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Telemetry Controlled Simultaneous Microstimulation and Recording Device for Studying Cortical Plasticity*

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Abstract — **This paper describes a telemetric interactive intracortical microstimulation (ICMS) and simultaneous recording device developed to deliver chronic microstimulation to the ipsilateral cortex and monitor evoked responses from the contralateral cortex. The embedded device was developed utilizing a Programmable System on a Chip (PSoC) microcontroller that can be remotely configured through Bluetooth. This device, with dimensions of 42 mm × 71 mm, can deliver monophasic, biphasic or pseudophasic stimulation pulses (peak current: ≤ 100 μA, duration: ≤ 10 ms, delay: ≤ 40 ms, repetition rate: 0.5 to 1 Hz) to a physiologically identified site in primary somatosensory cortex (SI) and record single and multiunit responses within 367 to 6470 Hz from a homotopic site in contralateral SI. This device was bench tested and validated *in vivo* in rat.**

I. Introduction

Cortical reorganization in the primary somatosensory (SI) cortex is a central neurological consequence that follows limb amputation [1] and post stroke recovery [2]. It is an innate mechanism that permits changes in the neuronal pathways and synaptic connectivity of cortical circuits providing the potential for lifelong ability to compensate for injury. Understanding this critical mechanism is necessary for developing alternative compensation strategies and rehabilitation therapies by modulating cortical circuits to aid in therapeutic treatment that follows amputation and the plasticity that occurs during rehabilitation in stroke patients.

Chronic intracortical microstimulation (ICMS) and physiological recording of neuronal firing are fundamental techniques used in modulating cortical connections to enable us to understand and characterize cortical plasticity [3–6]; however, limitations of continuous ICMS include potentially destroying neurons in the vicinity of the stimulation site and repeated monophasic stimulation may breakdown the ability of the electrode to deliver stimulation which could be offset by using bipolar stimulation. The approach of using stimulation to induce modulation of cortical circuits is based on Hebb's cell assembly theory wherein the connection between two neurons is strengthened when one cell repeatedly or persistently participates in the excitation and firing of the second cell [7]. ICMS typically requires the animal to be sedated and/or physically tethered to the stimulating and recording devices. These constraints could be minimized, if not eliminated, through the use of wireless telemetry based neural interfacing systems.

Wireless neural interfacing systems for microstimulation and recording neural activity have been rarely reported [8], [9]. Jackson and colleagues demonstrated *in vivo* in monkey an autonomous microcontroller-based neural device featuring separate stimulation and recording circuits; while it has the capacity to deliver 100 μA, the device is not remotely controlled nor is response activity monitored in real-time [8]. A portable telemetry stimulator, with the capacity to deliver up to 15 μA, and recording device was implemented by Ye and colleagues in freely behaving small animals [9]. We previously described a telemetry based system with the capacity to deliver up to 100 μA of current (tested to 5.0 hrs.) and record unit responses to study functional reorganization in rat cortex [10]. Investigating cortical plasticity in small freely behaving animals necessitates such functional capabilities into a cohesive system. This paper presents a novel wearable device for transcutaneous neurostimulation with these functionalities.

II. System Model

The complete system consists of two units: a base unit (computer) and a remote unit (embedded system). The system model is illustrated using the block diagram in Fig. 1. The base unit is a host computer system with Bluetooth connectivity and a custom software application to provide an intuitive graphical user interface (GUI), establish wireless communication with the remote unit, and remotely control the parameters for stimulation and recording. The remote unit is a hardware-software prototype board with a small form factor that contains (1) a Programmable System on a Chip (PSoC) microcontroller, (2) stimulator analog back end (ABE) circuitry, (3) recorder analog front end (AFE) circuitry, and (4) a Bluetooth module for wireless communication.

The reconfigurable system allows the user to select pulse shape (mono-, bi-, or pseudophasic stimulus) of either positive or negative polarity, amplitude, duration, delay, and frequency. This system also allows users to capture neuronal data in real-time through a wireless connection by specifying the number of responses to consecutive stimulations, the interval at which the responses will be collected, and the file location where data will be saved (.CSV format).

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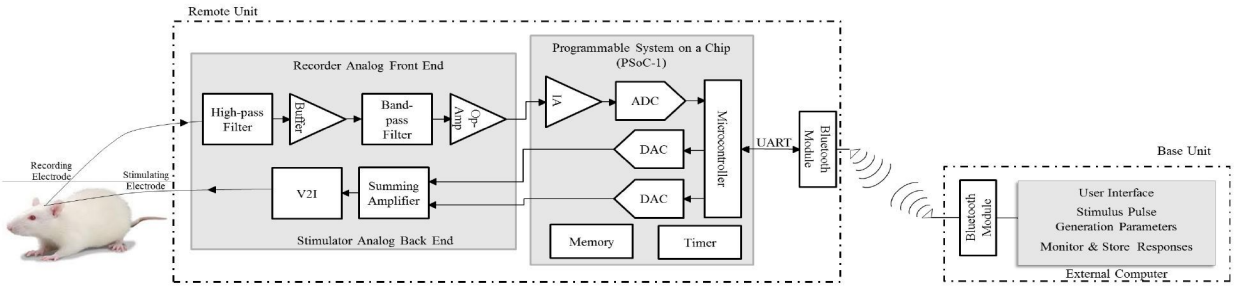

Figure 1. Block diagram of the two-unit system containing telemetry controlled simultaneous ICMS and recording capabilities.

III. Design and Fabrication

The system was designed to operate with stimulation and recording parameter ranges as outlined in Table I. The screen capture in Fig. 2 depicts the C# GUI used for remote management of these parameters. The printed circuit board (PCB) was designed using Eagle v6.3.0 (CadSoft Inc.). Dimensions of the fabricated PCB (Advanced Circuits) are 4.2 cm × 7.1 cm. The populated remote unit is photographed in Fig. 3. As presented, this embedded device is wearable within a backpack (not for implantation) in rodents or primates, and requires transcutaneous neurostimulator probes. This first generation design is more suitable for larger animal study, however optimization is possible to reduce the footprint and power consumption. The remote unit contains a PSoC-1 CY8C28452-24PVXI microcontroller unit (MCU) (1) (Cypress Semiconductor Corp.) for digital-computation, digital-to-analog conversion (DAC) of stimulation parameters, and for analog-to-digital conversion (ADC) of neural signals; buffer and peripheral ports for data storage and transmission; and a five pin MiniProg connector (2) for PSoC in-system serial programming (ISSP). The MCU operates at 24 MHz, with M8C CPU core, and contains 1 KB SRAM and 16 KB Flash RAM. The stimulator analog circuitry, shown by the red dashed outline in Fig. 3, features a differential amplifier (3), a 9-bit voltage-to-current converter (4), and a two pin connector (5) that feeds the stimulus pulse to a Platinum/Iridium (80%/20%) microelectrode (FHC Inc., USA) inserted into the cortex. The ground connector is attached to the skull. Neural response signals in contralateral cortex are transduced by another Platinum/Iridium recording

TABLE I. Stimulation and Recording Parameter Ranges

Function	Parameter	Value	Unit of Measure
Mode of Operation	Calibrate – Number of Pulses	0-255	count
	Chronic – Stimulation Duration	0-1440	min
	Stimulation Interval	0-1440	min
Stimulator	Amplitude (Anodic, Cathodic)	0-100	µA
	Duration (Anodic, Cathodic)	0-10	ms
	Delay (Anodic, Cathodic)	0-40	ms
	Frequency (repetition rate)	0.5-1	Hz
Recorder	Number of responses	0-255	count
	Recording Interval	0-1440	min

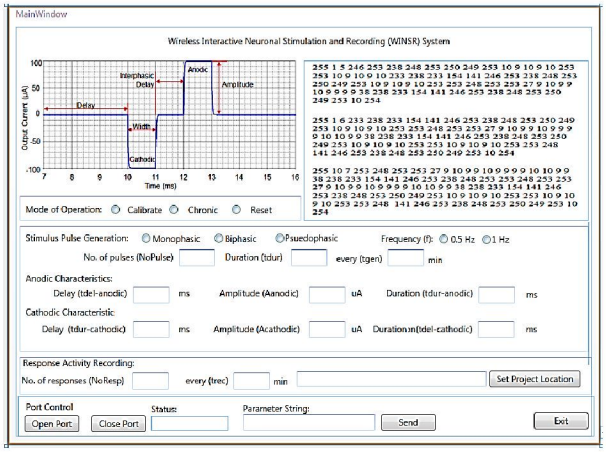

Figure 2. Screen capture of user interface to remote unit.

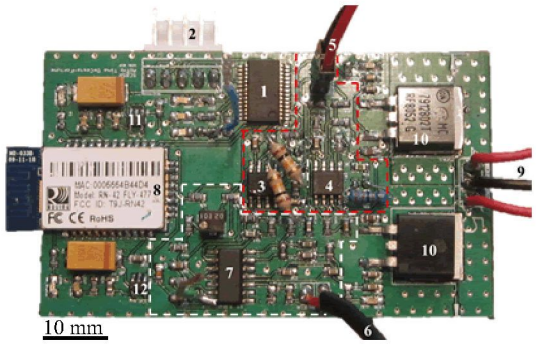

Figure 3. Photograph of the completed remote unit PCB. The board deminsions were 42 mm × 71 mm. Stimulator ABE (red dashed outline). Recorder AFE circuitry (white dashed outline).

microelectrode and fed into the recorder analog circuitry, shown by the white dashed outline in Fig. 3. The recorder AFE is comprised of a shielded copper co-axial cable (6) that receives the neural signals from the implanted electrode. Four OpAmps (7) are used for buffering, filtering and amplifying the analog signals. A Class-2 Bluetooth module (8) (Model: RN-42, Roving Networks, CA USA) is used for real-time interaction between the base and remote units. Power is provided from an external ±20 V battery (9) through two low-dropout (LDO) regulators (10) that generate ±12 V for the TL08x OpAmps (Texas Instruments), a 5.0 V LDO regulator (11) for the PSoC, and a 3.3 V LDO regulator (12) for the Bluetooth module.

The stimulator can deliver mono-, bi-, or pseudophasic microstimulation to a single microelectrode (100 kΩ at 1 kHz) inserted into a physiologically identified body part

representation in SI. The stimulator ABE is driven by the PSoC that generates two analog voltage signals corresponding to the anodic and cathodic pulse segments defined by the user. These signals are summed together using an operational amplifier. The combined waveform is then converted to current using a negative impedance converter, V2I, (OPA454, Texas Instruments) and is delivered to the microelectrode inserted into the cortex. Stimulation can be delivered as a set number of pulses (calibrate mode) or over a set period of time (chronic mode). After receiving the stimulation parameters, the stimulator operates autonomously; however, the parameters can be changed in real-time and retransmitted to the remote device.

The recorder acquires neuronal activity from a separate microelectrode (100 kΩ at 1 kHz) inserted into a homotopic site in contralateral SI. Transduced neural signals are commonly superimposed onto low frequency noise occurring at the electrode-tissue interface [11]. The recorder AFE first attenuates this noise with a high pass filter ($f_{c\text{-}HP}$ = 220 Hz) before buffering. Signals are then band-pass filtered through two cascading second-order multiple feedback (MFB) filters. The first MFB is a high-pass filter designed for $f_{c\text{-}BPH}$ = 6425 Hz and the second MFB is a low-pass filter designed for $f_{c\text{-}BPL}$ = 375 Hz. Overall gain of the recorder AFE (A_G) is 78.4 dB. After analog processing, employing ICMS signal as the trigger, the first 150 ms of each stimulation is sampled at 13 ksps, and transmitted wirelessly in real-time to the base unit via UART port of the Bluetooth module (SPP profile) for off-line storage and analysis.

IV. Experimental Results

A. Bench Test

ICMS range of operation was assessed on bench test by loading the stimulator with a maximal load (100 kΩ), and sweeping the intensity of a monophasic cathodic input pulse (5 µA increments) while measuring the output current with a µCurrent meter (www.EEVblog.com). System accuracy is demonstrated by comparison of the simulated and measured input-output characteristics as shown in Fig. 4. Similar input-output characteristics were observed for anodic stimulus pulses. Secondly, a 1.0 ms biphasic pulse with varying amplitudes (0-100 µA, 25 µA increments) was examined under the load conditions 0-220 kΩ. Linearity was maintained with loads ≤100 kΩ for stimuli ≤100 µA, and with loads up to 150 kΩ for stimuli ≤60 µA. Simulated and measured linearity results are presented in Fig. 5. Measured stimuli delivered across a resistor was used to evaluate accuracy of the delivered mono-, bi-, and pseudophasic waveforms with user-defined parameters, while output measurements were taken using the µCurrent meter previously described. Measured examples of a 1.0 ms 65 µA mono- (blue), a charge-balanced 1.0 ms 45 µA bi- (black), and a charge-balanced 1.0 ms 50 µA cathodic and 2.0 ms 25 µA anodic pseudophasic (red) are plotted in Fig. 6.

Recorder fidelity was determined by sweeping a 300 μV_{pp} sinusoid from 125 Hz to 10 kHz, while linearity was assessed by sweeping the amplitude of a 4 kHz sinusoidal input signal from 100 μV_{pp} to 500 μV_{pp} (Table II). Measured results revealed a 0.9-1.7 dB shift for signals below 300 μV_{pp}; which should not affect the desired functionalities.

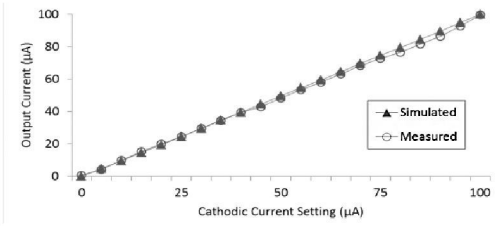

Figure 4. Stimulator transfer characteristic (simulated and measured) for a 100 kΩ resistive load with varying intensities (0-100 µA).

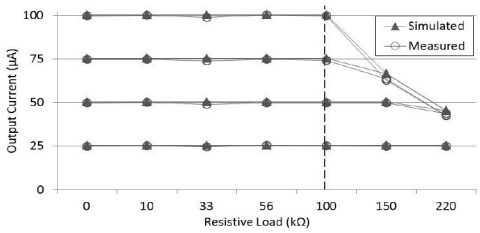

Figure 5. Stimulator output linearity (simulated and measured) under varying load conditions (0-220 kΩ).

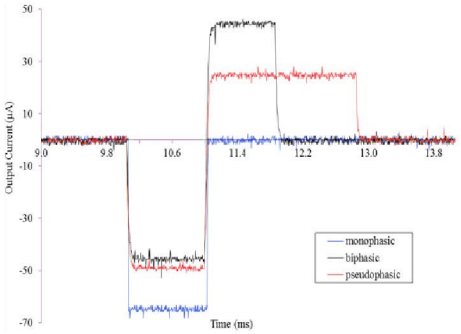

Figure 6. Examples of stimulus waveforms delivered to a 100 kΩ load.

TABLE II. Recorder Fidelity Summary

Environment	Gain (dB)	HPF (Hz)	LPF (Hz)
Simulation	78.4	375	6425
Measure	78.8	367	6470

B. In Vivo

System performance was evaluated in Sprague Dawley rat models. The experiments conformed to the Principles of Laboratory Animal Care (NIH publication No. 86-23, Revised 1985) and were approved by the University of Tennessee Health Science Center (UTHSC) Institutional Animal Care and Use Committee (IACUC). Three categories of real-time response activity in SI layer V (depth: 1,000 µm) dorsal wrist representation processed by the recorder AFE are presented: (1) spontaneous activity in the absence of microstimulation, (2) evoked responses to electrical peripheral stimulation of the contralateral dorsal wrist, and (3) evoked responses following microstimulation of the homotopic site in contralateral wrist cortex. A single trace of spontaneous activity recorded from multiple neurons is shown in Fig. 7; the difference in spike amplitude is reflective of the firing neuron's proximity to the recording electrode. Evoked response activity to peripheral stimulation (-70 µA, 1.0 ms duration, 1 Hz) of the dorsal wrist recorded in the corresponding contralateral SI layer V wrist

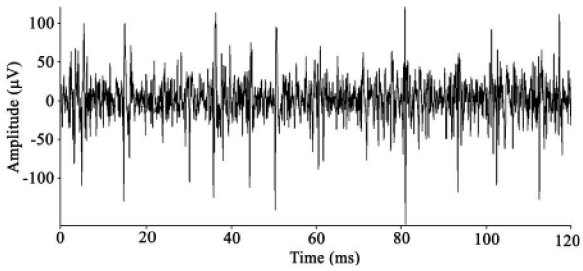

Figure 7. Real-time spontaneous spike activity recorded in SI layer V (depth = 1,000 μm) in the dorsal wrist representation.

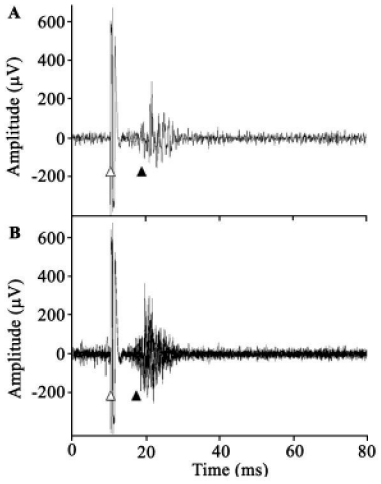

Figure 8. Real-time responses recorded in SI layer V (depth = 1,000 μm) dorsal wrist representation to peripheral stimulation (-70 μA, 1.0 ms duration, 1 Hz) of the contralateral dorsal wrist. **A:** Single evoked response. **B:** Composite of 5 evoked responses. Stimulus pulse and evoked response onset are denoted by the open and filled triangles, respectively.

representation is presented in Fig. 8 as (A) a single evoked response trace and (B) a composite of 5 evoked responses. Real-time evoked response activity between physiologically identified sites in the dorsal wrist representation in layer V of SI cortex is presented in Fig. 9. A single response trace is presented in Fig. 9A and a composite of 5 traces in Fig. 9B. The recorded evoked response latency corresponds to the reported response latency measured using commercial neurophysiological stimulating and recording equipment [10].

V. Conclusion

A telemetry controlled neuronal device is described here that delivers mono-, bi-, or pseudophasic chronic ICMS with real-time user-defined amplitude (0-100 μA), duration (0-10 ms), delay (0-40 ms), and frequency (0.5-1 Hz) to a maximum load of 100 kΩ and simultaneously acquires (A_G = 78.8 dB) real-time evoked response (ICMS triggered) activity within the frequency range of 367 to 6470 Hz. Functionality of the device on bench testing and *in vivo* validation in anesthetized young adult Sprague-Dawley rats have been demonstrated. The telemetry controlled embedded device, measuring 42 mm × 71 mm, is suitable to study cortical plasticity in small animals and primates. Further optimization can be achieved with custom ASIC designs.

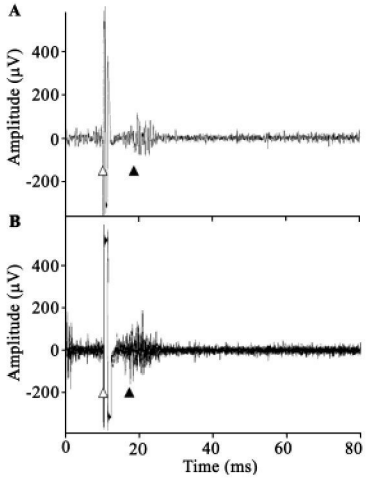

Figure 9. Real-time response activity in SI layer V (depth = 1,000 μm) dorsal wrist representation following ICMS (-75 μA, 1.0 ms duration, 1 Hz) delivered to a homotopic site in contalateral SI. **A:** Single evoked response. **B:** Composite of 5 evoked responses. Open and filled triangles denote onset of stimulus and evoked response, respectively.

References

[1] D. Borsook, L. Becerra, S. Fishman, a Edwards, C. L. Jennings, M. Stojanovic, L. Papinicolas, V. S. Ramachandran, R. G. Gonzalez, and H. Breiter, "Acute plasticity in the human somatosensory cortex following amputation.," *Neuroreport*, vol. 9, no. 6, pp. 1013–7, Apr. 1998.

[2] K. Roiha, E. Kirveskari, M. Kaste, S. Mustanoja, J. P. Mäkelä, O. Salonen, T. Tatlisumak, and N. Forss, "Reorganization of the primary somatosensory cortex during stroke recovery.," *Clinical Neurophysiology*, vol. 122, no. 2, pp. 339–345, 2011.

[3] G. H. Recanzone, M. M. Merzenich, and H. R. Dinse, "Expansion of the cortical representation of a specific skin field in primary somatosensory cortex by intracortical microstimulation.," *Cerebral Cortex*, vol. 2, no. 3, pp. 181–196, 1992.

[4] H. R. Dinse, G. H. Recanzone, and M. M. Merzenich, "Alterations in correlated activity parallel ICMS-induced representational plasticity.," *Neuroreport*, vol. 5, no. 2, pp. 173–6, Nov. 1993.

[5] P. Heusler, B. Cebulla, G. Boehmer, and H. R. Dinse, "A repetitive intracortical microstimulation pattern induces long-lasting synaptic depression in brain slices of the rat primary somatosensory cortex.," *Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale*, vol. 135, no. 3, pp. 300–10, Dec. 2000.

[6] G. J. Kalarickal and J. A. Marshall, "Rearrangement of receptive field topography after intracortical and peripheral stimulation: the role of plasticity in inhibitory pathways.," *Network (Bristol, England)*, vol. 13, no. 1, pp. 1–40, Feb. 2002.

[7] D. O. Hebb, *The organization of behavior*, vol. 911. Wiley, 1949, p. 335.

[8] A. Jackson, J. Mavoori, and E. E. Fetz, "Long-term motor cortex plasticity induced by an electronic neural implant.," *Nature*, vol. 444, no. 7115, pp. 56–60, Nov. 2006.

[9] X. Ye, P. Wang, J. Liu, S. Zhang, J. Jiang, Q. Wang, W. Chen, and X. Zheng, "A portable telemetry system for brain stimulation and neuronal activity recording in freely behaving small animals.," *Journal of neuroscience methods*, vol. 174, no. 2, pp. 186–93, Sep. 2008.

[10] T. DeCosta-Fortune, Q. Yang, N. Tyagi, A. DeJongh-Curry, C.-X. Li, and R. S. Waters, "Functional Modulation of Interhemispheric Forelimb Connectins in Rat," in *Program No. 363.21. 2009 Neuroscience Meeting Planner.*, 2009.

[11] G. Buzsáki, M. Penttonen, Z. Nádasdy, and A. Bragin, "Pattern and inhibition-dependent invasion of pyramidal cell dendrites by fast spikes in the hippocampus in vivo.," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 18, pp. 9921–5, Oct. 1996.