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A Bionic Neural Link for Peripheral Nerve Repair

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***Abstract*— Peripheral nerve injuries with large gaps and long nerve regrowth paths are difficult to repair using existing surgical techniques, due to nerve degeneration and muscle atrophy. This paper proposes a Bionic Neural Link (BNL) as an alternative way for peripheral nerve repair. The concept of the BNL is described, along with the hypothetical benefits. A prototype monolithic single channel BNL has been developed, which consists of 16 neural recording channels and one stimulation channel, and is implemented in a 0.35-μm CMOS technology. The BNL has been tested in in-vivo animal experiments. Full function of the BNL chip has been demonstrated.**

I. Introduction

Peripheral nerve (PN) injuries, such as brachial plexus nerve damage, are a highly debilitating medical conditions. Based on an early survey [1], there were nearly 500 new patients with brachial plexus injuries in 1987 in the UK alone. The situation is expected to be much worse in Asian countries as there are more motorcycle riders. PN injuries usually cause the loss of motor or sensory function, resulting in permanently paralyzed limbs. Existing medical techniques to treat PN injuries include nerve suture, graft, tube and transfer [2],[3]. Direct nerve suture can be very successful when the nerve is sharply cut or the injury gap (the segment of nerve lost or needs to be removed during the operation) is very small, though there are sometimes complications due to the trauma associated to the nerve dissection. For injuries with relative large gaps, nerve grafts are normally used. Autologous grafts are still the "Gold Standard" in the clinical treatment of peripheral injuries. The key in autologous grafts is to find a suitable donor nerve which matches the diameter, length, cross-sectional shape, area, and number of fascicles. Although autologous nerve grafts can partially recover nerve function, the results are still suboptimal [4]. Synthetic nerve tubes or conduits with biological compatible materials, as an alternative to autologous grafts, have also been reported, and some of them have been approved for peripheral nerve repair in clinical settings [3]. Nerve tubes have been found to be only suitable for the repair of injuries with small gaps, usually less than 3cm [3]. The recovery of nerve function relies on the regrowth of the nerve from the proximal side of the injury to the muscle fibers since the nerve on the distal side will degenerate very quickly (usually 48-96 hours) due to Wallerian degeneration [5]. Unfortunately, the regrowth rate is very slow, typically 1*mm*/day. For those injuries in the upper extremities, such as brachial plexus injuries, the nerve has to regrow a long distance to reach the muscle, and therefore the chance of nerve function recovery is usually poor [6]. On the other hand, Functional Electrical Stimulation (FES) has been used to re-animate paralyzed limbs [7],[8]. Recently, a single cortical neuron based FES capable of controlling the wrist movement of a monkey has been demonstrated [9]. However, they deal with a different problem where paralysis is caused by spinal cord injuries while the PN is intact. In this paper, a bionic neural link (BNL) for peripheral nerve repair is proposed to provide an alternative for restoring peripheral nerve function. The concept is described in Section II. The implementation of a prototype integrated BNL chip with sixteen recording channel and a single stimulation channel in a standard 0.35-μm CMOS technology is discussed in Section III. The measurement and animal experiment results are presented in Section IV, followed by the conclusion.

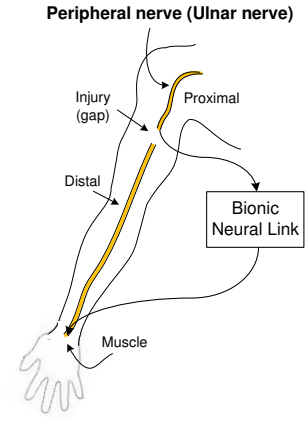

Figure 1. Concept of the proposed BNL

II. Concept of The Bionic Neural Link

The concept of the proposed BNL is shown in Figure 1. The BNL records extracellular action potentials (EAPs) from axons in a proximal peripheral nerve that is damaged. A spike detection circuit detects the EAPs and triggers a stimulator from which a biphasic pulse is generated and stimulates the muscles directly. When a peripheral nerve is severed in an injury, the neural signal paths are broken. The motor neuron signals cannot be transmitted from the brain to the limbs, resulting in paralyzed limbs. If the nerve injury cannot be repaired with existing medical treatments, the proposed BNL can be implanted to reconnect the neural signal path. The BNL bypasses the degenerated distal

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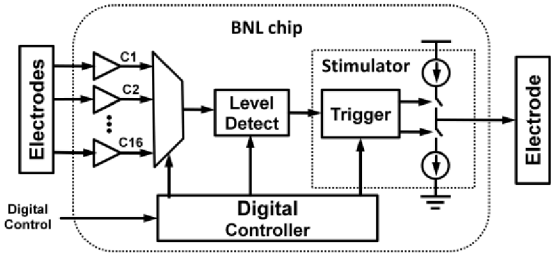


Figure 2. Block diagram of the proposed BNL.

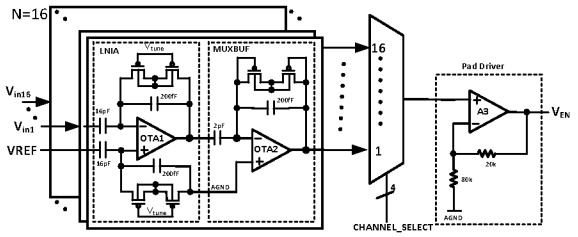


Figure 3. Neural amplifier

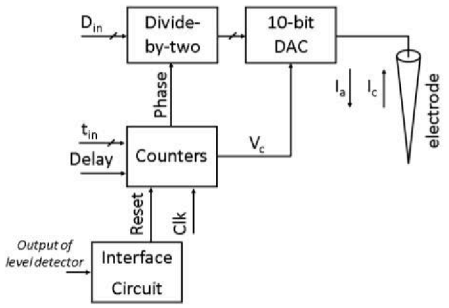


Figure 4. Biphasic muscle stimulator [10]

peripheral nerve and directly stimulates the muscles. It is therefore not affected by Wallerian Degeneration, and can provide instant nerve function recovery.

One of the challenges of the BNL is to map the recorded neural signals from the axons on the proximal side of the injury to the appropriate target muscles. However, it may be possible that once the neural signal path is re-established with the BNL, plasticity in the brain may help remap the relationship between motor neurons in the brain and their associated muscles. The patient can thus be re-trained to control their limbs. Recently researchers have shown that a single neuron in the motor cortex of a monkey can be used to control the artificially paralyzed wrist muscle to move a computer mouse [9]. This finding seems to contradict the early view that recording from a large population of neurons is needed in order to "decode" the mapping between the motor cortex and the limbs. This gives us hope that recording from a few axons in the peripheral nerve may well be enough to control the stimulation of the limbs through brain plasticity.

The proposed BNL may also be useful for nerve regeneration treatment. It has been known that denervated muscle will progressively atrophy [10]. Prevention of muscle atrophy in posttraumatic nerve repair is one of the major challenges in nerve regeneration treatment. In the case of upper extremity injuries, such as the brachial plexus, the nerve regeneration may take months to reach the muscle. By the time the nerve reaches muscle, the muscle may have already atrophied, and the nerve function will never recover. In this case, the BNL can be implanted to temporarily restore limb function and keep the muscle stimulated to prevent it from atrophying, while the nerve is regenerating towards the limb. The BNL can be subsequently removed after the nerve regeneration is completed.

The following sections report the initial results from this work. The primary motivation is to build an integrated single channel BNL to investigate peripheral nerve recording and muscle stimulation in animal experiments, as well as the function of the BNL.

III. BNL IMPLEMENTATION

The single chip BNL, as shown in Figure 2, comprises of 16 channels of neural amplifiers, a 16-to-1 analog multiplexer, a single channel level detector and a biphasic current stimulator. The neural amplifier records and amplifies the extracellular action potential (EAP) signal. The outputs of the 16-channel amplifiers can be time multiplexed to a single output pin for initial signal observation and channel selection. With an externally supplied threshold, the level detector circuit detects the incoming EAPs and issues a trigger signal to the stimulator. Up on receiving the trigger signal, the stimulator generates a biphasic pulse whose amplitude and duration can be programmed externally.

A. Neural amplifiers

Each element in the 16-channel electro-neurogram amplifier array consists of a low noise instrumentation amplifier (LNIA) [11] driving a multiplexer buffer (MUXBUF). A 16-to-1 multiplexer forwards one of the selected buffer's output to a Pad driver which can either drive an external digitizer or the on-chip level detector via an external jumper link.

Being the first stage of each amplifier channel, the LNIA needs to have a high enough gain to minimize the noise contributions of the subsequent signal chain. However, having a higher gain at the first stage requires the use of large input capacitors for the LNIA. This not only increases the total silicon area but also reduces the input impedance. Therefore, a 3 tiered gain distribution per channel is adopted. The LNIA is designed with a mid-band gain of 38.06dB, the MUXBUF contributes 20dB gain and the pad driver provides a final 1.93dB gain. The total mid-band gain for each channel would be 60dB. It must also have a low input referred noise to achieve an overall system input referred noise. Therefore, OTA1 is designed as a telescopic cascode OTA which have a low noise efficiency factor per unit biasing current amongst other single pole OTA structures.

The lowpass cutoff frequency of each channel is designed to be 6kHz. The highpass cut-off frequency for all channels can be programmed from 5Hz to 1 kHz. As the outputs of each MUXBUF need to be time-multiplexed at a rate of 1MHz to a single pad output, OTA2 is designed as a symmetrical OTA with a class AB output stage. This allows

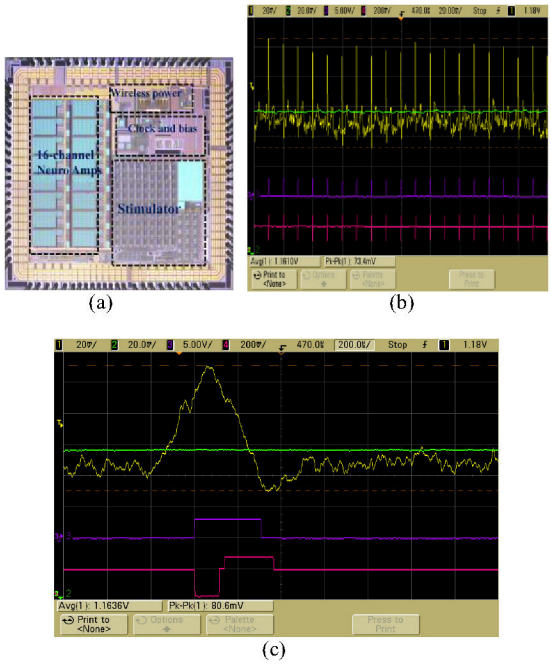


Figure 5. Electrical measurement results: (a) Chip microphotograph; (b) Measured output waveforms from neural amplifier, EAP detector and stimulator; (c) Zoomed-in view of signal EAP waveform.

it to consume a low quiescent current of only 1.5uA yet having a fast settling time of less than 0.5us.

B. EAP detector and biphasic muscle stimulator

The EAP detector is simply a comparator with a small hysteresis. The EAP is detected when it passes a threshold set externally. The stimulator block diagram is shown in Figure 4 [12]. The 10-bit DAC, consisting a nDAC (current sink) and pDAC (current source), generates the biphasic stimulation current. The current level can be programmed from 10μA to 10mA. The current in the anode phase is set to be half of that in the cathodic phase by the Divider. To achieve charge balance during the stimulation, the duration of the anodic pulse should be twice of that of the cathodic phase. The stimulation durations are programmed by the combination of clock frequency and the setting at t_{in} in discrete levels, i.e. 1, 3, 7 and 15 times of the clock period. For example, at a clock frequency of 125kHz, the stimulation pulse duration can be changed from 8μs to 120μs based on t_{in}. The interphasic phase duration, however, is fixed at 24μs to avoid possible monophasic effects which could lead to tissue damage. The charge mismatch achieved by the stimulator is less than 63nC (tested on a dummy resistive load without using the decoupling capacitor) [12], below the safety tolerance of 0.4μC/mm^2/stimulation-pulse.

IV. Experiment Results

A. Electrical measurements

The chip was fabricated in a CMOS 0.35-μm technology and the chip microphotograph is shown in Figure 5(a). The BNL chip is tested with a dummy EAP signal generator.

Figure 5 (b) and (c) show the measured output waveforms of the neural amplifier, EAP detector output and the biphasic stimulation pulse, respectively. The BNL functions correctly.

TABLE I
BNL Chip Performance Summary

Technology	0.35μm 2P4M CMOS
Supply voltage	3V
Total supply current	630 μA
Total chip area	3.6mm × 3.1mm
Neural Amplifier	
Static current consumption	~230μA (incl. bias, detector)
Signal gain	60 - 80dB (programmable)
3dB bandwidth	0.1Hz-100Hz to 5.89kHz
Input referred noise	5.7 μVrms (100Hz-5.89kHz)
Noise efficiency factor	2.58
Stimulator	
Static current consumption	~400 uA
Stimulation amplitude range	10uA to 1mA
Stimulation pulse width	8us to 120us
Interphasic delay	24us
Charge imbalance	< 63nC

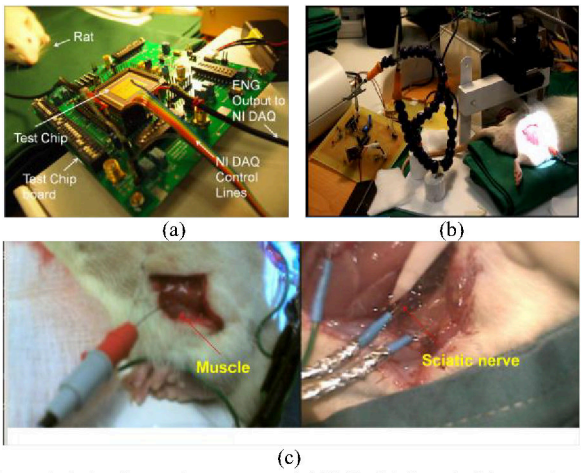
The measured total input referred noise of the neural amplifier is 5.7μV, from 100Hz to 5.89kHz. The performance summary is given in Table 1.

B. Animal experiment

An animal experiment was carried out using the BNL chip in a laboratory at the National University Hospital Singapore. The outputs of the biphasic current stimulator were coupled to 9V voltage boosters to drive the muscle stimulation electrode (the 9-V boosters can be easily integrated on the same chip when high voltage CMOS process is used). Figure 6 shows the experimental setup. The experiments were carried out as follows:

(1) A Wistar rat was first anesthetized, and surgical procedures were performed to expose the left sciatic nerve. A needle electrode was inserted into the sciatic nerve for neural signal recording and the stimulator output was connected to a dummy resistive load. The sciatic never was then slightly pinched with tweezers to generate the EAPs, which was then recorded by the BNL and stimulation pulses were issued. Figure 7 shows the waveforms of the recorded EAPs, detector output and biphasic stimulation pulse.

(2) With the recording electrode still in place, a concentric bipolar electrode for stimulation was inserted into the gastrocnemius muscle of the right leg. The sciatic nerve was then slightly pinched again with tweezers to generate the EAPs. Once the EAPs were detected, stimulation pulses were issued and a muscle twitch was observed. However, this time, a strong artifact due to the feedback from the stimulation electrode to the recording electrode was noticed, as shown in Figure 8. It can be seen that after the recorded EAP (top trace) passes the threshold of the detector, a trigger signal (2nd trace) is generated to start the stimulation. Immediately after the cathodic stimulation pulse (3rd trace), a large negative spike appeared at the neural amplifier output (top trace), followed by a positive spike. These spikes are caused by feedback from the stimulation electrode. The last trace is the voltage waveform on the bipolar stimulation electrode. The results show that the full BNL was functioning correctly, aside from the artifact observed. The artifact may be present because in the rodent animal model used in the experiment, the distance from the stimulation electrode to the recording



(a) (b)

(c)

Figure 6. Animal experiment set-up (a) BNL chip board, (b) experiment setup, and (c) recording and stimulation electrodes.

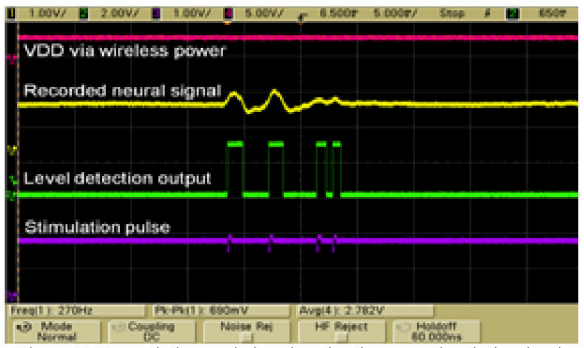


Figure 7. Recorded neural signal under dummy stimulation load condition (No artifact observed).

electrode is very short. This may not be a problem in a non-human primate model where the stimulation and recording sites are far apart. It has been found that the current level to elicit muscle contraction needs to be around 400 μA, resulting in average power consumption of 72μW under a 9V supply (for pulse duration of 100μS and stimulation frequency of 100Hz).

V. Conclusion

The proposed repair technique based on the BNL has the potential to overcome the bottleneck in existing medical treatments, especially when the peripheral nerve injuries result in large gaps or occur in the upper extremities. The BNL can also be used to temporarily restore limb function and prevent muscle from atrophying during nerve regeneration. The functionality of a single channel prototype BNL has been demonstrated both electrically and in an animal experiment. As the initial work reported here is for acute animal experiments, the wireless powered multi-channel implantable BNL will be developed in the future for chronic experiments.

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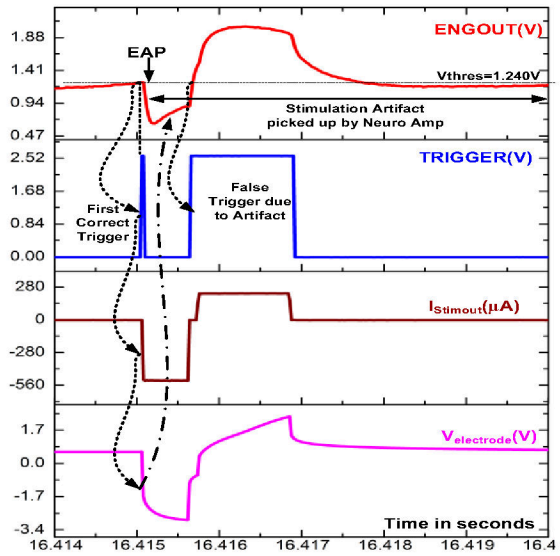

Figure 8. Full BNL results with stimulation electrode inserted in muscle (Artifact observed).

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