

*Northwestern University*  
*Department of Biomedical Engineering*

# **Implantable Phrenic Nerve Stimulator System**

## **Final Report**

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## **EXECUTIVE SUMMARY**

Children with Congenital Central Hypoventilation Syndrome (CCHS) need advanced breathing support to improve their quality of life. While the current state-of-the-art device has sufficient functionality, it uses outdated technology and is far from ideal for use in small children. This report proposes a design for a digital multi-setting implantable phrenic nerve stimulator. The technical feasibility of the system has been demonstrated with preliminary power and device calculations and initial system testing.

The functions of the multi-setting wireless stimulator include:

- Phrenic nerve stimulation
- Wireless communication between the implant and the outside world
- Wireless power management

While the system consists of an external transmitter and an implantable component, this report focuses on the components of the implant:

- Pulse generator circuit for phrenic nerve stimulation
- Wireless receiver for data reception
- Wireless receiver for power management

This work reports on development and initial testing of each component of the multi-setting implantable phrenic nerve stimulator. The report also includes recommendations on future steps and strategies for demonstrating system reliability and feasibility of the functional prototype.

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## **1 INTRODUCTION**

Children with Congenital Central Hypoventilation Syndrome (CCHS) need advanced breathing support to improve their quality of life. A mutation in the PHOX2B gene results in lifelong complications in the autonomic nervous system, including problems with breathing, cardiovascular, temperature, bladder, and colon control. In severe cases, patients with CCHS need constant ventilatory support and heavily depend on either mechanical ventilators or diaphragm pacers to generate breath.<sup>1</sup>

The proposed digital multi-setting implantable phrenic nerve stimulator will offer patients:

- Increased mobility
- Expanded range of activity levels
- Ability to perform water activities

While the complete system will consist of an external transmitter and an implantable component, most of the recent work has been done on the components of the implant:

- Pulse generator circuit for phrenic nerve stimulation
- Wireless receiver for data reception
- Wireless receiver for power management

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<sup>1</sup> Weese-Mayer, D.E, E.M. Berry-Kravis, I. Ceccherini, T.G. Keens, D.A. Loghmanee, and H. Trang. “An Official ATS Clinical Policy Statement: Congenital Central Hypoventilation Syndrome.” (Sept 21, 2016).

## **2 BACKGROUND**

### **2.1 Congenital Central Hypoventilation Syndrome**

Congenital Central Hypoventilation Syndrome (CCHS) is characterized by alveolar hypoventilation and autonomic nervous system dysregulation. See Appendix A for defined abbreviations. Children are born with this disease have a mutation in the PHOX2B gene. This gene encodes a transcription factor that contributes to the development of the autonomic nervous system. A mutation in the PHOX2B gene affects breathing, cardiovascular, temperature, bladder, and colon control. The exact location and variation of the mutation usually determines the severity of the disease. In the most severe cases, patients need to receive continuous respiratory support either through mechanical ventilation, diaphragm pacing, or a combination of both.<sup>2</sup>

Individuals with CCHS have diminished tidal volume, the volume of air displaced between inhalation and exhalation.<sup>3</sup> This results in hypoventilation and individuals with CCHS have a constant risk of becoming hypoxic and hypercarbic. However, these individuals lack the perception of asphyxia and cannot voluntarily adjust their breathing.<sup>2</sup> Thus, they require respiratory support for at least some period of time each day.

### **2.2 Phrenic Nerve Physiology**

The phrenic nerve system consists of two nerves - one on the left and one on the right side of the neck. Impulses from the inspiratory center of the brain travel through both sides of the phrenic nerve system and trigger diaphragmatic contractions on their respective sides of the body.<sup>4</sup>

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<sup>2</sup> Weese-Mayer, D.E., E.M. Berry-Kravis, I. Ceccherini, T.G. Keens, D.A. Loghmanee, and H. Trang. "An Official ATS Clinical Policy Statement: Congenital Central Hypoventilation Syndrome." (Sept 21, 2016).

<sup>3</sup> MediLexicon. <http://www.medilexicon.com/medicaldictionary.php?t=99389> (Oct 15, 2016).

<sup>4</sup> Avery Biomedical Devices. "Phrenic Nerve Damage Causes and Treatment." (<http://wwwaverybiomedical.com/phrenic-nerve-damage-causes-and-treatments/>). (Oct 16, 2016).

Figure 1 shows the location of the phrenic nerve in the body. According to Chin et al, there are no data evaluating the lifelong effects of pacing the phrenic nerve.<sup>5</sup>

### 2.3 Phrenic Nerve Stimulators

Electrical stimulation of the phrenic nerve allows for ventilation through diaphragm pacing.<sup>3</sup>

Diaphragm pacing generates inspiration by using the child's diaphragm as a respiratory pump, creating a negative pressure gradient that draws oxygenated air into the lungs. Electrode stimulation of the phrenic nerve causes the diaphragm to contract, leading to inspiration.<sup>2</sup> A schematic of a current phrenic nerve stimulation system can be seen in Figure 2.

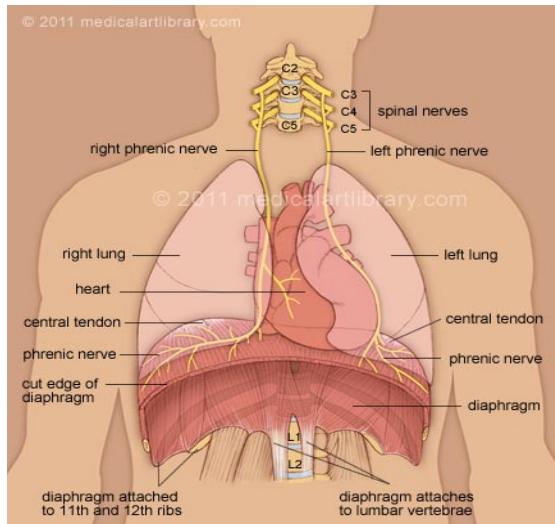


Figure 1: Phrenic nerve in body

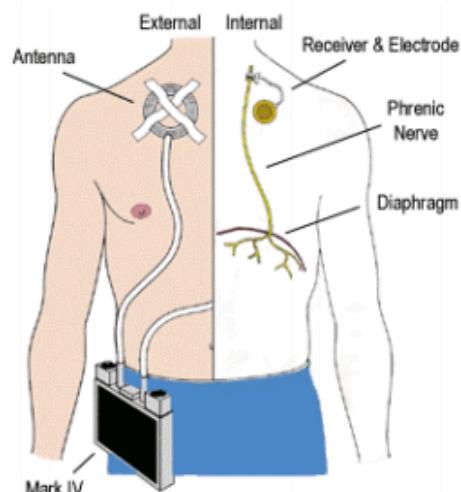


Figure 2: Phrenic nerve stimulation system

<sup>5</sup> Chin, A.C., D.B. Shaul, P.P. Patwari, T.G. Keens, A.S. Kenny, and D.E. Weese-Mayer. "Diaphragmatic Pacing in Infants and Children with Congenital Central Hypoventilation Syndrome." (Sept 21, 2016).

### ***2.3.1 Avery Breathing Pacemaker***

The Avery Breathing Pacemaker is the only current phrenic nerve stimulator with FDA approval.

The system includes the following components, shown in Figure 3:

- Implantable receiver connected to a specially-designed electrode
- External radio transmitter
- External radio antenna

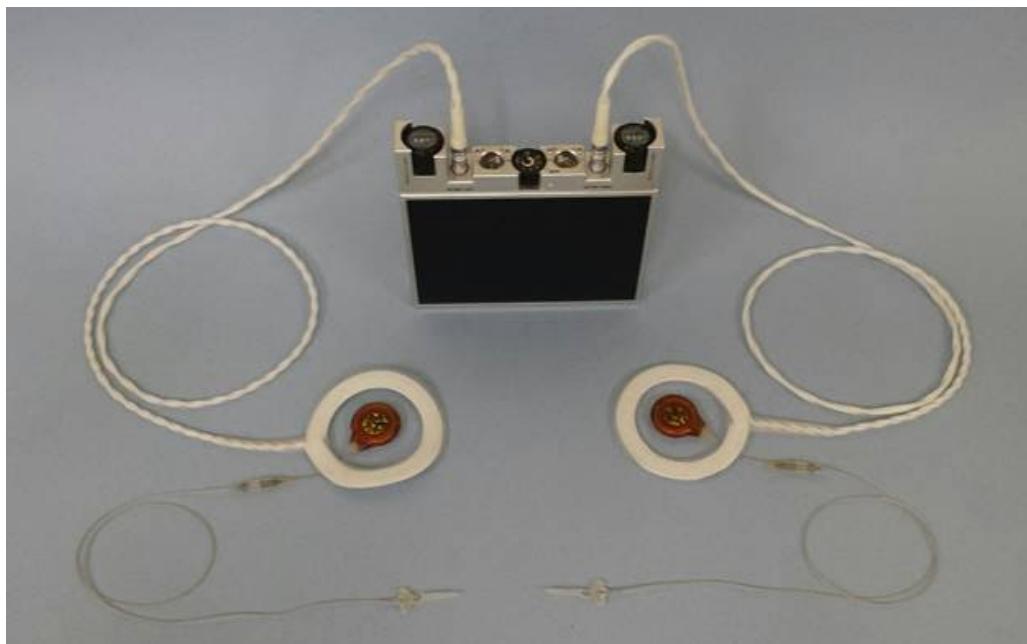


Figure 3: Avery Breathing Pacemaker components

#### ***2.3.1.1 Function***

The individual who uses this system undergoes an operation in which the receiver is implanted 5 cm below the clavicle, and the attached electrode partially encompasses the phrenic nerve. The voltage, current, frequency, and pulse width used to stimulate the phrenic nerve are calibrated by the individual's doctor. Usually, each patient who uses this technology is given two transmitters - one for periods of activity and one for rest.

When the device is in use, the antenna must be attached to the skin exactly above the implanted receiver. The antenna of the device must remain attached to the patient's body at all times in order for transmission to occur successfully.

The transmitter sends radio power pulses through the antenna to the receiver in the body, and the receiver converts this signal into electrical pulses that are transmitted to the phrenic nerve through the electrode. As a result of stimulation of the phrenic nerve, the diaphragm contracts and produces inspiration. After the patient's inspiratory period, the transmitter stops generating signals, which allows the diaphragm to relax and exhalation to occur.

#### *2.3.1.2 Advantages*

The advantages of the Avery Breathing Pacemaker compared to conventional positive pressure mechanical ventilators include:

- Greater patient mobility
- Use of 9 Volt batteries instead of proprietary rechargeable batteries
- Much lower weight - 2 lb vs. 15 lb mechanical ventilator
- Reduced costs - return on investments of 3-4 years and savings of \$18,000-\$30,000 per year thereafter<sup>6</sup>
- Reduced risks of pulmonary barotrauma and lower lobe atelectasis associated with positive pressure ventilation

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<sup>6</sup> Avery Biomedical (<http://www.averybiomedical.com/breathing-pacemakers/financial-advantages/>) (Oct. 23, 2016).

### 2.3.1.3 Drawbacks

The drawbacks of the Avery Breathing Pacemaker include:

- Weight and size of the transmitter box - weight = 2 lb, volume = 511 cm<sup>3</sup>. A small child must carry this weight while using the device
- Unintuitive user interface - the device has non-linear, poorly labeled dials (See Figure 4)
- Restricted mobility - antennae must be always attached to patient's body
- Required presence of the antennae on the body makes the system not waterproof
- System does not support multiple activity level settings, so each patient is forced to use two or three transmitters and mechanically switch between them when needed

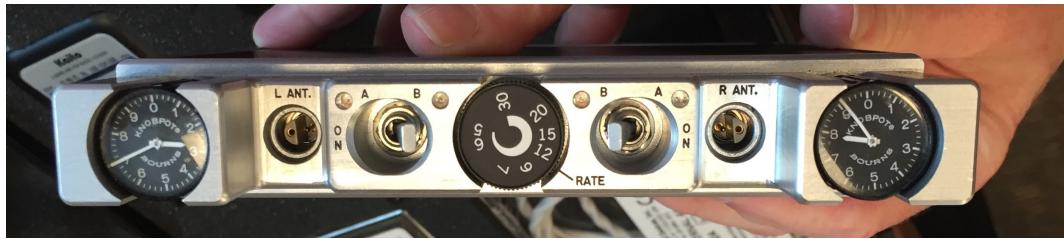


Figure 4: Avery Breathing Pacemaker transmitter

## 2.4 Device Needs

The multi-setting implantable phrenic nerve stimulator must fulfill the following needs.

- Reliable generation of breath
- Increased portability\*
- Reliable communication, processes, and pulse delivery
- Improved doctor control\*
- Intuitive user interface\*
- Support for more activity levels\*
- Ability to perform water activities

\*Compared to the current Avery Breathing Pacemaker device

## 2.5 Requirements

The requirements and specifications of the proposed device can be seen in Table 1.

Table 1: Requirements and Specifications

Requirement	Specification
Portability	< 2 lbs
Safety	Cannot heat up the surrounding tissue higher than +42 °C
Versatility (can support many activity levels)	How often user changes settings: how often physiological activity levels change
Ease of use	Training time required to learn
Reliability	Number of backup modes; Percentage of signals that are received and processed
Phrenic nerve stimulation	Frequency: 18 - 22 Hz Current: 2-10 mA Pulse Width: 150 - 300 µs Voltage: 3 - 5 V

### 3 PROPOSED DEVICE

#### 3.1 Device Concept

Various alternatives for the system were explored and can be seen in Appendix B. The concept of choice is a multi-setting implantable phrenic nerve stimulator, shown in Figure 5. The device will consist of a handheld external component that will allow the doctor and the patient to control the implant. The doctor will be able to change the breathing parameters, and the patient will be able to switch their own activity level settings (calibrated by the doctor) to adjust their breathing rate as needed. An example of the doctor and patient views of the external transmitter can be seen in Figure 6. The external transmitter will wirelessly communicate information and power to the implant to enable it to stimulate the phrenic nerve and ultimately generate breath.

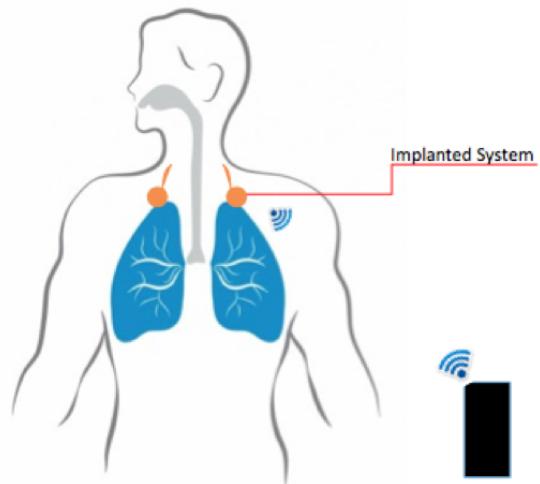


Figure 5: Proposed implant and external

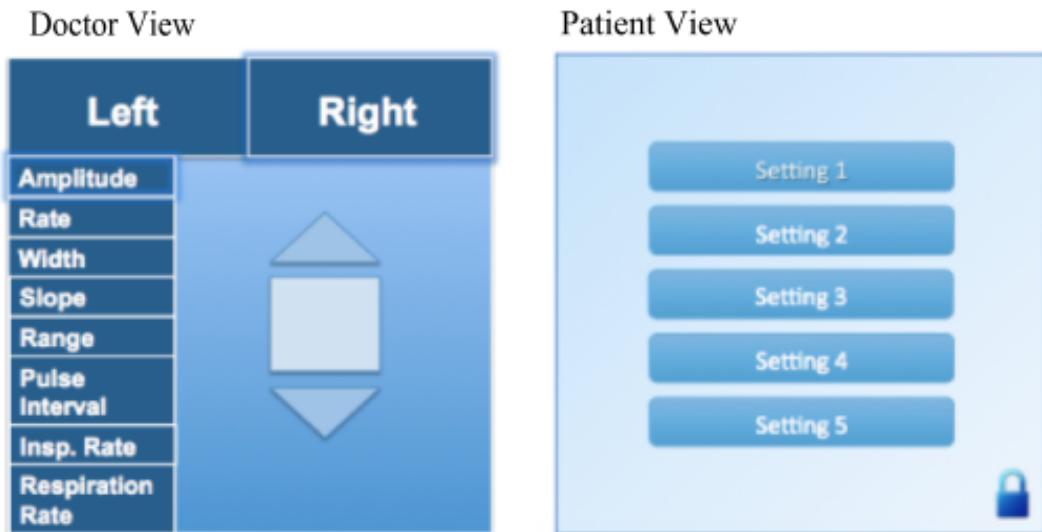


Figure 6: Doctor view and patient view of external transmitter

### 3.2 Implant Model

Preliminary ideation of the implantable component of the system can be seen in Figure 7. The implant will be placed in the chest cavity, while the charging and communication coil will be implanted subcutaneously. The circuitry of the device and a medical grade lithium ion battery will be housed within a hermetically sealed titanium case. The bipolar electrode connected to the circuit will partially encompass the phrenic nerve.

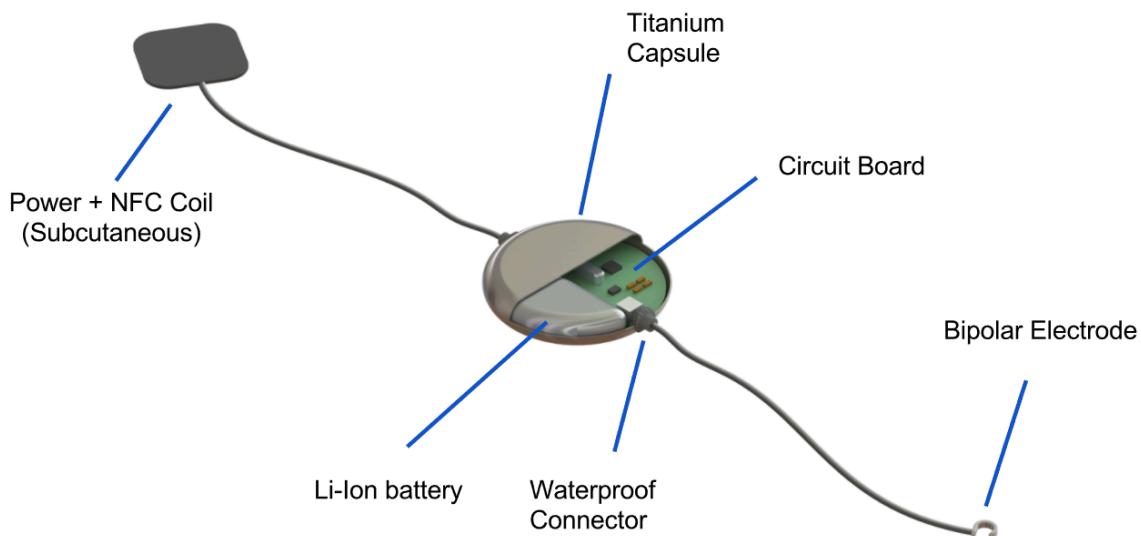


Figure 7: Proposed implant model

## 4 SYSTEM DESIGN

The functions of the overall multi-setting wireless stimulator system include:

- Phrenic nerve stimulation
- Wireless communication between the implant and the outside world
- Wireless power management

These can be subdivided into further functions, as depicted in Figure 8. These functions will be performed by a system comprised of an external and an internal component. The external component will house a digital display, a microcontroller, and radio and power transmitters. The

implant will house a microcontroller, radio and power receivers, a pulse generation circuit, and a bipolar stimulation electrode. Figure 9 shows the component diagram of the system.

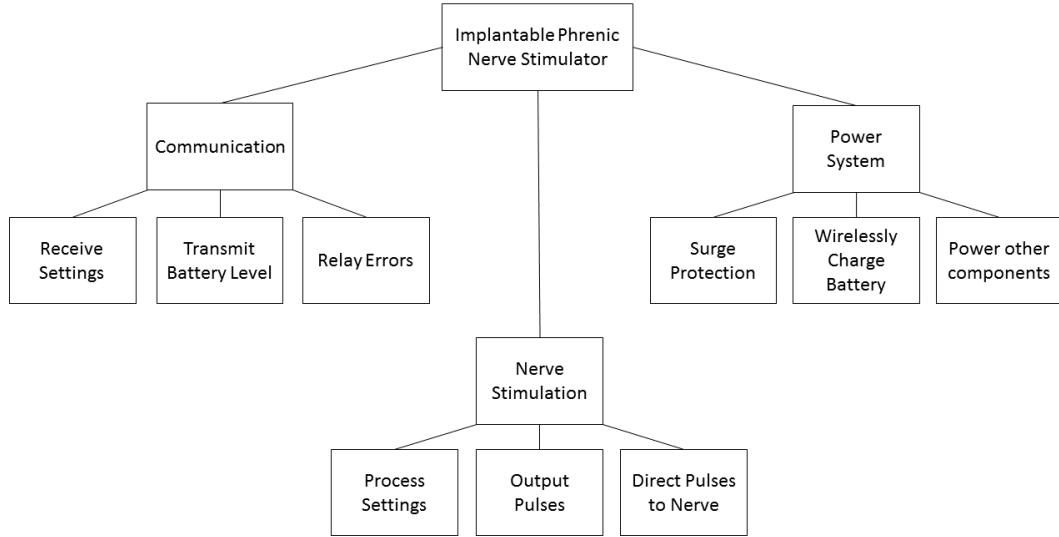


Figure 8: System Functionality Diagram

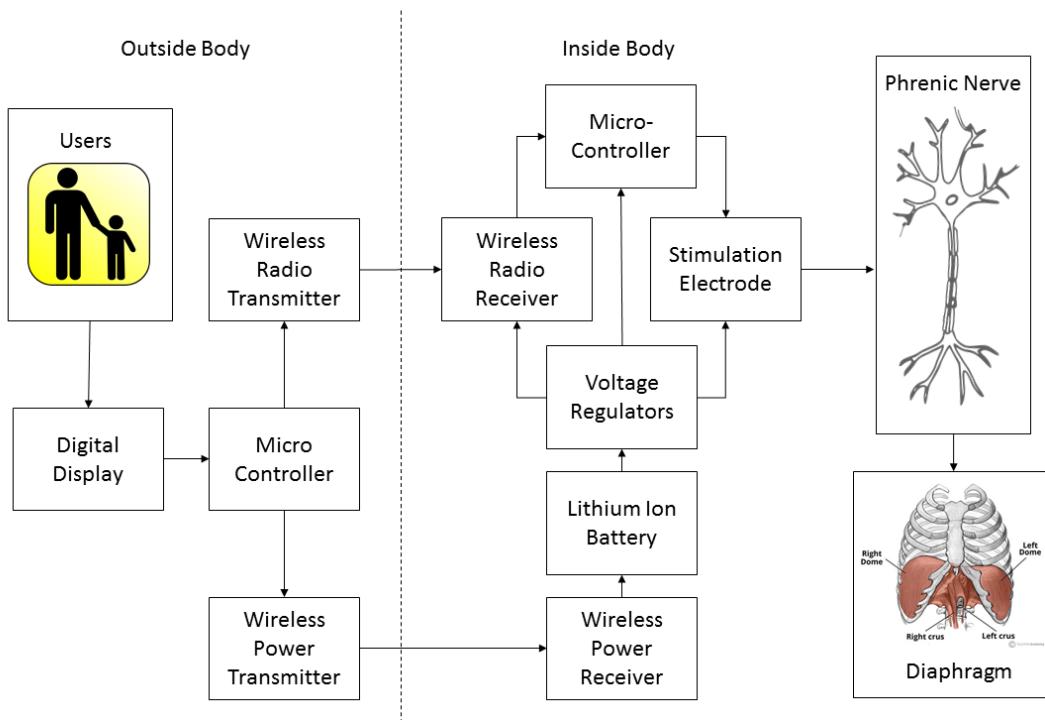


Figure 9: Component Diagram

## 5 TECHNICAL FEASIBILITY

### 5.1 System Feasibility

Two factors were taken into account when initially assessing the overall system feasibility. First, existing batteries must sustain device operations for at least a day of diaphragm pacing. Secondly, the system must perform reliably for multiple years. As this is an implantable system, surgical procedures to replace components must be minimized.

#### 5.1.1 Power Calculation

It was estimated that there would be three primary power draws: the microcontroller and communication chip operation, and the physical stimulation of the phrenic nerve. Using literature values for stimulation of the phrenic nerve and the datasheets for the electrical components, it was calculated that a fully charged lithium ion battery (LIR2450H, 3.7V, 190mAh) would be able to sustain the patient for just over a month before a recharge is necessary. The full power calculation can be seen in Appendix C.

#### 5.1.2 Device Life Calculation

The device life calculation used the datasheet for the Tenergy LIR2450H batteries.<sup>7</sup> Tenergy conducted maximum capacity retention testing up to 500 full charge and discharge cycles. Based on this testing, it was assumed that after 500 full charge/discharge cycles the battery would fail. Worst-case scenario capacity (about 70% capacity, from testing) for the entire duration of use was also assumed. Despite these worst-case scenario assumptions, the calculations seemed to indicate the battery would be adequate for decades of use. Real lithium ion batteries would almost certainly physically degrade in this time frame, and the electrical life of these batteries should be of no concern. The device life calculation can be seen in Appendix D.

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<sup>7</sup> “Tenergy Specification Approval Sheet”. ([http://www.all-battery.com/datasheet/34022\\_spec%20sheet.pdf](http://www.all-battery.com/datasheet/34022_spec%20sheet.pdf)) (2 Nov. 2016)

## 6 PULSE GENERATION

Referring back to Figure 9, the most important component of the system is the pulse generating circuit. The component consists of an analog circuit controlled by the microcontroller. For this, a low-power line of microcontrollers from STMicroelectronics, the STM8L line, was chosen. For ease of programming and debugging, the STM8L-DISCOVERY evaluation board from ST is being used. While reading this section, please refer to Appendix A for abbreviation definitions.

### 6.1 Analog Circuit

Nerve stimulation entails passing current through a nerve for a certain time. This current spike for some defined time is commonly known as a pulse. For the phrenic nerve, literature cites a requirement of 150  $\mu$ sec pulse duration, 0  $\mu$ A – 4.9 mA amplitude<sup>8</sup>, and 20 Hz frequency<sup>9</sup>.

Until recently, there have been two overarching ways of stimulating nerves: voltage controlled and current controlled stimulation. Both utilize the very familiar Ohm's Law:  $V = IR$ .

#### 6.1.1 Voltage Controlled Stimulation (VCS)

In voltage controlled stimulation, the circuit puts a certain voltage across the nerve, and because the nerve has a certain impedance (and, simplified even more, is just a resistive component R), the current passed through the nerve is simply  $I = V/R$ . The advantage of this method is the ease with which such a circuit can be controlled with a mere voltage. The downside is that if the resistance of the nerve would change - if the electrode shifts in place, for example - the circuit would provide much less current over the same amount of time, resulting in diminished

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<sup>8</sup> Hogan, James F., Hiroyuki Koda, and William W.L. Glenn. "Electrical Techniques for Stimulation of the Phrenic nerve to Pace the Diaphragm: Inductive Coupling and Battery Powered Total Implant in Asynchronous and Demand Modes." *Diaphragm Stimulation Symposium at Cardiostim* 1988.

<sup>9</sup> Agnew, W.F. and McCreery, D.B. "Considerations for Safety with Chronically Implanted Nerve Electrodes." *Epilepsia* 31(2) 1990. (Nov 9, 2016).

stimulation. In short, VCS offers energy efficiency and ease of implementation, while having lack of control over the amount of charge injected into the tissue.<sup>10</sup>

### ***6.1.2 Current Controlled Stimulation (CCS)***

Current controlled stimulation functions inversely. The circuit provides a course of constant current over constant time through the nerve, which provides a great deal of certainty about the strength of stimulation. However, if, again, the resistance of the nerve suddenly increases, the circuit must be able to supply extra voltage to the tissue to pass the same amount of current through the nerve. In short, CCS provides a safe and reliable source of charge, but is very energy inefficient compared to VCS.<sup>8</sup>

### ***6.1.3 Charge Injection into the Nerve***

However, what really matters in stimulation is the amount of charge injected into the nerve. Charge above a certain threshold causes cell membrane depolarization. Electric charge can be calculated by using the equation  $Q = It$ , where  $Q$  is electric charge passed through the nerve,  $I$  is the current passed through the nerve, and  $t$  is the amount of time over which this current was passed. However, there are ways of controlling injected charge other than voltage and current controlled stimulation.

### ***6.1.4 Voltage Controlled Capacitive Discharge (VCCD)/ Switched Capacitor Stimulation (SCS)***

The team has decided on an alternative method of nerve stimulation - voltage controlled capacitive discharge (VCCD) method. Instead of having appropriate current and voltage ready for stimulation and then “opening the floodgates” for the current to pass through the nerve for a time  $t$  (as in voltage- and current-controlled stimulation), appropriate amount of electric charge

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<sup>10</sup> Simpson, Jim, and Maysam Ghovanloo. "An Experimental Study of Voltage, Current, and Charge Controlled Stimulation Front-End Circuitry." *2007 IEEE International Symposium on Circuits and Systems*, 2007. doi:10.1109/iscas.2007.378401.

can be stored in capacitors until it is time for a pulse, and then it can be quickly discharged into the fluid surrounding the nerve, causing membrane depolarization.<sup>11</sup> The overarching equation behind this method is the simple capacitor equation  $C = Q/V, Q = CV$ . By knowing the capacitance of the circuit ( $C$ ) and charging it to full capacitance at voltage V, one can know precisely how much charge there is stored in the circuit. Then, these capacitors are isolated from the rest of the circuit and discharged into the tissue quickly. Assuming full discharge, one can calculate precisely how much charge ended up in the biological tissue. Studies show that VCCD/SCS provides the ease of implementation of VCS, while having the reliability compared to CCS. Energy efficiency of VCCD/SCS is between VCS and CCS.<sup>12</sup> A biphasic bilateral flow of equal charges would minimize nerve tissue damage under long-term stimulus.<sup>13</sup>

Figure 10 shows an example circuit that the team has experimented with in recent weeks, taken from *Design of Cardiac Pacemakers* by John G. Webster.

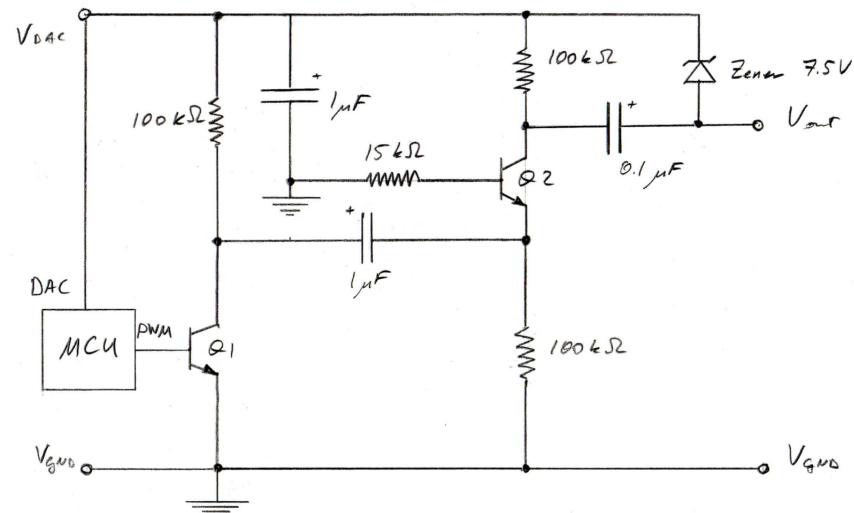


Figure 10: Switched Capacitor Circuit

<sup>11</sup> Rosellini, Will M., Paul B. Yoo, Navzer Engineer, Scott Armstrong, Richard L. Weiner, Chester Burress, and Larry Cauller. "A Voltage-Controlled Capacitive Discharge Method for Electrical Activation of Peripheral Nerves." *Neuromodulation: Technology at the Neural Interface* 14, no. 6 (2011): 493-500. doi:10.1111/j.1525-1403.2011.00398.x.

<sup>12</sup> Simpson, Jim, and Maysam Ghovanloo. "An Experimental Study of Voltage, Current, and Charge Controlled Stimulation Front-End Circuitry." *2007 IEEE International Symposium on Circuits and Systems*, 2007. doi:10.1109/iscas.2007.378401.

<sup>13</sup> Talonen, P., Malmivuo J., Baer, G., Markkula, H., Häkkinen, V. "Transcutaneous, dual channel phrenic nerve stimulator for diaphragm pacing". *Medical and Biological Engineering and Computing*. 1983. (Oct. 11, 2016).

The microcontroller provides two signals - an analog voltage level via the Digital-to-Analog Converter unit (DAC), and a time signal for pulsing via Pulse Width Modulator unit (PWM). When resting, the circuit capacitors are fully charged up to  $V_{DAC}$ . Then, the microcontroller passes a positive voltage to Q1 and then goes low at the end of the pulse. This results in a discharge of the capacitor circuit into the tissue.

## 6.2 Microcontroller Program

Figure 11 shows a simplified diagram of the microcontroller pulse generation program. There are two main operational states - inspiration (active pulsing, shown in blue) and expiration (low power sleep, shown in gray).

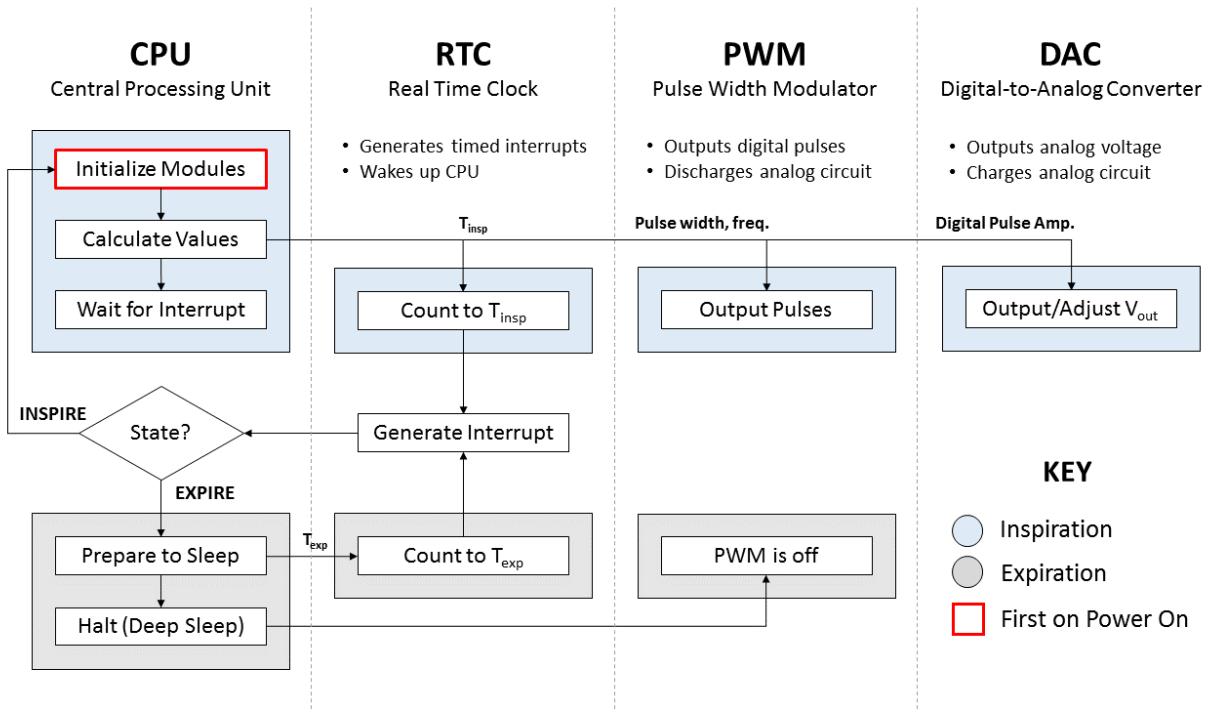


Figure 11: Microcontroller Program (Pulse Generator Only)

When the device is powered on, it initializes the necessary modules - Real Time Clock (RTC), Pulse Width Modulator (PWM) timed by a hardware timer TIM1, and Digital-to-Analog

Converter (DAC) unit. It then calculates certain values based on (so far) hard-coded physiological values of the patient, such as Breaths-per-Minute (BPM), Inspiration-to-Expiration ratio (I:E Ratio), and pulse width, amplitude, and frequency. It then passes those calculated values to functions that set up each module. Each module is then powered on for  $T_{insp}$  (inspiration time). After  $T_{insp}$ , RTC generates an interrupt, which causes the device to shut each module down and go to low power sleep for  $T_{exp}$  (expiration time). After that time, RTC generates another interrupt; this time, the device wakes up, and performs the initialization, calculations, and enabling again.

Next steps on this front, apart from changing the program based on improvements in the analog circuit, would be to implement I2C communication with an NFC tag that will be a link to the external reader and patient's choice of activity level settings.

## 7 COMMUNICATION

Near Field Communication (NFC) was determined to be the most fitting method for the purposes of the device, see Appendix E for other communication technologies that were explored. It not only performs at low power consumption values, but it also uses a widely available 13.56 MHz frequency, which complies with Federal Communications Commission (FCC) regulations.<sup>14</sup> It has been shown that the 13.56 MHz frequency band has minimal interaction with human tissues.<sup>15</sup> This technology is also fairly simple to implement in conjunction with a microcontroller. For instance, an example NFC tag IC from STMicroelectronics, the M24LR04E-R, only has eight pins to interface, two of which are used for power (positive

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<sup>14</sup> Philipp Gutruf (Postdoctoral Research Associate in the John Rogers Group) in discussion with authors, (Oct 27, 2016).

<sup>15</sup> Freudenthal, E., D. Herrera, F. Kautz, C. Natividad, A. Ogrey, J. Sipla, A. Sosa, C. Betancourt, and L. Estevez. "Suitability of NFC for Medical Device Communication and Power Delivery." (<http://robust.cs.utep.edu/freudent/homepage/pubs/2007-dembs-rfid-implant.pdf>) (Nov 25, 2016).

voltage and ground), one is used for extra energy output, and one pin acts as a signaling pin for indicating when RF communication occurs.

At this point in time, an NFC reader/tag kit from ST called M24LR-DISCOVERY has been explored and tested. It comes with a pre-programmed NFC reader board and a software Graphical User Interface (GUI), through which it is very easy to write and read data to and from the M24LR04E-R tag. The tag side is a development board that contains a Liquid Crystal Display (LCD) screen, a temperature sensor, and other components (see Figure 12). When the tag gets within the power transmission field of the reader, it powers up wirelessly and displays its stored data on the glass LCD.



Figure 12: NFC Reader and Tag

While communication between the reader and the tag through ST's GUI has been achieved, the ability for the STM8L152 microcontroller to read from the tag's EEPROM memory via I2C communication has not yet been programmed. However, source code has been located and obtained to do this - all that remains is to sift through code examples and compile code that would run in conjunction with the pulse generation program.

While the communication has not yet been fully incorporated into the system, the feasibility of this approach can be seen in widespread applications of the NFC technology in medical implantables.

## **7.1 John Roger's Lab at Northwestern University**

John Roger's lab at Northwestern has used NFC for wireless power transfer and data communication in optoelectronic systems for measures of physiological properties.<sup>16</sup> Roger's work to develop conformal skin-mounted measurement platforms uses NFC technology to wirelessly transmit data with sufficient bandwidths. NFC is also used in this application to supply sufficient power to operate components of the optoelectronic system, including, light emitting diodes, photodetector, and signal conditioning electronics.<sup>17</sup>

## **7.2 Pacemakers**

Pacemakers use NFC technology to transfer data bidirectionally to/from the pacemaker electronics. A small coil in the metal housing of the pacemaker transmits programming information from the pacemaker to an external programming coil.<sup>18</sup> Because pacemakers and the proposed system have very similar requirements and features, NFC technology is more than feasible in this application.

## **7.3 Testing**

The communication between the NFC reader and the NFC tag has been tested across pork skin and titanium. The communication signal did not diminish across pork skin; however, it was completely absorbed by a titanium sheet (0.018" thick, Grade 5, 6Al-4V), which was expected.

See Appendix F for further details.

Once the device is fully prototyped, we will test efficacy of communication across skin vs. air and distance at which communication starts to lose reliability

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<sup>16</sup> Kim, J., G.A. Salvatore, H. Araki, A.M. Chiarelli, Z. Xie, A. Banks, X. Sheng, Y. Liu, J.W. Lee, K-I. Jang, S.Y. Heo, K. Cho, H. Luo, B. Zimmerman, J. Kim, L. Yan, X. Feng, S. Xu, M. Fabiani, G. Gratton, Y. Huang, U. Paik, and J.A. Rogers. "Battery-free, stretchable optoelectronic systems for wireless optical characterization of the skin." *Sci. Adv.* 2016. (Oct 26, 2016).

<sup>17</sup> Kim, J., P. Gutruf, A.M. Chiarelli, S.Y. Heo, K. Cho, Z. Xie, A. Banks, S. Han, K-I Jang, J.W. Lee, K-T Lee, X. Feng, Y. Huang, M. Fabiani, G. Gratton, U. Paik, and J.A. Rogers. "Miniaturized battery-free wireless pulse oximeter system." *Advanced Functional Materials*. Manuscript Draft. (Oct 26, 2016).

<sup>18</sup> Yoo, H.J., and C. van Hoof. "Bio-Medical CMOS ICs." (Nov 26, 2016).

## **8 CHARGING**

To demonstrate the feasibility of wireless charging, the evaluation board STEVAL-ISB039V1 was tested across various materials. This evaluation board is designed to charge lithium ion batteries using the Qi wireless charging protocol with a power output of 1 W at short distances (several millimeters). See Appendix G for the other charging standards explored.

### **8.1 Interference Testing**

While staying within a several millimeter effective range, various materials were placed in between the transmitter and receiver coils to check for interference. It was generally found that organic materials of sufficient thinness, specifically pork skin, did not impede any power transfer (See Appendix H). In contrast, titanium completely blocked the power transmission signal (See Appendix I). This means that the receiver coil would have to be outside of any titanium casing, but that it otherwise is feasible to wirelessly charge a battery via this method in an implant, so long as the receiver and transmitter are within the transmission distance of the coils. This distance can be increased with larger coil sizes, or with larger power outputs, and as such is not limited to the several millimeter range the testing evaluation boards suffer from.

### **8.2 Next Steps**

Moving forward, the charging evaluation boards will be programmed to properly charge the lithium ion battery (LIR2450, 3.7 V) for the final prototype.

## **9 ENSURING RELIABILITY**

While current development work is focused on a proof-of-concept prototype, in the future it will be important to consider how this system could be made more reliable, particularly taking into consideration that diaphragm pacers are considered Class III devices by the Food and Drug Administration (FDA). Currently, none of the components being used for purposes of prototyping are medical grade. However, this section aims to validate that there are analogous medical grade counterparts to these components. In addition, possible failure modes will be explored and the implementation of failsafes will be proposed for use in later iterations.

### **9.1 Analogous Medical Grade Technologies**

The multi-setting implantable phrenic nerve stimulator consists of three major systems: pulse generation, wireless communication, and wireless battery charging. All three of these systems have equivalents in existing medical technology. Most notably, pacemakers and neurostimulators are related technologies that encompass the entire scope of the proposed device's needs.

Pacemakers are implantable devices that use electrical signals to control heart rhythms. They also require pulse generation, and so likely contain medical grade versions of components that are being used in prototyping. Pacemakers are also one of the justifications for the use of NFC technology to meet wireless communication needs, as existing pacemaker models already use NFC technology for transmitting data and programming features (See Section 7.2).

Another technology corresponding to the proposed device is neurostimulators. Neurostimulators are devices that deliver mild electrical stimulation to the epidural space near the spine, usually used as pain treatments. Similar to pacemakers, they also have a pulse generation system, but also have rechargeable batteries, wirelessly charged with a charging pad during sleep. As such,

neurostimulators indicate that medical grade versions of both pulse generation and wireless charging technology already exist, and are currently in use.

## 9.2 Failure Modes

Thus far, several possible failure modes that might occur in the final device have been identified. To minimize harm in the event of such failure modes, there are many possible failsafes that could be implemented. Several possible problems that may arise have been anticipated:

- Battery Depletion/Failure
- Microprocessor Malfunction
- Analog Circuit Failure

The failsafes for each of these failure modes are discussed below.

### *9.2.1 Battery Depletion/Failure*

The current design intends to track battery power remaining. If the battery percentage reaches critically low levels, the system may shift to a reserve battery for power and use a small speaker to produce audible alarms.

### *9.2.2 Microprocessor Malfunction*

Redundant microprocessors, which compare calculations and outputs with each other before proceeding with output to the nerve, can be placed into the system. If there are more than two microprocessors, a majority rules system could be used to override the erroneous processor, although this would require more power and more advanced programming.

### *9.2.3 Analog Circuit Failure*

A voltmeter could be used to measure the voltage output from the analog circuit, right before it arrives at the electrode. If this output is significantly different from the expected voltage output, than the system should alarm, and attempt to reset.

## **10 ANIMAL STUDY**

### **10.1 Purpose of Animal Testing**

The first step in illustrating feasibility of the proposed system is to demonstrate pulse generation on a phrenic nerve and to verify effective diaphragm stimulation and generation of breath. Testing the pulse generation function of the system in an animal model would provide a clear understanding of the effectiveness of each pulse in terms of physiological standards, which can be correlated to certain activity levels. With a validated pulse generation system, the most basic function of the device will be complete.

### **10.2 Animal Study Plan**

#### ***10.2.1 Animal Models***

The animal model options that are currently being explored are:

- Dogs
- Cats
- Rabbits

##### **10.2.1.1 Dogs**

Dogs have been used in phrenic nerve pacing studies in the past. The Avery Diaphragm Pacemaker was tested in an immature canine beagle model to investigate the functional and structural outcome of the diaphragm pacing system.<sup>19</sup> The dog diaphragm responds to continuous low-frequency stimulation and is similar to that of pediatric humans. Additionally, implantable medical device testing generally uses dogs as one of the experimental models.<sup>20</sup>

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<sup>19</sup> Marzocchi, M., R.T. Brouillette, L.M. Klemka-Walden, S.L. Heller, D.E. Weese-Mayer, B.S. Brozanski, J. Caliendo, M. Daoed, M.N. Ilbawi, and C.E. Hunt. "Effects of continuous low-frequency pacing on immature canine diaphragm." *American Physiological Society* 1990.

<sup>20</sup> U.S. FDA. "Animals Used For Experimentation." (<http://www.peta.org/issues/animals-used-for-experimentation/us-government-animal-testing-programs/food-drug-administration/>) (Oct 23, 2016).

### 10.2.1.2 *Cats*

Research studies to understand the properties of the phrenic nerve have used cats for many years. Thus, the characteristics of the phrenic nerve in cats are well known, which could be beneficial in the experiment. Resting membrane potential of cells is 40 - 70 mV and average membrane resistance is 2.0 - 4.2 MΩ.<sup>21</sup> The properties of the phrenic nerve fibers have also been explored.<sup>22</sup>

### 10.2.1.3 *Rabbits*

Due to their size and ease of handling, rabbits have been the animal of choice for implant testing.<sup>23</sup> Stimulation of the phrenic nerve in the rabbit has been performed in many studies, including devices that have been approved for use in pediatrics. Additionally, phrenic nerve innervation of the diaphragm in rabbits is similar to that in humans.<sup>24</sup>

## 10.2.2 *Study Parameters*

During the animal study, certain physiological parameters will need to be monitored to demonstrate the performance of the pulse generator in terms of relevant clinical standards for patients with CCHS. The following parameters were chosen due to their direct relation to ventilatory processes as illustrated in precedent studies with phrenic nerve stimulators.<sup>19</sup>

- Oxygen and Carbon Dioxide Levels
- Tidal Volume
- Transdiaphragmatic Pressure
- Respiratory Rate
- Nerve Conduction Time

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<sup>21</sup> Gill, P.K. and M. Kuno. "Properties of Phrenic Motoneurons." *J. Physiol.* 168 1963: 258 - 273. (Nov 9, 2016).

<sup>22</sup> Balkowiec, A. and P. Szulczyk. "Properties of postganglionic sympathetic neurons with axons in phrenic nerve." *Respiration Physiology*. 88(3) 1992: 323-331. (Nov 9, 2016).

<sup>23</sup> "A Practical Guide to ISO 10993-6: Implant Effects." *Medical Device & Diagnostic Industry Magazine* (1998).

<sup>24</sup> Muller Botha, G.S. "The Anatomy of Phrenic Nerve Termination and the Motor Innervation of the Diaphragm." *Thorax* 12(5) 1957: 50-56. (Oct 23, 2016).

#### *10.2.2.1 Oxygen and Carbon Dioxide Levels*

Oxygen and carbon dioxide levels are indicative of the effectiveness of breath in proper ventilation and are especially important in patients with CCHS in determining hyperventilatory symptoms.<sup>2</sup> While blood oxygen and carbon dioxide levels would be ideal, external breath-to-breath measurements with a capnometer will be sufficient in demonstrating stable levels for this study.

#### *10.2.2.2 Tidal Volume*

Measurement of tidal volume is one of the key characteristics determining adequate ventilation and is commonly used as a defining parameter of mechanical ventilator performance in order to minimize extraneous stressors on the body. Tidal volume will be measured with a spirometer during the animal study.<sup>25</sup>

#### *10.2.2.3 Transdiaphragmatic Pressure*

A common measurement of diaphragmatic performance, transdiaphragmatic pressure, will be measured with the placement of esophageal and gastric catheters, which will measure pleural pressure and abdominal pressure, respectively.<sup>26</sup> Transdiaphragmatic pressure will be derived from these values and is indicative of the contraction force of the diaphragm and the volume displaced by the contraction.

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<sup>25</sup> Ministry of Health. "Pediatric Intensive Care Clinical Practice Guideline: Pediatric Ventilation Guidelines" 2010. (Nov 19, 2016)

<sup>26</sup> DePallo, Vera A MD, McCool, Dennis MD. "Respiratory Muscle Evaluation of the Patient With Neuromuscular Disease". 2002. (Nov 16, 2016)

#### *10.2.2.4 Respiratory Rate*

Respiratory rate is another hallmark measurement of ventilation and respiratory processes.

Respiratory rate of the animal will be measured using a pulse oximeter.

#### *10.2.2.5 Nerve Conduction Time*

Phrenic nerve conduction time is representative of the effectiveness of the signal in stimulating diaphragm contractions and will be defined as the time between onset of the delivered signal to the time of a responsive compound diaphragmatic action potential.<sup>15</sup> This will be measured with a bipolar recording electrode inserted in the esophagus.

### **10.3 Moving Forward**

Moving forward, the team will begin preparations for animal testing and then perform the experiments. See Appendix J for more information on the animal study preparation.

#### ***10.3.1 IACUC Protocol Submission***

An Animal Study Protocol must be submitted to the Northwestern University Institutional Animal Care and Use Committee (IACUC) in order to perform the test. Moving forward, the protocol will be completed and submitted.

## **11 ETHICAL CONSIDERATIONS**

Since this device is being developed for a small affected population, a major moral consideration is the cost effectiveness of the development process and the societal impact of the device if fully developed and marketed. As a life-supporting device, the multi-setting implantable phrenic nerve stimulator must undergo several rounds of animal and clinical testing, thus requiring substantial funds to support development. Under the FDA, this device would be categorized as a Humanitarian Use Device as it affects “fewer than 4,000 individuals in the United States per year”.<sup>27</sup> In filing a Humanitarian Device Exemption, it is possible to reduce the requirements needed to acquire FDA approval, thus reducing development costs and increasing the feasibility of getting the product on the market.

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<sup>27</sup> FDA. “Humanitarian Device Exemption.” <http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/humanitariandeviceexemption/default.htm> (Nov. 27, 2016).

## **12 MOVING FORWARD**

### **12.1 Next Quarter Goals**

Next quarter, the goal is to deliver a functional prototype of the multi-setting phrenic nerve stimulator. To do this, the following must be completed:

- Development
- Modeling
- Testing

#### ***12.1.1 Development***

##### ***12.1.1.1 Charging Development***

The charger must be programmed to the specifications that are necessary to charge the implanted lithium ion battery.

##### ***12.1.1.2 Communication Development***

The communication chips must be programmed such that the external component can communicate the settings to the implant and the implant can communicate battery level and data to the external component.

##### ***12.1.1.3 Activity Setting Levels Development***

The capability to program at least five activity levels will be programmed into the device.

##### ***12.1.1.4 User Interface Development***

A rudimentary user interface for the external component will be developed to make the prototype easier to use in the animal studies.

## **12.1.2 Modeling**

### *12.1.2.1 Heat Propagation*

As with all electrical circuits, the implant will generate excess heat. In order to make sure that it is a safe amount of heat, testing needs to be conducted to verify that this implant can charge and function without generating a harmful amount of heat, and ideally, without causing discomfort.

Once all components of the prototype are done, heat generation testing can be done.

## **12.1.3 Testing**

### *12.1.3.1 Benchtop Testing*

Testing of the individual components will be done with a circuit model representative of the electrical properties of the phrenic nerve. See Appendix K for details on modeling the phrenic nerve electrically.

### *12.1.3.2 Animal Testing*

Discussed in Section 10 above, the phrenic nerve stimulator prototype will be tested on an animal model to see if the stimulator is effective at generating breath.

## **12.2 Beyond**

With a functional three-part system: pulse generation, communication, and charging, the proposed device will be able to deliver pulses at multiple activity levels with alternative settings and will be controllable through an intuitive user interface either in the form of a unit LCD or a cell phone app. In the future, the implant will be miniaturized so that it can ultimately be implanted in children with CCHS to provide them with advanced breathing support.

## **Appendix A: Table of Abbreviations**

<b>Abbreviation</b>	<b>Definition</b>
CCHS	Congenital Central Hypoventilation Syndrome
VCS	Voltage Controlled Stimulation
CCS	Current Controlled Stimulation
SCS	Switched Capacitor Stimulation
VCCD	Voltage Controlled Capacitor Discharge
DAC	Digital-to-Analog Converter
PWM	Pulse Width Modulation
RTC	Real Time Clock
I2C	Inter-Integrated Circuit Communication
NFC	Near Field Communication
FCC	Federal Communications Commission
IC	Integrated Chip
GUI	Graphical User Interface
LCD	Liquid Crystal Display
EEPROM	Electrically Erasable Programmable Read-Only Memory
FDA	Food and Drug Administration
IACUC	Institutional Animal Care and Use Committee

## Appendix B: Alternative Designs

Various system designs for an implantable phrenic nerve stimulator were explored. Three alternatives are described in this appendix:

- I. Digitized User Interface of the Current Avery Transmitter
- II. Multi-Setting Wireless Stimulator
- III. Implantable Biofeedback Device

Based on requirements and target specifications, Alternative II was chosen.

### 1.1 Alternative I: Digitized User Interface of the Current Avery Transmitter

#### *1.1.1 Description*

This alternative would digitize the user interface of the current Avery transmitter, while maintaining the function of the rest of the Avery device. The transmitter allows the doctor to control the following parameters: pulse amplitude, pulse rate, pulse width, slope, range, pulse interval, inspiratory rate, and respiration rate.

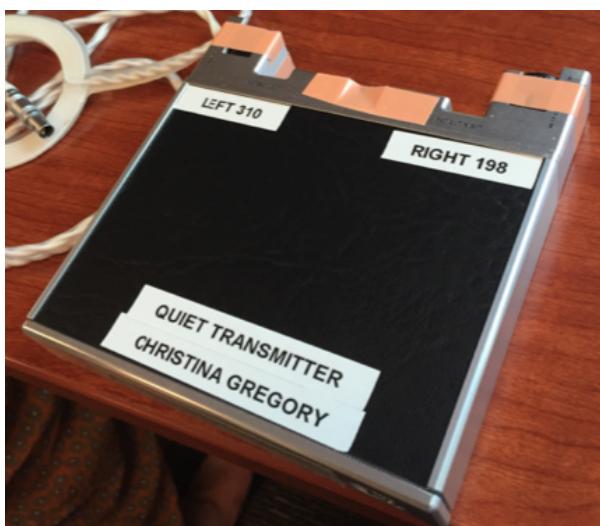


Figure 1: Current Avery Transmitter and Proposed Digital User Interface

As it can be seen in Figure 1, these parameters will be digitally displayed so the doctors know the value of the parameter being changed. With the current Avery transmitter, the doctor changes the settings on the back of the transmitter box with a screwdriver and arbitrarily sets the values; thus, this alternative would greatly improve control of the device by the doctor. However, each transmitter box would still only have one setting programmed, and the child would still have to carry around the transmitter.

The advantages and disadvantages that go along with each attribute of this alternative can be seen in Table 1.

Table 1: Attributes-Advantages-Disadvantages for Alternative I

Attributes	Advantages	Disadvantages
Digital User Interface of Transmitter	Easier for doctor to control	Still only 1 setting per transmitter box
Transmitter Box	Smaller than mechanical ventilator	Child always needs to carry around 2 lb box

### ***1.1.2 Needs Fulfilled***

This alternative will fulfill the following needs:

- Reliable generation of breath
- Improved doctor control
- Intuitive user interface

## 1.2 Alternative II: Multi-Setting Wireless Stimulator

### 1.2.1 Description

This alternative will include an external component that is smaller than the 2 pound Avery external transmitter. As it can be seen in Figure 2, the user interface of the external transmitter will have both a doctor view so that the doctor can digitally change the parameters and a patient view so the user can switch between settings when their activity level changes. The external transmitter, seen in Figure 3, will wirelessly communicate information to the implant from longer distances, so no wires will need to be attached to the child. The implant will be an active device that will communicate with the transmitter and change its pulse generation values based on the data it receives.

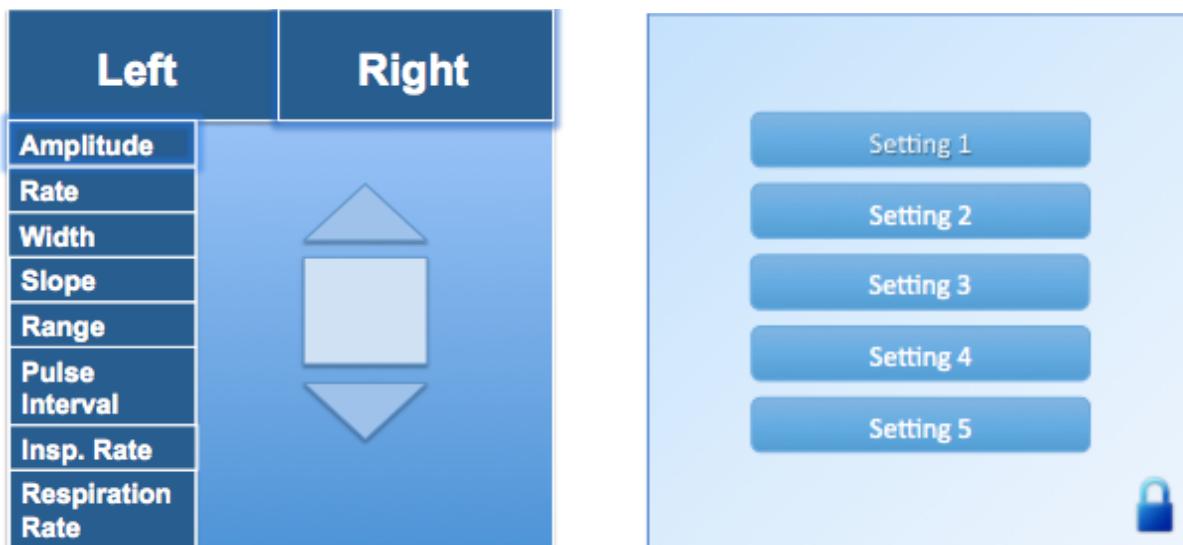


Figure 2: User Interface for Doctor (left) and Patient (right)

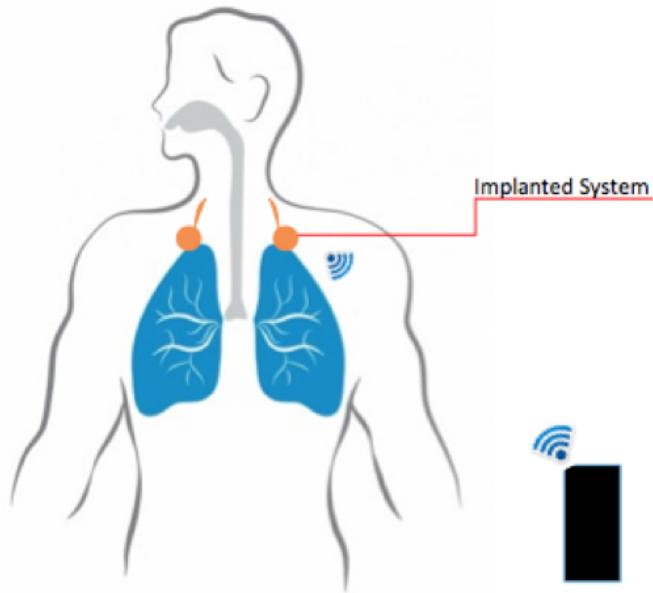


Figure 3: External and Implanted Components

The advantages and disadvantages that go along with each attribute of this alternative can be seen in Table 2.

Table 2: Attributes-Advantages-Disadvantages for Alternative II

Attributes	Advantages	Disadvantages
Wireless Communication	No wires attached to child Water activities	Less reliable than radio communication
Multiple Settings	Variety of activities	Complications of use
Rechargeable Battery	No additional surgery to change battery	Charge weekly

### ***1.2.2 Needs Fulfilled***

This alternative will fulfill the following needs:

- Reliable generation of breath
- Increased portability

- Reliable communication, processes, and pulse delivery
- Improved doctor control
- Intuitive user interface
- Versatility - accommodates more activities
- Waterproofing

### 1.3 Alternative III: Implantable Biofeedback System

#### *1.3.1 Description*

This alternative is fully implantable and there is no external component. As seen in Figure 4, an implanted CO<sub>2</sub>/O<sub>2</sub> sensor will sense the levels of carbon dioxide and oxygen in the blood and communicate the change in breathing that needs to occur to the implanted system. This alternative would give an accurate physiological response to every situation and is the ideal solution to the problem.

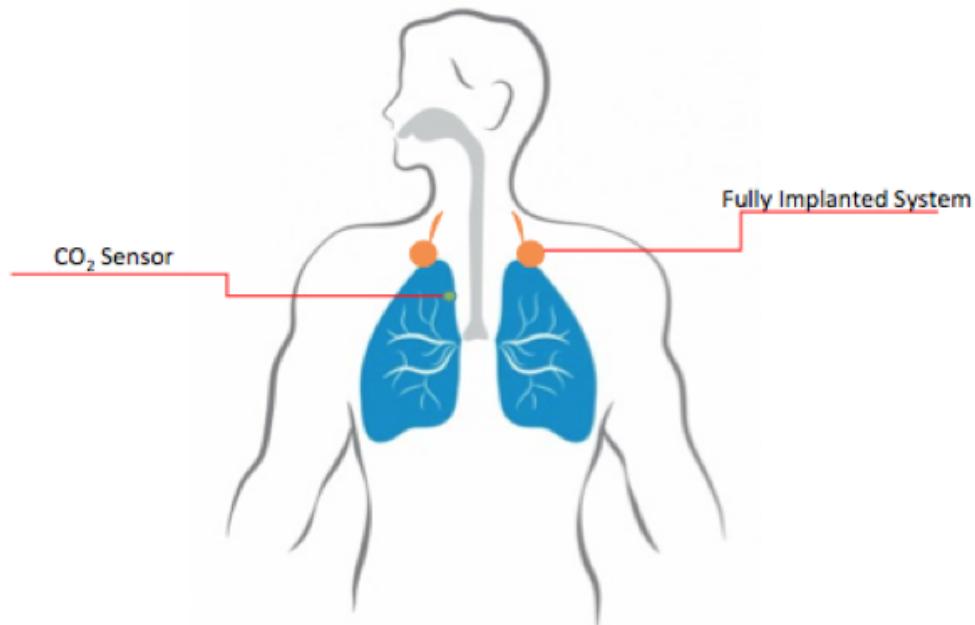


Figure 4: Fully Implantable Biofeedback System

The advantages and disadvantages that go along with each attribute of this alternative can be seen in Table 3.

Table 3: Attributes-Advantages-Disadvantages for Alternative III

Attributes	Advantages	Disadvantages
Fully Implantable	No external component	No external control Less failure recovery options
CO <sub>2</sub> /O <sub>2</sub> Sensor	Accurate physiological response to every situation	Technology does not exist

### ***1.3.2 Needs Fulfilled***

This alternative will fulfill the following needs:

- Reliable generation of breath
- Increased portability
- Reliable processes and pulse delivery
- Versatility - accommodates more activities
- Waterproofing

### **1.4 Decision Matrix**

A decision matrix, seen in Table 4, was created to compare the three alternatives and the Avery device to decide on a direction for the project. For each requirement, the solutions were ranked from 1 to 4, with 4 being the best. From this analysis, it was clear that Alternative II: Multi-Setting Wireless Stimulator was the direction the project should take. Alternative I would improve doctor control, but not necessarily solve the problem with

regards to the patient. Alternative III would need to incorporate technology that does not exist, the implanted CO<sub>2</sub> sensor. Also, the doctor would not have control over the device and any malfunction could be fatal. Therefore, Alternative II was chosen.

Table 4: Decision Matrix

Requirements	Specifications	Avery	Alt. I	Alt. II	Alt. III
Portable	< 2 lbs	1.5	1.5	3	4
Safe	Cannot heat surrounding tissue more than 42 C  Recovery time following surgery	3.5	3.5	2	1
Versatile (Accommodate more situations)	How often user changes settings : How often activity levels change	1.5	1.5	3	4
Easy to use	Training time required to learn	1	2	3	4
Recover errors	Number of backup strategies	2	3.5	3.5	1
Stimulate phrenic nerve	Frequency: 18 - 22 Hz Current: 20 mA Pulse Width: 150 - 300 µs Voltage: 3 - 5 V	1.5	1.5	3	4
Reliable (communication)	Percentage of signals that are received and processed	3.5	3.5	2	1
Cost to produce	N/A	N/A	3	2	1
Time to develop	< 33 weeks	N/A	3	2	1
Risk	N/A	N/A	3	2	1

## Appendix C: Power Management Calculation

### Nerve Stimulation

Parameter	Var	Value	Definition
<b>Phrenic Nerve Stimulation Parameters</b>			
Pulse Current <sup>1</sup>	$I_p$	Max. 2.2 mA	Max. current needed to stimulate phrenic nerve
Pulse Frequency	$f_p$	20 Hz	Frequency at which pulses are administered
Pulse Width <sup>2</sup>	$w_p$	Typ. $150 \pm 10 \mu\text{s}$	Time when pulse generator passes current
Inspiration to Expiration <sup>3</sup>	$R_{IE}$	1:3 to 1:2	Ratio of insp. time to exp. time for children
<b>Calculation Parameters</b>			
Stimulation Duty Cycle	$DC_{stm}$	(% duty cycle)	Ratio of pulse time to total inspiration time
Breathing Duty Cycle	$DC_{brt}$	(% duty cycle)	Ratio of inspiration time to total breath period
Total Duty Cycle	$DC_{tot}$	(% duty cycle)	Ratio of pulse time to total battery life
Battery Rating (nerve stimulation only)	$BR_{stm}$	(mAhr)	Value specifying how long a battery can last while supplying a certain current.
<b>Variables</b>			
Battery Life	$t$	(s)	Time between two recharge sessions

Assumptions:

- In the worst case scenario, the patient will be breathing with  $R_{IE} = 1 : 2$  and the electrode would not be implanted optimally, so pulse width will need to be higher than typical, i.e.  $w_p = 200 \mu\text{s}$ .
- For ease of calculation, battery only supplies stimulation process.

Then,  $DC_{stm} = w_p f_p = 200 \mu\text{s} \times 20 \text{Hz} = 0.004 = 0.4\% \text{ duty cycle}$  and  $DC_{brt} = R_{IE} = 50\% \text{ duty cycle}$

So, during patient inspiration, the phrenic nerve will need to be stimulated 0.4% of the time. Also, the patient inspires for 50% of the total battery life of the device. Hence, the total duty cycle of nerve stimulation is:

$$DC_{total} = DC_{stim} DC_{brt} = 0.4\% \times 50\% = 0.2\% \text{ duty cycle}$$

This means that stimulation occurs 0.2% of the total time of device operation until the next charging session. Assuming that the battery can last for time  $t$ , and the battery is only powering the nerve stimulation process, the battery rating is:

$$BR_{stm} = \text{time} \times \text{current} = (DC_{total} \times t) \times I = (0.2\% \times t) \times 2.2 \text{ mA} = 0.0044t \text{ mA}$$

It is important to note that variable  $t$  dictates actual battery rating based on how long the patient would like to be active until next battery recharge session. Conversely, it can be used to estimate device life based on a specified battery rating.

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<sup>1</sup> Le Pimpec-Barthes, Francoise, et al. "Diaphragm pacing: the state of the art." (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4856845/>) (Oct.12,2016).

<sup>2</sup> Avery Biomedical Devices. "Instruction Manual for the Avery Breathing Pacemaker System." (Oct 2, 2016).

<sup>3</sup> Perkin, Ronald M. *Pediatric Hospital Medicine: Textbook of Inpatient Management*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008.

## **Communication MCU**

Near Field Communications (NFC) will be used for data communication. STMicroelectronics provides a great NFC tag called **M24LR64E-R**. This IC can be powered by either a battery source or it can harvest energy from the NFC reader from outside of the patient. When communicating with the NFC reader, the tag can be used as an interrupt to a microcontroller.

Parameter	Var	Value	Definition
<b>M24LR64E-R Datasheet Parameters<sup>4</sup></b>			
Sleep Mode Current	$I_{c,sleep}$	Max. 30 $\mu$ A	Consumption while device is in sleep mode
Tx/Rx Mode Current	$I_{txrx}$	Max. 220 $\mu$ A	Consumption while device is communicating
Data Rate	$DR$	Min. 6.6 kbit/s	Rate at which data is communicated
Transmission frequency	$f_{txrx}$	13.56 MHz	Frequency at which data is communicated
<b>Other Known Parameters</b>			
Integer bit length	$l_{int}$	32 bits	Usual representation of an integer
<b>Calculation Parameters</b>			
Programming Frequency	$T_{prog}$	(s)	Time b/w subsequent programming sessions
Communication Time	$T_{txrx}$	(s)	How long it takes to exchange tx/rx data packet
Total Data Sent/Received	$d$	(kbits)	Data sent and received, including identification sequences and user data packets
Communication Duty Cyc.	$DC_{txrx}$	(% duty cycle)	% time the chip spends communicating
Sleep Duty Cycle	$DC_{c,sleep}$	(% duty cycle)	% time the chip spends sleeping
Battery Rating (communication only)	$BR_{comm}$	(mAhr)	Value specifying how long a battery can last while supplying a certain current.
<b>Variables</b>			
Battery Life	$t$	(s)	Time between two recharge sessions

Assumptions:

- The patient/parent switches settings of the device once every 5 minutes ( $T_{prog} = 5\text{min} = 300\text{ s}$ )
- The total data sent and received in one transmission is  $d = 0.66\text{ kbits}$  (for ease of calculations)
- Data does not get corrupted and does not need to be resent.
- For ease of calculation, the battery supplies only the communication chip.
- Battery supplies the communication chip 100% of the time (no energy harvesting function implemented)

With the above assumptions in mind,

- 1) The each transmission would then take the following amount of time:  $T_{txrx} = \frac{d}{DR} = \frac{0.66\text{ kbits}}{6.6\text{ kbit/s}} = 0.10\text{ s}$
- 2) Keeping in mind the estimation of how often the patient would reprogram the device, the duty cycle of communication would be:

$$DC_{txrx} = \frac{T_{txrx}}{T_{prog}} = \frac{0.10\text{ s}}{300\text{ s}} = 0.00033, \text{ or } 0.033\% \text{ duty cycle}; DC_{c,sleep} = 1 - DC_{txrx} \approx 1$$

- 3) So, if the battery only powered the communication MCU, the battery rating would have to be:

$$BR_{comm} = (DC_{txrx} \times t) \times I_{txrx} + (DC_{c,sleep} \times t) \times I_{c,sleep} = 0.00033t \times 220\text{ }\mu\text{A} + t \times 30\text{ }\mu\text{A} \approx 0.030t\text{ mA}$$

## **Microcontroller (PWM, ADC, other calculations and control)**

<sup>4</sup> "M24LR16E-R".

(<http://www.st.com/content/ccc/resource/technical/document/datasheet/45/6b/a2/02/63/ad/45/43/DM0047008.pdf/files/DM0047008.pdf/jcr:content/translations/en.DM0047008.pdf>) (Oct 27, 2016)

Microcontroller that will be used for pulse generation, storage of setting values, battery level detection, and possibly data logging will need to be an ultra-low power MCU. For these preliminary calculations, the datasheet for the STM8L151 MCU line was used.

Parameter	Var	Value	Definition
<b>STM8L151 Datasheet Parameters<sup>5</sup></b>			
Consumption in Run	$I_r$	Typ. 0.39 mA	Current consumed while in
Consumption in Act. Halt	$I_{ah}$	Max. 3.3 $\mu$ A	Current consumed while in Active Halt
CPU Clock (Run Mode)	$f_{CPU,r}$	125 kHz	Frequency of CPU operation
Active-Halt clock	$f_{CPU,ah}$	38 kHz	Low Speed Internal oscillator frequency
<b>Calculation Parameters</b>			
Stimulating duty cycle	$DC_{run}$	(% duty cycle)	Portion of the time the device is in Run mode
Sleeping duty cycle	$DC_{sleep}$	(% duty cycle)	Portion of the time the device is in Active Halt
Battery Rating (MCU only)	$BR_{MCU}$		Value specifying how long a battery can last while supplying a certain current.
<b>Variables</b>			
Battery Life	$t$	(s)	Time between two recharge sessions

Assumptions:

- When stimulating, the device is in “Run” mode 100% of the time. In reality, the program will be optimized, but this case was taken as the “worst case scenario”.
- When not stimulating, the device is in the “Active Halt” mode. That is, the CPU will be stopped, and only woken up by the Real Time Clock (RTC) at the beginning of next inspiration period.
- When in run mode, CPU clock is set at 125 kHz (by division of 16MHz internal oscillator).
- When in Active Halt mode, the device clock is set to Low Speed Internal oscillator (38 kHz).
- For ease of communication, the battery supplies only the MCU operation.

$$R_{IE} = 1 : 2; DC_{run} = DC_{sleep} = 50\% \text{ duty cycle}$$

$$BR_{MCU} = (DC_{run} \times t) \times I_{run} + (DC_{sleep} \times t) \times I_{sleep} = 0.50t \times 0.39 \text{ mA} + 0.50t \times 3.3 \text{ } \mu\text{A} \approx 0.20t \text{ mA}$$

### Total Consumption

Assumption here is that leakage current and heat losses are negligible.

Because the above consumption values are independent, they can be added together to get a total battery rating value:

$$BR_{TOTAL} = BR_{stm} + BR_{comm} + BR_{MCU} = 0.0044t \text{ mA} + 0.030t \text{ mA} + 0.20t \text{ mA} = 0.23t \text{ mA}$$

An average rechargeable coin cell battery, LIR2450 (Li-Ion) that can supply 3.6 V and 190 mAh can thus sustain the patient for:

$$t = 190 \text{ mAh} / 0.23 \text{ mA} \approx 830 \text{ hours} \approx 34 \text{ days, 14 hours}$$

So, by estimation, under worst case scenario (heavy communication usage, average battery, poorly optimized embedded program, need for maximum stimulation, etc.), **the device should be able to sustain the patient for at least one month on one recharge.**

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<sup>5</sup> “STM8L151/152”

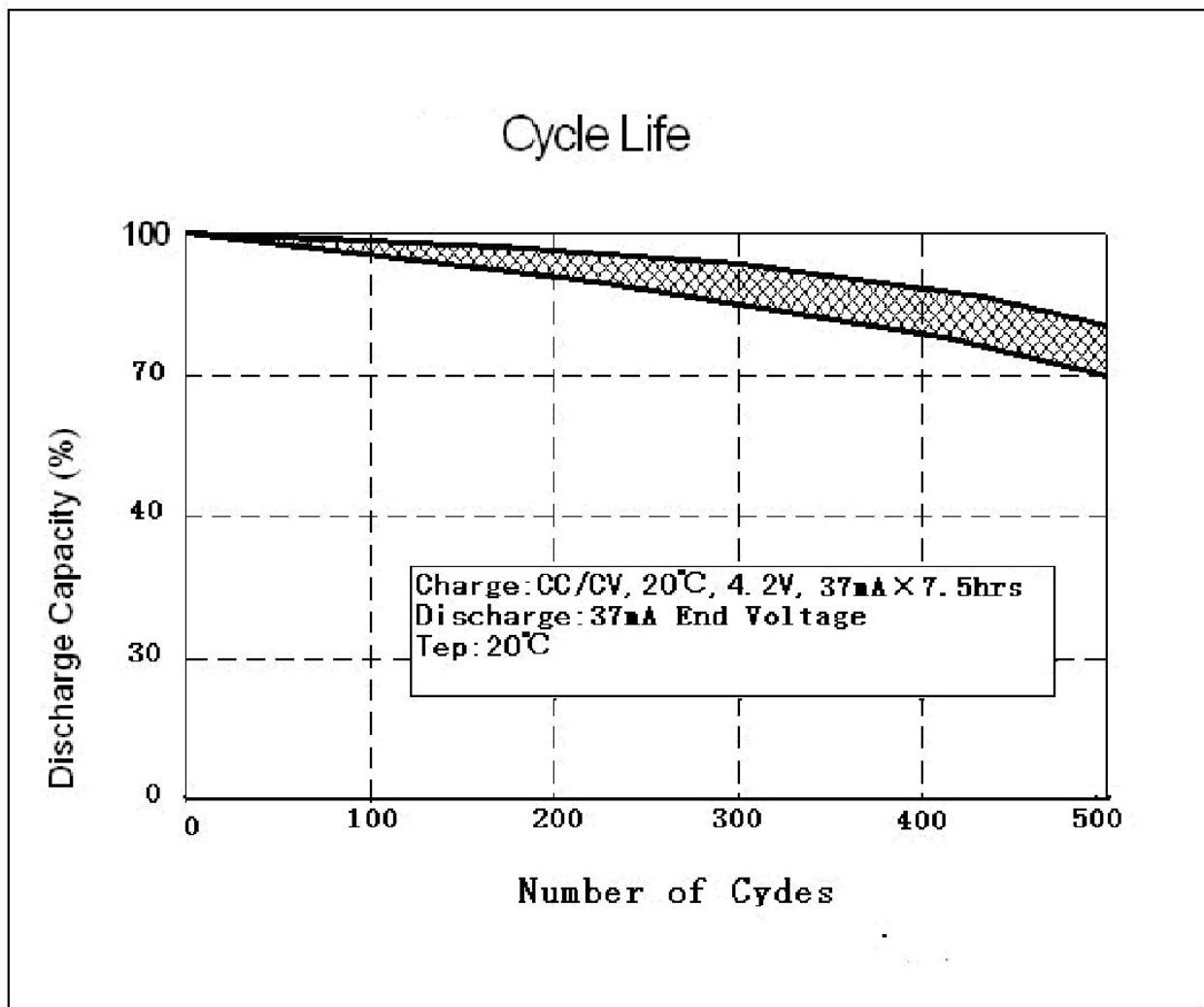
(<http://www.st.com/content/ccc/resource/technical/document/datasheet/12/49/3f/ce/27/db/47/2f/DM00027749.pdf/jcr:content/translations/en.DM00027749.pdf>) (Oct 5, 2016)

## Appendix D: Device Life Calculation

### Purpose

The purpose of this calculation is to approximate, if the Tenergy LIR2450H were to be used in the real device, the amount of time before the battery would need to be changed out via surgery.

The testing conducted by Tenergy and included in their data sheet (and as seen below) was conducted with lower temperatures than in the human body, and at higher loads with shorter time periods than would be necessary for our usage.<sup>1</sup> This means that the cycle life capacity would probably be different, but should be relatively close.



As can be seen, over 500 charging cycles, the capacity of the Lithium Ion battery decreases to about 70%. Based on the Power Calculation from Appendix A, this battery should last our device approximately 34 days on each full recharge.

<sup>1</sup> "Tenergy Rechargeable Li-ion Button Cell"

([http://www.all-battery.com/datasheet/34022\\_spec%20sheet.pdf](http://www.all-battery.com/datasheet/34022_spec%20sheet.pdf)) (Nov 6, 2016).

Parameter	Var	Value	Definition
<b>Battery Parameters</b>			
Cycle Life	$C_L$	70%	Capacity retained after 500 charge & discharges
Self-Discharge Rate	$R_d$	7%/month	Losses without electrode connections
<b>Power Calculation Parameters</b>			
Battery Life	$t$	34 days	Time battery can power device from full recharge, assuming 100% capacity still
<b>Calculation Parameters</b>			
Battery Life (after 500 Cycles)	$t_{500}$	(days)	Time battery can power device from full recharge, assuming 70% capacity
Device Life	$L$	(days)	Time until battery must be replaced

Assumptions:

- Worst case scenario: 70% capacity for the first 500 cycles
- Based on previous calculations, full capacity would last about 34 days
- After 500 cycles, battery ceases to function properly
- Cycle life does not change significantly based on temperature
- Self-discharge rate is negligible
- Battery was recharged optimally

With the above assumptions in mind,

- 1) Battery life at 70% retention of capacity (after 500 cycles) and involving self-discharge rate:  $t_{500} = (1 - R_d)(C_L)(t) = (0.93)(0.70)(34 \text{ days}) = 22 \text{ days}$
- 2) Device life, assuming that battery does not work after 500 cycles, is the late battery life times number of cycles:

$$L = t_{500} * 500 \text{ cycles} = 11000 \text{ days} = 30 \text{ years}$$

## Appendix E: Communication Technologies

For the multi-setting wireless system, various communication methods and chips were explored to determine the best method through which wireless signals could be delivered.

Bluetooth Low Energy (BLE), ANT, Medical Implantable Communication Service (MICS), and Near Field Communication (NFC) methods were evaluated with respect to the criteria defined in Table 1 and ranked from 1 to 4, with 4 being the best

Table 1: Communication Decision Matrix

Criteria	Units	BLE	ANT	MICS	NFC
Power Consumption	mA	2	1	3	4
Ease of Programming	hours	1	4	2	3
Circuit Interface	subjective	1	2	3	4
MCU Interface	subjective	1.5	1.5	3	4
Range of Comm.	meters	3.5	2	3.5	1
Ease of Compliance	FCC Regulations	1.5	1.5	3	4
Price	USD	3	2	1	4
<b>Total</b>		<b>13.5</b>	<b>14</b>	<b>18.5</b>	<b>24</b>

From this evaluation, it was determined that NFC methods would be most fitting for the purposes of the device. It not only performs at the lowest power consumption values among the options presented, but it also uses a widely available 13.56 MHz frequency, which complies with Federal Communications Commission (FCC) regulations.<sup>1</sup> Among

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<sup>1</sup> Philipp Gutruf (Postdoctoral Research Associate in the John Rogers Group) in discussion with authors, (Oct 27, 2016).

all of the options, this technology is also the simplest to implement in a circuit. For instance, an example NFC tag IC from STMicroelectronics, the M24LR04E-R, only has eight pins to interface, two of which are used to interface with an external antenna, two are used for inter-microcontroller communication, two are used for power (positive voltage and ground), one is used for extra energy output, and one pin acts as signaling pin for indicating when RF communication occurs.

The M24LR04E-R also has the following features:

- Electrically Erasable Programmable Memory (EEPROM)
- I<sup>2</sup>C communication interface - a standard inter-microcontroller communication protocol
- Dual-interface - it can either be powered by an electrical power source or by the NFC reader's RF field
- Energy Harvesting analog output, which relays unused power from the RF field of the reader out of the IC to be used for either charging or powering other parts of the circuit
- A pin toggled during RF communication. This can be used to indicate to the microcontroller that the communication occurred.<sup>2</sup>

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<sup>2</sup> "Dynamic NFC/RFID tag IC with 4-Kbit EEPROM, energy harvesting, I<sup>2</sup>C bus and ISO 15693 RF interface"  
(<http://www.st.com/content/ccc/resource/technical/document/datasheet/4e/fd/ac/70/b2/bc/43/fa/DM00038059.pdf/files/DM00038059.pdf/jcr:content/translations/en.DM00038059.pdf>) (Oct 27, 2016).

For preliminary prototyping, the M24LR-Discovery kit was chosen. The kit includes:

- M24LR04E-R NFC tag evaluation board. Notable features:
  - M24LR04E-R NFC tag
  - STM8L152 microcontroller (also used in STM8L-Discovery board)
  - Reset and User buttons
  - Digital LCD
  - 20 x 40 mm 13.56MHz inductive antenna etched on the PCB
  - SWIM connector for debugging the STM8L152 controller
- CR95HF NFC reader chip evaluation board. Notable features:
  - CR95HF-VMD5T 13.56 MHz multi-protocol contactless transceiver IC with SPI and UART serial access
  - 47 x 34 mm 13.56 MHz inductive antenna etched on PCB
  - STM32F103CB 32-bit microcontroller, with 128 Kbytes of Flash memory
  - USB for connecting to the host computer<sup>3</sup>

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<sup>3</sup> “Discovery kit for M24LR04E Dual Interface EEPROM with energy harvesting” (<http://www.st.com/en/evaluation-tools/m24lr-discovery.html>) (Oct 27, 2016).

## Appendix F: NFC Through Hand/Titanium Communication Test

### Purpose

The purpose of this testing was to verify that we can use NFC technology, and how it interacts with conductors (titanium) or organic tissue (my hand). The NFC evaluation board from ST 511-M24LR-DISCOVERY was used.

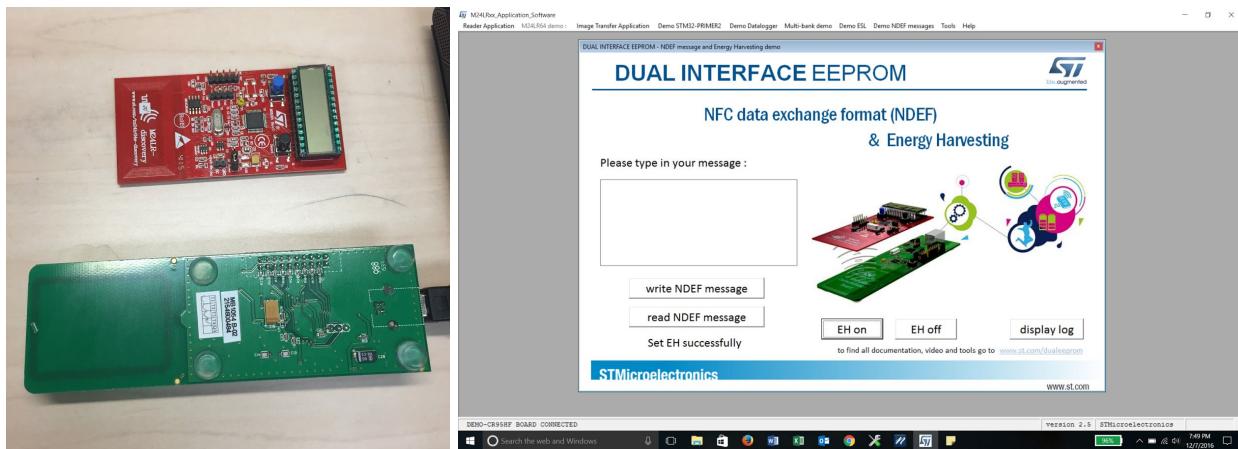
### Background

Titanium is often used in casings for implantables, due to its favorable biocompatibility and other useful properties. As such, we are considering it for a casing for at least part of our implant. However, titanium is also a conductor, and as such would probably absorb the EM waves being used to wirelessly communicate.

On the other hand, insulators tend not to interfere with EM waves, and organic tissues (which would have to be communicated through for sure) are usually primarily composed of insulators. We would not expect organic to interfere with the radio signals as a result.

### Procedure

First, it was verified that the evaluation board was functional. The receiver chip was programmed to harvest energy from the radio signal, and to output any text data stored in memory on the LCD. Text data was written to the receiver memory, and then the coils were aligned.



**Figure 1.** Left: Evaluation boards used, red being receiver coil and memory, green being transmitter controlled by computer. Right: GUI built by ST for control of evaluation board, used in testing for writing new text data into the memory of the receiver chip.

Upon confirming that the LCD was displaying the text data, the text data was changed, and LCD observed to confirm that the data updated.

This procedure was then repeated with titanium in between the coils, and with a hand between the coils, to see the effects of organic tissue, and conductors.

### Results

The initial baseline testing was successful in powering, and updating the data on the receiver chip.

The titanium clearly blocked the radio signals, preventing the coil from being powered, and prevented updating of data.

Placing a hand between the coils had no effect on transmission of either power or on updating the memory in the receiver chip.



**Figure 2.** From left to right: Control/baseline testing, titanium interference testing, hand interference testing. Note that control and the hand do not interfere with the radio signal, while the titanium completely blocks radio signal.

### Conclusions

Similar to wireless charging testing, and as expected based on EM theories, conductors completely absorb the radio signals, while organic tissue and air do not.

As such, these tests demonstrate that this technology is feasible to use in our implant prototype, since it can pass through organic tissues without problem. The receiver coil needs to be outside of any titanium or metal casing, and cannot have any metal between it and the pathway to the transmitter coil (outside the body).

## Appendix G: Charging Technologies

In order to power the implantable component of the device, wireless charging technology will be used to recharge the implanted lithium ion battery. There are several wireless charging standards that exist currently, including Qi, Power Matters Alliance (PMA), and Rezence. Qi standard was established earlier than others, currently has more worldwide use, and offers both magnetic induction and resonance charging.<sup>1</sup> PMA and Rezence are both marketed by the AirFuel Alliance, and constitute inductive and resonant technologies respectively. PMA is widely used in existing products, but it is not as prevalent as Qi. Rezence, on the other hand has not yet been introduced into consumer products.<sup>2</sup> A custom wireless charging solution could also be built from separate components, although this would be difficult and might have to be later changed for a full product. For these reasons, it was decided that Qi compliant charging technology would be most effective for this project. Full evaluation modules from STMicroelectronics were purchased, specifically the 1W Wireless Charger System from STMicroelectronics called STEVAL-ISB039V1.<sup>3</sup>

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<sup>1</sup> “Charging without Wires – A Solution or Laziness” ([http://batteryuniversity.com/learn/article/charging\\_without\\_wires\\_a\\_solution\\_or\\_laziness](http://batteryuniversity.com/learn/article/charging_without_wires_a_solution_or_laziness)) (Oct 26, 2016).

<sup>2</sup> “Wireless Charging is Still a Mess, but it Won’t Be Forever” (<https://www.wired.com/2015/11/wireless-charging-airfuel-rezence-qи-wpc/>) (Oct. 26, 2016).

<sup>3</sup> “STEVAL-ISB039V1- 1W wireless charger system Tx/Rx based on STM32F0 and STWLC03” ([http://www.st.com/content/ccc/resource/technical/document/data\\_brief/group0/86/18/61/83/d9/3d/4a/18/D\\_M00326828/files/DM00326828.pdf/jcr:content/translations/en.DM00326828.pdf](http://www.st.com/content/ccc/resource/technical/document/data_brief/group0/86/18/61/83/d9/3d/4a/18/D_M00326828/files/DM00326828.pdf/jcr:content/translations/en.DM00326828.pdf)) (Oct 31, 2016).

## **Appendix H: Pork Skin Charging Test**

### Purpose

The purpose of this testing was to see what effect, if any, a piece of pork skin (1.86 mm thick) inserted between the wireless charging transmitter and receivers we are using in prototyping (STEVAL-ISB039V1). This would have implications for placement of any transceiver coils, as well as casing materials, and lends support to the feasibility of implantable wireless charging systems.

### Background

For the purposes of wirelessly charging batteries, it is important to prove that skin does not interfere significantly with the electromagnetic (EM) radiation involved in wireless charging. Usually, only conductors would normally interfere with the EM waves, but it is important nonetheless to verify that it does not.

Pork skin is very analogous to human skin, and as such if wireless charging can be done through pork skin, human skin should be feasible as well. Although non-living pork skin was used, the only major difference would be a lack of blood circulation, which should not have much effect on EM wave penetration.

### Procedure

Three tests were done, control with only the plastic bag, pork skin in a plastic bag, and plastic wrap folded to be similar thickness to the pork and plastic bag. The Rigol DM3068 Digital Multimeter was used to measure current output as well as voltage, during separate trials. The wireless transmitter was powered via microUSB, and was running on its default factory settings (currently unknown exact parameters, but supposed to output steady voltage and current as possible). Voltage and current measurements were taken at separate times, with no major loads in the circuit.

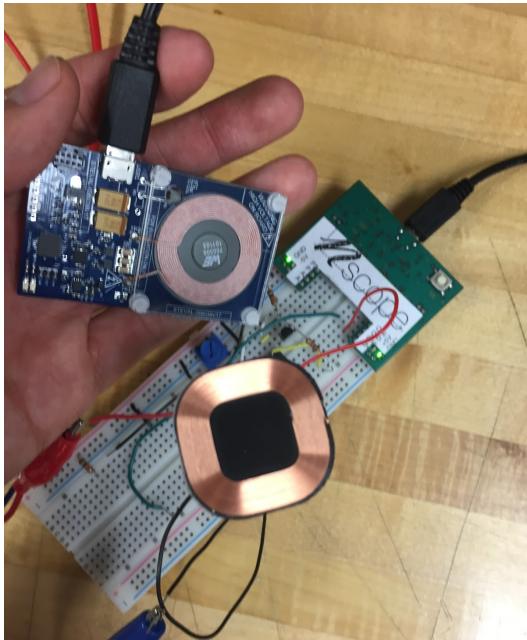


Figure 1. All materials used in testing.

The experiment was done using a single-case design. The receiver coil was repeatedly moved back and forth within/outside of charging distance, while voltage and current measurements were taken.

### Results

The plastic bag control performed as expected, with the receiver coil producing about 5V and 1.3 A.

Initial results with the pork skin (still in the plastic bag) yielded strange results. When coils were aligned laterally, they would detect each other for brief times, outputting the normal 5 V, but would repeatedly drop down to lower voltages. In addition, if the coils were separated further while the output was at the lower (~2.2 V) voltage, it would maintain, and slowly deplete to zero, a particularly strange behavior.

It was theorized that the thickness of the sample was the issue, as opposed to the pork. Because the evaluation board being used has a relatively low power output and small coils, it does not have a very large effective range. Thus, another control was made, where plastic wrap was

folded until it was about the same thickness as the pork in the bag (~1.75 mm). When placing the plastic wrap barrier between the coils, the same strange output patterns were observed.

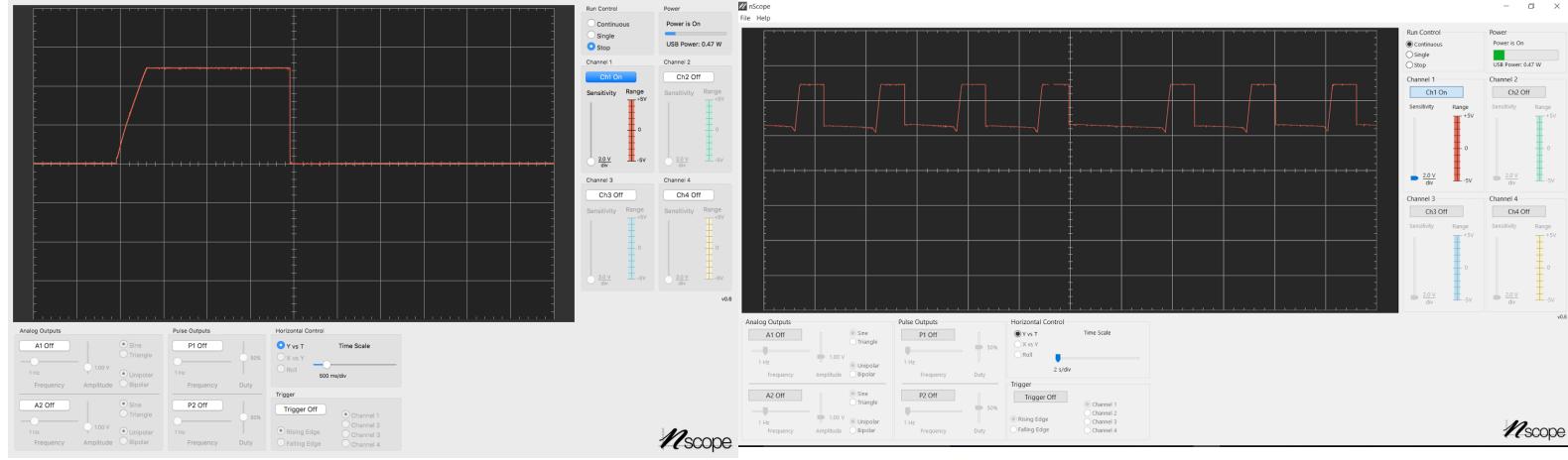


Figure 2. Representative voltage outputs from receiver coil upon placing receiver and transmitter in proximity. Left: Normal Functioning. Right: Just out of functional range.

Once some fat was stripped from the back of the skin in order to reduce the thickness, charging was seemingly completely unaffected by the presence of the pork skin, as seen in Table 1. The same could be seen with the plastic wrap control, where if compressed to less thickness, than the outputs became normal again.

Table 1. Maximum measurements found by condition. The pork skin only functioned equivalently to control when some fat was stripped away in order to lessen the distance between coils.

	Plastic Bag	Pork Skin
Max Voltage	5 V	5 V
Max Current	1.3 A	1.3 A

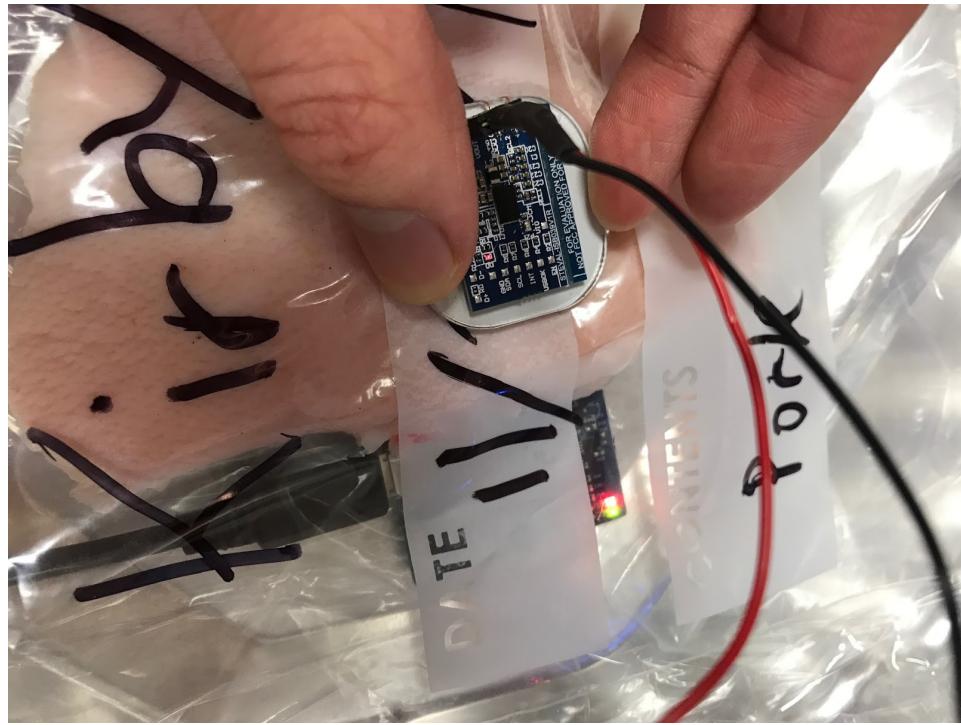
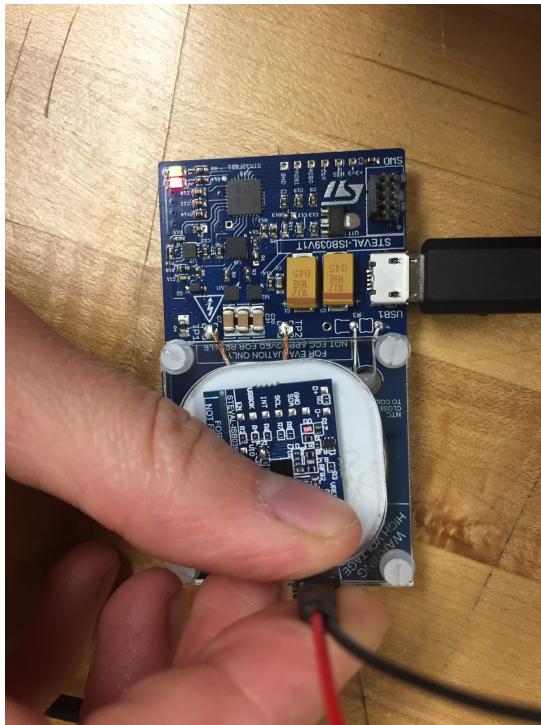


Figure 3. Left: Showing normal functionality (Notice the red LEDs on bottom right of evaluation board that indicate charging). Right: No charging detected when coils not in proximity.

### Conclusions

Looking at these results, it seems likely that charging can take place through organic tissue without a problem. The main concern is instead the distance over which charging can successfully take place.

It would be important to investigate at what depth the receiver coils could be implanted, so as to calculate what size/power of coil is necessary to transmit successfully.

It is also important to investigate heat generation from the charging process, which was not examined in this testing at all.

## **Appendix I: Titanium Charging Test**

### Purpose

The purpose of this testing was to see what effect, if any, a thin piece of titanium (0.018" thick) inserted between the wireless charging transmitter and receivers we are using in prototyping (STEVAL-ISB039V1). This would have implications for placement of any transceiver coils, as well as casing materials.

### Background

Titanium is often used in casings for implantables, due to its favorable biocompatibility and other useful properties. As such, we are considering it for a casing for at least part of our implant. However, titanium is also a conductor, and as such would probably absorb the EM waves being used to wirelessly charge the implant's lithium-ion batteries.

### Procedure

Two tests were done, control with only air between them, or experimental, with the thin sheet of titanium between them, covering the entire surface area of the coils. Voltage was measured using nScope, while the Rigol DM3068 Digital Multimeter was used to measure current output. The wireless transmitter was powered via microUSB, and was running on its default factory settings (currently unknown exact parameters, but supposed to output steady voltage and current as possible). Voltage and current measurements were taken at separate times, with no major loads in the circuit.



Figure 1. All materials used in testing.

The experiment was done using a single-case design. The receiver coil was repeatedly moved back and forth within/outside of charging distance, while voltage and current measurements were taken.

### Results

Overall, the titanium completely interfered with the wireless charging capabilities. We were unable to get the receiver to produce any significant amount of current or voltage with the titanium present, while in the control condition consistent, repeatable maximum outputs (seen below) were achieved.

Table 1. Maximum measurements found by condition.

	Control	Titanium
Max Voltage	5 V	0 V
Max Current	1.2 A	0 A

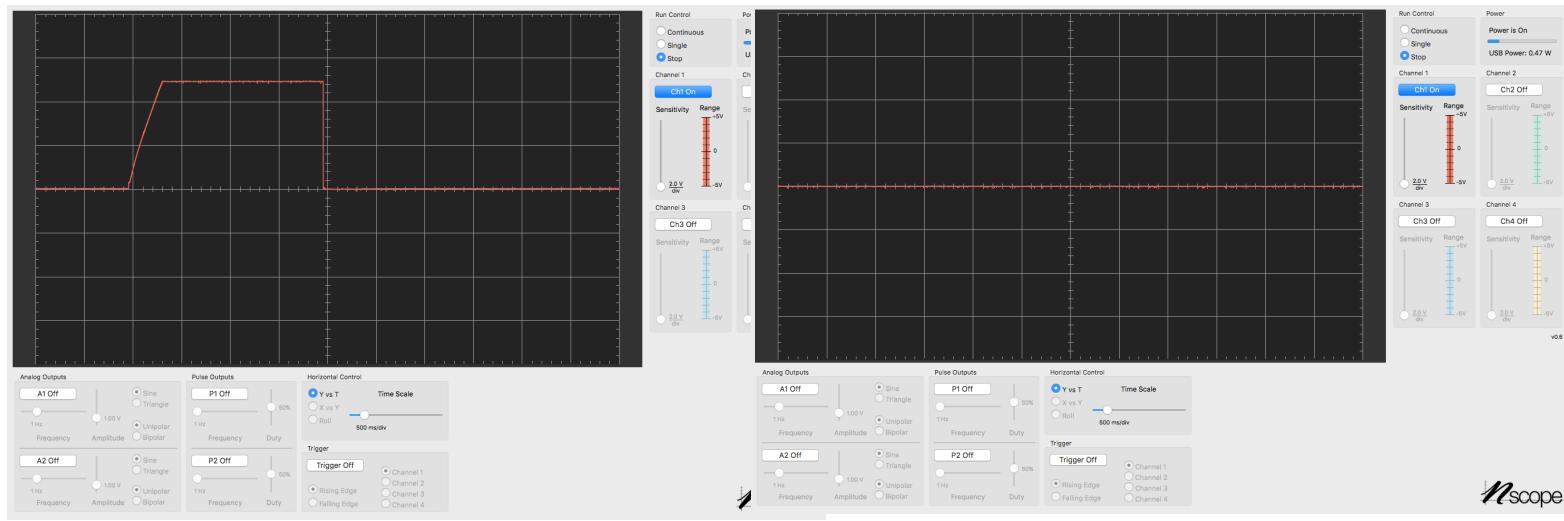


Figure 2. Representative voltage outputs from receiver coil upon placing receiver and transmitter in proximity. Left: control condition. Right: titanium present.

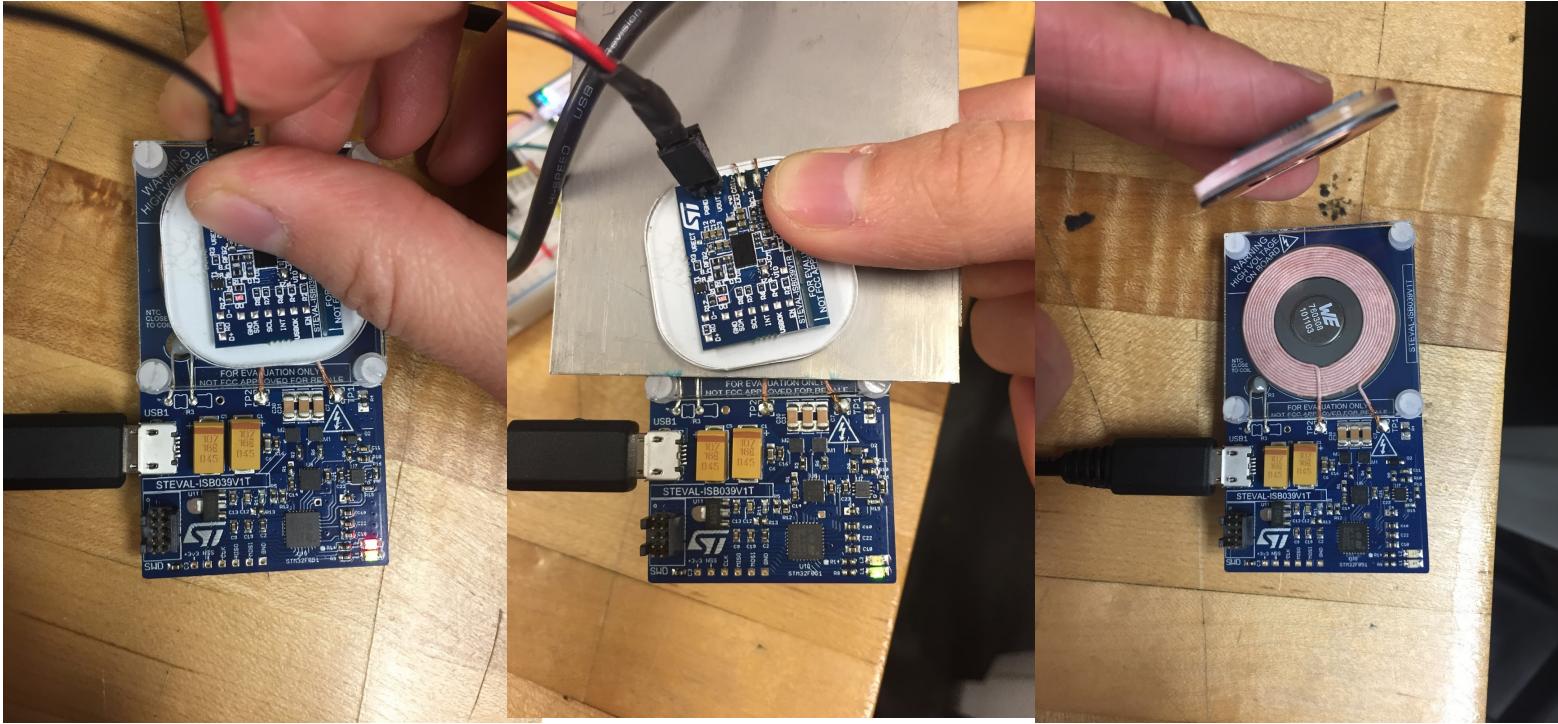


Figure 3. Left: control test, charging without titanium (Notice the red LEDs on bottom right of evaluation board that indicate charging). Center: No charging detected with titanium barrier. Right: No charging detected when coils not in proximity.

### Conclusions

Looking at these results, it is clear that there can be no titanium present between the coils of the transmitter or receiver if proper power transmission is to occur, at least with this evaluation board.

This also raises concerns about whether NFC can penetrate titanium casing. Further testing is necessary.

With an actual case, it would probably be a full hermetically sealed container, and as such would form a true Faraday cage with even more interference. Our true prototype might also utilize a more powerful transmitter. However, overall this is evidence that titanium casing would interfere with wireless magnetic induction charging.

Possible solutions include not using titanium for casing, or keeping the coils outside of the titanium casing.

## **Appendix J Animal Study Preparation**

### ***Meeting with Center for Comparative Medicine***

To clarify the steps and procedures necessary for setting up an animal study, the team met with Dr. Lisa Forman and Dr. Charlette Cain from the Center for Comparative Medicine at the Northwestern University Medical School. Options for animal models used in current studies for a possible protocol transfer were discussed and animal model options were narrowed down to canine, feline and rabbit models. Available resources were also discussed during this meeting and it was determined that animal care, veterinary services and surgery staff can be provided by CCM for the study at a per diem service charge rate. The team is in the process of completing pre-study trainings as well as constructing an independent protocol and an IACUC application.

### ***Training***

To perform an animal study, the team must undergo training required by the Institutional Animal Care and Use Committee (IACUC) Requirements.

- American Association for Laboratory Animal Science training class
- Occupational Health and Safety Program
- Facility Orientation

## Appendix K: Electrical Model of the Nerve

The phrenic nerve is composed of both myelinated and unmyelinated axonal fibers.<sup>1</sup> Therefore, electrical models of both myelinated and unmyelinated nerve models were explored to effectively illustrate the conductive properties of the nerve. These electrical representations can be seen in Figures 1 and 2 below.

### *Unmyelinated nerve model*

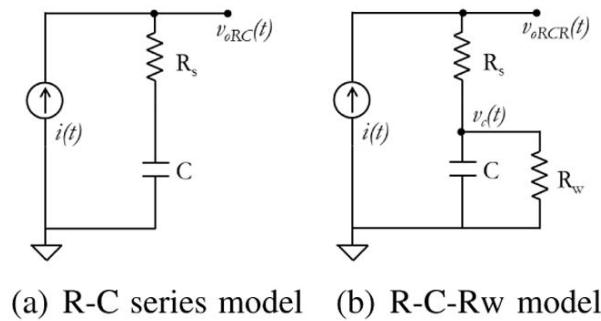


Figure 1 - Circuit to model an unmyelinated nerve<sup>2</sup>

### *Myelinated nerve model*

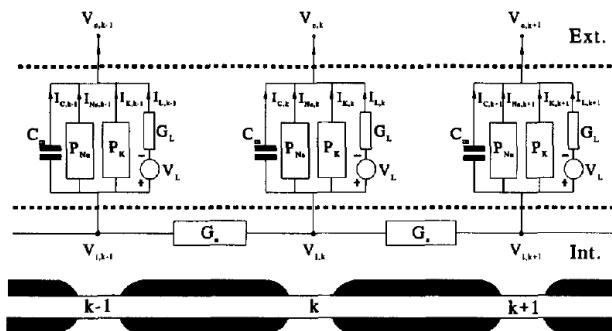


Figure 2 - Circuit to model myelinated nerve

<sup>1</sup> Balkowiec, Agnieszka, Sculczyk, Paweł. "Properties of postganglionic sympathetic neurons with axons in phrenic nerve". 1992. (Nov 13, 2016)

<sup>2</sup> Krishnan, Ashwati, Kelly, Shawn K. "On the Cause and Control of Residual Voltage Generated by Electrical Stimulation of Neural Tissue". 2012. (Nov 13, 2016).

Figure 1 represents an unmyelinated nerve fiber as a simple R-C series circuit while Figure 2 represents a myelinated nerve fiber. The myelinated model is still a variation of an R-C circuit, however, it takes various additional factors into account such as leak potential ( $V_L$ ), internodal leak conductance ( $G_L$ ) and the nodal membrane permeability for potassium ( $P_K$ ) and sodium ( $P_{Na}$ ).<sup>3</sup>

The electrical properties of the nerve could also potentially be simplified to a single resistor to model the most basic effect on the signal. Avery Biomedical used a  $1000\ \Omega$  resistor to test their devices and found that a 2 mA signal will generate a 2 V stimulus signal.<sup>4</sup>

Moving forward, the team will test each of these models to develop an understanding of the effect of the inputted pulse generation signals on the nerve and the conduction properties of the nerve. Nerve conduction time will be of particular interest as this will also be used as a measure in the animal study.

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<sup>3</sup> Frijns, J., Mooij, J., ten Kate, J. "A Quantitative Approach to Modeling Mammalian Myelinated Nerve Fibers for Electrical Prosthesis Design". 1994. (Nov 16, 2016).

<sup>4</sup> Martins, Tony. Avery Biomedical. Email Correspondence. (Nov 28, 2016).