

Battery-less Modular Responsive Neurostimulator for Prediction and Abortion of Epileptic Seizures

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Abstract—An inductively-powered implantable microsystem for monitoring and treatment of intractable epilepsy is presented. The miniaturized system is comprised of two mini-boards and a power receiver coil. The first board hosts a 24-channel neurostimulator SoC developed in a 0.13 μ m CMOS technology and performs neural recording, electrical stimulation and on-chip digital signal processing. The second board communicates recorded brain signals as well as signal processing results wirelessly, and generates different supply and bias voltages for the neurostimulator SoC and other external components. The multi-layer flexible coil receives inductively-transmitted power and sends it to the second board for power management. The system is sized at 2 × 2 × 0.7 cm³, weighs 6 grams, and is validated in control of chronic seizures in vivo in freely-moving rats.

I. INTRODUCTION

The vision of a fully-autonomous brain implant requires micro-systems that record neural signals at a high spatial resolution, process them in real-time, and efficiently modulate brain activity to avoid an undesired neurological outcome (e.g., a pathological brain state such as an epileptic seizure). Several implant designs that target such functionality have been reported [1]–[9]. However, chronic implantation constraints such as the ease of implantation and use, and long lifetime are often ignored, which prevents such systems from being used in long-term animal (e.g., rodent) studies and in clinics. A microsystem designed for long-term monitoring or treatment, must not only be good in brain neural signal recording, but also have a small form factor, be fully wireless and operate fully-autonomously.

Recording at high spatial resolution from a large section of the brain requires a large number of recording channels. Also to record both local field potentials (LFPs) and action potentials (APs), each of these channels must have a low-noise front-end that amplifies signals with amplitudes ranging from 10 μ V to 1mV and the bandwidth from sub-Hz to 10kHz [1]. To detect various neurological events, signal properties of each recording channel such as amplitude, power and phase as well as inter-channel information such as phase synchrony must be extracted. For a timely and effective responsive neuromodulation feedback, both power dissipation and stimulation latency must be minimized, which emphasizes the necessity of an on-chip implementation of such a signal processing unit.

An implantable/wearable microsystem such as the one for rodents presented here in Figure 1, must be able to communicate recorded data and signal processing results wirelessly and receive its energy from a battery or through magnetic induction. Using a battery that is suitable for chronic experiments (i.e., which can last more than a few months) increases the system weight and size significantly [4], [6]. Also if the system is implanted, a routine follow-up surgery is required once the battery is discharged [10]. On the other hand, inductive powering imposes no limitation on the system lifetime and can either be used to directly provide energy to the system or

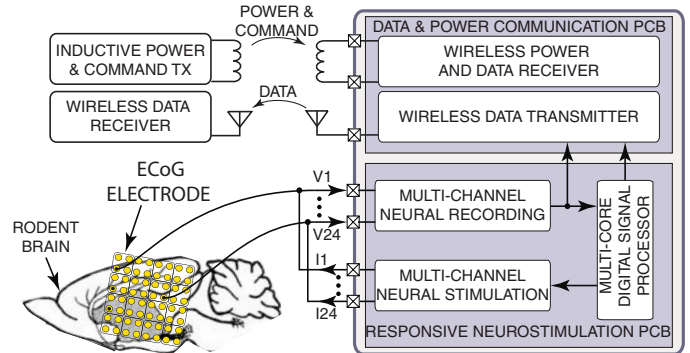


Fig. 1: Block diagram of the wireless closed-loop neurostimulator microsystem implanted on a rat's brain.

to recharge a smaller battery. Both of the wireless links for data and power must have a reasonable range (>10 cm) to ensure the ease of use. Also for the inductive link, the specific absorption rate (SAR) must be kept below the safety-permitted limit [11].

Recently reported wearable/implantable microsystem designs address some of these issues. In [4] a 32-channel closed-loop system is reported with promising in vivo experimental results. However, the system is battery-powered and lacks signal processing and stimulation units required for detection and control of neurological events. In [5] and [6] wearable closed-loop systems have been reported with in-vivo experimental results. The design in [5] has only four recording/stimulation channels and that in [6] has a low-data-rate wireless link, and both systems rely on a battery as the source of energy.

More recently inductively-powered implantable systems have been reported [8], [9]. In [8] the authors present an implantable micro-system with a very small form factor and 64 recording channels that enable high-spatial-resolution monitoring. However it does not have a signal processing unit or responsive neurostimulation. In [9], the system is equipped with both a signal processing unit and neurostimulation, but only has 8 recording/stimulation channels. Moreover, inductive links used in [8] and [9] for power delivery have 16mm and 6mm range, respectively, which requires the power transmitter to be located very close to the implant. This makes a freely-moving animal experiment impossible and poses challenges for convenient human use.

We have previously reported a 64-channel neurostimulator SoC (system on a chip) in [13]. The SoC in [13] transmits data within only a few centimeters and is powered using a wired connection. In [7] we reported a 64 channel SoC with a DC-coupled recording front-end, inductive powering, and multiple short/long-range data transmitters. However, both systems were tested using bulky packaged SoCs mounted on large bench-top boards, with monopole antennas, high-power controller FPGAs, making them non-implantable on a rodent or human subject.

To make the system implantable, the chip must be directly

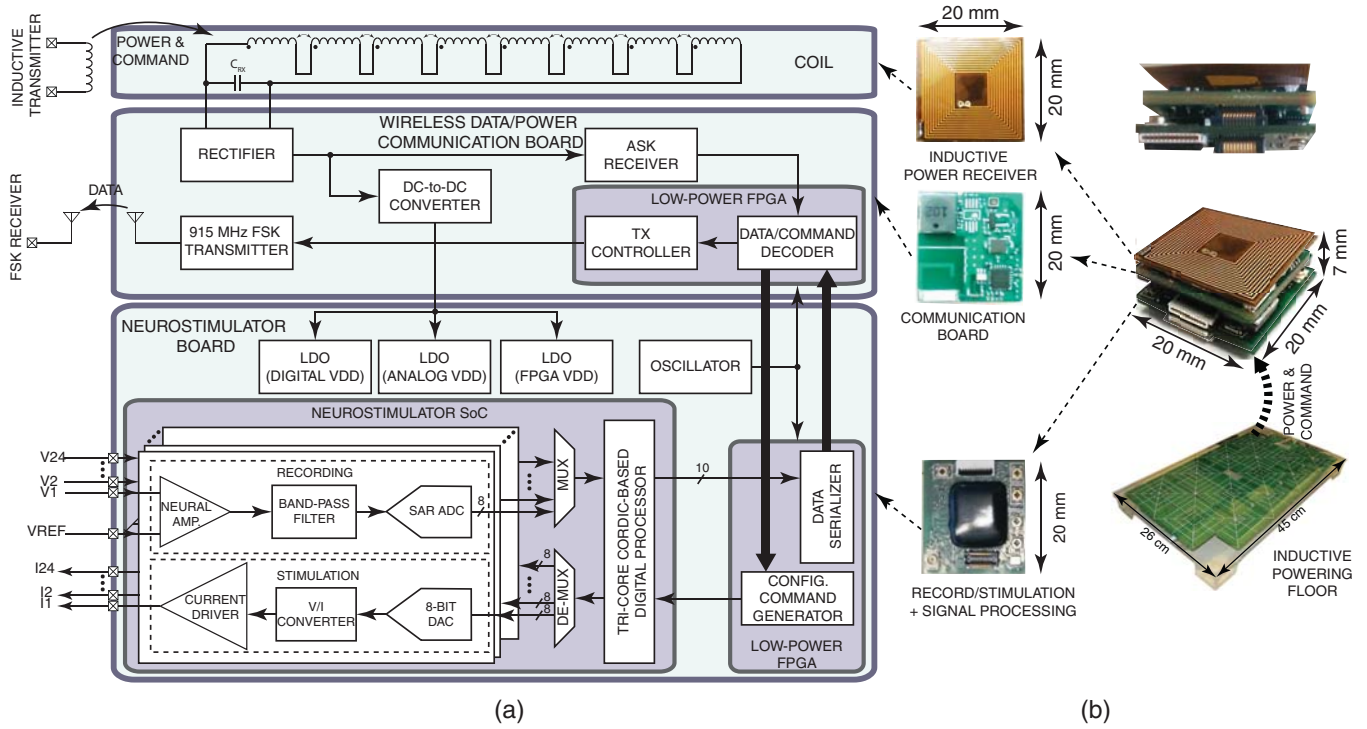


Fig. 2: (a) Simplified block diagram of the implantable inductively-powered closed-loop neurostimulator, (b) different components of the multi-PCB microsystem.

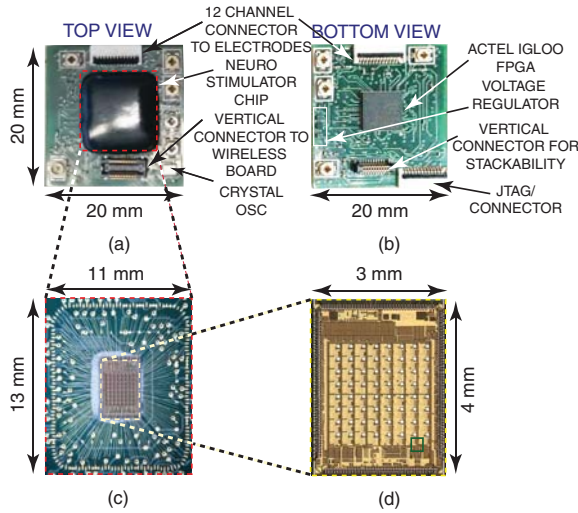


Fig. 3: Neurostimulator SoC wire-bonded to the neural interface PCB.

bonded to a PCB, and all the peripheral circuits must be either removed or replaced with low-power smaller versions to save area. Also, the digital chip controller implemented on the FPGA must be redesigned to fit inside an ultra-low-power FPGA that has X10 fewer logic elements. Since everything must fit within a 2 cm^3 implant, antennas must be redesigned and replaced with planar antennas implemented on the board.

This paper presents a 24-channel inductively-powered implantable microsystem for neural signal monitoring, on-chip signal processing and biphasic current-mode stimulation. A 12 mm^2 $0.13 \mu\text{m}$ CMOS SoC performs the core of signal recording, processing and stimulation [13]. The system transmits diagnostic data to the outside of the body wirelessly and receives its energy directly from an inductive powering link several centimeters away. The system's efficacy in epileptic seizure detection and abortion is validated in vivo on freely-

moving rats with temporal lobe epilepsy.

II. METHODS AND MATERIAL

Figure 2(a) shows a system block diagram of the implantable closed-loop neurostimulator. The system is comprised of the receiver coil, the wireless interface board and the neurostimulator board. The core of the system is the neurostimulator SoC which has 64 neural recording channels that receive and amplify EEG/ECOG signals from a microelectrode array implanted in the rodent brain. The amplified signals are filtered and digitized in each channel and then fed to an on-chip multi-core digital processor shared among channels, to extract their amplitude and phase information. The digital processor uses this information to detect an upcoming epileptic seizure and activate a subset of 24 current-mode stimulators available on the chip to abort it. The chip is interfaced with an on-board FPGA that serializes the chip output and sends it to the wireless communication board through a vertical connector bus. The FPGA uses the same bus to receive configuration commands from the wireless board.

The wireless interface board receives and modulates data from the neurostimulator board and transmits it using an on-board low-power FSK (Frequency Shift Keying) transmitter. It also receives inductively transmitted power from the receiver coil that is connected to it, rectifies the received signal and generates various DC supply and bias voltages for different blocks on both boards. An ASK receiver is also placed on this board to receive commands that are sent through the inductive link. Both boards share a crystal oscillator output as their global operating clock.

A. Rodent Headset

Figure 2(b) shows the miniaturized headset microsystem that is comprised of the two printed circuit boards (PCBs) and a coil powered by an inductive powering rodent cage floor [14]. As illustrated, the coil (top) is a polyimide-based

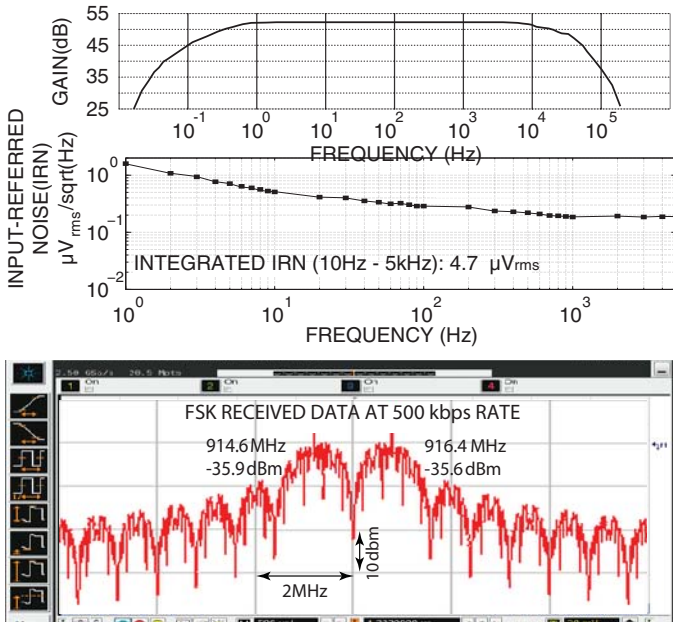


Fig. 4: Experimentally-measured frequency spectrum of the recording front-end (top), the input-referred noise (middle), and spectrum of the FSK transmitter signal measured at 1m distance (bottom).

flexible coil that receives power transmitted by means of near-field magnetic induction. The coil is connected to the first board (middle) that performs power management and supplies energy to different blocks of the system. In addition, this board contains an FSK wireless transmitter to communicate recorded data to the outside of the body. The second board (bottom) hosts the SoC, directly wirebonded on it and covered by epoxy, that performs multi-channel signal recording and digital signal processing for monitoring and detection of epileptic seizures. The chip also does automatic multi-channel responsive electrical stimulation for seizure abortion.

B. Closed-loop Neurostimulator Board

Figure 3(a) shows the top view of the neurostimulator board with the silicon SoC, shown in Figure 3(d), directly bond-wired to it as depicted in Figure 3(c). Figure 3(b) shows the bottom view of the neural interface board. As shown, the board hosts the neurostimulator chip as well as a low-power FPGA that serializes and sends recorded neural data to the wireless board and controls the SoC mode of operation using commands received from that board. Microelectrode or ECoG arrays used for in vivo experiments connect to two 12-channel connectors on this board using flat flexible cables. Vertical Panasonic connectors are used to connect this board to the wireless communication board on one side, and to additional replicas of the neurostimulator board on the other side. Due to the direct wirebonding constraints, only 24 channels of each SoC are used. For more channel count, more copies of the neurostimulator board are stacked vertically, each adding 24 to the total number of channels.

III. RESULTS

Figure 4(top) shows the amplitude response of the front-end amplifier from sub-Hz frequencies up to the MHz range. The amplifier nominally operates between 0.5 Hz to 10 kHz,

and its mid-band gain is measured to be over 53 dB for all of the channels. The experimentally measured CMRR (Common-Mode Rejection Ratio) at 10 Hz and 1 kHz is 75.4 dB and 71.5 dB, respectively. Both the high-pass and low-pass poles are adjustable, with the maximum bandwidth of 0.01 Hz to 10 kHz. Figure 4(middle) shows the integrated input-referred noise, which is measured to be $4.7 \mu\text{V}_{\text{rms}}$ when integrated from 10 Hz to 5 kHz, and $3.7 \mu\text{V}_{\text{rms}}$ for 1 Hz to 100 Hz. The noise efficiency factor is measured to be 4.4 for the 5 kHz bandwidth.

Figure 4(bottom) shows the frequency spectrum of the FSK wireless transmitter on the communication board that operates at 915 MHz. The experimental measurements show a maximum of 500 kbps data rate at 10 m distance, that constitutes a relatively high-throughput link for mid-range communications to a receiver connected to a computer base-station.

For freely moving rodent epilepsy studies, the implantable system is powered inductively. The powering system consists of a two-layer network of 16 planar high-Q ($Q=129$) inductive transmitter coils placed under a non-conductive rat cage floor, and a small multi-layer flexible receiver coil, both shown in Figure 2(b). The voltage received by the receiver coil is rectified and multiple on-board LDOs (Low DropOut regulator) and DACs (Digital to Analog Converter) are utilized to generate different supply and bias voltages required for the SoC and external components on both boards. The receiver coil is a $20\text{mm} \times 20\text{mm}$ stack of four flexible two-layer PCBs for a total of eight layers. The flexibility allows to tailor-fit the coil to the shape of the implantation site. The inductive powering system operates at 1.5 MHz, and achieves an overall wireless power transfer efficiency of up to 40% at a maximum distance of 15 cm.

The system was validated in a 100-hour study of chronic treatment of temporal lobe epilepsy (rat model) with four Wistar rats. The rats were divided into two groups, a non-treatment (i.e., without stimulation) and a treatment group (i.e., with closed-loop stimulation). Fig. 5(a) shows an example of in vivo on-line real-time early seizure detection in the non-treatment group. In the treatment group the SoC was configured to automatically trigger a closed-loop current-mode stimulation for the purpose of suppressing upcoming seizures. Fig. 5(b) illustrates the SoC-triggered stimulation upon a seizure onset detection in the treatment group. A comparative analysis is given in Table I where this work demonstrates advanced functionality among recently published state-of-the-art miniaturized SoC-based neural interfaces.

IV. CONCLUSION

A 24-channel wireless and battery-less implantable micro-system has been presented. The system records neural signals at high spatial resolution, processes them on-chip to predict epileptic seizures and performs multi-channel responsive current-mode electrical stimulation upon a prediction. A wireless transmitter communicates recorded neural activity as well as signal processing results to a remote computer. Energy is provided to the system using magnetic induction. Small form factor, light weight, lack of wires and autonomous operation make the system excellent for chronic implantation. The system was fully characterized electronically and was validated on freely-moving animals with temporal lobe epilepsy.

TABLE I: State-of-the-art miniaturized neural recording and/or stimulation SoC-based systems

Specifications	[5] TBIOCAS 2011 Mohseni	[4] TBIOCAS 2010 Meng	[6] TBIOCAS 2013 Genov	[8] JSSC 2015 Rabaey	[9] TBIOCAS 2015 Chen	THIS WORK
Targeted Application	Intracortical Microstimulation	Neural Monitoring	Rat ECoG Recording & stim.	Neural Monitoring	Closed-loop Neurostimulation	Epileptic Seizure Detection and Control
Power Diss. (mW)	0.42	142	N/R	0.225	< 10	5.8
Size (cm ³)	3.6 × 1.3 × 0.6	3.8 × 3.8 × 5.1	3 × 2.2 × 1.5	N/R	3 × 2.5 × 2.5*	2 × 2 × 0.7
Weight (gr)	1.7	N/R	12	-	20	6
Number of Rec. Channels	4	32	256	64	8	24
SIGNAL PROCESSING	YES	NO	NO	NO	YES	YES
Closed-loop Detection	YES	-	-	NO	YES	YES
Method	Spike-Discriminator	-	-	-	Phase & Magnitude	Phase Synchrony
NEURAL STIMULATION	YES	NO	YES	NO	YES	YES
# of Stim. Channels	4	0	64	0	8	24
Current Range	125 μA	-	20-250 μA	-	82.5-229 μA	10 μA - 1mA
ENERGY SOURCE	Battery	Battery	Battery	Magnetic Induction	Magnetic Induction	Magnetic Induction
Battery Lifetime (hr)	24	33	10	-	-	-
Receiver Coil Type	-	-	-	1-layer flex	1-layer flex	8-layer flex
Coil Separation	-	-	-	1.6cm	6 mm	<15cm
WIRELESS COMM.	YES	YES	YES	YES	YES	YES
Modulation	FSK	FSK	ZigBee	OOK	ASK	FSK
Frequency	433MHz	3.9GHz	2.4GHz	300 MHz	10 MHz	915MHz
Range	1m	>20m	N/R	N/R	6 mm	10m
IN-VIVO RESULTS	YES	YES	YES	YES	YES	YES
Sensitivity (%)	-	-	-	-	-	88-96
Selectivity (%)	-	-	-	-	-	89-97

*: Estimated, -: Not Applicable, N/R: Not Reported

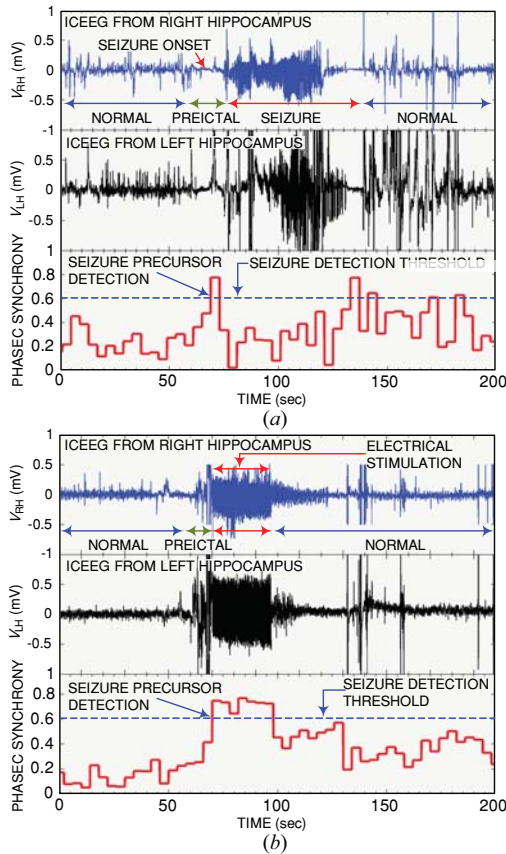


Fig. 5: Experimentally measured results: (a) an example of an early seizure detection in the non-treatment group, and (b) an example of a seizure abortion in the treatment group of rats.

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