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In Vitro and *In Vivo* Testing of a Wireless Multichannel Stimulating Telemetry Microsystem

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Abstract— **An inductively powered 64-site current microstimulating system, Interestim-2B, with a modular architecture and minimal number of off-chip components has been developed for neural prosthesis applications. Interestim-2B can generate any arbitrary current waveform and supports a variety of monopolar and bipolar stimulation protocols. A common analog line provides access to each site potential, and exhausts residual stimulus charges. *In situ* site impedance measurement capability helps indicating the defective sites in chronic stimulations. This paper also summarizes some of the *in vitro* and *in vivo* experimental results using a 16-site implant.**

Keywords— **Charge balancing, inductively powered, *in vitro*, *in vivo*, microstimulation, stimulation protocols, wireless**

I. Introduction

Real-time interfaces between the human nervous system and the external world through a class of implantable electronic devices, known as neural prostheses, can be used to restore sensory and motor functions lost through injury or disease [1]. Auditory and visual prostheses are two examples of the sensory function restoration based on neuronal electrical stimulation at different locations along the auditory and visual pathways. The common purpose of these sensory stimulating neural prostheses is to mimic the natural neurological function by establishing a direct or indirect link between an artificial sensor such as video camera or microphone, and those areas of the central nervous system (CNS) that organically receive information from their associated biological sensors such as eyes or ears [2], [3]. These are the main applications, considered in the design of Interestim-2B (IS-2B), a modular multichannel monolithic wireless microstimulation system. With minor modifications, IS-2B can also be used for direct brain stimulation to alleviate pain, control motor disorders such as Parkinson's disease, and reduce epileptic activity by stimulation of the cranial nerves, which are examples of motor function restoration.

Fig. 1 shows a simplified block diagram of the IS-2B wireless microstimulating system. The visual, auditory, or motor information is processed in a portable computer or PDA and converted to a series of digital commands that can generate a set of spatiotemporal stimulus pulses, based on the adopted stimulation protocol, at a 2D or 3D array of stimulating sites that is implanted in the targeted neural tissue. These commands are converted to a serial data bit-stream, frequency shift keyed (FSK-modulated), filtered, amplified, and transmitted across the skin through an inductive link between a pair of loosely coupled coils that set up a transformer. The IS-2B chip, which modular architecture is discussed in [4] and [5], extracts the serial data bit-stream and a constant frequency clock as well as a regulated 5V supply voltage form the received FSK carrier signal using its receiver and power conditioning blocks, respectively. A digital controller block converts the serial data bit-stream back into stimulating commands and controls digital to analog converters (DACs) and reference voltage/current generators to adjust the stimulus current amplitudes. It also controls current drivers that activate the selected stimulating sites by connecting them to V_{CC}, current source, *GND*, current sink, or common analog line (*CAL*) as explained in section II. Section III show some of the *in vitro* experimental results with a prototype implant that is fabricated based on the IS-2B ASIC. Section IV discusses

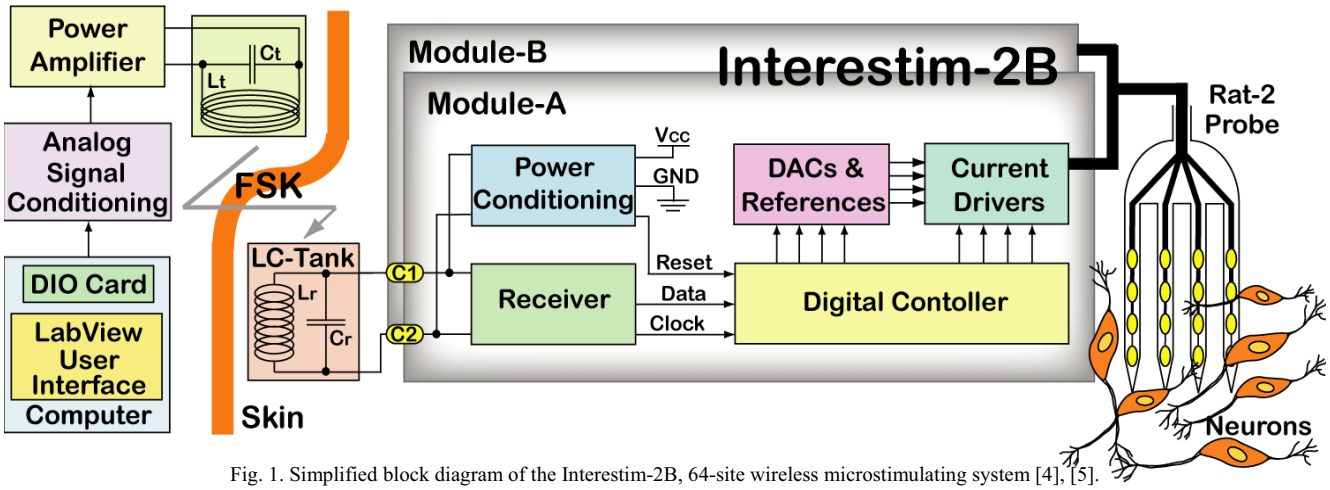


Fig. 1. Simplified block diagram of the Interestim-2B, 64-site wireless microstimulating system [4], [5].

an acute *in vivo* experiment with the IS-2B implant in the motor cortex, followed by concluding remarks in section V.

II. Stimulation Protocols

Every IS-2B chip consists of two identical 32-site modules each with a 6-bit user programmable address [5]. This would allow up to 64 modules to operate in parallel and drive up to 2048 stimulating sites. These modules can be all in a single implant or distributed in a network of stand-alone implants, powered by a single external coil. Each IS-2B module has eight current drivers (CD) that each of them is multiplexed between four stimulating sites [4]. Each CD_n (n = 0–7) is controlled by two specific status-bits (A_n, B_n) and two shared mode-bits (MD_0, MD_1) as shown in Fig. 2a.

The mode-bits can put the implant in four operating modes, which are summarized in Table 1A. Mode-0 is used to initialize the IS-2B by connecting the CD_n output to one of its four associated stimulating sites that is defined by the status-bits. Stimulation in Mode-1 occurs by connecting the sourcing site to a current source and the sinking site to *GND* in each phase of stimulation. For inter-phase or inter-pulse delay, both sites are switched to the high-z state and no current passes between them. In Mode-2 the sourcing site is connected to V_{CC}, while the sinking site is connected to a current sink. Since the currents passing through the sites that are connected to *GND* and V_{CC} are not controlled in modes 1 and 2, respectively, these modes are not suitable for multiple simultaneous active pairs. In these modes the current distribution among the active pairs, which depends on the site and tissue impedances, will be unknown and low impedance sites might exceed the safe charge injection limits. To solve this problem in Mode-3 both sourcing and sinking currents are controlled and therefore, this mode is safe for multiple simultaneous active sites at the expense of a slightly lower available headroom voltage compared to modes 1 and 2 [6].

In every stimulating mode (1–3), if $A_n = B_n = 1$, the selected site will be connected to *CAL*. *CAL* provides a mechanism to short out all the sites together after a burst of stimulating pulses, and cancels out (exhausts) the residual charges that might be accumulated at the sites due to small mismatches between sourcing and sinking stimulus currents [7]. Another function of the *CAL* is to provide access to the site potentials through implant test-points. The stimulating site potentials can be used to record the neural response to stimulus pulses, which indicates the effectiveness of stimulation and guides the user to place the microelectrode in a desired location and adjust stimulation parameters such as pulse amplitude, width, frequency, and delay. Site potential can also be used to measure the site and tissue impedances, as described in section III.B.

In addition to 32 stimulating sites, each IS-2B module has a reference electrode (*RE*), which can be connected to V_{CC}, *GND*, *CAL*, or stay at high-Z, as shown in Fig. 2b.

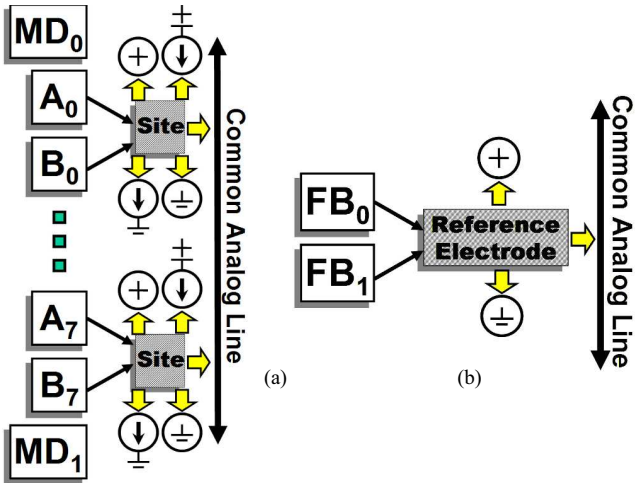


Fig. 2. (a) Stimulating sites and (b) reference electrode connections and control bits.

TABLE 1A
CURRENT DRIVER TRUTH TABLE

Mode	A_0	B_0	Site Status	Function
0	0	0	High-Z	Select Site0
	0	1	High-Z	Select Site1
	1	0	High-Z	Select Site2
	1	1	High-Z	Select Site3
1	0	0	High-Z	Passive
	0	1	Source	Bipolar stimulation between current source and *GND*
	1	0	*GND*	
	1	1	Source-*CAL*	Site imp. with current source
2	0	0	High-Z	Passive
	0	1	V_{CC}	Bipolar stimulation between V_{CC} and current sink
	1	0	Sink	
	1	1	Sink-*CAL*	Site-imp. with current sink
3	0	0	High-Z	Passive
	0	1	Source	Bipolar stimulation between current source and current sink
	1	0	Sink	
	1	1	*CAL*	Recording from site

TABLE 1B
REFERENCE ELECTRODE TRUTH TABLE

Mode	FB_1	FB_0	Ref. Electrode
0	0	0	High-Z
	0	1	V_{CC}
	1	0	*GND*
	1	1	*CAL*

Table 1B shows how the reference electrode is controlled by feedback-bits (FB_0, FB_1) in Mode-0. The main purpose of the *RE* is for monopolar stimulation. *RE* can be the implant metallic case or a large electrode far from the other sites. It should be noted that since the current design has a single supply (V_{CC} = 5 V), charge balancing in monopolar stimulation requires switching *RE* to V_{CC} and *GND* in cathodic and anodic phases of stimulation, respectively. An alternative option is to connect *RE* to an off-chip, low impedance virtual ground at $V_{CC}/2$ through *CAL*.

III. *In Vitro* Experiments

A prototype IS-2B implant, designed for acute wireless intracortical microstimulation and described in [4], is used in these experiments. This implant has a single 16-site micromachined silicon probe (called Rat-2) and each of its stimulating sites is directly connected to a CD output without multiplexing. Therefore, all 16 sites can be active simultaneously. The implant also provides access to V_{CC}, *GND*, *Clock*, and *Data* nodes as well as *CAL* for each of the two modules on the IS-2B chip through its test points. As a result, the IS-2B implant can be operated and tested both wirelessly and hardwired.

A. Pulsatile Stimulation

Fig. 3 shows part of the *in vitro* measurement setup. The iridium-coated, ~1000 μm^2 stimulating sites, which are connected to the implant via low access resistance platinum tracks on a silicon ribbon cable, were immersed in saline [4]. The average pre-stimulation site impedance at 1 kHz was measured 210 kΩ in magnitude and -76° in phase using HP4194 gain-phase analyzer. Biphasic bipolar stimulation pulses were applied to the Rat-2 probe before coating the implant, while monitoring site voltages and stimulus currents. The amount of charge that can be injected before saturating the CDs depends on the stimulus pulse width. For typical 0.1ms pulses, the stimulus current could be up to 130 µA on the average, which accounts for a charge injection density of 1300 $\mu C/cm^2$. This is within the safe limits for both iridium and iridium oxide (IrO_x), and no gas evolution was observed [8]. Fig. 4 shows sample 100 µA stimulus currents (upper traces) and differentially measured voltages (lower traces) across two active sites in Mode-3. The red traces show a charge-balanced pulse when both cathodic and anodic phases are 100 µs wide. The gray traces show the same pulse amplitude imbalanced by increasing the anodic width to 150 µs. The differential site voltage does not return to zero at the end of the anodic phase as opposed to the balanced case. Finally, the black traces show the same imbalanced situation, when both sites are connected to *CAL* at the end of the anodic phase. It can be seen that the residual charge is exhausted through *CAL* and the differential site voltage rapidly returns to zero.

B. In Situ Site Impedance Measurement

A useful feature of the IS-2B implant is its *in situ* stimulating site impedance measurement capability, which stems from the fact that the IS-2B chip can generate any arbitrary waveform, and every site potential is accessible through implant test points by electronically connecting the site under test (*SUT*) to *CAL*. For impedance measurement, 1 kHz sinusoidal current passes between the *SUT* and *RE*, while both are in saline. During the anodic half-cycle, the *SUT* is connected to a current source and *CAL* in Mode-1, and *RE* to *GND*. In the cathodic half-cycle the *SUT* is connected to a current sink and *CAL* in Mode-2, and *RE* to

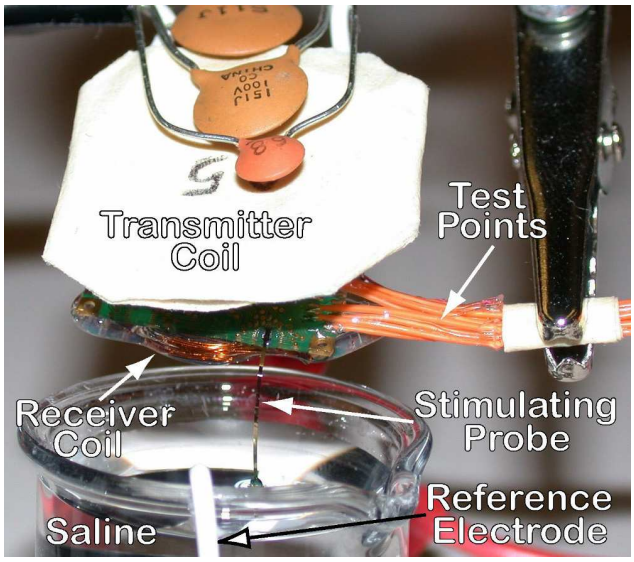


Fig. 3. Wireless and hardwired *in vitro* experiment setup.

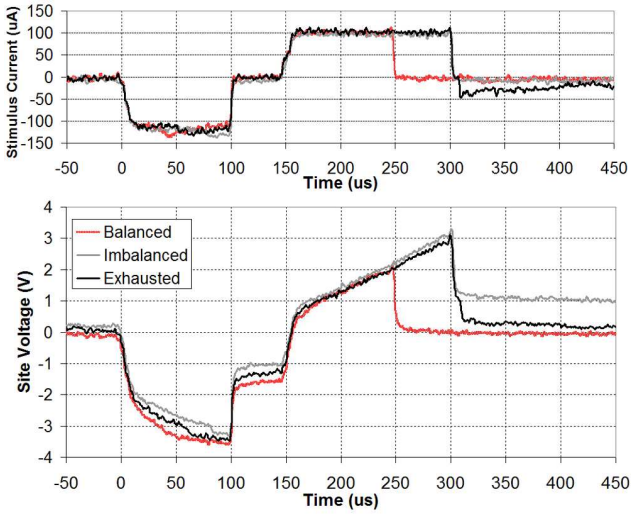
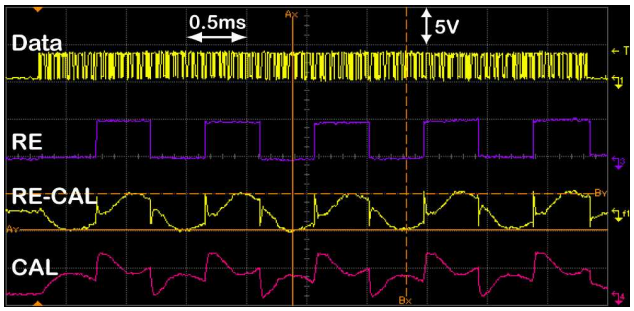
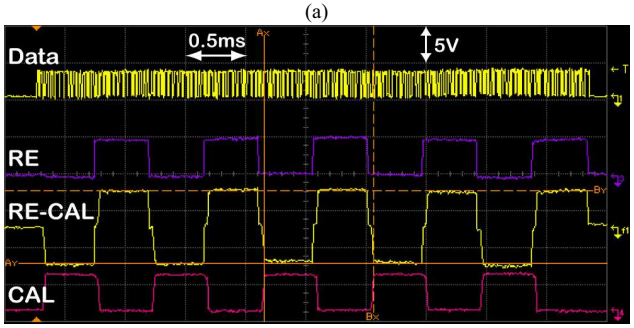


Fig. 4. Biphasic bipolar stimulus current and differentially measured voltage across a pair of active sites in saline.

V_{CC} (see Table 1). The resulting waveforms at *CAL* and *RE* are shown in Fig. 5. The magnitude of the *SUT* impedance can be calculated by dividing $V_{p\text{-}p}$(*RE-CAL*) (3rd trace from top) by peak to peak injected current, $I_{p\text{-}p}$. The average site impedance measured *in situ* was about 30 kΩ, which is much smaller than the pre-stimulation level. One reason is the site activation by stimulation, which forms iridium oxide films (IROF). The second reason is the non-linearity of the electrode-electrolyte impedance, which is amplitude dependent. The pre-stimulation impedance was measured at $V_{p\text{-}p}$ = 20 mV while *in situ* measurements were made at several volts. Post-stimulation measurement using HP4194 at $V_{p\text{-}p}$ = 1 V showed an average value of 45 kΩ, which is very close to the *in situ* results. In chronic experiments, it is more important to check for defective sites than measure the absolute site impedance values. Defects due to broken



(a)



(b)

Fig. 5. *In situ* site impedance measurement using IS-2B (a) normal site (b) high-impedance site.

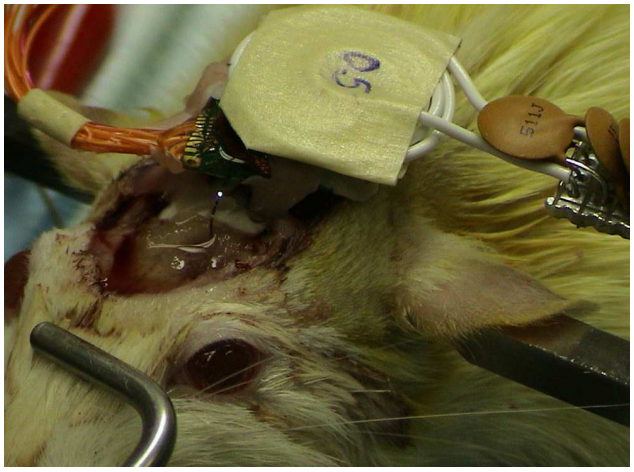


Fig. 6. Wireless *in vivo* stimulation in the rat motor cortex to wirelessly induce movements in the forelimb.

shanks, detached coatings, or leaky interconnect dielectrics can be detected by comparing their $V_{p\text{-}p}$ and waveforms with those of normal sites. In the first two occasions, the sine wave turns into a saturated square-wave as shown in Fig. 5b. Whereas in the 3rd case, $V_{p\text{-}p}$ reduces significantly.

IV. *In Vivo* Experiments

In order to assess the *in vivo* operation of the IS-2B implant, two male Sprague-Dawley rats (250-300 g) were acutely implanted with Rat-2 microelectrode arrays as described in [9]. Briefly, animals were anesthetized with a combination of Ketamine 75.0 mg/kg, Xylazine 7.5 mg/kg, and Acepromazine 1.5 mg/kg. The scalp was removed over the left hemisphere, and a 4 mm × 4 mm craniotomy was performed at 2.5 mm lateral and 2 mm anterior to bregma. The dura mater was removed and the tissue moistened with sterile saline. The motor cortex was approximately located stereotaxically and from vascular landmarks as identified in previous studies [10]. Subsequent location of the forelimb area of the primary motor cortex was determined using a single shank penetrating microelectrode. The IS-2B implant was fixed with dental acrylic on two screws mounted on the skull, and the Rat-2 microelectrode shanks were inserted below the surface of the cortex. The transmitter coil was held 5mm above the implant receiver coil, as shown in Fig. 6, and bursts of 20 bipolar, biphasic stimulus pulses at 200 Hz, 100–250 µs width/phase, and 10–100 µA amplitude were applied wirelessly to different site combinations. Meanwhile, the rat forelimb movements were independently observed by two of the authors.

V. Conclusions

Interestim-2B is an inductively powered 64-site current microstimulating system, which modular architecture is discussed in [4]. IS-2B stimulation protocols and some of the *in vitro* and *in vivo* experimental results are summarized in this paper. Additional *in vivo* experiments in motor cortex and midbrain auditory pathways are currently under way.

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