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Programmable Pulse Generator for Pain Relief Stimulation using Bioresorbable Electrodes

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***Abstract*—Neurostimulation therapies are often applied as an alternative method to pharmaceutical treatment for chronic pain relief. This paper demonstrates the design and implementation of a programmable Pulse Generator (PG) for analgesic nerve stimulation with 3 modes of operation: biphasic asymmetric, biphasic capacitor coupled, and monophasic Degradation On Command (DOC). The PG is implemented on 180nm CMOS technology and could generate up to $\pm$ 4mA current pulses in steps of 31μA (8-bit resolution) for pulse duration range of 1-256μs and stimulation frequency range of 16Hz-250kHz. During *in vitro* studies, capacitor-coupled biphasic stimulation provides electrode stability with only 5Ω impedance change for up to 14 million pulses. In the DOC mode, accelerated degradation of a bioresorbable electrode was observed after 24hrs of stimulation, when its impedance increased from about 100Ω to over 0.2MΩ at 500Hz. The compact, tunable and battery-powered pulse generator printed circuit board (PCB) shows promising results to perform *in vivo* animal studies for up to 30 hours of continuous stimulation with 26.4mW peak power consumption.**

***Index Terms*—Stimulator, Pulse Generator, Bioresorbable, Degradation On Command, Biphasic, Monophasic**

I. Introduction

According to the 2012 National Health Interview Survey, an estimated 11.2% of the U.S. adult population suffers from daily chronic pain [1]. Unfortunately, pharmaceutical treatments can lead to substance abuse and overdose, which has fueled the opioid epidemic. Therefore, alternative pain treatments, such as neurostimulation therapy via spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS), are often utilized [2]- [4]. Neurostimulation therapy is achieved by implanting one or more electrodes near a nerve or the spinal cord and applying an electrical stimulus to modulate the perception of pain. Nerve stimulation is a proven method of delivering long-term pain relief to patients without the use of pharmaceuticals. Further, long-term pain relief is often achieved even after cessation of stimulation, and chronic stimulation is not always required to treat chronic pain [3], [5]. Temporary implants, such as the Sprint PNS, have been developed to capitalize on this long-term analgesic effect.

This work presents the design and test results of a custom Application Specific Integrated Circuit (ASIC) chip for the external pulse generator (PG), with multiple modes of stimulation and programmable pulse features. The PG ASIC is integrated into a custom PCB for a standalone solution with a battery, power management, external clock and electrode connection port. Preliminary in-vitro studies using the compact PCB prototype demonstrate multiple modes for fast electrode degradation and long-term stimulation.

This paper is organized as follows. Section II provides a background of the challenges involved with neural stimulators for pain relief and introduces the proposed solution of specialized bioresorbable electrodes which need a custom PG for stimulation. Section III describes the circuit design and implementation of the custom PG with different modes of operation, including a dedicated mode for faster electrode degradation that is useful for bioresorbable electrodes. Section IV provides the measurement and benchmarking results of this work compared with the performance of other state-of-the-art stimulators. Section V demonstrates the efficacy of the presented work using two in-vitro studies. Section VI summarizes the contributions and possible future work.

II. Background

An electrical neural stimulator is a device that injects current into tissue via an electrode to modulate the action potentials of a group of neurons at the target site. Such devices are widely used for therapy, such as pain relief, epilepsy and Parkinson's disease. There are two major types of stimulators - constant voltage stimulators and constant current stimulators. Current stimulators are predominantly used for SCS and PNS due to their efficacy in stimulating nerves without saturating [6]- [8]. The standard of care for conventional SCS requires invasive surgical procedures and has a complication rate between 30-40% [9]- [10]. These complications include movement of the device in tissues, lead fracture, undesired sensations, and high-risk complications, such as surgical damage and infections.

Vanish Therapeutics, in collaboration with the University of Pittsburgh, is developing a fully non-surgical, bioresorbable PNS device to reduce complications and broaden the application of neurostimulation therapy. Resorbable metal lead and biodegradable insulation are used in a percutaneous PNS electrode design that can be delivered through non-surgical, ultrasound-guided insertion for effective analgesic stimulation. By replacing components of conventional designs with biodegradable materials, complications can be significantly reduced as seen with permanently-implanted stimulators or temporary devices that must be pulled out.

For the *in vivo* testing, a miniature Pulse Generator (PG) is needed that can be strapped to a rat's back. The pack consists of a PCB that will integrate the battery/power management

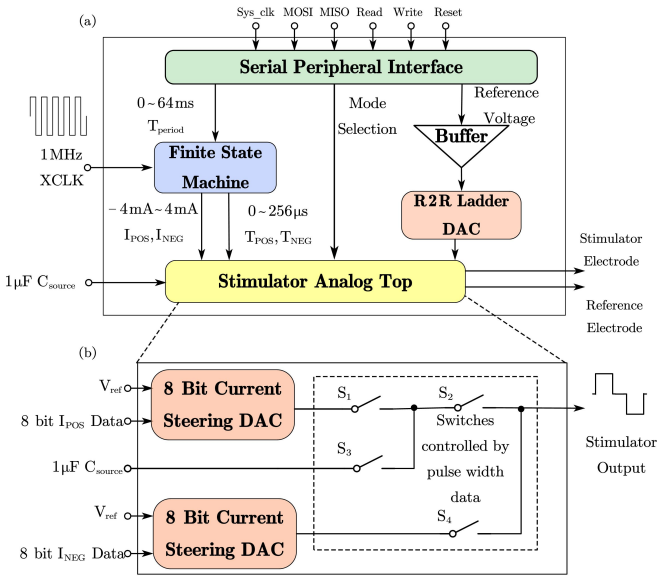

Fig. 1. Circuit block diagram of the pulse generator. (a) DUT block diagram. 6 IO pins are connected to Serial Peripheral Interface to transmit current pulse data. A 1MHz clock serves as reference clock. 1μF capacitor is used as coupling capacitor for biphasic capacitor coupled mode. (b) Stimulator analog top schematic. 4 MOSFET-based switches connect to 8-bit current steering DAC for bi-directional stimulation current pulse control.

module and a crystal oscillator, and a 2-way serial peripheral interface (SPI) block to communicate to a Host PC. The oscillator generates the reference clock, from which accurate timing signals are derived. The backpack will be connected to the Host PC to program or adjust the stimulation profile to maximize the longevity of electrode usage.

III. Pulse Generator Circuit Design

A custom integrated chip (IC) has been developed based on the PG architecture block diagram shown in Fig. 1. The IC provides the most vital PG functions as different modes of operation: analgesic stimulation and the Degradation On Command (DOC) waveform. The PG uses a current stimulator with programmable pulse amplitude, pulse width, and pulse period, which satisfy the specifications of clinically applied stimulations. The stimulation modes include biphasic (symmetric/asymmetric) pulses without capacitor coupling, biphasic capacitor-coupled (coupling in one phase only) pulses, and monophasic DOC pulses. To realize high-accuracy current control, a high-resolution digital-to-analog converter (DAC) is used [11]. In DOC mode, electrode degradation is accelerated by passing anodic current pulses with a programmable duty cycle. The DOC mode is particularly useful for bioresorbable electrodes since the electrodes can be degraded faster once the electrode impedance has reached a threshold where stimulation is not effective. By degradation on command, the electrodes can be safely replaced without the complications, such as infection, or metal residue in the tissues.

The pulse generator ASIC consists of several circuit blocks, as shown in Fig. 1a. The SPI block is used for 2-way digital communication to program (write and read) the internal register map. 16 internal registers, each 8-bit wide, are used to store the digital values for the stimulation mode of operation, pulse amplitude and pulse width in positive and negative phases, pulse period and inputs for bias voltage DACs (R-2R ladder structure). A digital finite state machine (FSM) block generates digital control signals TPOS, TNEG and TDOC based on the selected stimulation mode and internal register values to activate a switch matrix inside the analog top module as shown in Fig 1b. The analog top consists of two 8-bit segmented current steering DACs with the LSB 4bits binary coded and the MSB 4bits thermometer coded to minimize the integral and differential nonlinearity (INL and DNL) errors. The inputs to these DACs set the current pulse amplitude of the stimulator output in the positive and negative phases. Digital signals TPOS, TNEG and TDOC from the FSM control the switches (analog pass gates) to establish the pulse width in the positive and negative phases and the overall pulse period or stimulation frequency. The stimulation period can be tuned between 4μs to 64ms. Charge balancing was performed carefully so that minimal net charge is accumulated by balancing the total charge delivered and extracted in the positive and negative phases. Charge balancing is exempt during the DOC mode, where the residual charge delivered accelerates the degradation of the bioresorbable electrode.

IV. Measurement Results

The pulse generator PCB was validated in 2 stages. The first stage involved stimulating a known load impedance that models the bioresorbable lead and the underlying tissue using ideal and known values of resistors (R) and capacitors (C). With a resistive load of 1kΩ, three modes of stimulation were successfully validated with tunable pulse amplitude, width and duration, as shown in Fig. 2 for biphasic mode without capacitor coupling, Fig. 3 for biphasic mode with capacitor coupling in one phase, and DOC mode for Fig. 4. This setup establishes the efficiency, accuracy, and range of stimulation. In the second stage, the pulse generator was evaluated *in vitro*, as described in Section V.

The custom pulse generator ASIC was designed and fabricated in the TSMC 180nm process technology with a total chip area of $3mm^2$, as shown in Fig. 5. The chip was packaged and integrated into a custom compact PCB designed for the pulse generator, with dimensions 6cm x 4cm, as shown in Fig. 6. The PCB consists of a battery holder where two 3V coin cell batteries can be mounted to provide a 6V unregulated supply. The voltage regulator module can use this voltage to generate a 3.3V/5V regulated power supply for the stimulator device under test (DUT), the 1MHz reference clock source and the 1.5V voltage reference block. 6 IO pins are dedicated for SPI communication and 6 IO pins are designed to observe DUT internal state. An electrode connection port is provided in the PCB to connect to the stimulation electrode and the reference electrode biased at 1.5V. CR2032 battery with a capacity of 240mAh can support the PCB up to 30hr for the maximum current draw of 8mA. This PCB can fit onto a backpack design mounted on a rat for in-vivo studies.

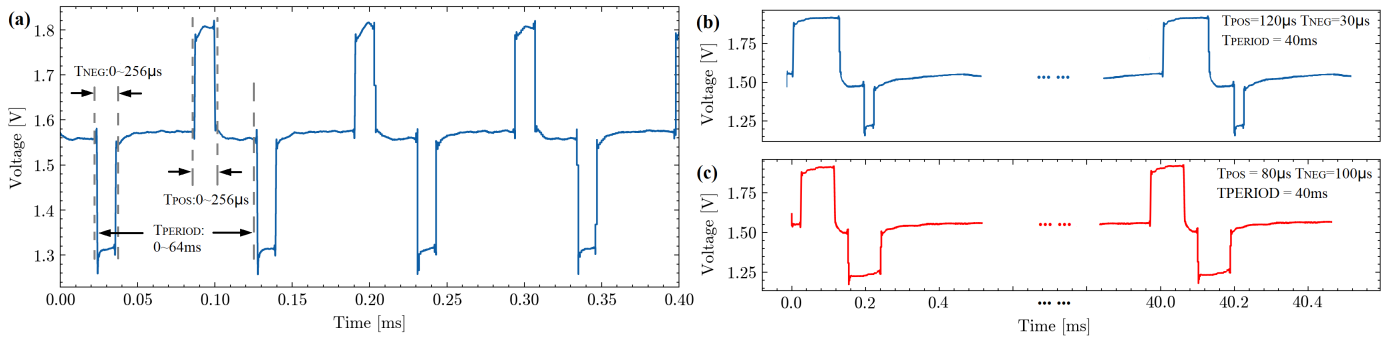

Fig. 2. Biphasic mode stimulator output without capacitor coupling. (a) Biphasic pulses with $T_{period} = 0.1ms$. Amplitude and pulse width in both phases set to 250μA and 12μs respectively. (b) Biphasic pulses with $T_{period} = 40ms$. T_{POS} and T_{NEG} are set to 120 μs and 30 μs respectively. Pulse amplitude is 400μA for both phases. (c) Biphasic pulses with same T_{period} and pulse amplitude of (b). T_{POS} and T_{NEG} are changed to 80μs and 100μs.

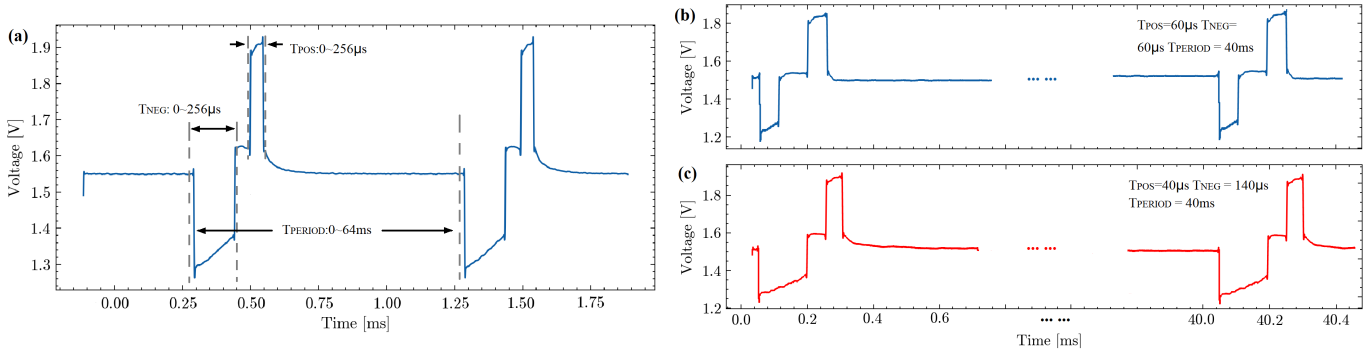

Fig. 3. Biphasic mode stimulator output with capacitor coupling in one phase. (a) Biphasic pulses with $T_{period} = 1ms$. Positive 350μA current pulse is set to 100μs and 200μA negative pulse is 300μs. (b) Biphasic pulse with $T_{period} = 40ms$. $T_{POS} = T_{NEG} = 60\mu s$. Pulse amplitude are set to 350μA and 200μA for positive and negative pulse.(c) Biphasic pulses with same T_{period} and pulse amplitude of (b). $T_{POS} = 40\mu s$ and $T_{NEG} = 140\mu s$.

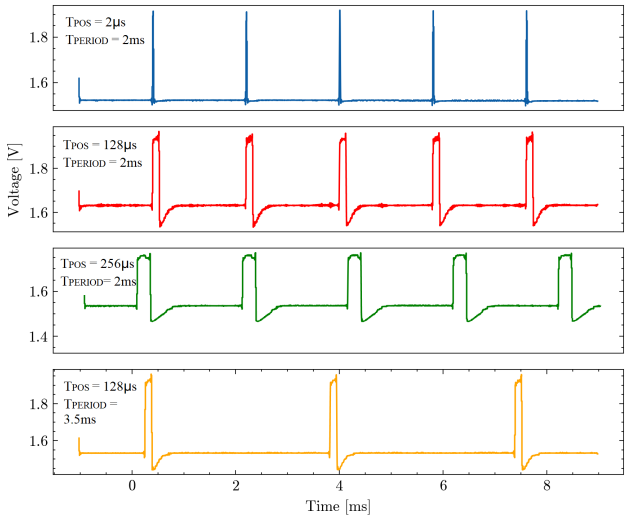

Fig. 4. DOC mode waveform with different pulse width and frequency. All pulses are set to 500μA. Blue, red and green pulse T_{period} are all set to 2ms. Blue: $T_{POS} = 2\mu s$. Red: $T_{POS} = 128\mu s$. Green: $T_{POS} = 256\mu s$. Yellow: $T_{period} = 3.5ms$ and $T_{POS} = 128\mu s$

V. Stimulator System *in vitro* Study

The DOC and biphasic stimulation modes were evaluated *in vitro* using a two-electrode setup in buffered artificial cerebrospinal fluid (aCSF, pH 7.4) solution, as shown in Fig. 7. The working electrode was an insulated degradable metal wire with 1cm exposed at the tip. A platinum foil was used as the counter/reference electrode. The solution was maintained at 37°C using an IsoTemp water pump system (HTP-1500, Adroit Medical Systems) and stirred at 150rpm using a small magnetic rod and stir plate. Electrochemical impedance spectroscopy (EIS) was used to measure changes to the working electrode indicative of degradation. Using the DOC mode (Fig. 4), the working electrode degraded substantially within 24hr of stimulation. During this time, the impedance increased from about 100Ω to over 0.2MΩ at 500Hz (Fig. 7B). When observing the wire, it was evident that the degradation progressed beyond the exposed tip and into the insulation (Fig7A). For the biphasic stimulation mode, the change in impedance when using two different waveforms was compared. The first waveform was an asymmetrical, biphasic square wave. The leading negative phase had an amplitude of 0.35mA and a pulse width of 50μs. The following positive phase had a smaller amplitude (0.14mA) but longer pulse width (125μs) to be charge-balanced. The second waveform was also charge-balanced and had a negative square wave as the leading phase followed by a positive capacitor-coupled (CC) phase. These waveforms were selected for their clinical relevance. The negative phase provides analgesic stimulation,

while the positive phase provides charge balancing. Reducing the amplitude of the positive phase through asymmetry or capacitor coupling will reduce the degradation of the electrode. After 14.4 million pulses, the biphasic stimulation caused the impedance to increase by 35Ω at 100Hz (Fig8A). However, the capacitor-coupled waveform caused an increase of only 5Ω at 100Hz (Fig8B). From these results, it is evident that capacitor-coupled stimulation provides improved electrode stability over asymmetrical, biphasic stimulation.

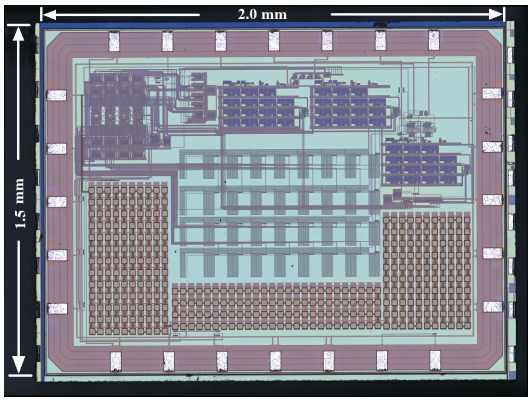

Fig. 5. Micro photo of die chip fabricated using TSMC 180nm technology.

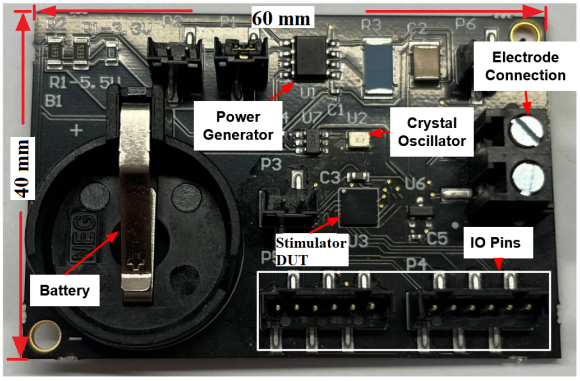

Fig. 6. Pulse generator PCB photo. Battery and voltage regulator provides DC supply to Stimulator DUT and the oscillator provides 1MHz clock. Electrode connection port is linked to DUT for bidirectional current pulse output.

VI. Conclusion

This paper demonstrates the design and implementation of a Pulse Generator for chronic pain relief stimulation with 3 modes of operation - biphasic with/without capacitor coupling and monophasic DOC. The PG has a programmable stimulation range of ± 4mA current with pulse width range from 1-256μs and 16Hz-4kHz stimulation frequency range. Target parameters for this work, derived from the commercial Sprint PNS device, are compared with other works and summarized in Table I. 24hrs of DOC mode *in vitro* test shows the working electrode has substantially degraded, as expected, from 100Ω to 0.2MΩ at 500Hz. On the other hand, capacitor-coupled biphasic stimulation provides sufficient electrode stability for up to 14 million pulses with only 5Ω change at 100Hz. The next step is to perform *in vivo* animal studies with the compact, tunable and battery-powered pulse generator.

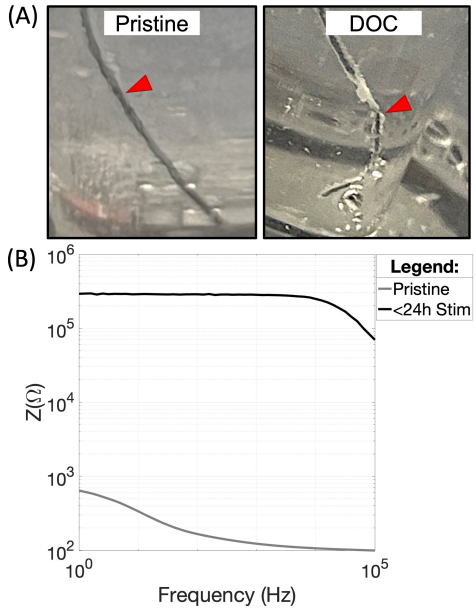

Fig. 7. (A) The red triangles indicate the location where the insulation begins on the working electrode before and after DOC. (B) The measured impedance of the working electrode before and after DOC.

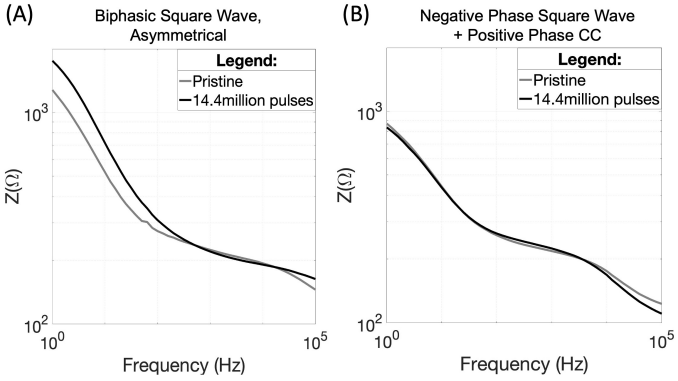

Fig. 8. The change in impedance of the degradable electrode after 14.4million pulses of stimulation with an asymmetrical biphasic square wave (A) and a positive phase capacitor-coupled (B).

TABLE I
Stimulator Performance Comparison Table

References	CICC'18 [12]	TBioCAS'22 [13]	TBME'18 [14]	This work
Process [nm]	65	180	40/HV180	180
Stimulation Modes	Biphasic	Biphasic	Biphasic, Arbitrary	Monophasic, Biphasic, DOC
Supply Voltage [V]	2.5	1.3,3.3	1.8, 1.2, 0.6	3.3
Stimulation Frequency Range [Hz]	0-2k+	15,50	1-250	16 - 250k
Maximum Stimulation Current [A]	400μ	750μ	5.1m	4m
Peak Power Consumption[W]	1.2m	2.6m	9.18m	26.4m

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