Verification of Targeted Design Specifications

A battery of verification tests were performed to determine which of the design specifications outlined for the Bifrost stimulator were met. As described by Table 1, a range of 1-5 tests were performed to determine the success of the alpha-prototype in meeting a given specification. Verification tests referenced are described in detail within Appendix section A1.

Table 1: A table listing all design specifications, associated verification tests (as listed within Appendix A1), and outcome of the verification tests for the Bifrost stimulator alpha prototype. The color coding for the Outcome column entries are green implies the specification was met or exceeded, red implies the specification was not met, and yellow implies an inability to test the specification. Note, room temperature was defined as between 20 and 25 °C.

Specification Number	Specification	Quantitative Metric	Verification Test(s)	Outcome
1	Operable relative humidity range	0-70%	2	Specification met
2	Usable for people in the following age range	12-80	3, 4, 6, 8, 9	Specification exceeded (12-82 age range)
3	Maximum time achieve pain blocking effect	5 minutes	14	Specification exceeded (12 second on-time)
4	Minimum device durability	28 days	4, 5, 6	Specification not met (drop durability failed)
5	Maximum device dimensions	17.8 cm X 17.8 cm X 10.2 cm (7 in X 7 in X 4 in)	7	Specification exceeded (final dimensions of 15.2 X 15.2 X 10.2 cm)
6	Maximum device weight	1.36 kg (3 lbs)	1	Specification exceeded (.67075 kg)
7	International Protection Marking rating	IP41	4, 5	Specification met (IP41 rating)
8	Maximum temperature of internal circuitry at room temperature	37.8 °C (100 °F)	8	Specification exceeded (maximum temperature of 26.3 °C)
9	Range of operable atmospheric temperature device	12.8-37.8 °C (55-100 °F)	8	Specification exceeded (operable between 4 and 37.8 °C)
10	Battery life	24 hours	9	Specification not met (6.5 hour battery life)
11	Maximum recharge duration	1 hour	10	Specification not met (1.5 hour recharge time)
12	Stimulation frequency	14-26 kHz	11	Specification met
13	Electrical stimulation amplitude (transmission voltage)	0.15-10 V	13	Specification met (0.383 V_{pp})
14	Input carrier frequency	5 MHz	12	Specification met
15	Maximum distance between implant blocker and external power source	4 cm	14	Specification unverified
16	Power Transfer Range	0.5 - 200 mW	13	Specification unmet (7.5 µW power output)
17	Time to completion	5 months	15	Specification met
18	Maximum cost for prototype	$500	15	Specification exceeded (actual cost of)

Note that verification test 15 was not completed within the performed verification plan due to lack of an available rat. The client informed the design team only 4 days before the *in vivo* verification test was planned and 9 days before the prototype deadline that the murine model intended for use was no longer available. Nonetheless, this verification test is critical to downstream validation of the Bifrost stimulator and is a key next step for proof-of-concept.

Overall, the device complied with the key mechanical and electrical specifications outlined. At face value, 13/17 or approximately 76.5% of the design specifications (that could be tested) were met. Although this is inherently promising as a strong majority of specifications were achieved, it is also critical to consider the relative importance of each specification. Aspects core to device functionality such as usability (specification 2), output signal waveform (specifications 12, 13, and 14) were met or exceeded. In addition, the device remained functional across all environments it is expected to come in contact with during 28-day timeframe of patient use. This includes output signal fidelity (i.e. fulfilling specifications 12, 13, and 14) across the listed temperature and humidity ranges (specifications 1, 7, and 9).

In contrast, a majority of the failed verification tests point to aspects of the prototype that can drastically be improved relatively trivially in later iterations. Namely, specification 4 associated with the durability of the device is bound to increase as a professional manufacturing workflow is leveraged for production of the market-ready version of the device. Custom insulation and support structures designed to fit the internal circuitry exactly will ensure greater durability. Further, conversion from analog to digital signal processing will increase the ability of the components to withstand force.

Failed specifications 10 and 11 are associated with the battery capacity of the system and its power consumption. These are more peripheral design elements that do not speak to the overall device ability to portably generate the intended waveform and are not critical to

proof-of-concept demonstrations. Further, there are known elements of the current prototype that can be augmented or replaced to facilitate increases in battery life and recharge speed. Currently, the entire system is based on analog signal processing. Namely, the 5 MHz and variable stimulating frequency between 14 and 25 kHz are generated as independent analog signals before being sent through another analog component (analog multiplier) for intended output waveform generation. Downstream, the design team plans to convert the circuitry from analog components connected via breadboards to a single PCB chip. This will reduce any inefficiency in power transfer between components. Further, transitioning from analog signal generation (i.e. with an analog multiplier) to digital signal processing will reduce the number of powered components and current draw from the battery to the signal generating components. Paired with pulse width modulation powerering, the battery usage should decrease by at least half. Further, as the space needed for electronic circuitry decreases, a larger battery can be installed. Currently, the installed 2500 mAh battery only takes up 0.78% of the volume of the stimulator. This can drastically increase as the circuitry is compacted, while still allowing the device to retain its portable nature.

Specification 16 is another aspect of the prototype that will assuredly be improved downstream and does not reflect on the proof-of-concept success. Power amplification systems are relatively common electronic components that can be integrated into the output of the current circuit to boost wattage. The reason this was not currently implemented is due to unknown factors such as the type of primary coil that will be used in the patient setting and the impedance between the primary coil and the skin. This is because, in RF power transfer systems, the impedances of the input and output of the coil must be matched to avoid harmful reflection of power back into the electronic system. This reflection of power could have fatal consequences on device functionality such as overheating and possible fire—potentially

harming the user. As such, only when these parameters are well understood can the design team proceed to integrate signal power amplification.

Validation Results

Validation testing was performed centered on three key criteria: wearability, functionality, and repeatability.

Device wearability was determined by assessing the prototype's ability to conform to the following requirements: (1) the device should be powered with batteries and should not need to be plugged in, (2) the batteries need to be rechargeable, (3) the device must be lightweight (less than 1.36 kg), (4) the device must also be holdable with reasonable dimensions. As demonstrated by Table 1, the final prototype conforms to specifications 2 (usability across the intended age range) and 6 (mass). Further, the device is battery powered and rechargeable albeit not to the expected standards described by specifications 10 and 11, respectively (Table 1). As described above, the shortcomings associated with design specifications 10 and 11 can be remedied in future iterations of the Bifrost. Thus, given that the device fulfills all four criteria outlined to define wearability, the prototype passes this validation requirement.

In terms of functionality, the prototype's ability to fulfill this aspect of the validation was initially planned through a three-tranched strategy. First, initial testing of the direct output signal waveform measured through electronic equipment (multimeter and an oscilloscope) was planned. Next, the design team planned to conduct *ex vivo* testing of signal transmission by analyzing the ability of a signal from the Bifrost stimulator connected to a primary coil to be delivered to a secondary coil through air. Finally, functionality would be assessed by conducting an *in vivo* test wherein the Bifrost would be used to power an implanted nerve stimulator fitted to

a sciatic nerve in an anesthetized murine model. However, 4 days prior to *ex vivo* and *in vivo* testing, the design team was notified by the client that the materials needed for testing would no longer be available. Given the prototype deadline was rapidly approaching (9 days remaining), the design team decided to complete all other planned design verification tests. During the drop durability test, the device failed during a 0.91 meter drop. As such, the team was unable to complete the remaining two tranches of functionality testing. Based on assessment of the prototype through direct waveform measurement, the intended waveform was successfully generated (fulfilled specifications 12, 13, and 14 from Table 1) prior to the drop test.

The last aspect of validation testing involved assessing the fidelity or reproducibility of the system output. It is critical for medical devices to consistently provide the same output to ensure patients can accurately complete the prescribed treatment course. Thus, the prototype was assessed for its ability to produce a repeatable output. Namely, the Bifrost stimulator was connected to an oscilloscope to measure its output signal across three trials separated by 20 minutes. The results of each trial and the percent differences are summarized in Table 2.

Table 2: A table listing the output carrier frequency, stimulating frequency, and peak-to-peak voltage across three trials equally spaced across one hour. Note, the carrier frequency was programmed to 5 MHz and the stimulation frequency was programmed to 14 kHz.

	Trial				
Parameter	1	2	3	Average	Average Percent Variation from Mean
Carrier Frequency (MHz)	4.98	5.04	5.07	5.03	0.66
Stimulating Frequency (kHz)	14.05	14.21	14.11	14.12	0.41
V_{pp} (V)	0.376	0.389	0.384	0.383	1.22

Based on the results of Table 2, it is clear that the system confers high fidelity in output signal parameters. Thus,based on the conducted tests, the device fulfills all facets of validation: wearability, functionality, and reproducibility.

Device Components and Diagrams

Parts List

The following parts list tabulated in Table 3 includes details for all of the parts used to build the final Bifrost prototype. First pages of the listed the datasheets can be found in Appendix E.

Table 3: Part list for components of the Bifrost Prototype. Note lead times refer to order lead time, (time from customer order received to customer order delivered).

Component (Number)	Price ($)	Specifications/Data Sheet	Lead Time (Days)	Source
Arduino Uno R3 (2)	44.00	https://www.farnell.com/datasheets/1682209.pdf	2	Arduino Online Store
Hitachi HD 44780 16x2 LCD Display (1)	5.99	https://www.sparkfun.com/datasheets/LCD/HD44780.pdf	1	Amazon
Rotary Encoder (1)	3.95	https://www.farnell.com/datasheets/1837001.pdf	1	Amazon
2500 mAh Battery (1)	15.99	https://www.adafruit.com/product/328	2	Adafruit
PowerBoost 1000 Charger (1)	19.95	https://learn.adafruit.com/adafruit-powerboost-1000c-load-share-usb-charge-boost/downloads	2	Adafruit
AD834 Analog Multiplier (1)	41.98	https://www.analog.com/media/en/technical-documentation/data-sheets/AD834.pdf	7	Digi-Key
SOP8 Board (1)	7.99	https://www.arieselec.com/products/data/19000-small-outline-prototyping-adapters.pdf	2	Digi-Key
AD9850 DDS Synthesizer (2)	46.80	https://www.nooelec.com/store/downloads/dl/file/id/24/product/86/ad9850.pdf	1	Amazon
Prototyping Board (2)	3.04	1 x 8 x 5 cm	0	Micro Center
Battery Charger (1)	9.99	5V & 2.5A power supply with Micro USB output, https://www.amazon.com/Raspberry-Power-Supply-Adapter-Charger/dp/B0719SX3GC	6	Amazon
Potentiometer (1)	5.99	https://components101.com/sites/default/files/component_datasheet/potentiometer%20datasheet.pdf	1	Amazon
Switch (1)	0.71	https://www.alliedelec.com/m/d/4b01369cd497d0a29d14c860eb221183.pdf	2	Allied Electronics
10KOhm Resistor (1)	0.05	https://www.alliedelec.com/m/d/5c22b21fcadf6efc3f053d50cbf71e24.pdf	2	Allied Electronics
Storage Container (1)	12.00	10.2cm x 15.2cm x 15.2cm	0	Target
Total	**252.27**	**N/A**	**N/A**	**N/A**

In addition to these enumerated resources, unquantified amounts of standard prototyping materials such as solder, single core wire,and heat shrink tubing was used to connect the components. Further, hot glue was used to adhere components such as the LCD screen, power switch, and frequency control knob (rotary encoder) to the device casing and seal any gaps.

Further, the following prototyping equipment was used in device construction: soldering iron, heat gun, oscilloscope, multimeter, and drill.

Circuit Drawings

Circuit diagrams presented represent the carrier frequency (5 MHz) generating component (Figure 1), the variable stimulating frequency generating component (Figure 2), and the composite circuit diagram describing all connections within the Bifrost stimulator and the overall device output (Figure 3). Please note that all perpendicularly crossing wires within the diagrams do not represent connected wires and simply are overlaid due to the 2D nature of these drawings. In the below diagrams, some powered components (such as the AD9850, LCD screen, and potentiometer in Figure 2) are linked to a +5V output and ground in arrow notation and not explicitly a depicted battery. This is simply to ensure readability of the diagram and as there a variety of equally valid configurations that can be employed to successfully complete the circuit. Each of these sources may be powered through the 5V and GND pins voltage out pins on the Arduino Uno R3 or directly from the battery source used to power the Arduino components. The decision between these two options should be made based on the spatial configuration of the devices and length of wire needed to make the different connections within each option.

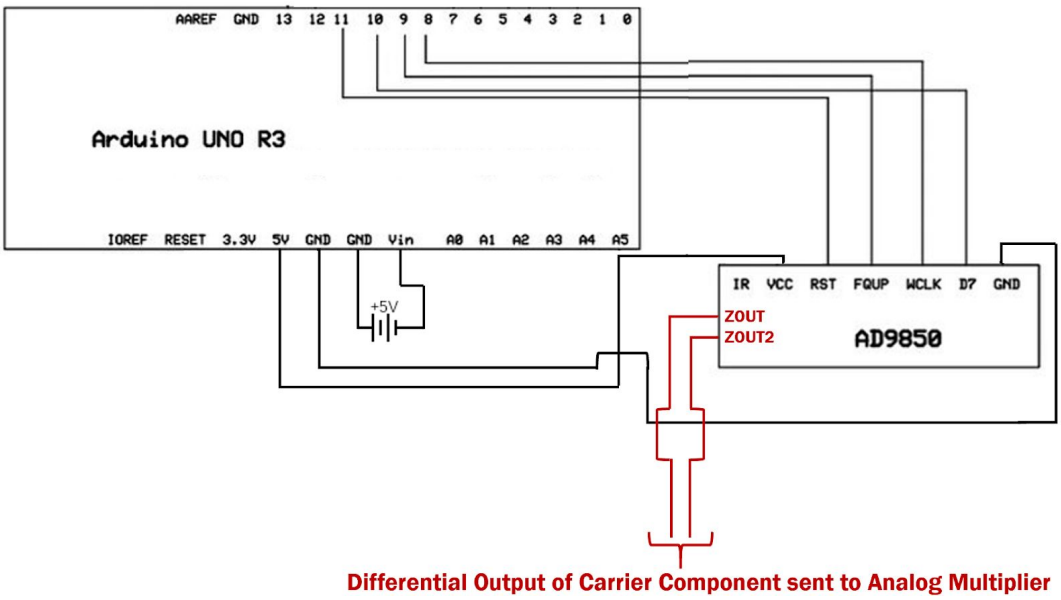

Figure 1: Circuit diagram of the Arduino Uno and AD9850 function generator chip used to develop the 5 MHz carrier frequency voltage signal. No user-facing interface is present to alter the output of this component as the carrier frequency is determined by the client's bioresorbable nerve inhibitor the Bifrost will be paired with and will never need to be changed. Note that the two analog outputs from the AD9850 chip (ZOUT and ZOUT2) are highlighted in red to represent the output of this circuit component within the Bifrost prototype.

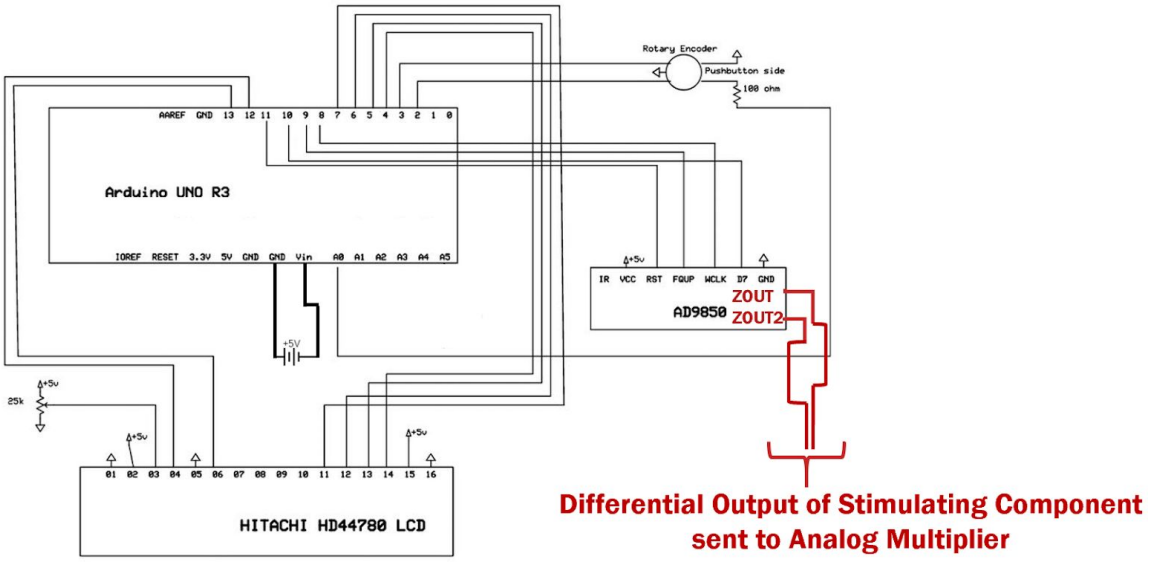

Figure 2: Circuit diagram of the Arduino Uno and AD9850 function generator system used to develop the 14-25 kHz variable stimulating frequency voltage signal. Further, the Arduino logic board was connected to an LCD screen and rotary encoder. The LCD display displays the stimulating frequency output by the AD9850 chip and the rotary encoder allows the user to alter the outputted stimulating frequency. Further, a potentiometer connected to the LCD display is used to control screen contrast.

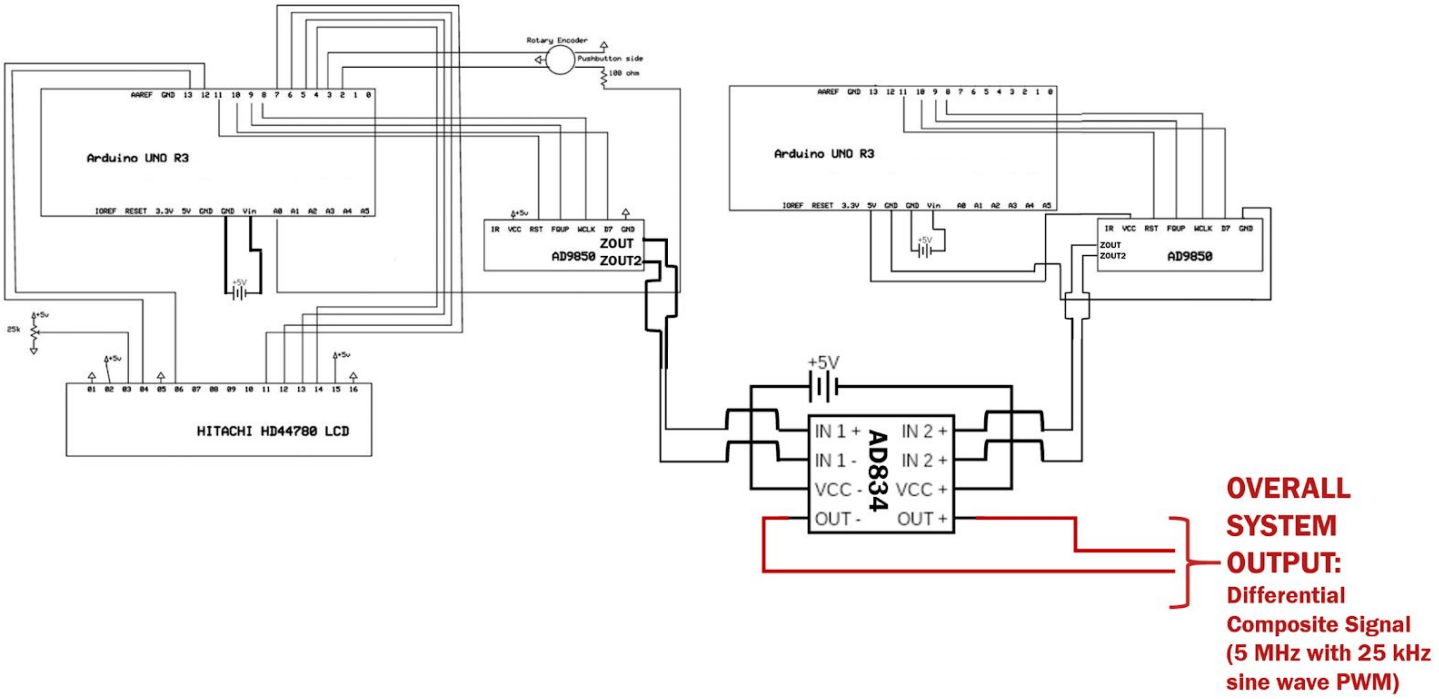

Figure 3: Circuit diagram representing complete connection of all electronic components within the Bifrost prototype. Circuits depicted in Figure 2 and Figure 1 are connected to the AD834 high frequency analog multiplier's differential input pins to generate the composite, overall output waveform (highlighted in red).

Wiring Diagrams

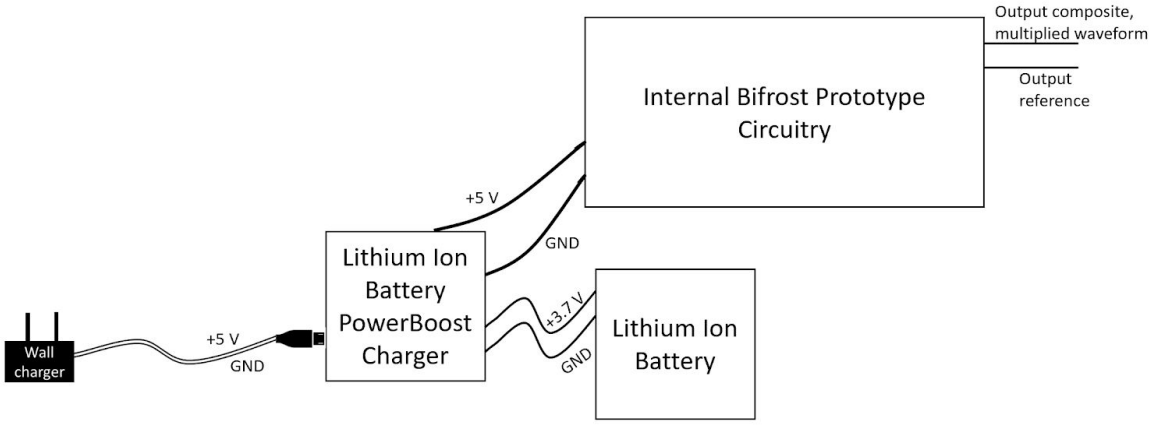

Figure 4: Wire diagram demonstrating the overall input and output connections between the Bifrost stimulator and the outside. Note that ground is abbreviated as GND within the drawing. Further, both the PowerBoost and the lithium ion battery used to power the stimulator are located within the prototype but drawn outside in this diagram clarity.

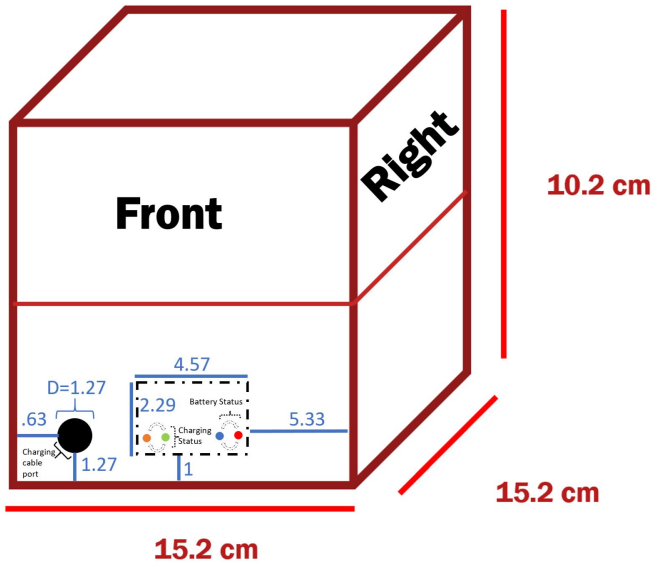

Figure 5: Mechanical drawing of the front view of the Bifrost stimulator. The left, black circle represents a hole that needs to be drilled into the casing for the charging cable to pass between the inside and outside of the device. The dashed box represents the battery status chip (PowerBoost 1000 charger) and is placed on the inside of the casing. As it is an electrical component it is insulated by the plastic casing but still visible due to the casing's translucent nature. The charging status switches between orange (charging) and green (fully charged) while the battery status switches between blue (healthy) and red (low battery). Note that the figure is not drawn to scale and all measurements are in centimeters.

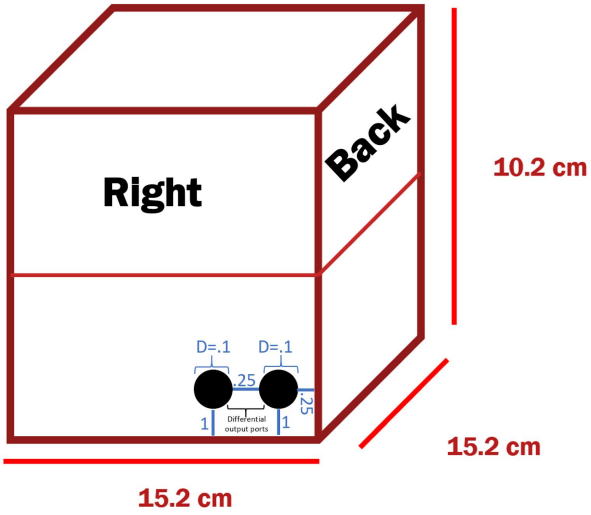

Figure 6: Mechanical drawing of the right view of the Bifrost stimulator. The two circles represent 0.1 cm holes to pass the differential output waveform from the inside of the casing to the outside. Note that the figure is not drawn to scale and all measurements are in centimeters.

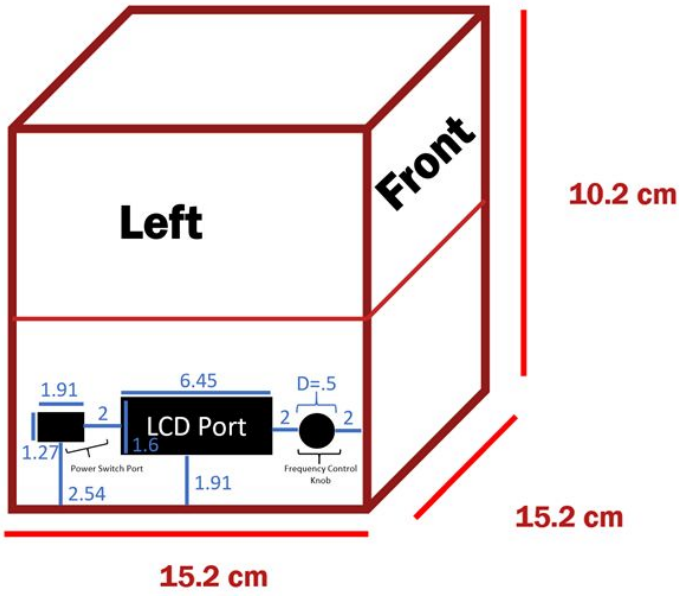

Figure 6: Mechanical drawing of the left view of the Bifrost stimulator. Each port and the knob represent shapes that need to be drilled out of the casing to allow for user access of the power switch, LCD screen, and frequency control knob (from left to right in the diagram). Note that the figure is not drawn to scale and all measurements are in centimeters.

Software Code Flow Diagrams

Coding diagrams presented demonstrate logic flow for each of the methods the Arduino Uno R3 logical processor is equipped with in the Bifrost device. The actual code employed can be found in Appendices C1 through C3 and the visualization presented in this section was facilitated through the use of the code2flow (code2flow.com) platform.

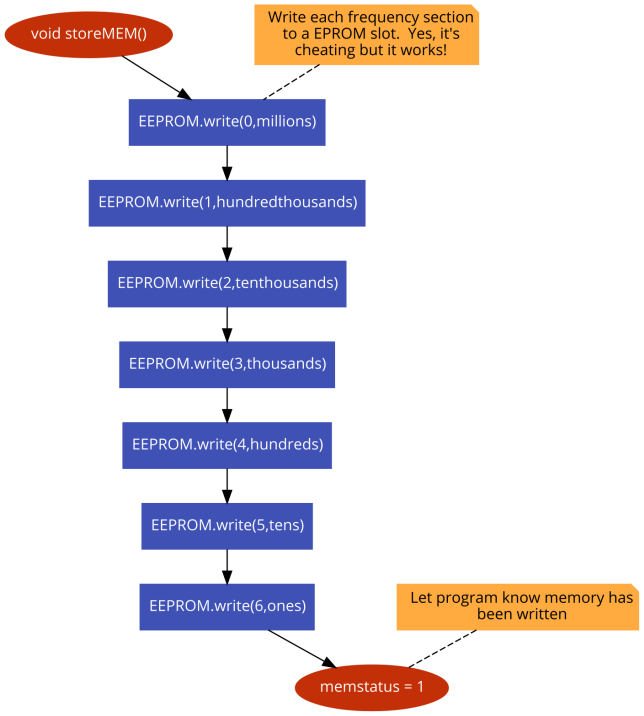

Figure 7: Software flow diagram depicting a method that assigns numbers as shorthand for different increments in base-10 to be used by other methods for frequency changes.

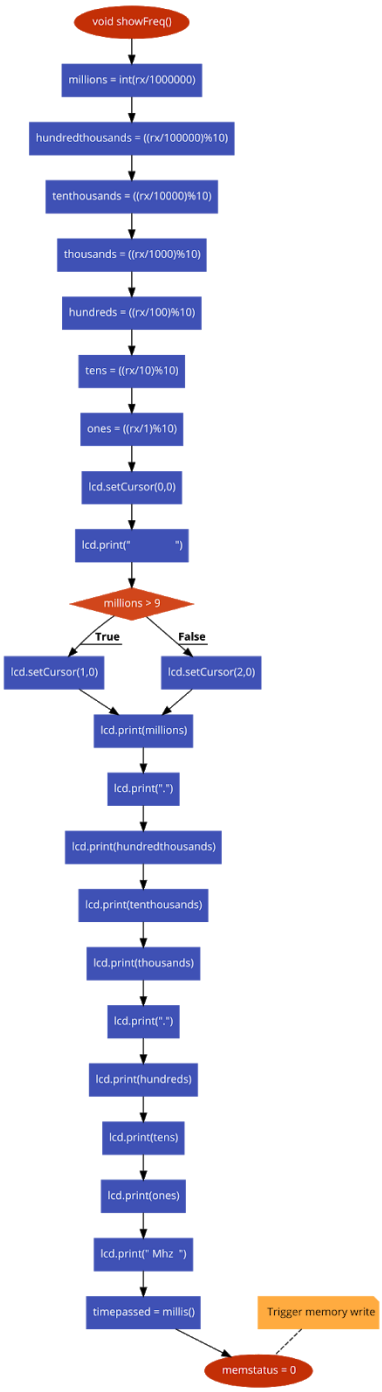

Figure 8: Software flow diagram demonstrating how the current set frequency (variable rx) is passed to the LCD display for representation to the user.

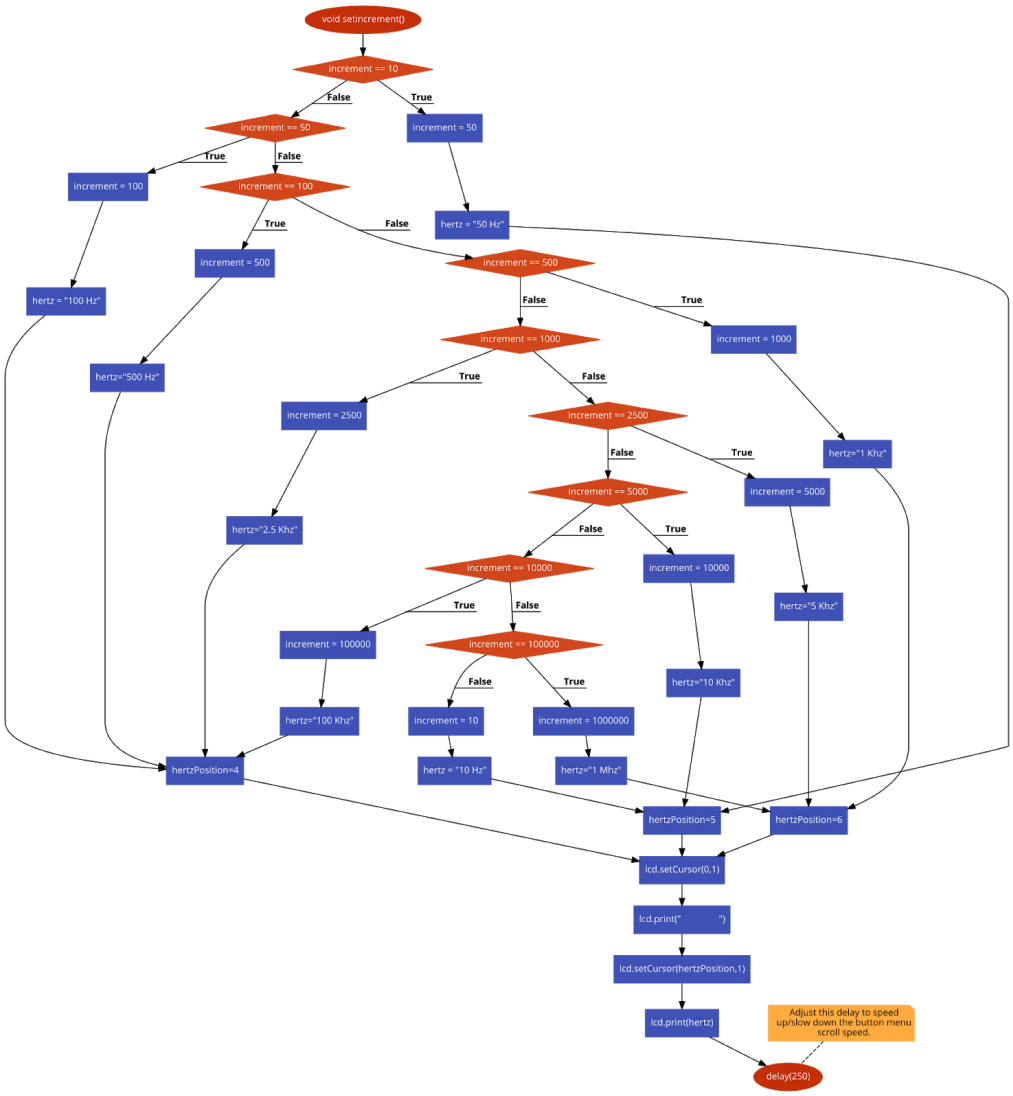

Figure 9: Software flow diagram depicting how pushes of the rotary encoder are read to change the increment frequency for every turn of the encoder.

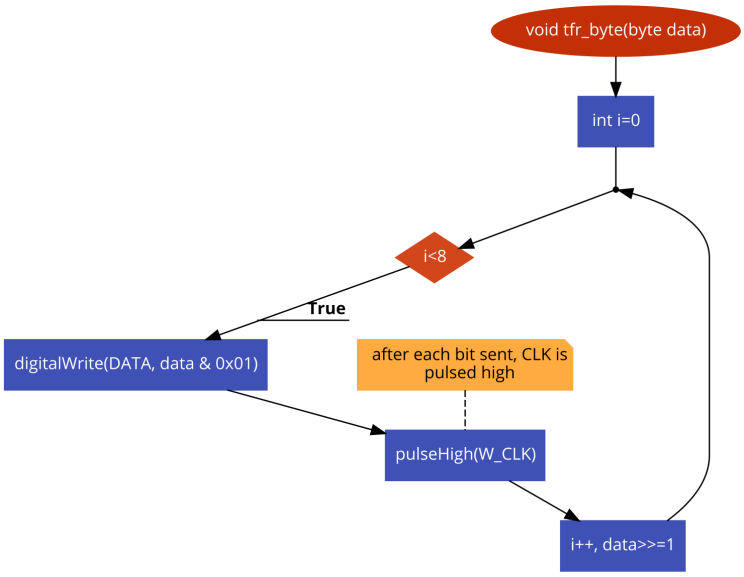

Figure 10: Software flow diagram depicting the tfr_byte method that splits the input variable, data, into bits to send to the AD9850 chip one at a time.

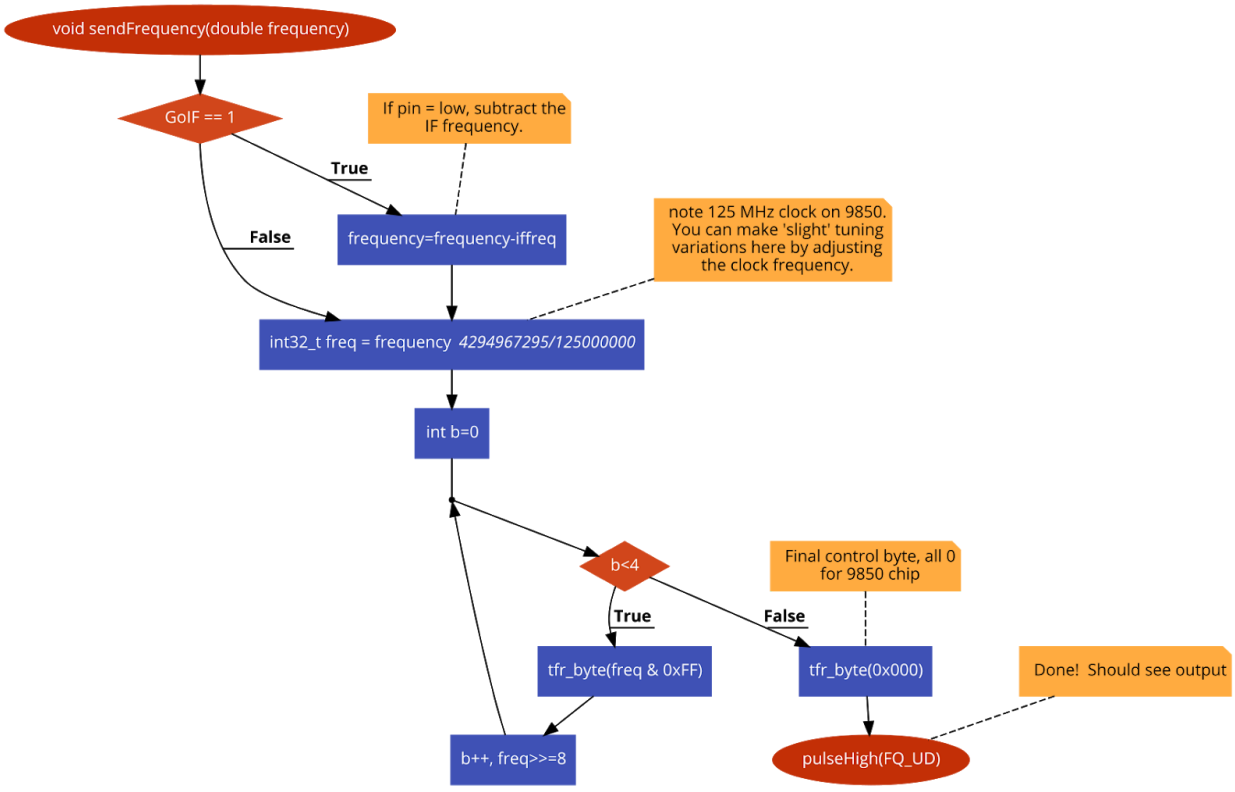

Figure 11: Software flow diagram representing the sendFrequency method that takes in a double representing the desired frequency signal and sends the appropriate message to the AD9850 chip to cause a change in that frequency.

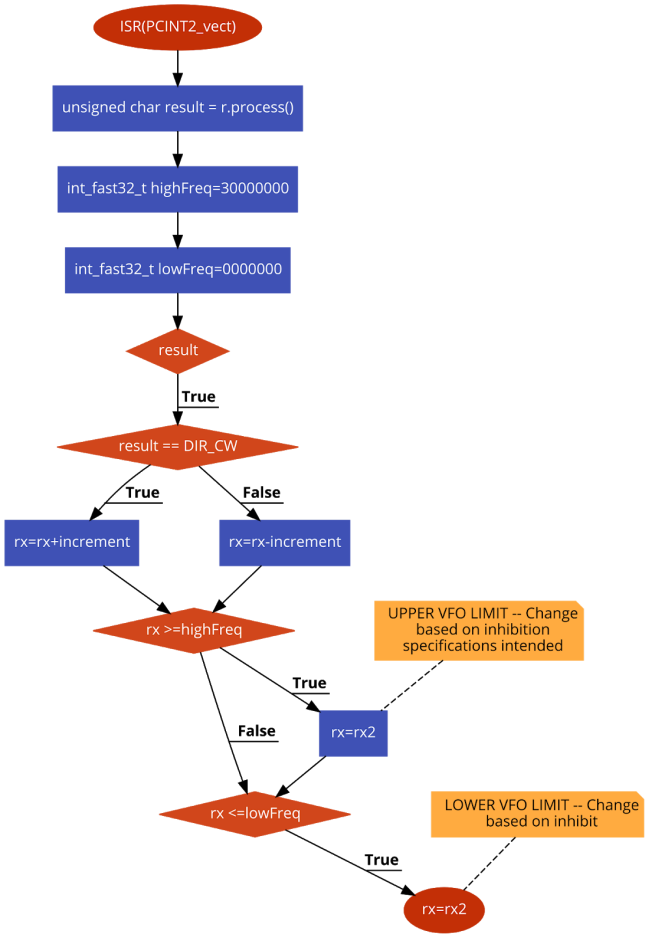

Figure 12: Software flow diagram depicting the method that ensures turns of the rotary encoder do not cause the frequency request sent to the AD9850 chip to go above or below the set frequency output limits represented by double-type variables highFreq and lowFreq, respectively.

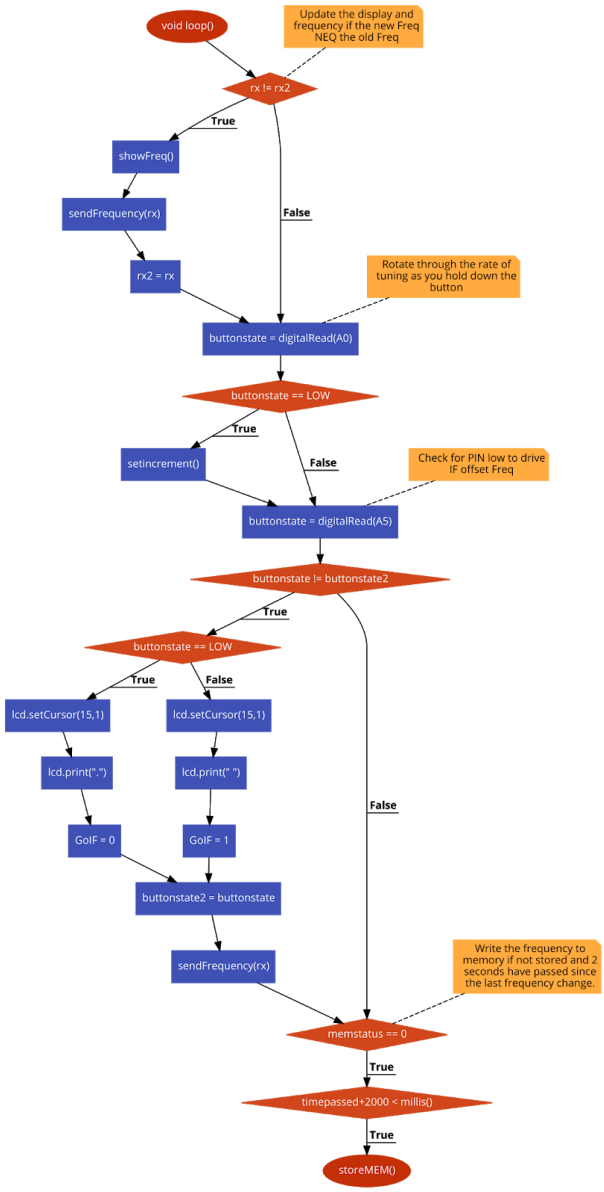

Figure 13: Software flow diagram depicting the continuous check between the currently set frequency and that reported by changes in the rotary encoder to ensure the AD9850 chip is outputting the desired frequency in real time.

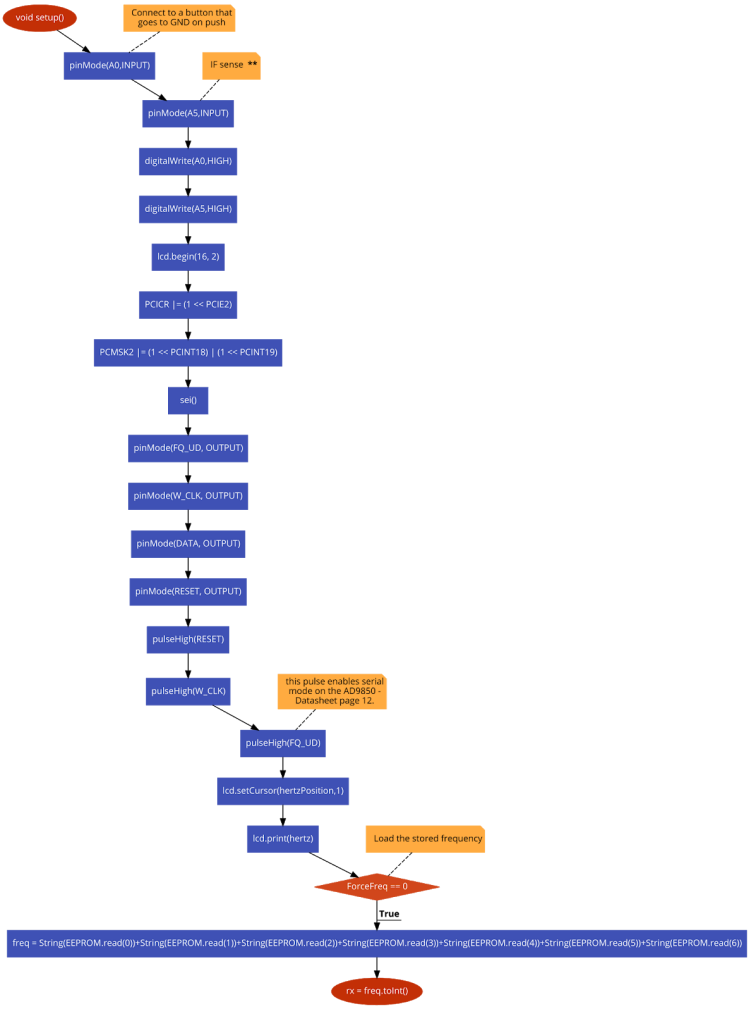

Figure 14: Software flow diagram depicting the initialization of the LCD and AD9850 boards upon startup of the Arduino Uno R3 system.

User Interface and Images of Completed Prototype

The Bifrost User Interface (UI) is comprised of three key panels: frequency control, device status, and waveform output.

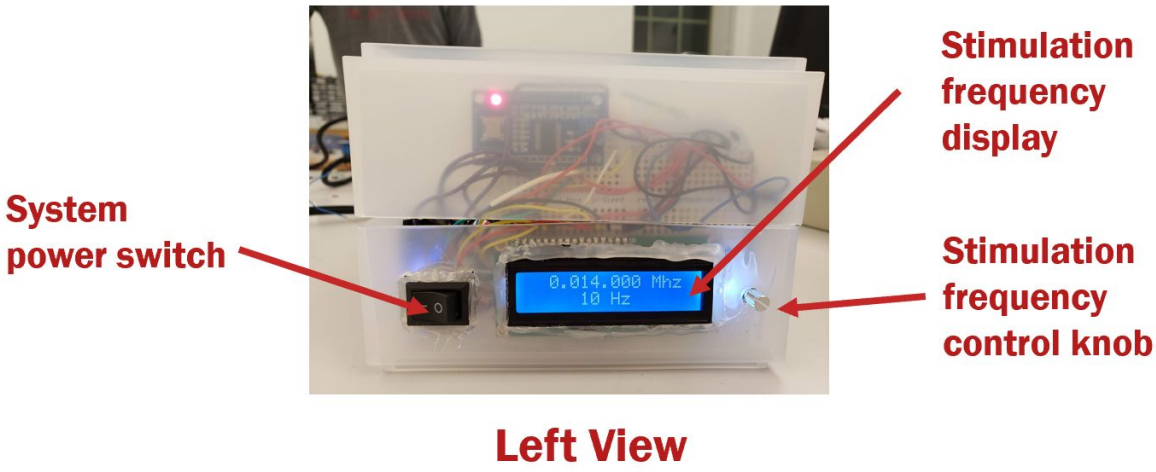

Figure 15: Frequency Control panel of the Bifrost Device. This includes a power switch for the whole system, a display of stimulation frequency, and a frequency control knob.

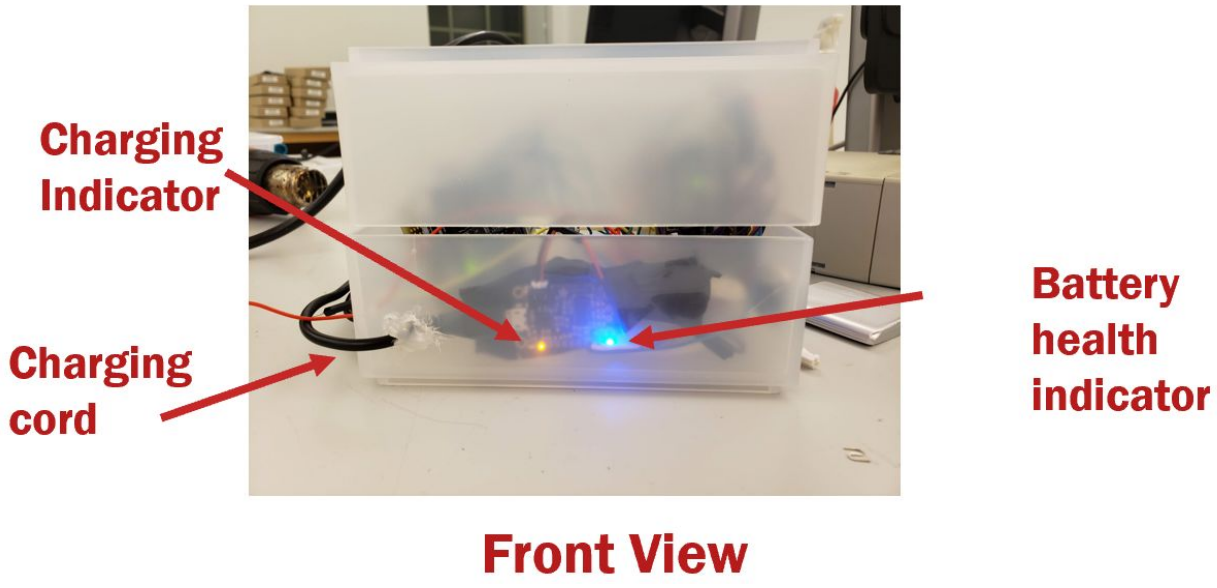

Figure 16: Device Status panel of the Bifrost Device (front view). The power status of the device is communicated via a system of LED bulbs on the device status panel. As described in Figure 5, charging status (left LED) switches between orange (charging) and green (fully charged) while the battery status (right LED) switches between blue (healthy) and red (low battery).

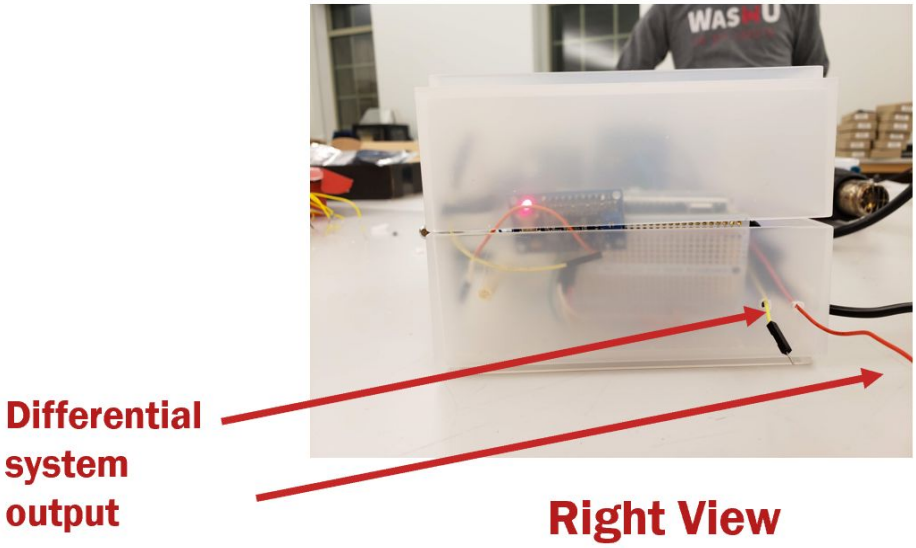

Figure 17: Output Panel of the Bifrost (Right View). The differential output of the system is transmitted via two wires exiting the lower half of the Bifrost's output panel.

Ergonomic Optimization

During development of the Bifrost prototype the wide age range of the end-user was considered. To facilitate high usability and accommodate the undoubtedly diverse patient population the device will interface with, the user interface was segmented into three panels (Figures 15, 16, and 17). Each of these panels organized the different aspects of the device. All frequency controlling aspects of the device were sequestered to the Left Panel (Figure 15). The battery status of the device and charging (both associated with device powering) were organized on the Front Panel (Figure 16). Finally, the waveform meant to be sent to the primary coil was placed on the separate, Right Panel (Figure 17). This was because in the planned use-case, the Right Panel would likely be obscured by a primary coil and placed on the location of the patient's body where the inhibitor was implanted. As such, any information presented on this panel would be lost to the user during therapeutic use. Instead, information was contained to the Front and Left Panels of the device that would likely be visible even during use.

Alongside this, universe color language was employed on the battery status indicator as shown in Figures 5 and 16. Green is used to depict fully charged, orange is used to describe charging, and red is used to describe low battery. This ensures that, even with limited instruction, a user would be able to intuitively use the device.

While ergonomic factors were considered in the development of the alpha prototype of Bifrost, this can be further optimized downstream through collaboration with a human factors engineering.

Safety Analysis and the Regulatory Landscape

Design Safe Analysis

Overall, hazards of operating the Bifrost device may be broadly categorized as thermal and electrical. The device relies on magnetic induction and associated control systems. If the load (i.e. the body) and source impedances are not properly matched, the energy may be reflected from the load and back to the source (i.e. Bifrost stimulator), which diminishes power transfer efficiency and may damage the source as a result of excess heating[6]. Some of the elements within the Bifrost's circuitry such as the analog multiplier heat up very quickly if connected improperly or shorted. Lithium polymer batteries are designed to operate within a safe voltage range from 3V to 4.2V. However, over-charging above 4.2V could be dangerous and eventually cause fire. As given by DesignSafe, heat risk is categorized as "slight" to "serious" depending on the identity and experience of the operator.

The second major risk posed by the Bifrost is a result of electrical shock. The Bifrost is built from several electrical components powered by a Lithium Ion Polymer Battery (3.7V, 2500mAh). The threat posed by electrical shock may arise from significant exposure to water (i.e. a bathtub) and improper handling of the battery and other circuit components. Risks relating

to electricity are categorized as “slight.” It is important to note that while the alpha prototype is IP41 rated, downstream iterations of the prototype can include more secure plastic casing improving the waterproof nature of the stimulator.

The users of the Bifrost are categorized in three main groups: clinical (doctors and nurses), device technicians, and patients (including family members and caretakers). Each of these users face both the electrical and heat related hazards given above. However, device technicians will be trained extensively to safely handle the device and avoid these hazards. In contrast, patients need not be aware of such risk mitigation strategies, yet they must also be protected from these dangers. Therefore mitigation strategies must not require prior knowledge or training related to electronic hardware. These strategies include warning labels, proper clinician and patient training, and use of thermal and electrical insulators within casing.

Note, the Design Safe Analysis report that led to these conclusions can be located in Appendix D.

Food and Drug Administration Approval Plan

Within the United States, the Food and Drug Administration (FDA) is the regulatory body that determines whether any new medical technology can enter the market. It is important to recognize that the Bifrost will be submitted to the FDA together with the bioresorbable nerve inhibitor as it is a composite system that together serves to abate pain. This is best characterized by the FDA’s GZJ product code (defined as transcutaneous electrical nerve stimulator for pain relief). This implies a Class II specification - allowing the pain inhibiting system to obtain market approval through the accelerated 510k pathway. In discussions with Graematter, Inc. (an FDA/regulatory consulting agency), a strong history of GZJ devices successfully entering the medical device marketplace through the 510k

mechanism have been discovered. Over 570 neuro-pain management devices have gained market approval. Given that the Bifrost system emits voltage amplitudes lower than other 510k Class II, GZJ devices (882.5275 emits up to 20 V), it is clear that there is a history for FDA endorsement for similar devices.[7] The implantable nerve stimulator is produced with magnesium, silicon dioxide, and PLGA. Magnesium is an essential mineral present in the human body in large amounts, mostly in bones.[8] People obtain most of the magnesium in their bodies through their diet. Silicon dioxide is one of 370 Generally Recognized As Safe (GRAS) substances as classified by the FDA. The Select Committee on GRAS substances said in a written opinion that silicon dioxide and various silicates occur abundantly in the earth's crust, are present in practically all natural waters, animals, and plants, and are part of the normal human diet. PLGA is biocompatible and biodegradable, exhibits a wide range of erosion times, has tunable mechanical properties, and, most importantly, is an FDA approved polymer[2]. Confidence is further bolstered by the fact that the 510K mechanism has also been previously approved for bioresorbable devices (888.3030).[9] Further, key predicate devices for the Bifrost (FDA regulation codes 882.5275 and 882.5890) have gained approval without clinical trials.[7,10] These facts are summarized in Figure 18.

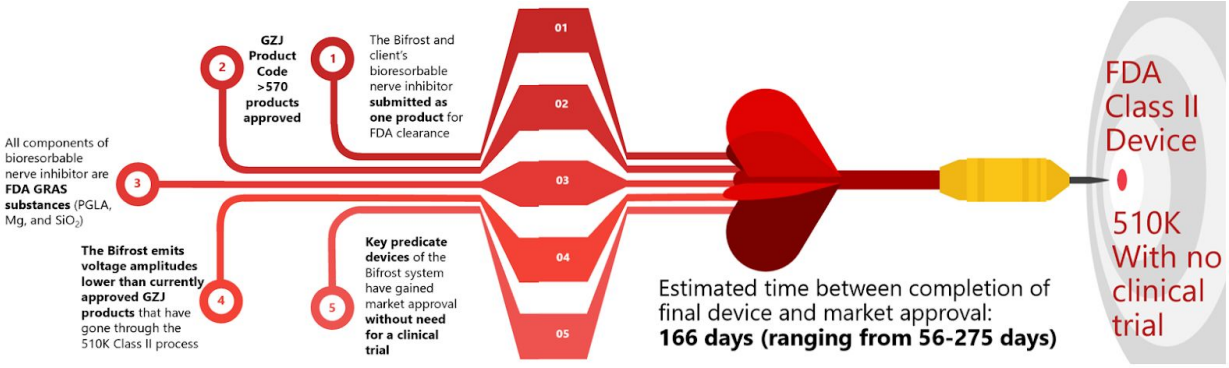

Figure 18: A pictorial depiction of the five key aspects of the Bifrost and its associated nerve stimulator that indicate likelihood of FDA market approval through the Class II 510K mechanism. Note, estimation of time between completion of final prototype and market entry is based on analysis of previous GZJ approval time course. This will significantly reduce costs and time to entry to obtain FDA approval compared to a Class III PMA process.