Wireless Simultaneous Stimulation-and-Recording Device to Train Cortical Circuits in Somatosensory Cortex

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Abstract — **We describe for the first time the design, implementation, and testing of a telemetry controlled simultaneous stimulation and recording device (SRD) to deliver chronic intercortical microstimulation (ICMS) to physiologically identified sites in rat somatosensory cortex (SI) and test hypotheses that chronic ICMS strengthens interhemispheric pathways and leads to functional reorganization in the enhanced cortex. The SRD is a custom embedded device that uses the Cypress Semiconductor's programmable system on a chip (PSoC) that is remotely controlled via Bluetooth. The SRC can record single or multiunit responses from any two of 12 available inputs at 1-15 ksps per channel and simultaneously deliver stimulus pulses (0-255 μA; 10 V compliance) to two user selectable electrodes using monophasic, biphasic, or pseudophasic stimulation waveforms (duration: 0-5 ms, inter-phase interval: 0-5 ms, frequency: 0.1-5 s, delay: 0-10 ms). The SRD was bench tested and validated in vivo in a rat animal model.**

I. Introduction

Maladaptive cortical reorganization and changes in neuronal pathways and synaptic connectivity of cortical circuits in somatosensory cortex (SI) are central neurological consequences that often follow limb loss [1] and cortex related stroke injuries [2]–[4]. Understanding the neural pathways and mechanisms for functional reorganization in deafferented cortex can lead to the development of compensation strategies and rehabilitation therapies that modulate cortical circuits. Low current intercortical microstimulation (ICMS) is capable of modulating cortical pathways and circuits and could prove useful in treating phantom limb pain and stroke.

Chronic repetitive ICMS can strengthen and alter cortical pathways and circuits. This notion is based on the ideas of Hebb, who speculated that the connection between two neurons is strengthened if the first neuron repeatedly brings about activation of a second neuron [5]. Methodologies based on stimulation and recording with microelectrodes and arrays are widely used in both in-vivo and in-vitro investigations of the nervous system. ICMS is typically used in anesthetized and/or tethered animal preparations. However, there is a rapidly growing need for neuroscience platforms, which can perform simultaneous chronic recording and stimulation of neural tissue in a completely wireless fashion together with powerful signal processing software to facilitate the analysis of the chronically recorded signals. We have developed a SRD that eliminates experiment sedation and the need for tethering, and can be used in freely moving animals.

Wireless systems for simultaneous stimulation and recording have been infrequently reported [6], [7]. The Neurochip has been used to artificially connect two sites in motor cortex of awake monkeys and has the capacity to deliver up to 200 μA current; this device, designed for primates, is much too large for use in rats, and is not remotely controlled nor is the activity monitored in real time [6]. A device appropriate in size and functionality for rat has been developed by Ye and colleagues [7], but this device has limited battery life (< 2 hours), and the stimulator is synchronized using off-circuit wireless signals prohibiting accurate synchronization with neural recordings. Our SRD offsets these limitations along with offering an open platform and compatibility with other biopotential signal applications. To the best of our knowledge, our SRD is the first telemetry-controlled device capable of simultaneously stimulating and recording in brain tissue.

Our model system for testing the SRD is the rat forelimb barrel subfield (FBS) that lies in layer IV of SI. The FBS is arranged in cell clusters associated with the representation of punctate regions of the forelimb skin surface [8]. Individual barrel clusters form part of vertically arranged cortical columns [9]. Layers III and V send strong projections to contralateral SI [10] and terminate at sites having similar receptive fields in layers III and V [11]. The presence of this interhemispheric projection, and the fact that stimulation of the forelimb only evokes responses in contralateral SI raised the question whether this interhemispheric pathway could be altered to carry information from the ipsilateral forelimb to the ipsilateral SI and whether strengthening the pathway could lead to its expression in the ipsilateral cortex. We tested the hypothesis that chronic ICMS enhances the interhemispheric pathway and induces cells in the ipsilateral SI to respond to input from ipsilateral forelimb using our SRD.

II. System Overview

The SRD is a wireless brain-computer-interface (BCI) system capable of simultaneous recording and stimulation, and is constructed using commercially available components. An illustration of the SRD system is shown in Fig. 1. Biopotential signals are amplified, filtered, and digitized by a digital electrophysiology interface chip. Digitized data is transferred to a core processor, buffered, and then transmitted to a host PC via Bluetooth for offline analysis. The SRD is capable of simultaneously recording (1-15 ksps/channel) from any 2 of 12 available channels or sweeping through all channels, two channels per sweep. Stimulation is provided

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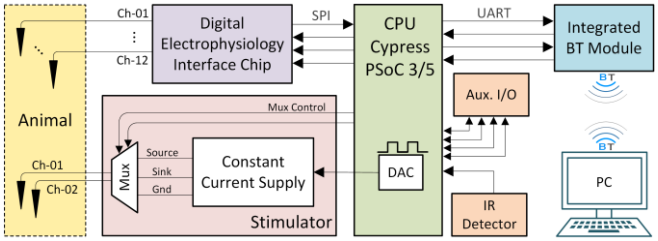

Figure 1. System overview showing interconnections between PSoC CPU, Bluetooth module, host PC, stimulator, digital electrophysiology interface chip, and tissue interface.

using a constant-current stimulator (0-255 µA) capable of delivering adjustable monophasic or biphasic waveforms to a user selected monopolar electrode. Current is steered to the desired electrode via a multiplexer. In addition, the SRD has one IR receiver that can be used for synchronizing external devices and 4 additional auxiliary input/output pins for user defined digital or analog purposes. The user can visualize captured data, save data to file, and control the SRD's operating parameters (filter bandwidths, sample rate, stimulation amplitude) using a custom graphical user interface (GUI). SRD operating modes include autonomous, continuous sampling (1channel only), externally triggered stimulation, and external triggered recording.

III. System Design

A. System Core and Wireless Communication

The core processor for the SRD is a Cypress Semiconductor PSoC3 (CY8C3866LTI-30) programmable system-on-a-chip. The PSoC manages all aspects of the device including timing events, analog sampling control, stimulus control, and wireless communications. The selected PSoC can operate at 67 MHz using a 8051 CPU core, and contains 8 KB SRAM and 64 KB Flash RAM. The PSoC3 and PSoC5 general purpose input/output pins offer an any-signal-to-any-pin routing that helps optimize PCB layout, shorten design time, and allow for a large degree of solder-less rework within the SRD. An example of this versatility is the ability to exchange the PSoC3 with a PSoC5 LP for increased memory and processing speed without requiring printed circuit board (PCB) layout changes. The SRD PCB capable of being used with freely moving rats (Fig. 2) will be placed inside a wearable 3D printed backpack.

Wireless communication is facilitated using a RN-42 (Microchip Technology, Inc.) Bluetooth module configured for serial port profile (SPP) mode. Experimental parameters and digitized signals are transmitted via the Bluetooth connection between a host PC and SRD.

Figure 2. Photo of our current SRD PCB (27 mm x 48 mm) next to a US quarter dollar for reference.

B. Data Acquisition Subsystem

Analog biological signals are digitized using a RHD2216 (Intan Technologies) digital electrophysiology interface chip. The key features of the RHD2000 series chips include: programmable analog and digital filters, 16-bit ADC, 30 ksps/channel sample rate, bipolar or unipolar configurations, in-situ electrode impedance measurement capability, and serial peripheral interface (SPI). The RHD2216 is a fully integrated 8 × 8 mm quad-flat no lead (QFN) package and requires no external components other than two bypass capacitors. The SRD was configured for 12 unipolar channels or 6 bipolar channels at a maximum sample rate of 15 ksps/channel. However, with minor PCB changes the SRD could use 12 bipolar channels, and with additional source code changes the SRD could use all available channels on the selected Intan chip model (16, 32, or 64 channels). Further code changes could also enable the SRD to act as a real-time closed-loop system capable of providing stimulation based on acquired cortical signals and enable real-time cortical spike discrimination.

Sample rate, filter bandwidths, channel selection, and various data acquisition timing parameters can be adjustable using a GUI discussed later. The RHD2216 internal programmable filters include one analog low-pass filter (3 pole Butterworth, 100 Hz – 20 kHz), one analog high-pass filter (1-pole, 0.1 Hz – 500 Hz), and one digital high-pass filter (one pole IIR, 0.07 Hz – 16.5 kHz at 15 ksps).

C. Stimulator Subsystem

The SRD stimulator is designed to deliver monophasic or biphasic stimulation constant current waveforms in a monopolar electrode configuration. Timing and current amplitudes are available for user configuration in the GUI. Users can control stimulation frequency, delay, duration, and inter-phase interval.

Implementation of the constant current hardware is achieved by generating both a constant current sink (cathodic current) and a constant current source (anodic current) using two of the PSoC3 built in current mode digital-to-analog converters (IDAC). Each current source is subsequently directed into a matched-pair MOSFET current mirror (ALD1105, Advanced Linear Devices, Inc.) to increase compliance voltages to ±10 V. The overall current is directed through an analog multiplexer to steer current to a user selectable electrode. Included in the SRD stimulator design are options for inline blocking capacitors and the ability to short electrodes to ground for reducing tissue damage caused by charge imbalances [12], [13].

The current SRD uses one stimulator circuit with two outputs, but is scalable to two simultaneous stimulators with as many outputs as are available in current multiplexer offerings using the present design implementation.

D. Power Supply Subsystem

One single-cell lithium-polymer battery (850-1000 mAh) serves as the primary SRD power source. Power rails are generated for each of the three power domains: digital, analog, and stimulation. A dual low-drop-out regulator provides separate 3.3 V to digital and analog components while two switching DC/DC converters provide ±10 V for stimulation current and stimulator components.

E. Graphical User Interface (GUI)

The SRD user interface software was developed using Microsoft Visual C#. The GUI allows the user to interact with the SRD for establishing Bluetooth connection, setting experimental parameters, visualizing acquired signals, and saving signals to file. Fig. 3 shows a screenshot of the GUI with the various graphical elements. Elements of the GUI layout include: SRD operating modes; settings for data acquisition, stimulation, and calibration; options for saving signals to file; settings for graph details; and signal graphs.

IV. Experimental Results

A. Bench Testing

Simulations, prototyping, and bench testing were performed to ensure that the SRD would meet the desired project specifications. Simulations included in preliminary tests were performed on power supply designs, stimulator design, and analog filter performance using Altium Designer (Altium Limited) and/or MATLAB (MathWorks, Inc.). Additionally, bench testing of all four subsystems (power, recording, stimulation, and communication) have been performed. Summary of bench test results include: (1) the SRD prototype consumed an average of 30 mA without optimized firmware code and can operate more than 24 hours on a 1000 mAh battery, (2) SRD stimulator successfully produced accurate biphasic current waveforms in saline and in vivo using platinum/iridium (Microprobes, 100 kOhm at 1 kHz) electrodes at desired stimulation specifications (Fig. 4), (3) Bluetooth communication provided a sufficient and reliable connection for desired data transfer rates and two-way communication for setting experimental parameters.

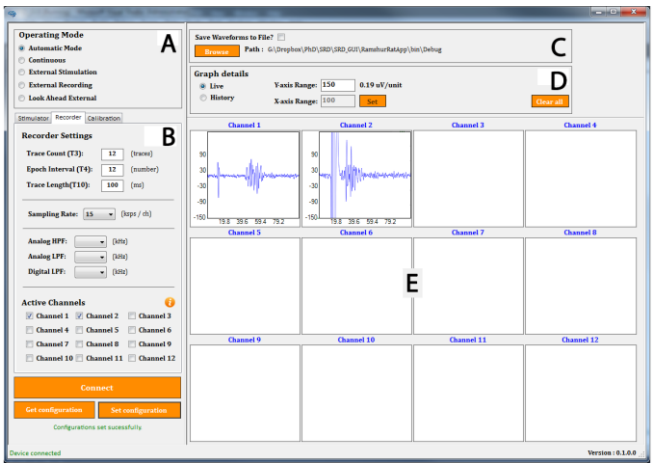

Figure 3. Graphical user interface. (A) Modes of operation. (B) Experiment settings including settings for data acquisition, stimulation, and system calibration. (C) Options for saving data to files. (D) Graph details. (E) Graphs area with examples of an ipsilateral peripheral evoked response

B. In-Vivo Testing

In Ketamine/Xylazine (100 mg/kg, i.p.) anesthetized rats (n=5), extracellular electrodes (carbon-fiber, platinum-iridium) and forelimb mechanical or electrical stimulation were used to map homotopic forelimb representations in both SI cortices (layer V). The SRD was then connected and used to deliver single biphasic ICMS pulses (1ms duration, 1 Hz) to one electrode and record evoked responses in contralateral SI from a second electrode to determine response thresholds.

Microstimulation amplitudes were adjusted to 1.5 × thresholds and chronic stimulation was delivered for 0.5 to 3 hours. Responses to 20-50 consecutive microstimulations were recorded at the beginning, during, and end of chromic stimulation to determine level of enhancement. To examine functional reorganization ipsilateral evoked responses following forelimb electrical stimulation of the ipsilateral forelimb were collected. Electrical forelimb stimulation and SRD recording was synced using a custom external IR sync pulse and the SRD's built-in IR receiver input. Again, 20-50 consecutive peripheral evoked responses were captured prior to, during, and following chronic ICMS. Lastly, electrolytic lesions (5 µA, 10 s) were made at both stimulating and recording sites using a customized current source.

An example of an interhemispheric enhancement is shown in Fig. 5. Prior to chronic ICMS, baseline responses were recorded (Fig. 5a) and compared at time intervals following chronic ICMS. An example of enhancement is shown in Fig. 5b (enhancement is defined as an increase in response amplitude and/or response duration).

Chronic ICMS not only produced enhancement of the evoked response, but lead to functional reorganization in the ipsilateral SI, whereby neurons became responsive to new input from ipsilateral forelimb. Results are shown in Fig. 6.

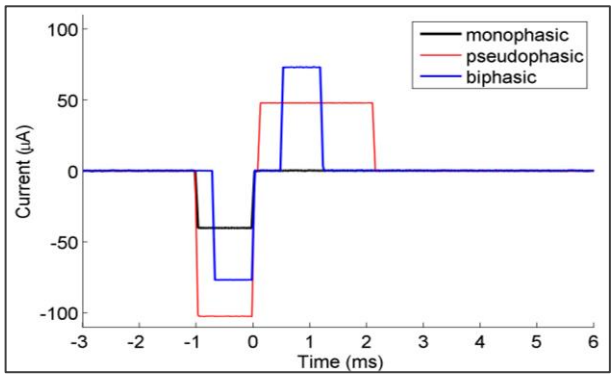

Figure 4. Oscilloscope traces of monophasic (black), pseudophasic (red), and biphasic (blue) stimulation waveforms produced using the SRD with a 10 kΩ resistive load. Traces were offset in time for waveform comparisons.

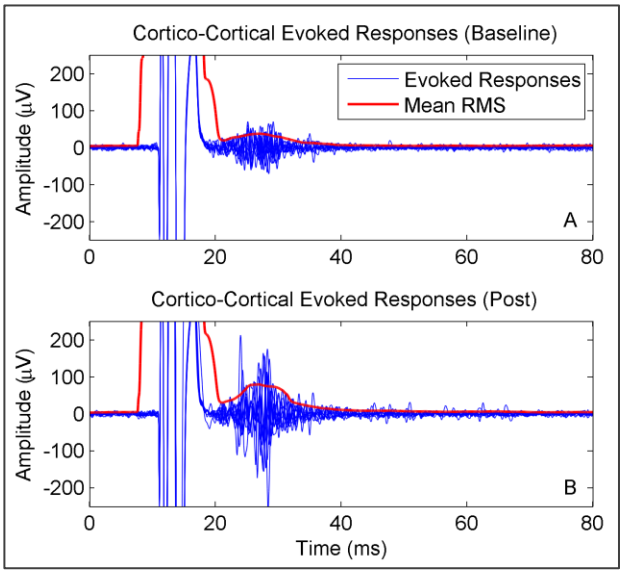

Figure 5. Evoked responses (n=10, blue) to ICMS using the SRD (A) prior to chronic ICMS and (B) following chronic ICMS. Mean windowed RMS shown in red. (ICMS = 30uA, biphasic, 1 ms duration, 1 Hz)

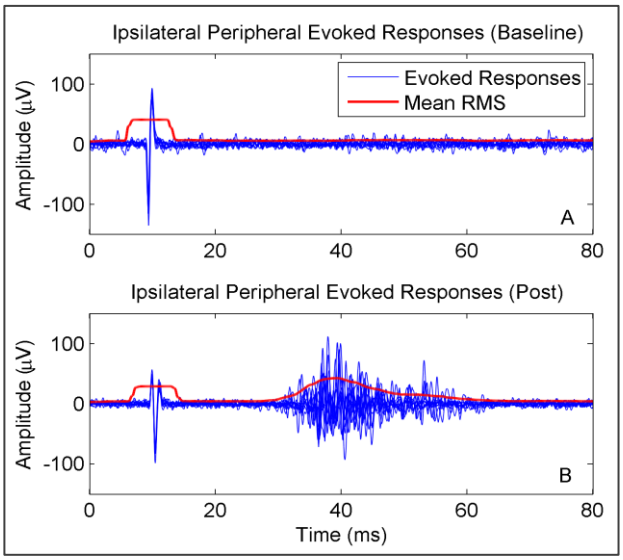

Figure 6. Evoked response (n=10, blue) to electrical stimulation of ipsilateral forelimb using the SRD (A) prior to chronic ICMS and (B) following chronic ICMS. Mean windowed RMS shown in red. (ICMS = 30uA, biphasic, 1 ms duration, 1 Hz)

V. Conclusion

We described the design and implementation of a telemetry controlled SRD that can simultaneously record single and multiunit responses and deliver mono-, bi-, or pseudophasic ICMS and tested its validity in an anesthetized in-vivo rat animal model. We demonstrated that the SRD was capable of (a) delivering chronic ICMS to an interhemispheric pathway in SI cortex, (b) recording evoked responses in the contralateral SI showing that the stimulation enhanced the interhemispheric pathway, and (c) demonstrating that the enhancement led to the functional expression of new input in the enhanced SI.

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