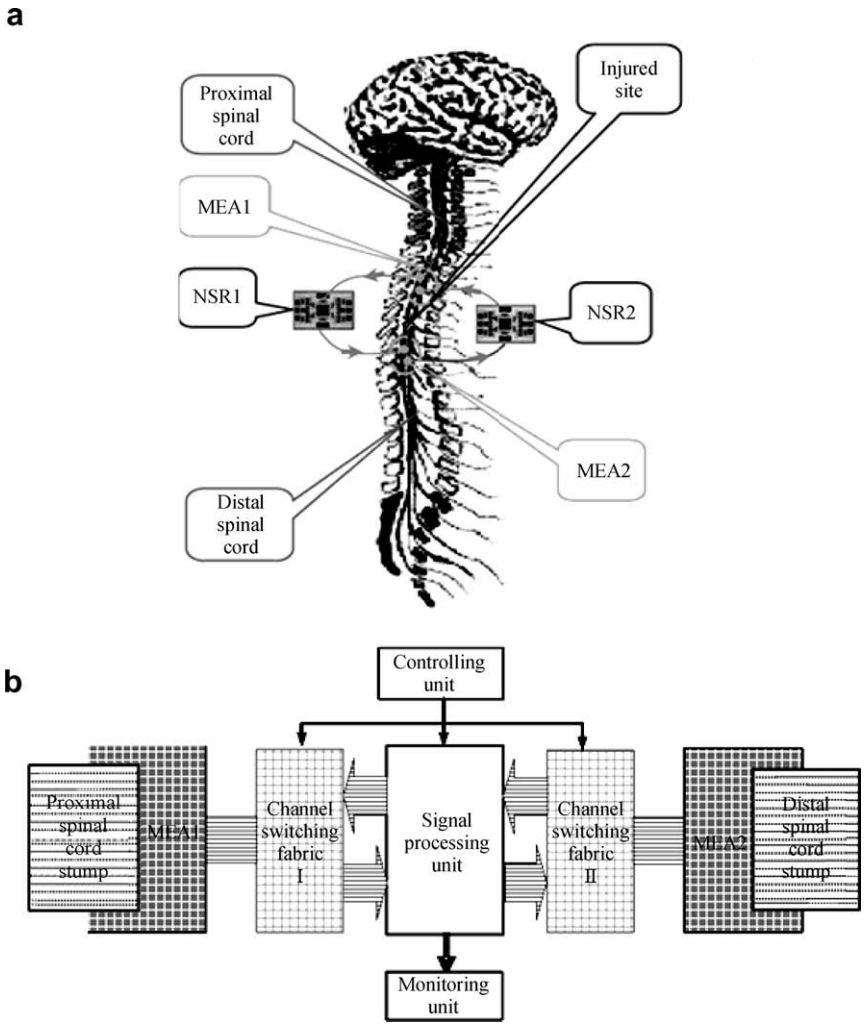

Fig. 1. Concept of the channel bridging and signal regeneration of an injured spinal cord by using two NSRs (a) and the block diagram of the microelectronic module along with two MEAs (b).

two amplifiers can generate two signals with 180° phase difference, which can be used to amplify the signal further so as to obtain an effective stimulating voltage to drive the following microelectrodes [13]. For simplicity and low-power application, all signals are processed in an analogue domain. The active band-filtering stage realizes only a filtering function to remove noises and interferences of the 50 Hz power supply.

For our study, three types of electrodes, self-developed microelectronic systems, and a series of commercial instruments have been used.

The hook-type electrode (Quanshui Experimental Devices Co., Nanjing, China) was made of two parallel metal wires pressed into the surface layer of a hook-formed plastic plate. The cuff electrode arrays of different sizes were obtained from the Fraunhofer Institute for Biomedical Engineering, Germany. Its substrate was made of polyimide (Pyralin PI 2611, Du Pont), the contact metal platinum/iridium, the conductive strips gold, and the bond pads solderable layer [14]. Two cuff-type MEAs with different contact configurations, which are 3×4 and 3×6, were used to form four and six channels of the triple-electrode system, respectively. The self-made needle electrode arrays were made of acupuncture needles whose body was covered with Parylene except for the tip (Cookson Electronics Specialty Coating Branch, Shanghai). Fig. 2(a) shows one four-needle electrode array. The aluminum sheath was used to wrap the needles for supporting and shielding. A three-arm stereotactic positioner (Shanghai Alcott Biotech CO. Ltd.) was used to hold and position the three-needle electrode arrays as shown in Fig. 2(b). The three regions to be positioned were the spinal cord, the left sciatic nerve, and the right sciatic one.

The microelectronic systems for *in vitro* experiments were realized by using the printed circuit board (PCB) technique. Besides simple discrete devices such as resistors and capacitors, precision operational amplifiers OP27 or MAX4168 (Maxim, USA) were chosen for all gain stages [15,16]. In the system, there are eight groups of low-noise high-gain amplifiers, analogue signal processing units, and FES units. The gain of each amplifier can be switched among 10 values: 1, 10, 50, 100, 200, 500, 1000, 2000, 5000, and 10,000. One amplifier plus one signal processing unit can form a neural signal detector or monitor. An FES unit

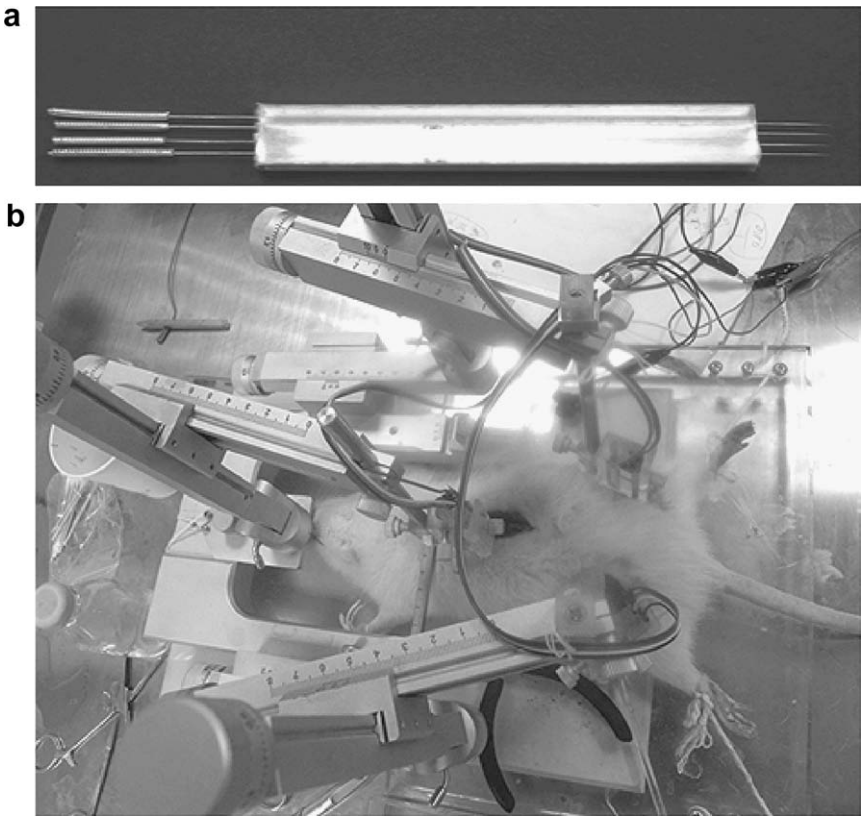

Fig. 2. Four-needle electrode array made by the Institute of RF- and OE-ICs, Southeast University, China (a) and photograph of the three-arm stereotactic positioner for holding and positioning three-needle electrode arrays (b).

can be used alone or combined with a neural signal detector to build up an NSR-channel. That means, a maximal of eight NSR-channels can be built up. One applicable possibility is that four channels are used for downward signal regeneration and the others for the upward one. The function transforming and gain adjusting were carried out by the switches and potentiometers on the front board of the box.

The integrated circuits (ICs) for implantable systems were designed in the so-called fabless mode [12,13]. A 0.6 μm CMOS 2P(oly)2 M(etal) technology (CSMC, Wuxi, China) was chosen as the foundry for the chip fabrication. The computer-aided design programs Smart-Spice (Silvaco, Silicon Valley, USA) and Zeni (Huada, Beijing, China) were used for the circuit simulation and the layout design, respectively. The chips were fabricated through the Multi Project Wafer (MPW) service of ICC, Shanghai, China. The sizes of the die and the packaged chip were 2.82×2 and 14.2×14.2 mm, respectively.

The measuring instruments of both the PCB- and IC-type microelectronic systems mainly include an arbitrary pulse generator (Agilent 33220A, USA) and an oscillograph (Tektronix TDS5104, USA). The same pulse generator and oscillograph were also used in the animal experiments as the pulse signal source of the FES driver and for signal monitoring and recording, respectively.

All animal experiments were completed in the laboratory of the Southeast University and Jiangsu Key Laboratory of Neuroregeneration of Nantong University and performed in compliance with the Medicine Institutional Animal Care and Use Committee of Nantong University and national regulations and policies.

3. Experimental results

Using all three types of electrodes and the discrete or integrated microelectronic neural regenerating systems mentioned above, we have carried out, in the last 4 years, 15 animal experiments, and a total of 100 toads, 48 rats, and 3 rabbits were used as models in the experiments. The significant results obtained are as follows.

3.1. In vitro nerve signal regeneration from a toads' left leg to the right one

First, the spinal cord of a toad was destroyed and then, two hind limbs were separated and the relevant sciatic nerves were exposed. In this experiment, two five-needle electrode arrays were used to pierce into the toad's left and right sciatic nerves, respectively. The schema of the channel bridging and signal regeneration are shown in Fig. 3(a), and the experimental results are shown in Fig. 3(b). Here, an FES signal was stimulated by a pulse

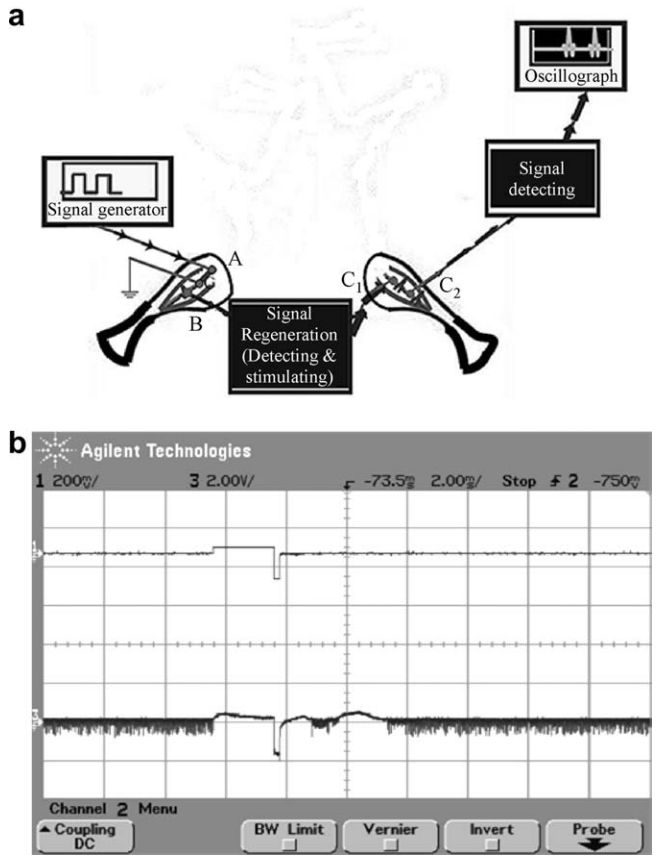

Fig. 3. Schema of neural channel bridging between sciatic nerves in toads' legs (a) and the stimulating signal on point A in the left sciatic nerves and the regenerated nerve signal on point C_2 in the right ones (in top–down direction) (b).

generator with a needle electrode on point A. Another needle electrode was employed to detect the nerve signal activated by the foregoing one from A on point B. Grounded electrodes were arranged on point G between the stimulating and detecting electrodes to realize the artefact suppression. Then, a nerve signal regeneration chip was used to transmit the nerve signal from the left sciatic nerve to the right one. After that the regenerated signal was added on the right sciatic nerve through a needle electrode on C_1. Finally, a nerve signal was detected from another needle electrode on C_2 by an oscillograph, as shown in Fig. 3(b).

After the aforementioned *in vitro* experiments, *in vivo* ones were carried out. Sprague–Dawley (SD) rats weighing about 350 g were used in the following experiments. We anesthetized them with chloral hydrate (300 mg/kg), exposed the spinal cord in L_{10} (approximately 5 mm wide and 15 mm long) and removed dura mater over the exposed area.

3.2. Mapping relation between spinal cord stimulation and the motion of muscles

A series of important "mapping", that is, the relation between the stimulating points in the spinal cord and the reaction parts of the body, were tested by means of the cuff-type MEAs and needle-type electrode arrays. Up to now, we have determined more than 30 spinal cord points, at which the distinguishable reaction of limbs could be watched. For data reading, the upper border of a defined vertebra, the posterior median sulcus, and the surface of the spinal cord were used as the origins of the *x*-, *y*-, and *z*-coordinates, respectively. Adding voltage to a needle-type electrode array, which was inserted into the spinal cord with a distance of 0.6 mm left from the posterior median sulcus and at a depth of 1.8 mm from the surface of the spinal cord at vertebra L_1, for instance, we found the actions of the toe of the left hind foot. It was also found that with a needle-type electrode array, most threshold values of the stimulating voltage could be lower than 1 V, while with a cuff-type MEA, the threshold values were mostly higher than 3 V.

3.3. Nerve signal regeneration from the left leg to the right one

The schema of our experiment of the channel bridging and signal regeneration on the rats' sciatic nerves is shown in Fig. 4(a), and the experimental results are shown in Fig. 4(b). An FES signal generated by a pulse generator was supplied to the hooked electrode A, which was interfaced on the ventral spinal cord of the rat where the corticospinal tract runs downwards. The first cuff MEA, B, was encircled on the intact left sciatic nerve to detect the neural signal for regeneration, while the others were on the distal stump of the transected right one. The first channel joined to C_1 was used to evoke a new neural signal, and the second one to C_2 for monitoring the regenerated signal.

Under the condition of narcotism and external stimulation, the signal waveforms shown in Fig. 4(b) were obtained from four electrodes, respectively. Then, the pulse generator was switched off and the waveforms were captured from electrodes A, B, C_1, and C_2 (Fig. 4(c)). In this case, the spontaneous neural signal was regenerated from the left sciatic nerve to the right counterpart and detected successfully.

A pattern recognition raster diagram for signal C_2 was created (Fig. 4(d)), by adopting the coding method used by Mazurek et al. [17] and Jones et al. [18]. It is well known that each pulse corresponds to a neural spike. Therefore, the spike numbers of the five bursts from B, C_1, or C_2 are 10, 9, 6, 3, and 1.

3.4. Nerve signal regeneration between the spinal cord and transacted sciatic nerve

The schema of the channel bridging and signal regeneration from the spinal cord to a sciatic nerve of a rat is shown in Fig. 5(a), and the experimental waveforms are shown in Fig. 5(b). Here, the spontaneous neural signal was detected by A from the intact spinal cord and sent into the neural signal regenerator. After being amplified and

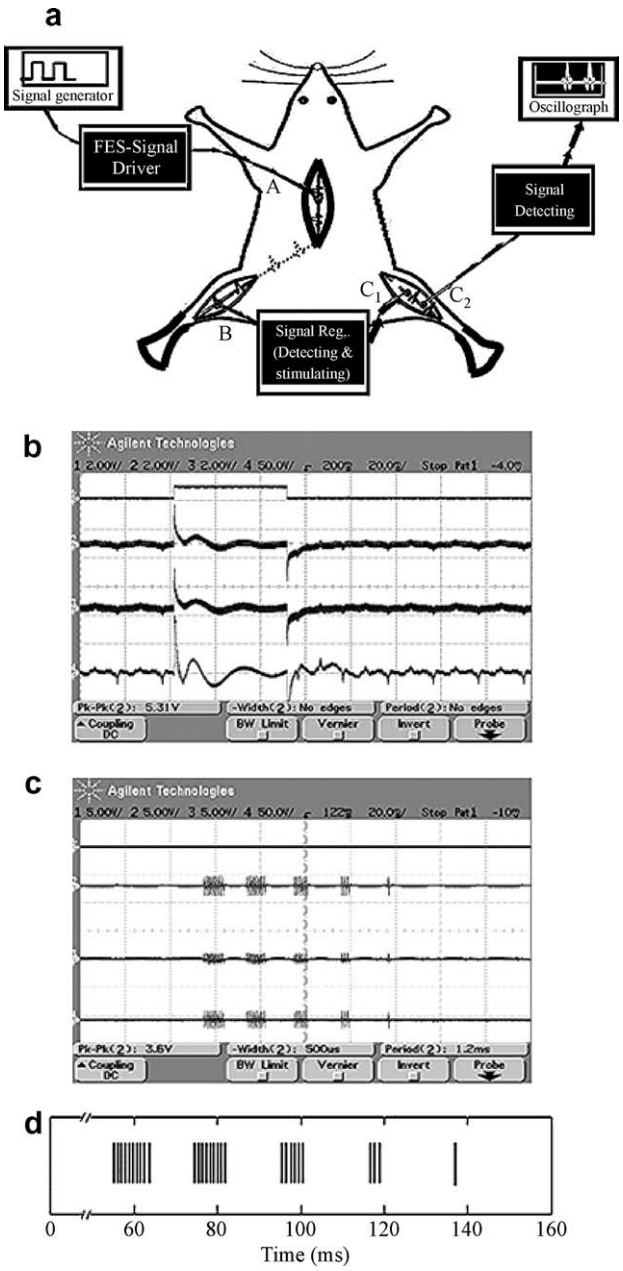

Fig. 4. (a) Schema of neural channel bridging between sciatic nerves with evoked potential spikes from the spinal cord. (b) Four waveforms recorded from electrodes A, B, C_1, and C_2 (in top–down direction) with stimulation on A. (c) Four waveforms recorded from the same electrodes without stimulation on A. (d) The raster diagram of signal B in (c) obtained by means of pattern recognition.

processed, a related FES signal was generated and applied onto B_1, which was joined to the distal stump of the transacted left sciatic nerve. The neural spikes evoked by B_1 were detected by B_2, which was interfaced to the site near B_1, and sent to the oscillograph.

An interesting phenomenon was observed. After the system was switched on, the muscle near the distal stump of the transacted left sciatic nerve bundle twitched irregularly. At the same time, we monitored the waveforms from A, B_1, and B_2 as shown in Fig. 5(b).

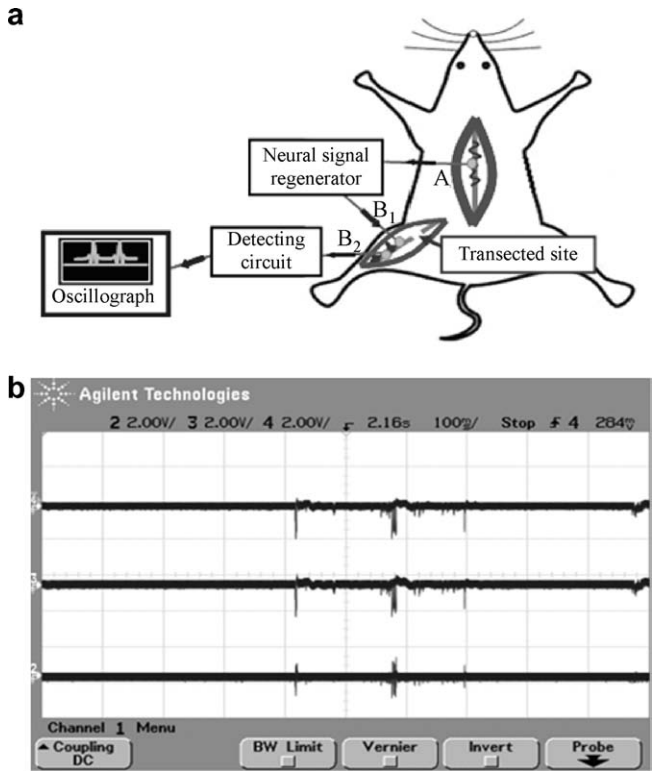

Fig. 5. Schema of the channel bridging and signal regeneration from the spinal cord to a sciatic nerve bundle of a rat (a) and three signal waveforms recorded from A, B_1, and B_2 (in top–down direction) while the left sciatic nerve of the rat was flickering (b).

3.5. Bi-directional nerve signal regeneration of the transacted spinal cord

Based on the experiments above, we carried out the bidirectional signal channel bridging and regeneration experiment on the transacted spinal cord of a rabbit, as schematically shown in Fig. 6(a), and the signal waveform shown in Fig. 6(b). Two cuff MEAs of large dimension ($\Phi \approx 10$ mm) were used. Electrode A_2, neural signal regenerating circuit NSR1, and electrode B_1 formed the neural signal regeneration channel in the downward direction while B_3, NSR2, and A_4 formed the neural signal regeneration channel in the upward direction.

First, the rabbit was narcotized, and an external stimulating signal was applied to evoke the neural spikes. In order to avoid self-oscillation, we adjusted the gain, G, of the neural signal regenerators NSR1 and NSR2 from >500 to <500 and obtained the signal waveforms recorded from A1, B2, B3, and B4 (in top–down direction) as shown in Fig. 6(b). Then, under the condition that there was no external stimulation and the inner side of the right thigh of the rabbit was knocked, the signal waveforms recorded from B4, A4, and A3 (in top–down direction) were captured, as shown in Fig. 6(c). The result demonstrated that the motorial and sensory signals were regenerated in the bidirectional system.

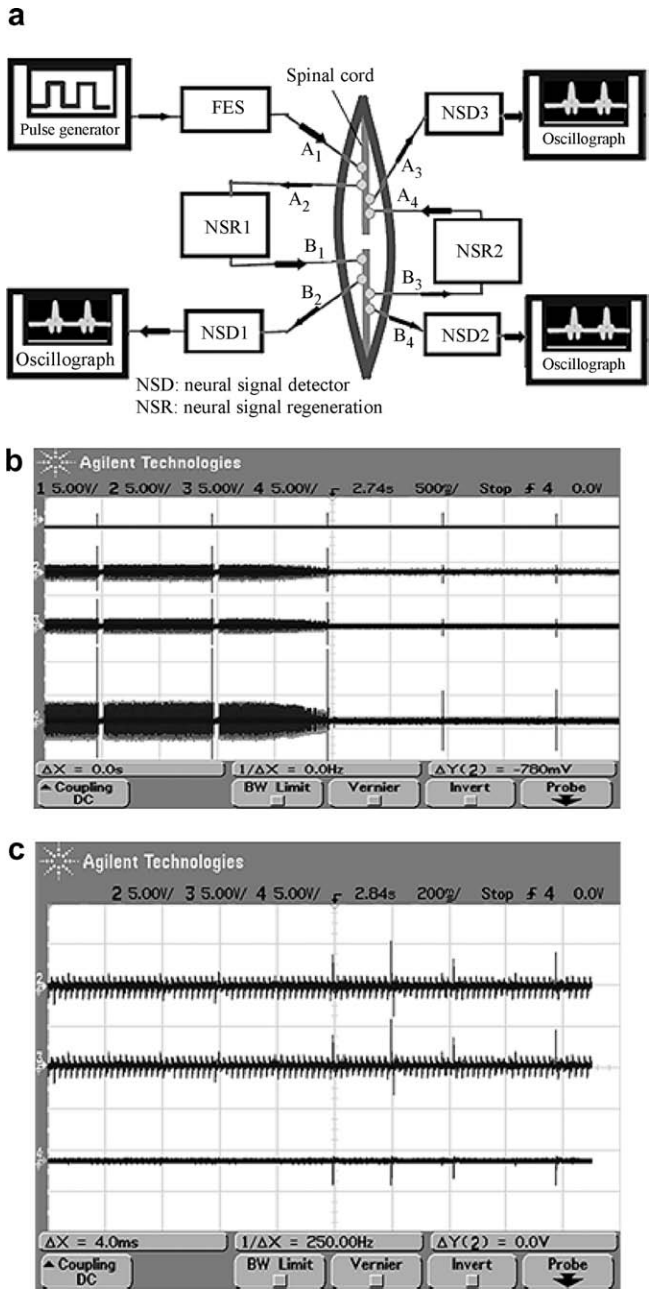

Fig. 6. (a) Schema of the signal channel bridging and bidirectional signal regeneration experiment on the spinal cord of a rabbit. (b) Signal waveforms recorded from A_1, B_2, B_4, and A_3 (in top–down direction) when we adjusted the gain, G, of the neural signal regenerators NSR1 and NSR2 from $G > 500$ to $G < 500$. (c) Signal waveforms recorded from B_4, A_4, and A_3 (in top–down direction) under the condition that the inner side of the right thigh of the rabbit was knocked.

4. Discussion

A nervous system is, in fact, a complex communication network. Its function is mainly to realize the generation, processing, transmission, and reception of neural signals. Like an interrupted physical (sonic, optical, or electrical) communication system, an injured spinal cord means that a part or all of the transmission channels are interrupted and neural signals cannot be transmitted through the injured section. Our idea for the channel bridge and the signal regeneration of an injured spinal cord is to build up such a system in which the transmission channels of the neural signals are bridged by means of an embedded microelectronic device or module instead of a nervous graft as made by Richardson et al. [2] and David et al. [3].

The possibility that a microelectronic system can be applied to connect the injured spinal cord is based on the fact that a neural signal travelling in a nerve fibre is similar to an electromagnetic wave travelling along a transmission line or cable. Therefore, it is possible to detect or monitor the neural signal with proper electrode or electrode array. The challenge in detecting signals from a spinal cord is that an array of electrodes should be arranged properly such that the unnecessary signals from the nearby nerve fibres can be shielded.

We choose cuff-type MEAs at first. As indicated by its name, the cuff MEA becomes columnar when it is inserted into the spinal cord and automatically encircles the cord. Therefore, the cuff MEA has the advantage that for interface with the spinal cord or nerve, it is non-invasive and self-grasping. Another advantage is that all signals in the spinal cord or nerve surrounded by the cuff MEA are detectable in principle. For the primary experiments, four-channel MEAs with 12 contact dots were selected for all of the sciatic nerves and spinal cords of rats, and for the experiments with the spinal cords of rabbits, six-channel MEAs with 18 contact dots were used. For clinic patients in the future, MEAs with channel numbers of 16, 32, 64, or more should be feasible. One disadvantage of today's cuff MEAs is that their contact dots are interfaced with the perineurium of the spinal cord and not directly with the nerve fibres to be bridged. Thus, its threshold value for an evident reaction is high and the selectivity is poor. Therefore, we have developed a needle-type electrode array, with which the threshold valve could be reduced to <1 V. However, such electrode arrays are difficult to fix on a spinal cord. In order to overcome the disadvantages of both the cuff- and needle-type electrode arrays, a new type of MEA by incorporating the cuff structure with needle-type electrode arrays has been developed and will be reported.

The channel bridging and signal regeneration is significant for the following three cases:

(1) An injured spinal cord. This is the main goal of this study.
(2) An injured peripheral nerve. The inosculation of the injured peripheral nerves needs a long time, sometimes many months, while the microelectronic-embedded channel bridging can be made directly at the accident site to maintain the activity of the distal peripheral nerves.
(3) An artificial channel from the spinal cord to a peripheral nerve.

In Fig. 4(a), we choose both the left and the right sciatic nerves because the cuff MEAs are 12 mm long and it is difficult to wrap two cuff MEAs around one sciatic nerve. Another argument for this schema is that the action of the left leg can be regarded as a reference to the right one.

The essential characteristic of the experimental systems shown in Figs. 3–6(a) is that they are of the hybrid electro-nervous system because, in each system, there is at least one electronic system, one nervous system, one electro-to-nervous interface, and one nervous-to-electric interface. The most important is that the electronic system can be embedded into the nervous system.

Our goal of the animal experiments is to demonstrate whether the hybrid electro-nervous system functioned as desired.

In the *in vitro* toad's experiment, when the stimulating signal was added to the point A and the nerve signal regeneration chip did not work, we could just observe the twitch of the left hind limb of the toad. Then, after the chip was switched on, the right hind limb began to twitch synchronously with the left one. At the same time, we monitored the waveforms from C_2, which is shown in Fig. 3(b). The upper was a stimulating signal added to the left sciatic nerve from signal regeneration, while the nether detected a signal from the right sciatic nerve. As can be seen, after a direct electrical coupling signal, two pulses appeared in the nether. Both maxima of the widths of the two pulses were all about 1 ms, which is well known as the typical value of one of the nerve signals. Therefore, we can conclude that a nerve signal has been regenerated by the microelectronic chip system successfully.

From Fig. 4(b), we can see the following characteristics:

(1) The evoked potential signal, from B, is differentiable from the FES square waveform applied to electrode A. This might be due to the nonlinearity of the nervous network.
(2) The waveform of the evoked potential signal, from B, is similar to those obtained by Watkins et al. [19], which means that the detected waveform is a neural signal.
(3) The positive potential spike from B, which is evoked by the rising flank of the square wave from A, corresponds to the starting point of depolarization of neurons. Furthermore, the regenerated signals from C_1 and C_2 include a main spike with a period of about several milliseconds. This result is comparable with the one given by Patrick et al. [20] and Linderman et al. [21], which means that it is the neural spikes, which are evoked by the rising flank of the square wave from A, that are regenerated from the left sciatic nerve to the right one.
(4) In the waveforms from B, C_1, and C_2, there is a ringing procedure with decaying amplitude. This phenomenon can only be explained again by the nonlinearity of neural networks.
(5) The waveform from C_2 is especially interesting. At first, it is similar and synchronous to the ones from B and C_1. With this argument, we can say that the spike from C_2 is a regenerated version of the one from B. Secondly, the narrower the spike from C2 , the stronger the ringing becomes, and the period of the ringing is shorter than the counterparts from B and C_1. All these characteristics reveal that the waveform is more independent of the evoking spike from C_1.

All the signals, from B, C_1, and C_2, shown in Fig. 4(c), are typical spontaneous neural spikes. Comparable results are the waveforms obtained by Vetter et al. [22].

In comparison with the experiments on the left and right sciatic nerves, the signal regeneration from the spinal cord to a sciatic nerve bundle, as shown in Fig. 5(a), is more interesting, because it is an artificial transmission system completely. The observed twitch of the muscle near the sciatic nerve bundle in the left leg of the rat and the waveforms shown in Fig. 5(b) indicate that the distal stump of the interrupted left sciatic nerve has been bridged to the spinal cord.

In the bidirectional experimental system in Fig. 6(a), we observed an oscillation when the gain of the neural signal regenerators was greater than 500. This is not surprising since the bidirectional neural signal regenerating system along with the nervous network may form a closed feedback loop under special conditions. According to the cybernetics, a closed feedback loop will oscillate by itself when the loop gain is $\geqslant 1$ and the loop phase is equal to $2n\pi$ ($n = 0, 1, 2, \ldots$). When, in our case, the system does oscillate, it gives us an important indication: the channel bridging system is established. Then, the next task is to adjust the selectivity and the parameters of the electronic system such that the self-oscillation is suppressed and the system functions correctly.

Through the preceding experiments, we are confident that a microelectronics-embedded signal channel bridge can be established between the proximal and distal stumps of an interrupted nerve bundle. Moreover, both the evoked and spontaneous neural signals can be regenerated by such an artificial electronic system.

Acknowledgements

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