Towards a Miniaturized Brain-Machine-Spinal Cord Interface (BMSI) for Restoration of Function after Spinal Cord Injury

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***Abstract*—Nearly 6 million people in the United States are currently living with paralysis in which 23% of the cases are related to spinal cord injury (SCI). Miniaturized closed-loop neural interfaces have the potential for restoring function and mobility lost to debilitating neural injuries such as SCI by leveraging recent advancements in bioelectronics and a better understanding of the processes that underlie functional and anatomical reorganization in an injured nervous system.**

This paper describes our current progress towards developing a miniaturized brain-machine-spinal cord interface (BMSI) that is envisioned to convert in real time the neural command signals recorded from the brain to electrical stimuli delivered to the spinal cord below the injury level. Specifically, the paper reports on a corticospinal interface integrated circuit (IC) as a core building block for such a BMSI that is capable of low-noise recording of extracellular neural spikes from the cerebral cortex as well as muscle activation using intraspinal microstimulation (ISMS) in a rat with contusion injury to the thoracic spinal cord. The paper further presents results from a neurobiological study conducted in both normal and SCI rats to investigate the effect of various ISMS parameters on movement thresholds in the rat hindlimb. Coupled with proper signal-processing algorithms in the future for the transformation between the cortically recorded data and ISMS parameters, such a BMSI has the potential to facilitate functional recovery after an SCI by re-establishing corticospinal communication channels lost due to the injury.

I. Introduction

Existing brain-machine interface (BMI) technology is designed to either record from the brain and use the recorded neural activity as the source of command for controlling the external environment [1], or stimulate the brain (or other parts of the nervous system) to modulate a dysfunctional neural pathway or transmit a particular type of sensory information [2]. While the existing BMI technology has shown a tremendous potential for augmenting the quality of life in patients afflicted with neural injuries and neurological disorders, a new generation of neuroprostheses is already emerging that aims to combine neural recording, neural signal processing and microstimulation functions in a single device for closed-loop operation. These neuroprosthetic devices create an artificial connection in the nervous system by converting neural activity recorded from one cortical area to electrical stimuli delivered to another cortical area [3] or muscles [4] in real time, and have been shown to induce neuronal plasticity for functional reorganization in both intact [5] and injured [6] nervous systems.

Similar activity-dependent stimulation approaches can also be envisioned to facilitate functional recovery after a spinal cord injury (SCI), a debilitating neural injury that can be caused by a traumatic blow to the spine damaging the nerve axons that carry sensory-motor signals back and forth between the brain and the rest of the body. Specifically, given that the neural circuits above and below the lesion generally remain intact [7], a brain-machine-spinal cord interface (BMSI) neuroprosthesis can potentially bridge the damaged connections by converting in real time the neural command signals recorded from the cerebral cortex to electrical stimuli delivered to the spinal cord below the lesion. Such an approach would require developing a corticospinal interface integrated circuit (IC) capable of low-noise intracortical spike recording and distinct muscle pattern activation via intraspinal microstimulation (ISMS), as well as developing appropriate signal-processing algorithms (and hardware-efficient architectures for their real-time implementation) for the transformation between the cortically recorded data and stimulation parameters [8].

This paper reports on our progress towards developing such a BMSI and is organized as follows. Section II presents the system architecture of the IC, and Section III presents the results of biological investigations to study the effect of various ISMS parameters (e.g., stimulus rate, number of pulses within an ISMS train, monophasic *vs.* biphasic, etc) on movement thresholds in both normal and SCI rats. Section IV presents a summary of the measured electrical performance of the corticospinal interface IC as well as its functionality *in vivo*. Finally, Section V draws some conclusions from this work.

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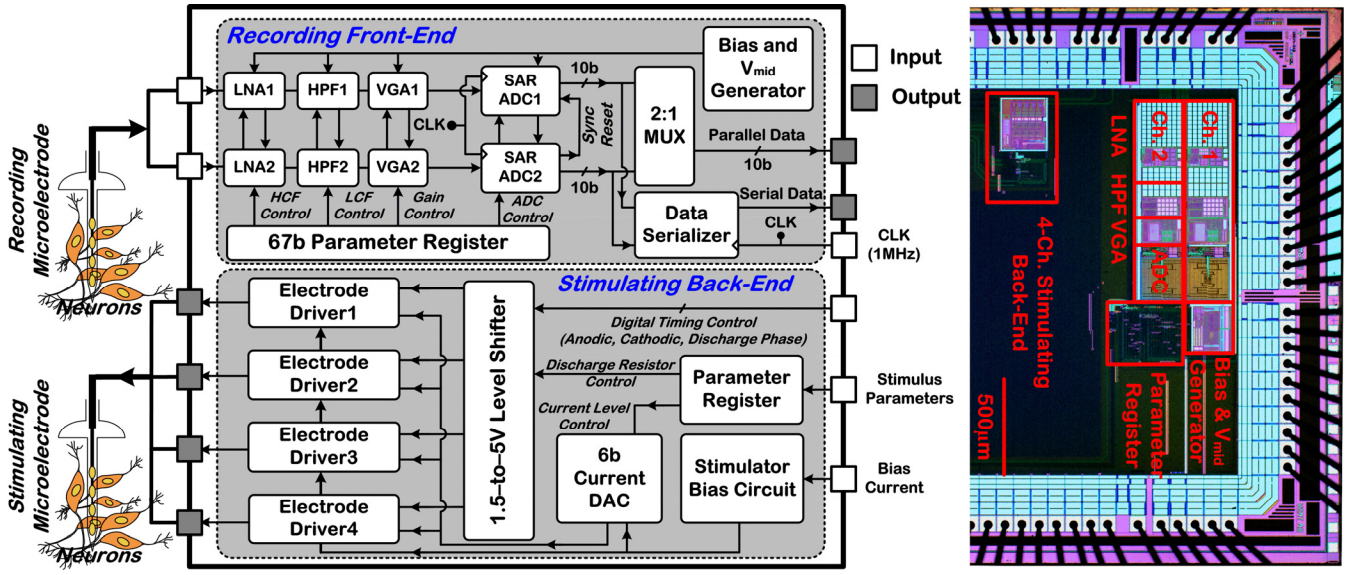

Fig. 1. System architecture and die micrograph of the corticospinal interface IC fabricated in AMS 0.35µm 2P/4M CMOS.

II. System Architecture

Fig. 1 shows the IC architecture designed to interface with the cerebral cortex and the spinal cord via a pair of implanted microelectrode arrays [9]. The IC incorporates two identical recording channels with digitally programmable gain and bandwidth for ac amplification, dc baseline stabilization, highpass filtering and 10b digitization of the recorded neural spikes. A 2:1 multiplexer and a data serializer block allow the user to access the digitized output of one channel in parallel or both channels in serial fashion, respectively. The IC also incorporates 4 identical stimulating channels to deliver ISMS trains of charge-balanced monophasic or asymmetric biphasic current pulses (0 to ~100µA) followed by passive discharge. In its nominal mode of operation for benchtop and *in vivo* testing purposes, the stimulating back-end is programmed to stimulate the spinal cord sequentially on all four channels with a programmable inter-channel delay to evoke four different limb movements in the subject. All current pulse parameters such as amplitude and duration as well as frequency and number within an ISMS train are also programmable for the IC.

III. Effect of ISMS Parameters on Movement Threshold

Biological experiments were initially carried out in four adult, male, Fischer 344 rats using commercial laboratory equipment to determine the effect of various ISMS parameters on movement thresholds (i.e., minimum current required to evoke a visible joint or muscle movement). These tests were conducted in two normal rats and two rats that had received a contusion injury to the thoracic spinal cord at level T8-T9 more than four weeks prior to the neurophysiological procedure. On the day of these experiments, the rats were anesthetized with isoflurane and placed in a spinal stabilizer, and the thoracic and lumbar spinal column was exposed.

A silicon-based microelectrode array (*NeuroNexus Technologies*) with stimulus site impedance in the range of 120–140kΩ at 1kHz was inserted into the spinal cord at the lumbar level. The position of the stimulus sites ranged from ~500–2,800µm below the surface of the posterior spinal cord, with the medio-lateral position ~250–1,500µm lateral to the midline. The current return-path electrode was secured to the animal's tail. All electrophysiological experiments were conducted under ketamine anesthesia.

Both monophasic and biphasic current pulses (with passive discharge) were used to determine the relative efficacy of each ISMS mode for evoking hindlimb movements. In each rat, movement thresholds were determined in at least 60 spinal cord sites. The ISMS responses typically consisted of movements of the hip, knee, ankle or toes, with movement thresholds typically ranging from ~15–25µA. While monophasic anodic pulses resulted in slightly lower movement thresholds, there was no significant difference between these conditions, as shown in Fig. 2.

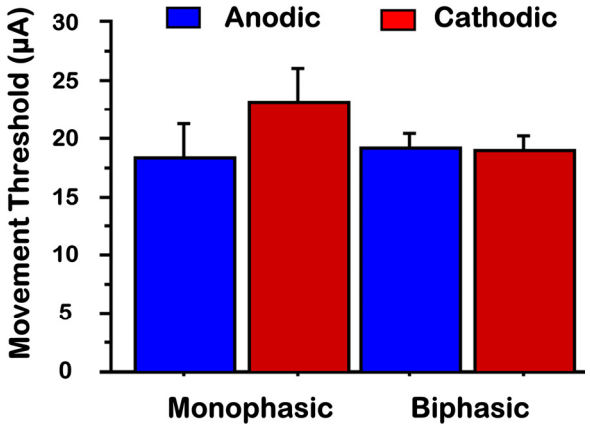

Fig. 2. Movement thresholds using monophasic (anodic and cathodic) or biphasic (anodic- and cathodic-leading) stimulation in an SCI rat. ANOVA: $F_{(3,165)} = 1.141$; $p = 0.3343$. Number of pulses in ISMS train = 5. Stimulation rate = 300Hz. Error bars are standard error of the mean (SEM).

Fig. 3 shows the movement thresholds in an SCI rat using monophasic (anodic and cathodic) stimulation with 5 current pulses in the ISMS train at stimulation frequencies in the range of 100–500Hz. While there was a trend towards lower thresholds with higher frequency using anodic pulses, the differences were not significant.

Fig. 4 depicts the movement thresholds in a normal rat using biphasic (cathodic-leading) stimulation at 300Hz, comparing different lengths of ISMS current pulse train (i.e., # of pulses). Post-hoc comparisons showed that movement thresholds were significantly lower when 13 or 5 pulses were used as compared to one pulse. However, even using a single pulse, the movement threshold was only 16 ± 3.2µA, which was well within the stimulus current range of the IC.

Fig. 5 shows the comparison of movement thresholds in a normal and SCI rat using biphasic (cathodic-leading) stimulation at a rate of 300Hz with 5 current pulses in the ISMS train. This experiment was performed to determine whether the movement thresholds were considerably higher after spinal cord injury. As can be seen, while thresholds in the SCI rat were significantly higher statistically, the actual difference was quite small (< 3µA).

IV. Experimental Results

A prototype IC was fabricated in AMS 0.35µm two-poly four-metal (2P/4M) CMOS, measuring ~2.9mm × 2.9mm including the bonding pads (see Fig. 1.) Electrical performance of individual circuit blocks was initially characterized in benchtop measurements, and their *in vivo* functionality was verified in biological experiments with anesthetized laboratory rats in accordance with guidelines approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Kansas Medical Center. Table I tabulates the measured performance of the recording and stimulating blocks of the IC.

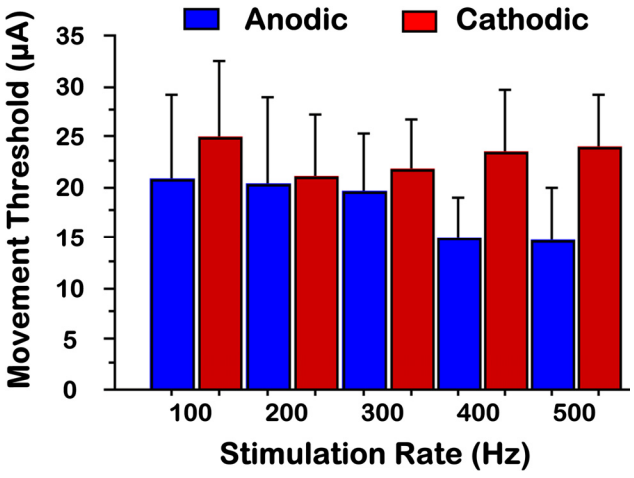

Fig. 3. Movement thresholds using monophasic (anodic and cathodic) stimulation at different stimulation frequencies in an SCI rat. ANOVA: $F_{(9,50)} = 0.256$; $p = 0.9832$. Number of pulses in ISMS train = 5. Error bars are SEM.

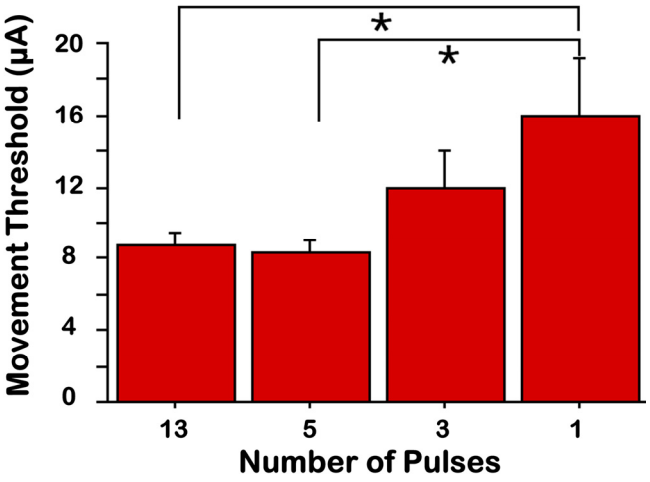

Fig. 4. Movement thresholds as a function of number of pulses in ISMS train using biphasic (cathodic-leading) stimulation in a normal rat. ANOVA: $F_{(3,85)} = 6.359$; $p = 0.006$. Stimulation rate = 300Hz. Error bars are SEM.

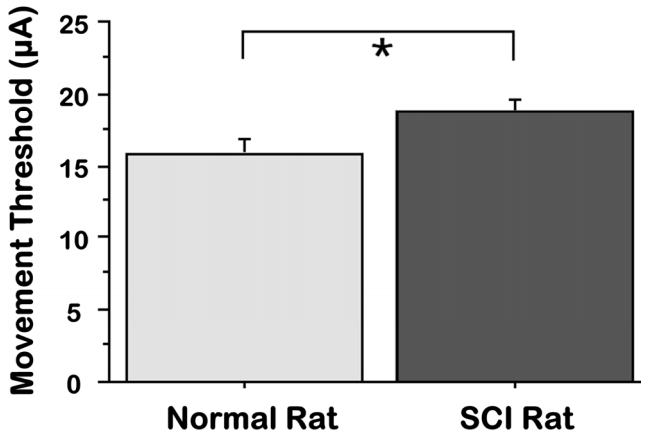

Fig. 5. Movement thresholds in a normal and SCI rat using biphasic (cathodic-leading) stimulation. ANOVA: $F_{(1,173)} = 4.327$; $p = 0.0390$. Stimulation rate = 300Hz. Number of pulses in ISMS train = 5. Error bars are SEM.

Table I

Summary of Measured IC Performance

RECORDING FRONT-END		**STIMULATING BACK-END**		
AC Gain @ 1kHz	49 – 65.6dB		**Anodic**	**Cathodic**
High f_{3dB} Low f_{3dB}	5 – 11.9kHz 0.2 – 460Hz	Voltage Compliance (Max. I_{OUT})	4.75 (of 5V)	4.85 (of 5V)
Input Noise Voltage	$3\mu V_{rms}$ (0.5Hz – 50kHz)			
NEF	2.47 (272Hz – 10kHz)	Max. I_{OUT}	100µA	33.3µA
CMRR/PSRR	56 / 63.4dB	Output Imp.	> 100MΩ	
INL/DNL	< ±1.15 LSB	INL (LSB)	< ±0.59	< ±0.50
SNDR/ENOB	56dB / 9b @ $f_{s,max}$ = 65kSa/s	DNL (LSB)	< ±0.62	< ±0.58
Power Dissipation	31.9µW @ 1.5V (0.2Hz – 11.9kHz; f_{CLK} = 1MHz)	Supply Sensitivity	-69nA/V	-10nA/V
		Current Efficiency	96.1%	94.7%

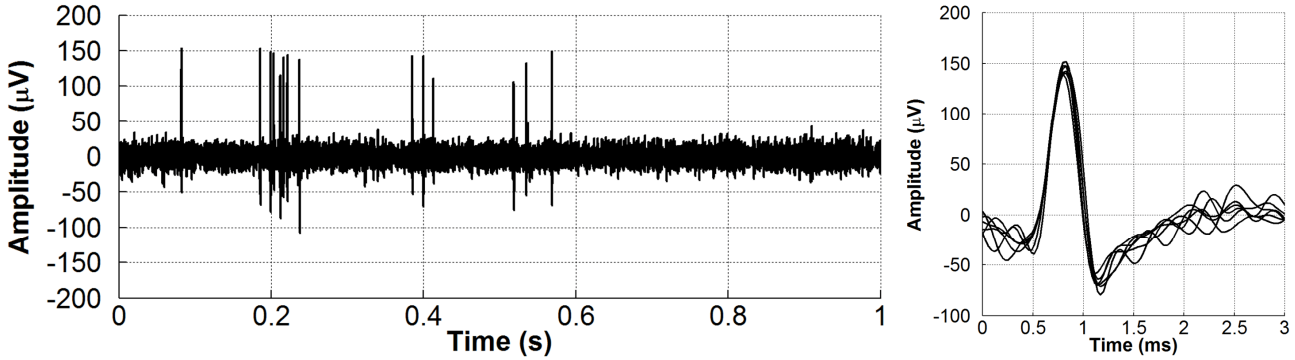

Fig. 6. 1-second window of recorded data from the rat's cerebral cortex using the IC and an expanded view of several neural spikes discriminated offline.

For *in vivo* tests, a recording microelectrode array was acutely implanted in the sensory cortex of a ketamine-anesthetized rat. Fig. 6 shows a 1-second window of recorded data from the rat's cerebral cortex and an expanded view of several evoked neural spikes extracted from the data using offline spike discrimination. All amplitudes are shown as input-referred.

Next, following the same procedure as previously described, a second rat was anesthetized with isoflurane and placed in a spinal stabilizer, and the thoracic and lumbar spinal column was exposed. This rat had also received a contusion injury to the thoracic spinal cord at level T8-T9 more than four weeks prior to the *in vivo* experiment. Under ketamine anesthesia, a stimulating microelectrode array was acutely implanted in the rat's spinal cord below the level of the contusion injury, and the IC was used to deliver single-channel ISMS to the spinal cord with a single monophasic current pulse (anodic, 25μA, 200μs) followed by passive discharge. Fig. 7 shows the fine-wire electromyography (EMG) signals recorded with benchtop equipment from two muscles in the rat's hindlimb (with the horizontal black bar indicating the onset and duration of the stimulus current pulse), demonstrating successful muscle activation via ISMS in the rat's spinal cord by the IC.

V. Conclusion

This paper reports on our progress towards developing a miniaturized brain-machine-spinal cord interface (BMSI) that is envisioned to facilitate functional recovery after a spinal cord injury (SCI) by converting in real time the electrical activity recorded from the cerebral cortex to electrical stimuli delivered to the spinal cord below the level of the injury. A corticospinal interface IC as the core building block of such a BMSI was developed, electrically tested via benchtop measurements, and evaluated *in vivo* using both normal and SCI rats. The effect of various stimulation parameters on movement thresholds in the rat hindlimb was also investigated to further guide the IC design. In future work, appropriate signal-processing algorithms require development for the transformation between the cortically recorded neural data and spinal cord stimulation parameters for closed-loop operation.

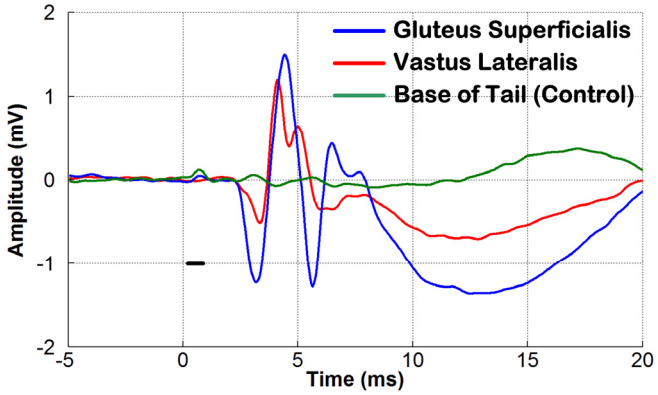

Fig. 7. Recorded EMG signals from two hindlimb muscles of an SCI rat activated via ISMS in the rat's spinal cord using the IC. The horizontal black bar depicts the onset and duration of the single stimulus current pulse (monophasic anodic with passive discharge).

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