The Bifrost

Verification & Validation Report

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Client: Dr. Matthew MacEwan

BME 401A: Senior Design

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Introduction

For updates on the team's design specifications, project timeline, and responsibilities see the Appendix. Before the verification and validation plans are described, it is important to distinguish between verification and validation when reporting the efficacy of the device. The Project Management Body of Knowledge (PMBOK) Guide published by the Institute of Electrical and Electronic Engineers (IEEE)[1] sets official definitions for validation and verification. Validation is "the assurance that a product, service, or system meets the needs of the customer and other identified stakeholders. It often involves acceptance and suitability with external customers."[1] Validation may be broken down further into several categories including "prospective" and "retrospective."[1] Since this project will end at the end of this semester, the validation will be limited in scope to the prospective type. This means that it will be conducted before the item is officially released for clinical use to make sure the client will be satisfied in the future. Verification, in contrast, is "the evaluation of whether or not a product, service, or system complies with a regulation, requirement, specification, or imposed condition. It is often an internal process."[1] Since design specifications were set at the beginning of the semester and confirmed with both the client and the instructor of the class, these will be the metrics used for the final verification plan. A number of additional, more minor specifications were also added.

Verification Plan:

Bifrost verification can be divided into two categories: mechanical (any physical properties of the device including usability and durability) fidelity and electrical (any signal transmission properties associated with the device relevant to signal transmission) fidelity. Note, for all relevant tests, an oscilloscope will be used to verify signal waveform and a multimeter will be used to measure V_{pp} and power outputted by the Bifrost.

Mechanical Verification:

1) Mass (fulfilling specification number 6):

The Bifrost device will be weighed via a calibrated lab balance to ensure it is below the client specified 1.36 kg.

2) Humidity (fulfilling specification number 1):

The Bifrost will be placed in an incubator with humidity controls and tested for output signal fidelity (i.e. fulfilling specifications 11, 12, 13, and 15). The onboard humidity sensor will be used to report the relative humidity the Bifrost is exposed to during testing to ensure the 0-70% range expected by the client is met.

3) Usability (fulfilling specification 2):

The Bifrost device is intended for use by patients without assistance or input from a medical worker. As such, individuals across a wide age range (12-82) will be allowed to use the device. Each individual will be given instructions about how to use the device and then asked to complete the following tasks 30 minutes later: 1) turning the device on/off 2) tuning the device to the intended stimulation frequency. The user will also be asked if the LCD screen within the Bifrost is readable. Users will not be implanted with a bioresorbable nerve inhibitor and will operate the device in abstraction.

4) Water-resistance (fulfilling specifications 2, 4, and 7):

The Bifrost is expected to come in contact with low amounts of sweat/other physiological fluids. To test the fidelity of the device in this situation, the Bifrost will be placed on a surface sprayed with water as per the International Electrotechnical Commission (IEC) test for IP1 (water).[4] Specifically, the device will be placed upright and rotated at 1 RPM while spraying it with 1 mm of water.[4] It will then be turned on and tested for output signal fidelity (i.e. fulfilling specifications 11, 12, 13, and 15).

5) Solids resistance (fulfilling specifications 2, 4, and 7):

The Bifrost will not only be isolated to clinic use and may come into contact with foreign objects and materials. To ensure it is usable under these conditions, the device will be tested for IP4 (solid particles) classification.[4] The Bifrost will be powered on and small screws, wires, and other objects ≥1 mm in length will be dropped from 6 inches above the device.[4] It will then be assessed for output signal fidelity (i.e. fulfilling specifications 11, 12, 13, and 15).

6) Drop durability (fulfilling specification 4):

The Bifrost is expected to withstand physical damage due to accidents during its 28-day use cycle. Due to the time constraints of the design project, it will not be possible to observe device function after 28 days of daily use. However, to replicate the potential physical damage the device would need to withstand, it will be dropped from 4 feet (approximate waist height) followed by vigorous manual shaking (with hands) for one entire minute. Then, the Bifrost will be turned on and tested for output signal fidelity (i.e. fulfilling specifications 11, 12, 13, and 15).

7) Dimensions (fulfilling specification 2 and 5):

The Bifrost is expected to be a portable device a patient can use for pain management throughout the day. So a standard ruler will be used to measure the final length, width, and height and ensure it conforms to the 17.8 cm X 17.8 cm X 10.2 cm requested by the client.

8) Temperature (fulfilling specification 2, 8, and 9):

The Bifrost is expected to function across a range of temperatures it will normally face in a 28-day use cycle in the hands of a patient. As such, the device will be placed in a temperature-controlled incubator and tested for output signal fidelity (i.e. fulfilling specifications 11, 12, 13, and 15) across the 12.8-37.8 °C range requested by the client. The onboard temperature sensor on the Bifrost will also report the temperature range the device was exposed to. It is also important for the Bifrost device to not overheat and potentially harm the

patient during use. The device will be left on for a period of one hour at room temperature (20 °C) and the temperature will be recorded through the onboard temperature sensor. This will ensure that the device circuitry does not raise the Bifrost temperature to more than 37.8 °C (i.e. body temperature) at any point during use as per the client requirements.

Electrical Verification:

Electrical verification contains an assessment of the battery life of the system, the output signal waveform fidelity, and output signal voltage and power parameters

9) Battery life (fulfilling specifications 2 and 10):

The Bifrost's portability is contingent on successful battery powering. To measure battery life, the device will be plugged in with a fully charged battery source. Then the output signal will be tested for ability to fulfill specifications 11, 12, 13, and 15. After this, the time until the battery source connected to the Bifrost is fully drained (i.e. Bifrost no longer emits a signal) will be measured to ensure it conforms to the client's specification.

10) Time course from battery fully drained to fully charged (fulfilling specification 11):

Battery recharge ability will be measured by taking a fully drained battery and measuring the time to full charge with a 2 A micro-USB charger to ensure it takes no longer than 1 hour.

11) Stimulation frequency (fulfilling specification 12):

An oscilloscope will be used to record the Bifrost's stimulation frequency outputted by the AD9833 signal generator via an oscilloscope to verify emission of a 14-26 kHz sine wave.

12) Carrier frequency (fulfilling specification 14):

The Bifrost's carrier frequency will be measured by recording the waveform out of the AD9850 signal generator through an oscilloscope to ensure a 5 MHz signal can be produced.

13) Overall voltage amplitude and power transmission (fulfilling specifications 13 and 16):

The Bifrost's output voltage signal's peak-to-peak voltage sent to the primary coil will be tested to ensure it is within the 0.15-10 V range specified by the client. The power transmission of the Bifrost between 0.5 and 200 mW will also be verified with a multimeter.

14) Nerve inhibition parameters (fulfilling specifications 3 and 15):

First, the team will place a set of stimulating electrodes (proximal to the soma and distal to the axon terminal) and a set of recording electrodes (proximal to the axon terminal) on a rat sciatic nerve with the client's bioresorbable stimulator already implanted. The Bifrost will then be powered on and its ability to inhibit the nerve signal sent by the stimulating electrodes (as measured by the recording electrodes) will be observed at varying distances from the nerve inhibitor (as measured by a standard 12-inch ruler). Further, the time between powering the Bifrost and first observation of inhibition will also be measured.

15) Cost and Time (fulfilling specifications 17 and 18):

The project is on track to be completed in 5 months (July to December 6, 2019) and the cost of the initial prototype is $744. This is outside the bounds set within the design specifications, but the client will cover the additional cost.

Validation Plan

The validation plan should ensure that the wants and needs of Dr. MacEwan and his lab are satisfied. Dr. MacEwan was explicit with the goals for the project from the beginning of the semester. He wants the transmitter/controller to be wearable (defined here as wireless and lighter than 1.36 kg). The device must also supply enough power to activate the implanted nerve stimulator via wireless/RF transmission. He would like to see it work in a murine cadaver, and he would be more impressed if it could work in an ambulatory murine model. From this statement, it is clear that the primary categories for this prospective validation will be wearability, functionality, reproducibility, and repeatability.

In regards to wearability, the client currently uses a bulky, immobile function generator for powering his implantable nerve stimulators. Their current setup is unsustainable as a long term solution, and the client is looking for a more long-term powering device that would be clinically viable. This is why he needs the prototype to be wearable. Wearability will be tested as follows: (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 stated above, these considerations must be met to achieve the client's goal of making the device independent of bulky function generators and amplifiers in the lab. This will move the product closer to the ultimate goal of clinical viability.

Next, the device must function properly, especially to transmit power to the implanted nerve stimulator at the correct frequency (including the carrier frequency). The testing will be performed in 3 tranches. Initial testing will be entirely limited to circuit validation with electronic equipment such as a multimeter and an oscilloscope. Later, testing will be *in vivo* in a murine model. Again, input from lab members was used to ensure that the prototype would be validated. A PhD student in Dr. MacEwan's lab told the team that the Bifrost must be able to produce 3V across a resistor *ex vivo*. Since the device is powering an inductor, power must be successfully transmitted from the primary coil to the secondary coil wirelessly which can simply be measured with a multimeter across the secondary coil. With *ex-vivo* testing complete and the device's ability to wirelessly transmit power confirmed, *in-vivo* testing may begin. The Bifrost will be used to power an implanted nerve stimulator in a murine model shortly after experimentation by other lab members.

Finally, reproducibility and repeatability will be considered. Reproducibility is the closeness of the agreement between the results of measurements of the same procedure

carried out by different parties. This would be great to accomplish, but not a necessity, due to the constraints of the Senior Design Course. The instructor has said in class that he only expects an alpha prototype, not a beta prototype. The difference between these two types of prototypes is as follows: an alpha prototype functions when the engineering team is operating it, and a beta prototype works when the user is operating it.

Repeatability or test–retest reliability is the closeness of the agreement between the results of successive measurements of the same measure carried out under the same conditions of measurement. In other words, the measurements are taken by a single person or instrument on the same item, under the same conditions, and in a short period of time. This is a more reasonable test that can be accomplished by the project's deadline. For the purposes of this project, pulses of power need to be delivered to the implantable device repeatedly, which means the precision of the device must high. To operationalize this, the Bifrost will be tested on the same rat and in the same trial but separated by 20 minutes. Variability of less than 5% will be required for this test. In summary, prospective validation testing will specifically include wearability, functionality, and repeatability.

Discussion of FDA Process

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.[5] 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.[2] 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).[6] Further, key predicate devices for the Bifrost (FDA regulation codes 882.5275 and 882.5890) have gained approval without clinical trials.[5,7] This will significantly reduce costs and time to entry to obtain FDA approval compared to a Class III PMA process.

Overall Status of the Project

The team has successfully built a miniaturized, battery powered function generator on a breadboard that is capable of producing a 5MHz sinusoidal signal. This was verified with an oscilloscope. Next, this module will be miniaturized and the breadboard will be removed. Work has also begun to build the second function generator capable of producing a 14-26 kHz signal. Once complete, the two signals will be multiplied together to produce the desired waveform.

Appendix

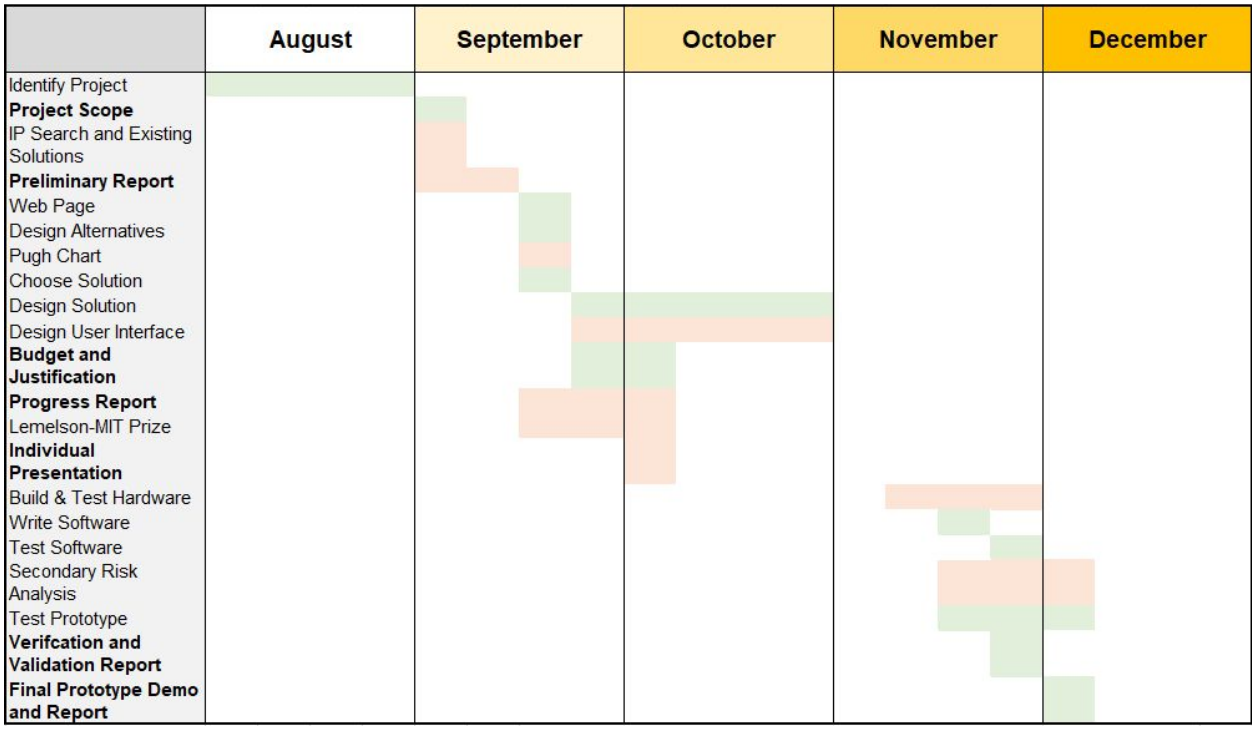
Updates to design specifications:

Table 1: A table outlining all specifications the Bifrost device must conform to. Note that specification numbers are referenced in this report within the Verification Plan and verification tests outline tests described in the Verification Report.

Specification Number	Specification	Quantitative Metric	Verification Test(s)
1	Operatable relative humidity range	0-70%	2
2	Usable for people in the following age range	12-80	3, 4, 6, 8, 9
3	Maximum time achieve pain blocking effect	5 minutes	14
4	Minimum device durability	28 days	4, 5, 6
5	Maximum device dimensions	17.8 cm X 17.8 cm X 10.2 cm (7 in X 7 in X 4 in)	7
6	Maximum device weight	1.36 kg (3 lbs)	1
7	International Protection Marking rating	IP41	4, 5
8	Maximum temperature of internal circuitry	37.8 °C (100 °F)	8
9	Range of atmospheric temperature device can withstand	12.8-37.8 °C (55-100 °F)	8
10	Battery life	24 hours	9
11	Maximum recharge duration	1 hour	10
12	Stimulation frequency	14-26 kHz	11
13	Electrical stimulation amplitude (transmission voltage)	0.15-10 V	13
14	Input carrier frequency	5 MHz	12
15	Maximum distance between implant blocker and external power source	4 cm	14
16	Power Transfer Range	0.5 - 200 mW	13
17	Time to completion	5 months	15
18	Maximum cost for prototype	$500	15

Updates to design schedule:

Table 2: Updated Gantt chart outlining the current project timeline. Team member responsibilities are delineated by color. Green represents Aadit's responsibilities, and red represents Joe's.



Updates to team responsibilities:

Table 3: Updated team responsibilities.

Person	Responsibilities
Aadit Shah	Software (app, Bluetooth communication, UI), optimization of the device-implant interface, client communication, course communication, posting updates to team website
Joe Beggs	Durability Testing, Hardware components (battery, inductor coil, circuitry), optimization of signal-generator:signal-generator interface, verification that purchased components align with design requirements

References

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