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ELECTRICAL INHIBITOR FOR TOCOLYSIS

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ABSTRACT

Preterm birth (*PTB*) *is one of the leading causes of neonatal morbidities and mortalities. Limited methods are available to physicians for mitigating PTB, thus posing an urgent need to develop effective methods for its prevention. In prior research, a benchtop electronic uterine control device* (*EUCD*) *was developed for tocolysis through injection of current pulses. However, the benchtop version is wall tethered and constrains patients to hospitals, i.e., it is unsuitable for deployment in out-patient or home settings. This paper focuses on the development of a mechatronics-based, low-cost, battery-powered, portable, and reproducible EUCD, which is suitable for use in home and clinical environments. The developed mechatronic version is validated for electrical performance with resistive load-tests, which indicate that the mechatronic device can generate current pulses similar to the existing benchtop EUCD. Furthermore, the signals generated from the device are evaluated for repeatability using coefficient of variation* (*CV*) *analysis and the results indicate that the mechatronic version can produce repeatable frequency* (*1—100Hz*), *amplitude* (*1—17mA*), *and pulse width* (*1—120ms*) *modulated current signals. An internet of medical things* (*IoMT*) *methodology is discussed to enable seamless transition of the developed device from a clinical environment to a home-based setting for remote use by the patients.*

Keywords: electrical stimulation, internet of medical things, medical device, preterm birth, pulse generator, tocolysis.

INTRODUCTION

PTB refers to childbirth before 37 weeks of gestational age. It is one of the leading causes for mortalities in children and mothers worldwide affecting over ~15 million children annually [1]. The overall yearly costs associated with creating awareness and hospitalization for PTB account for ~$26 billion only in the USA [1]. Moreover, the chronic and debilitating effects of neonatal complications associated with PTB require frequent hospitalization, which increases the costs associated with healthcare needs of neonates. Around 10% of the children born are PTBs [1,2], which poses an urgent need to develop effective strategies and medical devices to prevent PTBs.

The major reasons for PTB occurrences are: (*i*) spontaneous labor, (*ii*) rupture of membrane, and (*iii*) induced labor due to fetal/mother health [3]. Several studies have sought to understand the background and causes of PTB, however, limited evidence is available to narrow down potential indicators [4]. Some of the major precursors observed include, but are not limited to, family history and age of maternity [3]. Primary preventive interventions for preterm labor are administered to pregnant women in the form of nutritional supplements and education. Secondary interventions for women with PTB precursor include: (*i*) antibiotic treatment for infections, (*ii*) progesterone supplements, and (*iii*) cervical cerclage [5]. Finally, tertiary interventions for women posing an immediate risk of preterm labor consist of tocolytic (from the Greek words τόκος, childbirth or labor and λύσις, to loosen or stop) drugs [6]. While tocolytic drugs can delay the childbirth by up to 72 hours facilitating growth of the fetus, these drugs are toxic and are

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withdrawn after few dosage [7]. Because of maternal-fetal side-effects, there are no sustainable medical means of stopping premature labor; thus, there is an urgent need for biomedical devices that can effectively control premature uterine contractions.

During both normal and preterm labor, synchronous contractions of the uterine muscle fibers are responsible for generating enough force to deliver the fetus from the uterus. Prior literature substantiates the foci of electrical activity in the uterine smooth muscles that trigger the mechanical contractions of the uterus leading to the delivery of offspring in mammals [8].

Electrical current pulses can be utilized to inhibit uterine contractions in mammals [9]. Moreover, the study of [9] showed that uterine contractions resume upon the withdrawal of current pulses, thus demonstrating the reversible nature of the tocolytic effects induced by the electrical inhibition. Based on these animal studies, for current injection via the posterior vagina, a benchtop device was created that has proven to safely stabilize the uterine contractions in humans without damage to the fetus/mother [7]. In yet another study [10], weak current pulses were injected in several mammals (e.g., rabbits, rats, and humans) and it was found that these current pulses can generate tocolytic effects. However, due to the need for clinical trials to demonstrate the safety and efficacy, at present there are no approved devices on the market and no facilities currently offer electrical inhibition-based tocolysis.

To reinforce the goals of March of Dimes and to reduce the PTB occurrences [2], it is critical to deploy EUCD for tocolysis in various medical and non-medical settings. In our prior efforts, we have documented the development of a mechatronics-based low-cost prototype for grasp rehabilitation [11], which is currently being used at several patients' homes for grasp performance assessment and telemedicine [12]. In a similar spirit, this paper discusses the design and development of a mechatronics-based, low-cost prototype for electrical inhibition, which is capable of being rapidly prototyped for testing and deployment at multiple medical and non-medical facilities.

The existing benchtop device being used for electrical inhibition and tocolysis is described in Section 1.1. Drawing inspiration from the existing device, the mechatronic version is developed, and its design is documented in Section 1.2. The mechatronic version of the EUCD is tested with resistive loads to compare its performance with the existing device and the results are illustrated in Section 2.1. Section 2.2 discusses an IoMT approach to develop connected medical devices for electrical tocolysis, which utilizes the ubiquitous internet for telemonitoring. Finally, Section 3 offers some concluding remarks, describes the limitations of the current work, and suggests future directions to overcome some of these limitations for commercial viability of the developed device.

1. METHODS

1.1 Benchtop EUCD setup

The transvaginal application of a current pulse to the uterine muscle during the time of the contractions controls the frequency and strength of uterine contractions [7,10,13]. A manually operable, benchtop current pulse generator, with dimension 150mm × 150mm × 50mm is shown in Figure 1. It was utilized in [7,10,13] to regulate the frequency, amplitude, and pulse width of current pulse trains to the uterine muscle via an intra-vaginal catheter fitted with electrodes. The benchtop device can generate modulated current pulses with 1Hz to 100Hz frequency, 1ms to 120ms pulse width, and 1mA to 17mA current amplitude. By demonstrating resistive load test results for safety, this device received an investigational device exemption (IDE) from the Food and Drug Administration (FDA) in 2008 for testing with patients. Since receiving the approval, this device has been used by physicians in human clinical trials demonstrating its efficacy and safety in preventing preterm uterine contractions without any damage to the child or the mother [7].

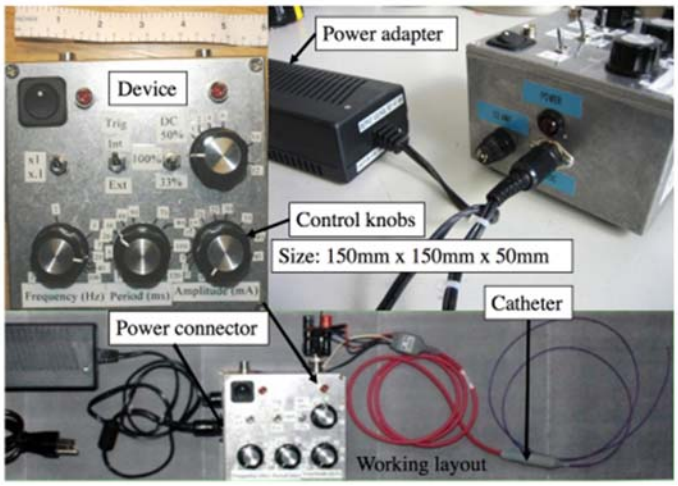

FIGURE 1: BENCHTOP EUCD AND WORKING LAYOUT

1.2 Mechatronic design of EUCD

A mechatronic version of the EUCD is built on a breadboard by utilizing off-the-shelf, low-cost electronic components for reproducibility. The current pulse generation functionality of the benchtop EUCD is achieved with (*i*) a 555 timer in the astable mode for frequency modulation, (*ii*) a 555 timer in the monostable mode for duty cycle modulation, and (*iii*) an LT3092 as a current source for current pulse generation. Suitable resistors, capacitors, and rotary potentiometers were chosen based on calculations to match the frequency, pulse width, and amplitude modulation ranges of the benchtop EUCD. Figure 2 shows the schematic diagram representing the signal flow of the electrical components in the mechatronic prototype. Figure 3 shows the solderless breadboard version of the mechatronic EUCD prototype used for testing.

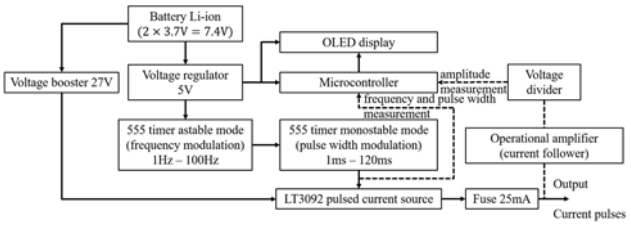

FIGURE 2: MECHATRONIC EUCD SCHEMATIC AND SIGNAL FLOW DIAGRAM

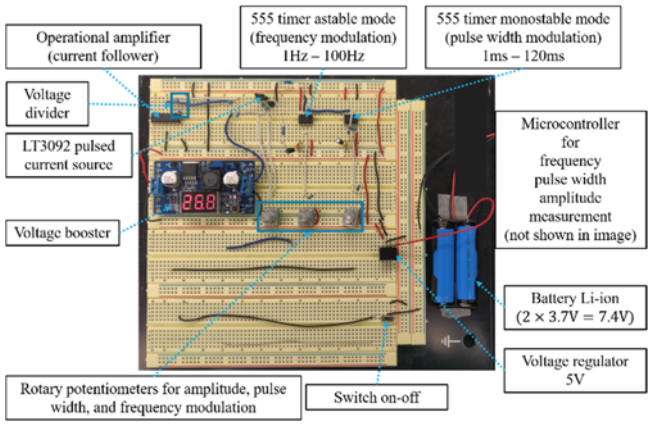

FIGURE 3: MECHATRONIC EUCD PROTOTYPED ON A SOLDERLESS BREADBOARD

Eagle CAD was used to design and replicate the breadboard circuit layout on a printed circuit board (PCB) of dimension 99mm × 55mm. The PCB was machined and the components were assembled on it to develop a low-cost reproducible version of the EUCD. A 3D printed enclosure was also designed to house the battery and PCB with electronics. A microcontroller was fitted on the PCB to sample the current pulse output through: (*i*) a current follower connected to a voltage divider that is tapped through an analog to digital converter pin for amplitude measurement and (*ii*) a digital input-output pin for pulse width and frequency measurement. The microcontroller was additionally connected to an OLED display where the measured frequency, pulse width, and amplitude of the generated current pulses are displayed for ease of use by the clinicians. The output current pulses are tapped through a Bayonet Neill-Concelman (BNC) cable output similar to the design of the benchtop EUCD of Section 1.1. Figure 4 shows the mechatronic prototype of the EUCD consisting of a 3D-printed enclosure (125mm × 65mm × 45mm) and the OLED display.

FIGURE 4: MECHATRONIC EUCD PROTOTYPE WITH AND OLED PLACED IN A 3D PRINTED ENCLOSURE

2. RESULTS AND DISCUSSION

2.1 Experimental testing, data collection, and results

Medical devices such as cardiac pacemakers require clearances prior to testing with subjects. An intuitive approach to ease the approval procedure and commence the use of the developed device in clinical environments is to prove that the developed device can generate current pulses comparable to any existing devices. In a similar vein, we utilized resistive loads to compare the signals obtained from the mechatronics *versus* benchtop EUCDs. Several resistive loads utilized in generating the results used for the FDA IDE certification of the benchtop device were used to perform electrical load tests on the mechatronic EUCD for comparison. Pico Scope 4224 with 12-bit resolution at 100-kilo samples per second was used for recording all the measurements on Picoscope6 software interface. The maximum voltage measurements for various resistive loads obtained from both the benchtop and mechatronic EUCDs are plotted in Figure 5. The plot indicates that the performance of the mechatronic EUCD is identical to the benchtop EUCD.

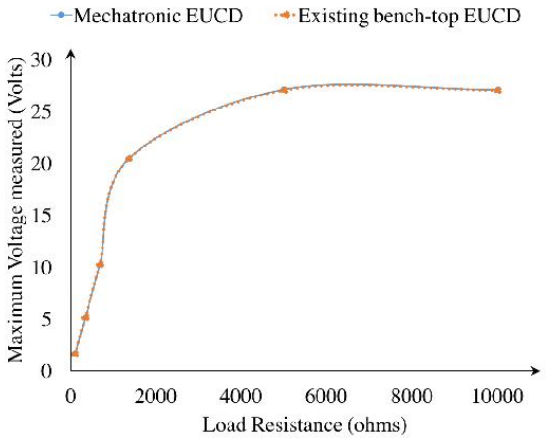

FIGURE 5: LOAD TEST RESULTS FROM THE BENCHTOP AND MECHATRONIC EUCD

Figure 6 illustrates the pulse width, frequency, and amplitude modulation achievable with the breadboard version of the mechatronic device. All the measurements were taken through a 50ms time window. From top to bottom, Figure 6 plots indicate a variation of frequency, pulse width, and amplitude with a 390Ω load. Table 1 lists the values of achieved pulse width, frequency, and amplitude measurements recorded in two iterations and three days for repeatability testing. The repeatability of the device is characterized using the coefficient of variation ($CV = \frac{\sigma}{\mu} \times 100$) [14], where μ and σ denote the mean and standard deviation, respectively. It was observed that the coefficient of variation is less than 1% for all the measured values of frequency, pulse width, and amplitude, except when the frequency is 1Hz for which the CV is less than 4%. The small values of the CV indicate that the newly developed mechatronic device produces repeatable current pulses.

TABLE 1: PULSE WIDTH, FREQUENCY, AND AMPLITUDE MODULATED CURRENT SIGNAL CONNECTED TO A 108Ω RESISTIVE LOAD FOR REPEATABILITY MEASUREMENT

Measuring parameter setting		Pulse width (ms) (10Hz-10mA)			Frequency (Hz) (10ms-10mA)			Amplitude (mA) (20ms-10Hz)		
		10	**40**	**80**	**1**	**25**	**90**	**5**	**10**	**15**
Day 1	Trial 1	9.92	40.05	80.01	1.00	25.09	90.07	5.04	10.09	15.07
	Trial 2	10.10	40.07	80.13	1.05	25.06	90.02	5.07	10.09	15.04
Day 2	Trial 1	10.05	39.89	80.05	1.07	25.01	90.08	5.09	10.03	15.09
	Trial 2	9.97	40.09	79.85	1.09	25.05	90.06	5.01	10.03	15.04
Day 3	Trial 1	10.02	40.02	79.94	0.99	25.18	89.88	5.10	10.06	15.04
	Trial 2	10.07	39.92	80.12	1.00	24.96	90.01	5.01	10.08	15.24
	μ	10.02	40.01	80.02	1.04	25.05	90.02	5.06	10.06	15.09
	σ	0.06	0.08	0.10	0.04	0.05	0.07	0.05	0.02	0.07
	CV	0.62	0.19	0.12	3.75	0.19	0.08	0.097	0.25	0.48

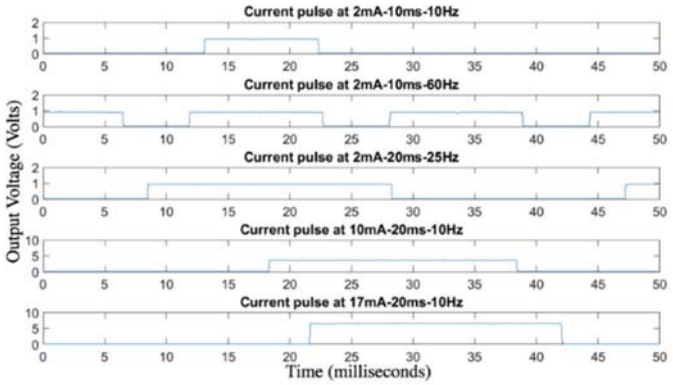

FIGURE 6: PULSE WIDTH, AMPLITUDE, AND FREQUENCY MODULATED SIGNAL OBTAINED FROM THE SOLDERLESS BREADBOARD VERSION OF THE DEVICE SAMPLED ON PICOSCOPE 4224 WITH 390Ω RESISTIVE LOAD

2.2 IoMT for at-home use of electrical tocolysis

The benchtop EUCD tethers patients to an external apparatus and requires them to be bed-ridden throughout the therapy process. The prospect of PTB is a stressful situation for mothers [15] and isolating them from their home and family to in-patient hospital facilities in such a situation can contribute to additional emotional toll on them. The development of mechatronic EUCD, documented in Section 1.2, provides an evidence that a low-cost, small foot-print, reproducible design of EUCD is feasible.

The future of medicine is being revolutionized by development of implantable bioelectronic devices [16]. Drawing insight from research literature, we propose the development of an insertable, smartphone-controllable, wirelessly chargeable, IoMT-based EUCD medical device that can be inserted by physicians into the patient's birth canal in a single out-patient visit. The inserted EUCD will generate current pulses to inhibit the preterm uterine contractions, whether in an out-patient clinical facility or at home, until the completion of the gestation period at which time the inserted EUCD will be removed allowing for a full term birth.

Miniaturization of electronics and advancements in computing and communication technologies have led to the development of connected devices and wireless IoMT solutions. Furthermore, advancements in information and communication technologies have improved the connectivity of medical devices with pervasive smartphones, tablets, and computers to communicate with the universal internet for real-time data transfer and user assistance. Such connected devices have been leveraged for myriad healthcare applications such as monitoring blood pressure, blood glucose level, etc. Recent advancements have showcased the development of an implantable cardiac pacemaker that connects with a smartphone application and improves the accessibility to patient follow-up information [17]. Inspired by the implantable and connected device from Medtronic, Inc., USA, among others, we will leverage smartphone and Bluetooth low energy (BLE) communication to connect with the insertable EUCD.

Wireless energy transmission has witnessed breakthrough developments in transferring power to implantable devices up to a depth of 10 cm inside the body [18]. Additionally, two unique smartphone interface designs are conceived to connect with and operate the insertable EUCD with different functionalities: (*i*) a patient user interface with device turn on-off feature and (*ii*) a clinician user interface with pulse width, frequency, and amplitude parameter adjustment features (Figure 7).

In prior efforts, we have utilized BLE and smartphones to develop medical devices for assessment of eye-contact behavior for children with autism spectrum disorder [19]. The mechatronic version of the medical device designed in Section 1.2 will require the following modifications for converting it to an IoMT insertable EUCD: (*i*) the rotary potentiometers will be replaced with programmable digital potentiometers for control from the microcontroller; (*ii*) the microcontroller will be upgraded with a BLE powered microcontroller for wireless connectivity with the smartphone; (*iii*) the microcontroller will require a programmable memory for storing the pulse characteristic information set by the clinician/physician for later usage; and (*iv*) the circuit board must be miniaturized to be insertable and to host a catheter terminal. A conceptual

schematic of the IoMT for electrical tocolysis application is represented in Figure 7. It illustrates a typical clinician-patient interaction in hospital setting. Following the insertion of the EUCD, patient seamlessly continues to receive electrical tocolytic therapy. Furthermore, connected smartphone application will alert concerned authorities during any emergency.

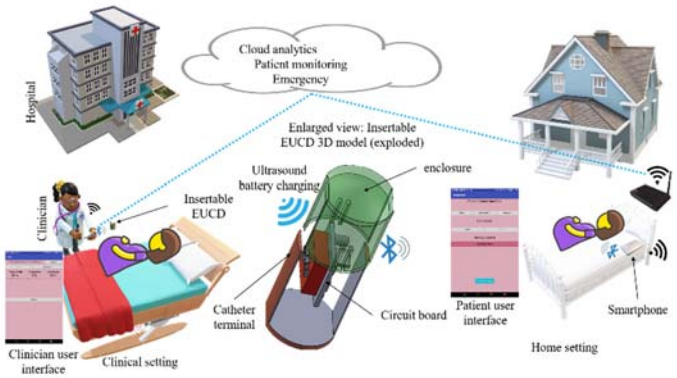

FIGURE 7: SCHEMATIC REPRESENTATION OF INSERTABLE EUCD FOR AT-HOME USE

3. CONCLUSION

In this paper, we presented the design, development, and testing of a mechatronics-based, low-cost, and reproducible EUCD for tocolysis. Furthermore, a PCB prototype with OLED display, easily usable by physicians, was created. The experimental testing for repeatability indicates that the developed EUCD can produce repeatable current pulses with accurate pulse width, amplitude, and frequency modulation. The device was also tested with various resistive loads (100Ω to 10,000Ω) and the results were found to be consistent with the existing benchtop EUCD. These testing results enable the benchtop device to be listed as a predicate for the FDA IDE certification of the mechatronic EUCD. Although the developed mechatronics EUCD functionalities are identical to the existing benchtop EUCD for electrical performance, further evaluation such as leakage test, mechanical load test, cybersecurity, and subject efficacy tests are required for commercial viability of the developed device. We believe that the developed EUCD falls under Class II (special controls) devices with an analogous approval procedure as a cardiac pacemaker, requiring extensive data-driven evidence to prove the efficacy for commercial viability. Our strategy is to gain FDA IDE for the mechatronic EUCD followed by the deployment of reproduced version at multiple medical centers. The efficacy results from the use of multiple devices will provide a secure pathway for commercialization of these devices. Our future work will also focus on adopting the framework of medical devices with connected technology by developing an at-home use EUCD for tocolysis.

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