Towards a Fully Implantable Closed-Loop Opto-Electro Stimulation Interface for Motor Neuron Disease Treatment

Fangqi Liu, Dai Jiang, and Andreas Demosthenous
Department of Electronic and Electrical Engineering,University College London,
London, United Kingdom
e-mail:fangqi.liu.14@ucl.ac.uk

***Abstract*—This paper presents a fully-implantable closed-loop opto-electro stimulation interface for motor neuron disease studies, designed for experiments with freely moving rodents. A low power consumption Bluetooth data link is used to wirelessly control 64 opto-electro stimulation channels and receive neural recording data. The implant is powered by a wirelessly rechargeable lithium-ion battery, which can support 2.5 hours continuous operation with a stimulation output up to 10 mA. The battery is recharged using a QI standard wireless inductive power link, which can deliver >100 mW power at a distance of 2 cm. The total size of the implant system is 29 mm × 20 mm × 13 mm. The performance of the proposed system is compared with state-of-the-art.**

Keywords—***Electrophysiological recording, integrated circuits, motor neurone disease, optogenetics, opto-electro stimulation***

I. Introduction

Motor neuron disease (MND) is a devastating illness which leads to progressive degeneration of upper and lower motor neurons. The development of MND is often accompanied with rapid deterioration of motor function loss [1]. MND has been ranked as the third most common neurological disorder disease after Alzheimer's and Parkinson's diseases [2]. Engrafting embryonic stem cell derived motor neurons into peripheral nerve environments offers the potential for reinnervating denervated muscles [3], but the engrafted neurons are not connected with the central neural system that needs to be regulated using electrical stimulation [3]. Functional electrical simulation generates local electrical field which often stimulates both the target neurons and undesired peripheral neurons (e.g. endogenous and engrafted neurons) and causes considerable discomfort. In comparison with electrical stimulation, optical stimulation can deliver more precise stimulation of target neurons. The genetic modification of cells with channelrhodpsin2 (ChR2) to be light sensitive can be applied on a specific neuron population [4].

A stimulation interface that can be used as a research platform for studying and developing optogenetic methods for MND treatment has recently gained research interest. To support long term *in vivo* animal tests, the stimulation interface needs to address the following requirements: 1) The device needs be biocompatible and the whole platform be a small size to be fully implantable to avoid infections in long-term tests. 2) It needs to provide reliable power to the device implanted in small freely moving animals. Studying the activities of the motor neuron requires the test animal to have free movements in a certain area which brings challenges to system powering. The supplied power needs to be high enough to support current

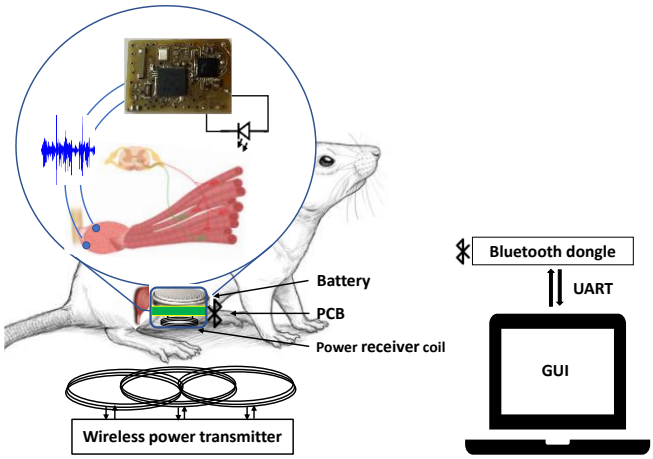

Fig.1. Concept of the proposed system implanted in a rodent.

stimulation and be stable while the animal is moving. 3) The device needs to have a reliable wireless communication link. A closed-loop system for both controlling stimulation and receiving real-time recording data is desired. In particular, the link must have sufficient signal strength when implanted because the skin and tissues degrade the radio signal. The link should have high data rate to be capable of transmitting real-time recorded neural signals such as EMG signals. In addition, the power consumption of the wireless data link needs to be minimized.

Although previous research has successfully developed stimulation interfaces for animal tests, it is still challenging to provide long-term *in vivo* tests with completely free animal movement due to device size and powering constraints. The work in [5] proposed a device that can be applied on rodents for both heart optogenetic and electrocardiography recording. However, it requires a percutaneous connection to an external device for powering and communication purposes. The system demonstrated in [6] is capable of providing synchronized optogenetics and electrophysiology recording in small animals, but it is powered by a percutaneous connection to an external battery. The design in [7] reports a fully implantable device; which is powered by a small wireless telemetry link and high power transmitting efficiency. However, since the system is powered by a micro-coil on an ASIC, the movement of the test subject could cause decoupling of the inductive link that leads to wireless powering failure.

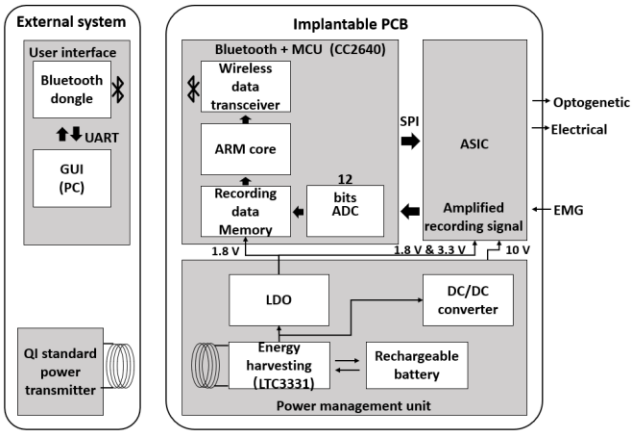

Fig. 2. The structure of proposed system.

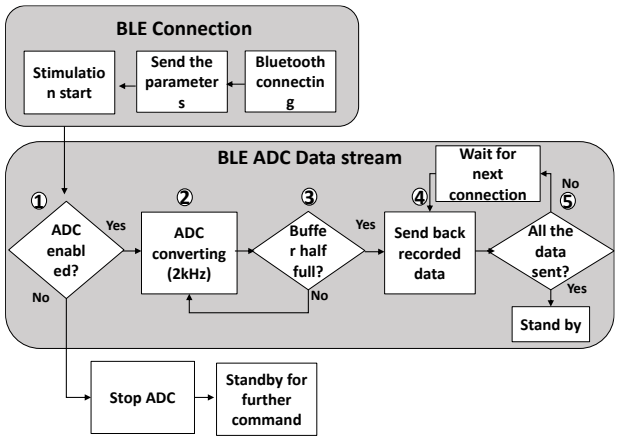

Fig. 3. The flow chart of the wireless communication

This paper presents a fully implantable multi-channel stimulating and recording platform for closed loop opto-electro stimulation. The concept of the proposed implantable interface is shown in Fig. 1. The platform can be implanted in rodents for delivering both optogenetic and biphasic electrical current stimulation. The local EMG signal can be recorded via a low power Bluetooth communication link. The system is powered by a lithium-ion battery, which is rechargeable via a wireless inductive link.

The rest of the paper is organized as follows. Section II describes the design and implementation of the system. Section III presents the measured performance of the developed device. Concluding remarks are drawn in Section IV.

II. System Implementation

The proposed system consists of an external part and an implant part as shown in Fig. 2. The external part contains a PC based graphic user interface (GUI), which is used to control the stimulation parameter and to receive recording data via a Bluetooth low energy (BLE) link. The power transmitter provides power for recharging the implant battery via the inductive link. The implantable part of the system contains a microcontroller that manages the stimulation settings and data communication. A custom chip (ASIC) generates stimulation pulses and records the EMG signal according to received settings. The recorded signal is sampled by the ADC in the microcontroller and sent back to the PC via the Bluetooth. The power management unit contains an integrated energy harvesting circuit (LTC3331) for power supply using the battery or for recharging the battery via the inductive link.

A. The Closed-Loop Data Commnuication Link

The data communication between the PC based GUI and the implant uses a BLE link. A CC2640 microcontroller with BLE 5.1 has been implemented as the communication link. This is because it has ultra-low power consumption (less than 12 mW) with a data transmission rate up to 2 Mbps. For the downlink data transmission (PC to the implant) the user set stimulation parameters (in the GUI) are transmitted to the Bluetooth dongle via a USB cable. The Bluetooth dongle wirelessly transmits the parameters during the Bluetooth connection interval. In the implant, the parameters are received by the microcontroller (CC2640), which further packages the data to be communicated to the ASIC via an 8 MHz SPI. The ASIC generates either monophasic or biphasic stimulation pulses. According to the received parameters the microcontroller initiates the ADC sampling.

For the uplink data transmission (implant to PC) the local EMG signal is recorded from the electrodes and transmitted to the ASIC. To meet the input voltage scale of the ADC the recorded EMG signal is amplified in the ASIC with a programable gain ranging between 500 and 5000. The amplified signal is sent to the ADC in the microcontroller for digitization. The sampling frequency of the 12-bit resolution ADC is 2 kHz. The digitized signals are sent to the GUI via the Bluetooth link.

B. Powering and Wireless Battery Recharging

The movement of the animal may cause the decoupling of the inductive link. To improve the system stability, a rechargeable battery is included for powering the implant during the stimulation. A 3.6 V rechargeable lithium-ion coin battery (LIR2450) with a diameter of 24 mm is used. The battery is connected to the energy harvesting module (LTC3331), whose built-in boost converter boots the battery output to 5 V. This relatively high voltage is needed to improve the stability and efficiency of the DC/DC converter for generating the 10 V stimulation compliance voltage. The dual output LDO is powered by the 5 V output from the LTC3331 to generate outputs of 3.3 V and 1.8 V. To minimize power consumption the microcontroller is powered by 1.8 V and the ASIC is powered by both 1.8 V and 3.3 V inputs.

The energy harvesting module recharges the battery (floating voltage: 4 V) using the power received from the inductive link. Since the stimulation is also powered by the energy harvesting module, the recharging only works at the time the stimulation is inactive. When the implant is in sleep mode (no stimulation outputs), the buck DC/DC of the LTC3331 converts the high voltage energy (between 6 V and 15 V) received on the receiver coil to charge the battery. If the link is inactive the fully charged battery can deliver 10 mA, 50 % duty circle stimulation current at 50 Hz for 2.5 hours

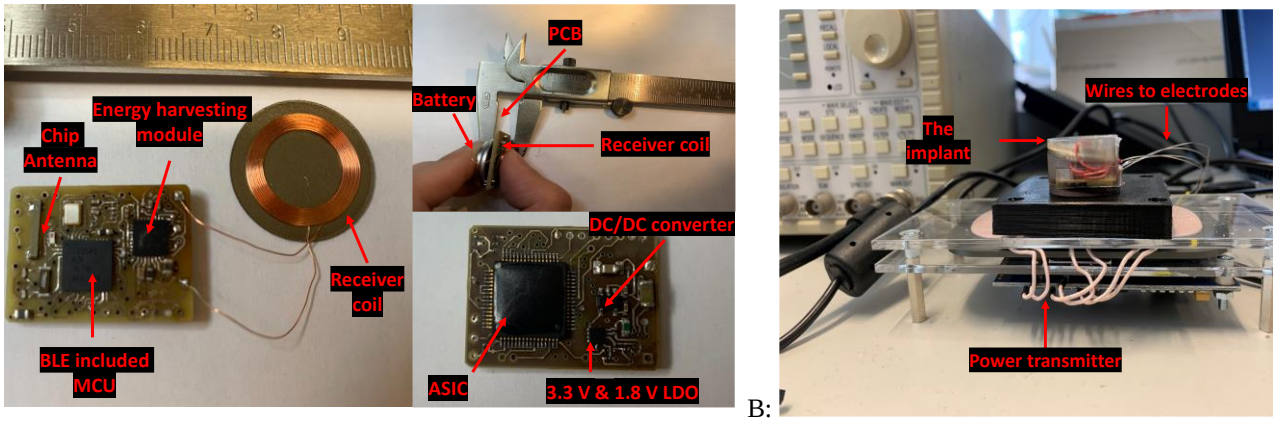

Fig. 4. (A) The manufactured PCB with the receiving coil. (B) The sealed implant on the power transmitter.

TABLE I. SYSTEM CHARACTERSTICS

Parameters	*Value*
Maximum output current	10 mA
Data transmision power consumption Tx/Rx at 0 dBm	12 mW/10.5 mW
Power consumption	35 mW
Recording / stimulation channels	1/64
Maxmum wireless data transmitting rate	2 Mbps
Maximum wireless transmitting power	>100 mW
Bluetooth working distance	0-2 m
Wireless recharging distance	1-2 cm
Implant device weight	4.33 g
Battery life	2.5 h

The QI standard based commercial inductive transmitter (STEVAL-ISB047V1) is used for wireless power transmission. The transmitter can deliver up to 5 W power with a carrier frequency of 126.7 kHz. The implant receiver coil is a commercial wireless inductive coil (WR222230-26M8-G). In order to compensate for the implant depth and the rodent's size the working distance of the transmitter is set to between 1 cm and 2 cm. The transmitter contains three transmitting coils, which are capable of recharging the implanted battery in an animal with free movement over an area of 9 cm × 4.5 cm.

C. *The ASIC*

The details of ASIC used in this study for generating stimulation pulses were presented in [8]. The bidirectional stimulator ASIC is capable of mixed opto-electro stimulation and electrophysiological signal recording. The ASIC comprises four stimulator units, each featuring 16-channels for optical and electrical stimulation using arbitrary current waveforms with an amplitude up to 16 mA and a frequency from 1.5 Hz to 50 kHz. The stimulators can be programmed to work individually or together for synchronized stimulation. The ASIC also contains a programmable amplifier gain up to 74 dB. The ASIC was implemented in a 0.18-µm CMOS technology.

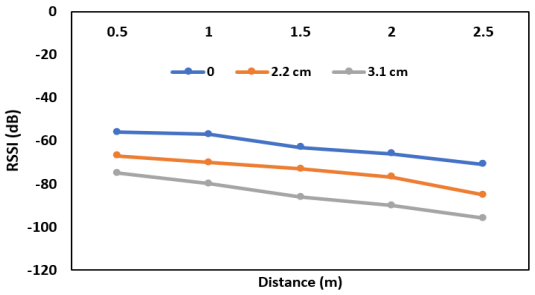

Fig. 5. Measured BLE signal strength at different distances.

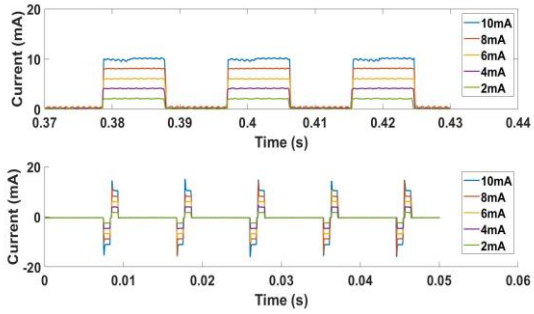

Fig. 6. Measured monophasic and biphasic stimulation outputs.

III. PERFORMANCE AND RESULTS

The system was fabricated on a 4 layer PCB with minimum size to be implanted in rodents after encapsulation. To date the device has been tested on dummy loads and experiments with rodents are planned. The specification of the implant system is shown in Table 1.

A. *PCB Size and Dimension*

The fabricated PCB of the implantable system is shown in Fig. 4. The top side of the PCB contains the microcontroller, Bluetooth antenna, and energy harvesting integrated circuit. The bottom side of the PCB contains the ASIC, DC/DC converter, and the dual output LDO. The device is designed to be implanted under the belly of the test animal so that the battery can be recharged by the wireless transmitter placed under the animal. The receiver coil, PCB and battery are

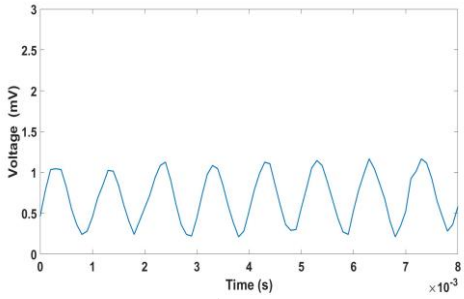

Fig. 7. Recorded output signal from a 150uV sinusoid simulating an EMG signal.

TABLE II. COMPARSION WITH STATE-OF-THE-ART

	[5]	[9]	[11]	[10]	This work
Year	2017	2018	2019	2021	2021
Max stimulation (mA)	198	5	3	0.8	10
Fully implantable	No	No	Yes	Yes	Yes
Wireless powering	No	No	<40 mW	230 mW	>100 mW
Power consumption (mW)	111	172	12	42	35
Max data rate	2 Mbps	2 Mbps	< 76 Kbps	2 Mbps	2 Mbp
Size (mm)	18×25×10	33×36×15	10×12×3	43×39×10	29×20×13

organized in a sandwich structure as shown in Fig. 4(a). The coil is at the bottom layer since the wireless power transmitter is placed under the test subject as shown in Fig. 4(b). The PCB is placed at the middle layer, whilst the battery is on the top.

B. BLE Signal Strength

To increase the signal strength of the BLE, a chip antenna is used as shown in Fig 4 (a). To test the signal strength after it is implanted in the animal, animal skin was used to cover the device and measure the BLE signal strength (RSSI). The measured RSSI at distance of 0.5 m, 1 m, 1.5 m, 2 m and 2.5 m with skin thickness of 0 cm, 2.2 cm and 3.8 cm are shown in Fig 5. With the skin thickness of 2.1 cm the RSSI at the distance of 2 m is -74dB. Under this condition, the BLE is still able to establish a reliable connection for transmitting the recorded EMG signal to the PC.

C. Stimulation and Recording

The remotely controlled stimulation outputs on dummy loads were measured. The monophasic outputs for optogenetic stimulation were measured on a dummy load resistor of 50 Ω. The output current of 10 mA, 8 mA, 6 mA, 4 mA and 2 mA for driving the LEDs for optical stimulation at a frequency of 50 Hz and a duty cycle of 50 % is shown in Fig. 6 (upper panel). The symmetrical biphasic pulse for electrical stimulation was tested on a 100 Ω resistor. The output current of 10 mA, 8 mA, 6 mA, 4 mA and 2 mA at a frequency of 100 Hz are shown in Fig. 6 (lower panel). The cathodic phase has a pulse width of 800 µs, which is identical to that of the anodic phase.

To test the recording performance, a dummy signal from a signal generator (TGA1241) provided a sinewave signal with 150 mV amplitude, and 1.5 V offset at 1 kHz frequency. The generated output was further attenuated by 1000 times to simulate the level of an EMG signal on the recording electrodes. The received output on the GUI is shown in Fig. 7.

D. Comparison With Other Work

The performance of the proposed system compared with other state-of-the-art optogenetic systems [9] [10] [11] [5] is shown in Table II. The proposed system is fully implantable.

IV. CONCLUSION

A fully implantable interface for opto-electro stimulation for completely free animal movement has been presented. The system is powered by a battery which can deliver continuous stimulation for 2.5 hours with stimulation intensity up to 10 mA and with EMG signal recording functionality. To support long term continuous testing *in vivo*, the battery can be recharged using a wireless power transmitting inductive link, which is capable of wirelessly delivering 100 mW power at a distance of 2 cm. The device is remotely controlled by a BLE based communication link with low power consumption. The maximum data transmission rate is 2 Mbps with transmitting distances up to 2 m. The size of the fabricated implant system is of 29 mm × 20 mm × 13 mm which is suitable for implantation in small animals. The next step of this work will be to encapsulate the device and implant it to conduct *in vivo* animal tests.

REFERENCES

[1] J. E. McLeod and D. M. Clarke, "A review of psychosocial aspects of motor neurone disease," *J. Neurol. Sci.*, vol. 258, no. 1–2, pp. 4–10, 2007.

[2] K. Talbot, "Motor Neurone Disease," *Postgard Med J*, vol. 78, pp. 513–519, 2002.

[3] D. C. Yohn, G. B. Miles, V. F. Rafuse, and R. M. Brownstone, "Transplanted mouse embryonic stem-cell-derived motoneurons form functional motor units and reduce muscle atrophy," *J. Neurosci.*, vol. 28, no. 47, pp. 12409–12418, 2008.

[4] T. A. Marie, F. Eva, R. Linda, S. O. Juan, R. Patrick, and S. Thomas, "Let There Be Light—Optoprobes for Neural Implants," *Proc. IEEE*, vol. 105, pp. 101–138, 2017.

[5] L. L. Gagnon, G. Gagnon-Turcotte, A. Popek, A. Chatelier, M. Chahine, and B. Gosselin, "A wireless system for combined heart optogenetics and electrocardiography recording," *Proc. - IEEE Int. Symp. Circuits Syst.*, pp. 17–20, 2017.

[6] G. Gagnon-Turcotte, L. L. Gagnon, G. Bilodeau, and B. Gosselin, "Wireless brain computer interfaces enabling synchronized optogenetics and electrophysiology," *Proc. - IEEE Int. Symp. Circuits Syst.*, pp. 17–20, 2017.

[7] T. Yousefi *et al.*, "An Energy-Efficient Optically-Enhanced Highly-Linear Implantable Wirelessly-Powered Bidirectional Optogenetic Neuro-Stimulator," *IEEE Trans. Biomed. Circuits Syst.*, vol. 14, no. 6, pp. 1274–1286, 2020.

[8] D. Jiang *et al.*, "An integrated bidirectional multi-channel opto-electro arbitrary waveform stimulator for treating motor neurone disease," *Proc. - IEEE Int. Symp. Circuits Syst.*, vol. 2021-May, pp. 2–6, 2021.

[9] A. Zhou et al., "A wireless and artefact-free 128-channel neuromodulation device for closed-loop stimulation and recording in non-human primates," *Nat. Biomed. Eng.*, vol. 3, no. 1, pp. 15–26, 2019.

[10] A. Shon, J. U. Chu, J. Jung, H. Kim, and I. Youn, "An implantablewireless neural interface system for simultaneous recording and stimulation of peripheral nerve with a single cuff electrode," *Sensors (Switzerland)*, vol. 18, no. 1, pp. 1–26, 2018,.

[11] H. Zhang *et al.*, "Wireless, battery-free optoelectronic systems as

subdermal implants for local tissue oximetry," *Sci. Adv.*, vol. 5, no. 3, 2019.