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Towards Closed-Loop Neuromodulation: A Wireless Miniaturized Neural Implant SoC

Wentai Liu*, Po-Min Wang, and Yi-Kai Lo

University of California, Los Angeles, Los Angeles, CA, USA 90095

Abstract

This work reports a platform technology toward the development of closed-loop neuromodulation. A neural implant based on the SoC developed in our laboratory is used as an example to illustrate the necessary functionalities for the efficacious implantable system. We also present an example of using the system to investigate the epidural stimulation for partial motor function recovery after spinal cord injury in a rat model. This hardware-software co-design tool demonstrate its promising potential towards an effective closed-loop neuromodulation for various biomedical applications.

Keywords

Neuromodulation; closed-loop; system-on-a-chip (SoC); neuroprosthetics; bioelectronics; implant; stimulation; recording

1. INTRODUCTION

Neuromodulation, whether invasive or non-invasive, is an emerging and promising method to restore or enhance dysfunctional biological systems by modulating proper nervous systems. Electrical stimulation has ostensibly become a common method in neuromodulation for various applications. Well-known examples include retinal prostheses to restore eyesight for the blind¹, spinal cord implant for pain relief² and vagus nerve stimulation for weight control³. It is important to point out that most neuromodulation devices adopt an open-loop scheme which requires the user to manually change the stimulation parameters, thus lacking safety, selectivity, specificity and adaptability. Effective and safe neuromodulation requires intelligent control to dynamically adjust the stimulation pattern in response to the subject's physiological state as well as the environmental condition.

Many features must be incorporated to support the closed-loop operation. The development of the aforementioned closed-loop systems for clinical purpose is still limited. Recently, a closed-loop system was presented to induce baroreflex for blood pressure control⁴. However, the system is not implantable and relies on wires connecting the stimulator and the pressure sensor with the external controller, impeding its clinical usage. A cortical implant incorporating wireless power and data transmission technology has also been demonstrated

* wentai@ucla.edu; www.seas.ucla.edu/IBR.

for real-time seizure control⁵. Nonetheless, the system does not support adaptive power regulation to stabilize the potential power fluctuation at the implant side due to environment changes such as coil displacement. The unexpected power loss would decrease the efficiency of the power link and even lead to the malfunction of the implant. A recent work has proposed a brain-spine interface for alleviating gait deficits after incomplete spinal cord injury⁶. A wireless rechargeable battery is used to power the implanted stimulator. However, a set of pre-loaded stimulation parameters is used in this study and the only real-time adjustable parameter is the stimulation onset frequency. The system thus lacks the feasibility and capability to perform real-time and dynamic tuning of the stimulation patterns to reflect the subject's varying physiological states. Equally important, a neural implant must be capable of monitoring the electrode-tissue interface to ensure an effective and safe stimulation protocol. Devastating damage to the electrode or biological tissue can be avoided if the bio-impedance at the electrode-electrolyte interface can be monitored to not only ensure the robustness of the electrode but also help define the safe stimulation parameters to ensure the electrode overpotential is well within its water window. A stimulator with versatile programmability to generate flexible waveform is also preferred to facilitate the selective stimulation⁷⁻⁹. The capability of performing selective and focal stimulation to specific nerves would greatly ameliorate the treatment efficacy. An implant fulfilling the above features must also be miniaturized to reduce its surgical invasiveness, which would greatly enhance patients' acceptability.

This paper starts with the required functionality for a closed loop neuromodulation. Due to the importance of closed-loop neuromodulation, we then report a platform technology consisting of SoC developed in our laboratory that has incorporated the necessary functionalities for a closed-loop implant, heterogeneous packaging technique, and GUI interface, that is ready to be rapidly retuned for various biomedical applications. The SoC integrates all required functional blocks mentioned above for the closed-loop control of the power regulation, stimulation safety control and adaptive stimulation in response to the subject's varying physiological states. A dedicated rendezvous device and a versatile GUI have also been implemented and would be demonstrated with the neural implant to realize a closed-loop system.

2. DESIGN REQUIREMENTS FOR CLOSED-LOOP WIRELESS NEUROMODULATION

Key design requirements for a neural implant including wireless power link, wireless data link and high-compliance voltage for stimulator have been discussed in our previous¹⁰ and others' works^{5,11}. In this section, we will discuss some additional design considerations related to the design and development of a closed-loop implant.

2.1 Wireless power regulation

Among various wireless powering schemes, inductive powering is the most popular mechanism because of its high power transmission efficiency under the size constraint of implant. An inductively powered neuromodulation system should adaptively stabilize the power fluctuation at the implant side when there is a displacement or misalignment between

the implant and external powering coils. The received power at the implant side coil can be significantly affected by the coupling coefficient changes due to environment change, including coil misalignment caused by movement of the subject, or loading condition changes (i.e. the power consumption of the implant changes). Under such considerations, undesired power loss might lead to malfunction of the implant while excessive power delivery, on the other hand, increases the risk of violating the safety regulations (i.e. IEEE SAR regulation). It is therefore critical to realize a dynamic control mechanism while ensuring system stability to regulate the received power at the implant side. We have developed and implemented an adaptive power telemetry for inductively-powered biomedical implants¹². Class-E power amplifier with optimized coil pair is used for wireless power transfer. The loading and/or coupling coefficients change is dynamically compensated by sensing the implant's power information and transmitting it back to the primary power transmitter in order to adjust the level of delivered power. Details for designing the adaptive power telemetry and system stability analysis can be found in our prior work¹².

2.2 Stimulation safety control – safe stimulation parameters

The electrical charge per stimulation phase and the charge injection limit are common guidelines to avoid electrode degradation and tissue damage¹³. The electrode overpotential during stimulation should also always stay within its water window to protect the electrode. One troublesome issue being neglected in most stimulator systems is that even when the stimulation parameters are under the limit of charge per phase and charge injection limit, there is still the possibility that the electrode overpotential can exceed its water window¹⁴, resulting in irreversible damage. A possible solution is to carefully design the stimulation parameters while considering the equivalent circuits of the electrode-tissue interface. Common implants examine the impedance by delivering a sinusoidal signal and measuring the electrode voltage due to the simplicity of its circuit implementation, but this method only can be used to evaluate the reliability of the electrode and the proximity between the electrode and targeted tissue. Conventional electrochemical impedance spectroscopy (EIS) has been widely used to obtain the electrode-electrolyte impedance at a broad spectrum¹⁵ but it is challenging to realize this sophisticated approach in a neural implant. An effective approach developed in our laboratory performs time domain analysis on the electrode-tissue impedance: a biphasic stimulus as a by-product supported by most stimulators is injected into the electrode-tissue interface and the electrode potential are measured at three specific time points to estimate the equivalent circuit model of the bio-impedance¹⁴. The advantages of this approach are it is less hardware-consuming and can provide more information about the neural interface for designing effective and safe stimulus.

2.3 Stimulation safety control - charge balance

Biphasic electrical stimulation is widely adopted to ensure a zero Faradic charge residual at the stimulation site. When a non-zero residual charge is established at the stimulation site, a DC current flows into the surrounding tissue and creates neural damage as a result of the excessive generation of toxic byproducts from electrochemical reactions, pH changes, gas formation, and electrode dissolution. Conventional approach discharges the electrode residual voltage by shorting the electrode to the ground electrode after stimulation. Its effectiveness largely depends on the electrode impedance (electrode time constant), the

amount of residual charge, and the time period between each stimulating pulse. One reported closed-loop approach is to adjust the current intensity of either the leading or compensating phase of the stimulus. However, a perfect matched biphasic current stimulus is difficult to achieve as a result of the intrinsic mismatch of current sink and source drivers caused by semiconductor process variations (~1-2%). Others have also proposed inserting predefined short pulses to neutralize the residual voltage after sensing the remaining electrode overpotential, but the inserted short pulses might result in unwanted neural responses. To overcome the above shortcomings, we have developed and demonstrated a closed-loop approach for charge balancing¹⁶. Instead of spending significant efforts to match the biphasic current amplitudes or designing sophisticated charge compensating circuits, the sensed electrode voltage is sent to a proportional-integral-derivative (PID) controller to precisely control the width of either the anodic or the cathodic current pulses. This approach has the advantage of precisely controlling the compensating charge because the resolution is determined by the product of the minimal stimulation intensity and fine pulse width adjustment inherently supported by the stimulator.

2.4 Real-time adaptive stimulation

A critical and paramount feature for the closed-loop implant is the capability of adapting the stimulation parameters in real-time. As mentioned above, most implants stimulate with pre-loaded patterns when sensing abnormal physiological signals, while a more effective stimulation might involve adaptive stimulation parameters in response to the biological signals of interests. A recent example is the commercial stimulator for pain reduction¹⁷. With the goal of helping patients adjust parameters as pain changes along with changing posture, a three axis-accelerometer is used to recognize the body position and activity for the adjustment of stimulation parameters, but the stimulator is only capable of supporting six different parameters and only stimulation amplitude can be adjusted. An immediate and promising application is motor function recovery for spinal cord injuries. The stimulation parameters (i.e. stimulation frequency, intensity, pulse width, and selection of stimulating electrodes) need to be adjusted on the fly according to the patients' EMG responses or possibly spinal cord local field potential to improve the treatment efficacy¹⁸. We envision that adaptive closed-loop stimulation will be an indispensable feature for implants as there is rare implants/SoCs supporting such an important functionality.

2.5 Closed-loop system architecture and algorithm deployment

An intelligent algorithm capable of generating an optimal stimulation for different biomedical applications is necessary to achieve an effective and safe neuromodulation. There are two approaches widely adopted to execute the control algorithm for the closed-loop implant: 1) preloading the re-configurable firmware in the implant^{19,20}, and 2) configuring the algorithm in the external controller that communicates with the implant^{21,22}. An example adopting the first approach can be found in prior work²⁰ in which the firmware is preloaded in the implant. This approach allows the implant to operate independently but the flexibility of exploring different computation algorithms is somewhat limited because some pre-processing of the physiological signals has inevitably taken place in the implant. On the other hand, the second method allows researchers to investigate potential algorithms for closed-loop control under the premise that the raw data can be faithfully transmitted to

the external controller for processing. Although this approach would burden the design of the wireless link, it is suitable for the closed-loop system that is still in the stage of investigating the optimal control algorithm. One potential application is the spinal implant for motor function recovery of the paralyzed¹⁸ which adopts an external controller to facilitate the investigation of sophisticated algorithms to adaptively alter multi-dimensional parameters including pulse width, stimulation frequency and pulse number in the pulse train, etc.

2.6 Focalized and selective stimulation

Selectivity and focality are also important concerns in electrical neuromodulation. An effective neuromodulation should be capable of selectively activating the desired nerve fibers/neurons of interest while avoiding others. One prominent example is the high-density retinal stimulator in which tens or hundreds of electrodes are placed within the $\sim 5\text{mm} \times 5\text{mm}$ fovea region to partially restore vision in the blind^{10,23,24}. However, concurrent stimulation of adjacent electrodes within such a limited space incurs poor resolution as the delivered charge from the stimulating electrodes would inevitably spread to nearby tissues. In light of this challenge and need, a multi-channel stimulator should be able to independently configure the stimulation parameters in each driver and support various waveforms. This would allow the shaping and steering of the electric field at the stimulating electrode to improve the stimulation spatial resolution¹⁰ and accordingly perform selective nerve stimulation.

3. CLOSED-LOOP SOC

We have developed a mixed-signal, mixed voltage SoC which is capable of supporting closed-loop neuromodulation^{18,25}, as shown in Fig. 1. This SoC is composed of wireless power and data telemetry, multi-channel stimulation with flexible and versatile stimulator, multi-channel recorder, as well as electrode impedance sensing and on-chip power sensing circuitries, all are the necessary components for realizing a closed-loop system. Through inductive powering, the power management circuit generates four different voltages to power both analog and digital circuits. The on-chip digital controller governs the SoC operation. Physiological signal is recorded and digitized by the multichannel recorder and the ADC, while the multiple-channel stimulator empowers versatile and flexible stimulation parameters in each stimulation driver. The impedance sensing circuit monitors the electrode-tissue interface to ensure safe stimulation and the electrode reliability, as well as also reads the electrode overpotential for the purpose of maintaining stimulation charge balance. Power fluctuation due to environment or loading condition change is detected by the power-sensing unit. The wireless receiver and transmitter constitutes a pseudo full-duplex bi-directional data link at a data rate of 2Mb/s to link the SoC and the rendezvous device. The recorded physiological signal/electrode-tissue impedance/electrode residual voltage/received power of the SoC can thus be transmitted to the external controller for signal analysis using customized algorithm and the new command can be sent to the SoC once a decision is made. Detailed validation and characterization of the SoC can be found in our prior work¹⁸.

4. APPLICATION EXAMPLE USING THE SOC

An example of using this SoC is the application of motor function recovery for the spinal cord injured. It has been reported that more than 1 million Americans have suffered a spinal cord injury (SCI) and there are more than 12,500 new cases each year. Each paralyzed patient faces an estimated lifetime cost of >\$1.1 million for the treatment and postsurgery care²⁶. It is important to point out that our prior works and others have shown the potential that epidural stimulation helps paralyzed subjects to partially regain the abilities of walking and stepping¹⁸²⁷, but currently there is no appropriate and suitable solution available for researchers to advance this recent breakthrough and further investigate the optimal stimulation strategy along with the underlying biological mechanism. We have thus been developing an implantable system based on the SoC to fill this technology gap.

The conceptual diagram for the spinal cord implant system is shown in Figure 2 using a rat model with a spinal cord injury. The core of the system is the miniaturized implant. We developed a heterogeneous assembly and packaging process in our laboratory to miniaturize the neural implant to integrate the SoC, power and data coils, flexible epidural stimulation electrode, EMG wire electrodes, and 0201-SMD passive components on a polyimide substrate with a volume of 0.5 cm³ and a weight of 0.7 g²⁵. The spinal cord implant is implanted subcutaneously. The flexible epidural electrode array is inserted into epidural space for spinal cord stimulation while the EMG wire electrodes are sutured to the leg muscles for kinetics recording. The rat then carries a rendezvous device (RD) to link the implant and an external control device held by the researchers. The recorded physiological signal is relayed by the RD to the external controller (e.g., tablet /mobile phone/personal computer) for signal analysis. At the same time, the new command (e.g., updated stimulation parameters) from the external controller is transmitted to the implant through the RD in response to the recorded signal. A mobile app based on iOS system has been developed to control the RD through WiFi link. The app provides researchers with full modular control over all of the stimulation and recording parameters. Stimulation parameters of up to 160 channels supported by the SoC can be independently configured with a preview panel in the app (Figure 3(a) and (b)). The app supports real-time display of selected recorded waveform sent from the implant (Figure 3(c)). EMG signals recorded from the paralyzed rat's flexor and extensor leg muscles of are demonstrated. The two recorded EMG signals fire sequentially, indicating that this rat was stepping and using his flexor and extensor muscles alternatively. The recorded data can be further processed by a control algorithm embedded in the mobile device to dynamically modify the stimulation parameters, achieving a closed-loop implant system.

In order to explore the optimal stimulation patterns, through the optimization of software and hardware co-design, the versatile stimulator is capable of generating various stimulation waveforms. Figure 4 demonstrates selected stimulation waveforms supported by the implant system. In one example, each stimulation channel is configured independently (Figure 4(a)). In addition, the stimulator supports not only continuous pulse waveform but also user-specified pulse train with flexible pulse period and pulse number per burst (Figure 4(b) and Figure 4(c)). The pulse period can be set from the range of milliseconds to the time frame fulfilling the use's need. Furthermore, the stimulator supports arbitrary stimulation

waveforms defined by the user. Two examples of pseudo sinusoidal and triangular waveforms delivered from the implant are illustrated in Figure 4(d).

5. CONCLUSION

With the advent of bioelectronic medicine and electroceutical that aim to treat medical conditions through electrical neuromodulation²⁸⁻³¹ targeting at the molecular mechanism which directly relates to a diseases, more emphases should be placed on the development of closed-loop implants to ensure safe and effective neuromodulation. There have been abundant engineers working on implant development, yet the lack of in-depth knowledge and experience in neuroengineering and physiology somewhat limits the practicality and efficacy of their designs. On the other hand, scientists studying specific biological/medical problems might not have appropriate engineering skills and knowledge to develop new tools to meet their needs. Experts fluent at speaking both engineering and science languages are thus desperately required to bridge this technology gap. In this paper, we share some of our insights and prior works in developing neuromodulation implant and demonstrate a closed-loop system based on a SoC fulfilling the requirements toward closed-loop neuromodulation. The system can serve as a platform technology to be applied generally to different biomedical applications. A prominent example given here is the spinal cord stimulation for motor function recovery of the paralyzed. The SoC and the system have demonstrated the restoration of the walking and stepping function of a paralyzed rat²⁵.

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Figure 1.

The system diagram and chip microphoto of the SoC, revised from our prior work²⁵.

Figure 2.

The system diagram of the implant system using the rodent model. A mobile device serving as the external controller communicates with the rendezvous device (RD) that can be carried by the subject. An implant is subcutaneously implanted to perform epidural stimulation and EMG recording. The RD then links the implant and the mobile device through WiFi.

Figure 3.

Interface of the iOS based mobile App. The bottom panel in the home screen allows researchers to select three different model to set up stimulation/recording/file saving. (a). In the stimulation control page, each stimulation channel or a group of channels can be independently selected. (b) After indicating the channel, this page let users to set parameters and preview the waveform. (c) Real-time display of the recorded waveform. In this example, two channels of EMG recording waveform are displayed.

Figure 4.

Versatile and flexible stimulation waveform: (a) Stimulation channel with independently configurable parameters (e.g., start delay, pulse width, intensity, inter-pulse delay and starting polarity). (b) User-specified pulse train with a period of 100 ms and a pulse number per group of five. (c) User-specified pulse train with a period of two s and a pulse number per group of 10. (d) Pseudo-sinusoidal waveform and pseudo-triangular waveform.