The Bifrost

Progress Report

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Updates from Preliminary Report

After consideration of potential design alternatives, it became clear that opioids are an extremely effective method for both acute and chronic pain management. However, its fatal flaw (addictive nature) makes it paramount to find better ways to abate pain. With that being said, the team decided to revise the initial need statement to:

"A **non-addictive** method for pain management after surgery that does not require additional surgeries would lead to a better quality of life for patients by eliminating side effects of medication and better control of the pain."

Namely, a switch between "non-opioid" to "non-addictive" was made. This is as an opioid treatment such that addiction incidence rate is effectively 0 will confer the necessary benefits and remove current shortcomings needed for the target population.

No changes were made to design specifications, design schedule, or team responsibilities.

Statement of Design Alternatives

There are a number of both existing and brainstormed solutions that have potential to solve the problem of opioid abuse in a postoperative setting. Of course, novel ideas will require a full design process for implementation. Even existing solutions will need some level of design to meet the design requirements set forth in the preliminary report. In general, the design alternatives fall into one of several categories: bioresorbable infrared (IR) or radio frequency (RF)-powered wireless power transfer

method coupled with a bioresorbable stimulator (transcutaneous), dissolvable batteries for implant, quantitative acupuncture, and a restricted opioid regimen.

Wireless powering of bioresorbable stimulator (transcutaneous)

Any device designed must be coupled with a dissolvable receiver. Given the stringency of implanted device properties necessary for resorbability, there are two primary modes of wireless power transfer possible: magnetic induction or infrared laser.

Optical charging methods utilize a photovoltaic cell integrated in the implant. The power can be transmitted from an external source via a laser diode in the near-infrared (near-IR) or infrared region (IR) and received by an array consisting of photovoltaic cells directly connected to the nerve blocker.[6] With regard to safety, IR and near-IR frequencies have very low interactivity with biological tissue (as seen in Figure 1) and are therefore quite safe. Generally penetration depth and wavelength are directly proportional and can allow sufficiently deep penetration to deliver power to the device. Once the radiation reaches the photo-voltaic cell, it is converted into electrical current to charge and operate the implanted nerve blocker. These devices can generate power on the order of hundreds of microwatts. For reference, this is on the lower end of the range set forth in the design specifications.

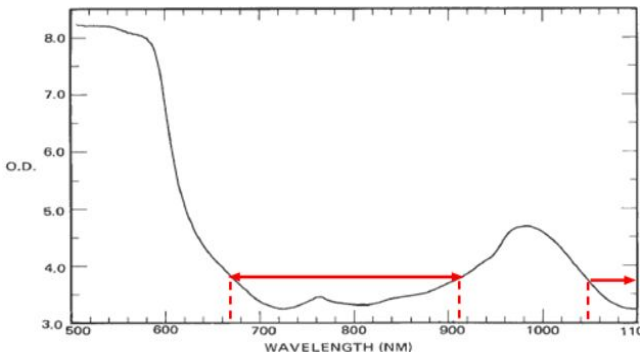

Figure 1: A depiction of the tissue absorbance of light across the near-infrared and infrared range.[1] Ranges of light with limited tissue absorbance are indicated with red arrows.

As aforementioned, the implanted photovoltaic array, along with the nerve blocker itself, must be bioresorbable per the design requirements set forth by the client. One such candidate technology developed by the Rogers Group at Northwestern University are Biodegradable Monocrystalline Silicon Photovoltaic Microcells.[7] This technology is very new and has not yet been commercialized, but John Rogers is a collaborator with the client and thus may provide access to this technology.

Induction is a relatively common modality for wireless power transfer in the biomedical community. While both ultrasonic coupling power transfer and capacitive coupled transfer are also known modes of short range power transmission, they are less effective and not often leveraged in biomedical technology.[8] According to Faraday's Law of Induction, electromagnetic induction is governed by the following equation for a solenoid with N turns of wire:

$$\varepsilon = -N\frac{d\Phi}{dt}$$

Therefore, the induced voltage ε in the receiving device may be increased with a greater number of turns of wire or by increasing the magnetic flux (Figure 2).

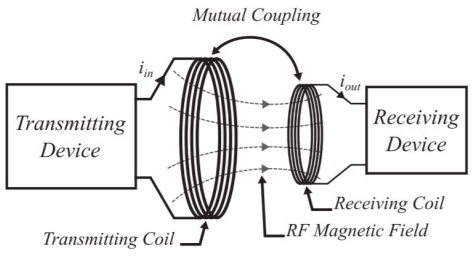

Figure 2: Schematic of inductively coupled power transfer.[9]

The latter may be accomplished in a number of ways including altering the magnetic field with time. This method of power transmission allows for short-range transfer between a receiving coil (inside the body) and the transmitting coil external to the body. However, optimal efficiency of inductive coupling is lost when the modality is translated to design specifications necessary for physiological compatibility. Often, inductors are rendered as planar coils for biomedical applications which do not function well as highly permeable coupled transfer systems.[10]

Dissolvable batteries for implant

Current battery-powered biomedical implants are effective at managing pain, but limited by the need for explanation of the non-resorbable battery. The associated risk factors of an additional surgery put into question the value add in comparison to traditional opioid treatment. If instead, these biomedical implants could be powered by resorbable modalities of power, they could prove highly effective. The recent advent of resorbable, silk-based batteries could feasibly be applied in pairing with current bioresorbable stimulators. These batteries dissolved in a buffered protease solution over a 45 day time course at physiological temperature (Figure 3).

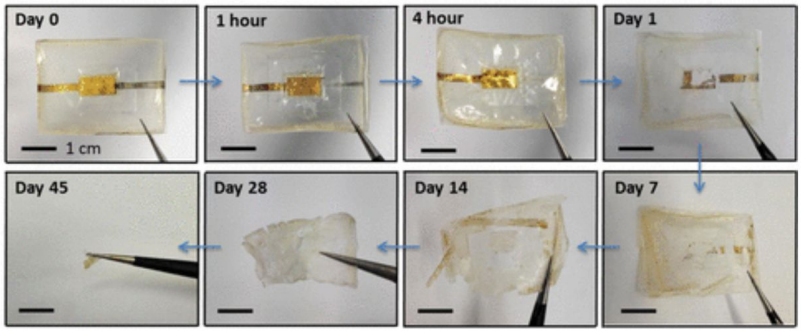

Figure 3: A temporal sequence of a dissolvable AZ31|SF-[Ch][NO3]|Au-SF battery degrading over days when placed in a buffered protease solution at physiological temperature (37 C).[2]

However, it is important to note that stable open-circuit voltages only lasted for 64 minutes in saline buffer. Even with the addition of a nonimmunogenic crystallized silk film to further encapsulate the battery, the battery was able to maintain a stable output voltage for 109 min. Nonetheless, neither of these time courses are on the same scale as that needed for an implant used in post-operative pain management. Although the temporal nature of battery degradation is appropriate, its functional components lose capability too quickly for feasible application. In addition, these batteries have not been validated for use in humans - implying a large financial burden and time investment prior to entry into the marketplace.

Quantitative acupuncture

Traditional acupuncture is a form of Eastern medicine that has been used to abate pain for centuries. However, this form of treatment currently requires in-person sessions with an individual trained in acupuncture and can cost $50-95/session with a normal treatment course of 5-6 weeks (up to two sessions/week).[11,12] Not only is this quite costly, but requires patients to travel frequently to a location for therapy. If this therapy could perhaps be augmented to a more autonomous process that a patient could perform at home, it could be more widely applicable. In this paradigm, the patient would be instructed by a software tool to perform acupuncture on target sites on their body. Requiring a smartphone, this application would use image processing and understanding of the operated site to assist the user in placing the acupuncture needles in the correct locations. Furthermore, this would allow for a standardized treatment course. For example, the application would inform the user optimal times to perform

acupuncture which could initially occur at high frequencies and decrease over the course of the treatment course based on a variety of factors including pain perceived by the patient, physician assessment, and site of operation. Effectively, the only cost in this quantitative, at-home approach would be the cost of sterile acupuncture needles and software.

However, there still remain concerns with this approach. The ability for a patient to perform acupuncture successfully in a safe-manner would need to validated. In addition, an accurate enough image processing algorithm would require a vast dataset of images. The minimum angles/images needed for proper targeting would need to be studied. Finally, it would require the patient to have reliable smartphone technology (some phones may be ineligible depending on the image resolution needed for proper targeting). In addition, this entire approach is based on acceptance of acupuncture as an effective medical treatment by the biomedical community.

Opioid treatment plan to prevent addictiveness

Although opioid treatment is undoubtedly psychologically and physically burdensome due to its addictive nature, it is clear this class of pharmaceuticals are exceptionally effective at pain management. Although the initial problem statement was outlined as non-opioid solutions to pain management, in reality, if the control over the usage of these drugs could be improved to significantly reduce incidence of addiction there is no medical need to remove these drugs from the standard of care.

Current opioid prescriptions are quite generalized (either told to be taken every 6-12 hours or on an as needed basis). Implementation of a more personalized

prescription strategy that was variable and dependent on patient risk factors and the severity of operation could be effective. This would allow for patient-specific plans to wean of opioids to minimize the risk of addiction. Although this strategy may prove to be effective, this approach would require large datasets of patient outcomes across different cultural and socioeconomic backgrounds.

In addition, this regimen could incorporate truly tamper proof bottles that would only dispense small amounts of drug based on physician-prescribed frequencies. This would limit patient control of opioid usage and ideally facilitate an increase in physician-patient conversations about pain management (e.g. to readjust dispensal dosage). This may prove to be a low-cost, safe intervention; however, it does not ensure a lack of addiction post-treatment. Patients during the treatment course may be limited by the frequency of drug dispensation, but may develop an addiction nonetheless and attempt to seek out opioids through illicit channels after the original treatment course has ended.

Further, using objective measures of patient pain levels, such as nociceptive neuronal activity, could inform the physician as to the appropriate rates of opioid dispensation.[4] Pain is currently quasi-quantified in the clinic by patients selecting the face from a number of facial expressions–ranging from smiling to grimacing–that best matches their level of discomfort (Figure 4).

Figure 4: Standard survey given to patients experiencing chronic pain as a measure to quantify their level of discomfort.[3]

As one might imagine, this method is quite subjective and ineffectual communication between the physician and patient could cause errors when doctors have to make important clinical decisions. Patients in pain are notorious for both understating and overstating their degree of pain. Also, some patients experiencing chronic pain may be incapacitated in some way and unable to properly articulate their level of discomfort.

A more quantitative and objective approach could more closely match opioid dispensation to the actual levels of patient pain using fairly standard equipment, such as EEG, that could detect when nociceptive axons are activated following noxious stimuli.[5] The physician would apply various noxious stimuli to the patient to produce a standard curve between stimulus intensity and nociceptive nerve activity. This standard curve could then be used to quantify pain in an outpatient setting and determine the appropriate amount of opioid medication to be dispensed by the tamper-proof pill bottle. In other words, the medication would be dispensed on an “as-needed” rather than “patient-controlled” basis.

Finally, psychological studies in the past have demonstrated that animals in most pleasant and social environments develop addiction at lower incidence rates. Current behavioral therapy sessions can be quite costly which has led to low rates of implementation. However, if an automated approach to therapy could be used to supplement opioid prescription, it can serve to help patients better manage opioid side effects. The patient would be equipped with a biometric sensing device (capturing physiological parameters such as heart rate, respiration, body temperature, sweat response). In addition, an EEG reading patch could be applied near the site of operation to obtain quantitative measures of nociception. This would work synergistically with a software tool capturing qualitative psychological data points (mood, pain). Together, the software tool would provide behavioral therapy support as the patient progressed through their pain management treatment - only altering a psychiatrist or other mental health provider after a certain level of risk is surpassed.

Overview of Chosen Solution

In order to choose a solution from the given design alternatives a number of factors must be taken into account, each with varying degrees of importance. These factors include user interface considerations such as form factor, reliability, and durability; and manufacturing analysis including maintenance, feasibility, and ease of manufacturing. A Pugh matrix was employed to accomplish this task (Table 1). Note that Pugh matrices are used to inform the decision of chosen solution, but ultimately it is up to the design team to accept or reject the results of the Pugh matrix analysis.

Table 1: Pugh matrix quantifying the appeal of the different solutions based on a number of different criteria. Each criterion is assigned a weight that is multiplied by the respective scores for each proposed solution. The total normalized score for each solution is that solution's raw score divided by the maximum raw score. Therefore the highest score of one is for induction powered WPT (highlighted in green).

	Solution				
Criteria (weight)	**IR-powered WPT**	**Induction-powered WPT**	**Dissolvable Batteries**	**Quantitative Acupuncture**	**Restricted Opioid Regimen**
Current Related CPT/ICD-10 Codes (2)	10	10	10	0	10
Patentability (5)	10	10	0	0	7
Scalability (2)	8	9	8	5	8
Cost (4)	6	7	2	10	9
Mobility (9)	8	9	10	6	5
Reliability (8)	6	8	4	4	3
Safety (10)	10	10	5	6	2
Feasibility (9)	7	10	4	8	8
Ease of Manufacturing (3)	6	10	7	10	7
Form Factor (6)	7	9	8	8	10
Durability (8)	7	9	3	6	10
Friction to Adoption (1)	10	10	10	1	4
Maintenance (3)	5	4	6	5	3
Total (Raw)	534	629	373	410	442
Total (Normalized)	**0.85**	**1.00**	**0.59**	**0.65**	**0.70**

As per the Pugh Matrix, is it is clear that a RF-based transcutaneous, wireless powering device for an extant bioresorbable implant is the best design solution. It will afford the user with effectively limitless mobility, allow for the physician to obtain quantitative information of patient progression in their pain management, adds no complications, does not increase the risk of infection, requires no additional surgeries, and harbors no risk of addiction. As bioelectric stimulation is already present in the field, limited friction should be present in entering the marketplace. At the same time, the

novelty of a wireless bioelectric pain inhibitor should confer patentability. This technology will leverage pre-existing electronic circuitry components that can be obtained inexpensively - especially en masse. Maintenance will be limited to battery replacement and the patient can use the device without needing to ingest any medication or performing an invasive procedure.

The design chosen would need to conform to the specifications listed in Table 2. These parameters were determined by the properties of the implant bioelectric blocker and empirically observed power delivery needed to achieve nerve blocking by the MacEwan group.

Table 2: A table outlining the necessary power and transmission specifications required of the wireless power transmitter for the bioresorbable nerve inhibitor.

Specification	Quantitative Metric
Electrical stimulation frequency	14-26 kHz
Electrical stimulation amplitude (transmission voltage)	0.15-10 V
Input carrier frequency	5 MHz
Maximum distance between implant blocker and external power source	4 cm
Power Transfer Range	0.5 - 200 mW

Preliminary Consideration of Solution to Initial Design Specifications

Referencing the Design Specifications in listed in the Preliminary Report (Table 3), this solution can feasibly conform to all desired specifications. Given that the device will house an LCD unit and only a few buttons it will be usable for the broad age range indicated. Electronic components chosen appear to be rated for the listed temperature and humidity but this will be verified empirically through the onboard temperature and humidity sensor once a prototype is complete. The same uncertainty applies to device

battery life, its recharge speed, durability, and weight. Given the bioelectric modality, the user should be able to abate pain through wireless stimulation momentarily after activating the device. Further, cost is below the $500 maximum price as per Table 4.

Table 3: A table with key specifications that the solution to manage postoperative pain must conform to.

Specification	Quantitative Metric
Operatable relative humidity range	0-70%
Usable for people in the following age range	12-80
Maximum time to achieve pain blocking effect	5 minutes
Battery life[1]	>1 week
Maximum recharge duration[1]	3 hours
Minimum device durability	28 days[2]
Maximum device dimensions	15.2 cm X 15.2 cm X 7.6 cm (6 in X 6 in X 3 in)
Maximum device weight	1.36 kg (3 lbs)
Maximum temperature of internal circuitry[1]	37.8 °C (100 °F)
Range of atmospheric temperature device can withstand	12.8-37.8 °C (55-100 °F)
Time to completion	5 months
Maximum cost for prototype	$500

[1]Considerations for potential solutions that may involve circuitry components.
[2]Not fully waterproof, but resistant to low amounts of sweat and other liquids it may be transiently exposed to. Initial prototype may not be fall proof but the final iteration will require a capacity to survive a minimum of 2 drops from 2 meters.

Estimation of Price

Based on search for pre-existing electronic components for an alpha-prototype (i.e. proof-of-concept) the following components were selected. Price was primarily determined by the electronic equipment needed onboard to achieve the necessary output signal described in Table 2. The estimated price of $101 remains considerably lower than the maximum of $500 (Table 3). However, it is important to note that additional elements may be added to improve device battery life, durability, and usability. Nonetheless, these expenses are not predicted to exceed the stated budget.

Table 4: A table listing the cost per component of the chosen solution.

Part	Cost (USD)
3D Printed Housing Unit	0.00
energyShield 2 Basic - Rechargeable Battery for Arduino (portable battery)	29.95
SparkFun Electronics PRO MINI SIGNAL GENERATOR SHIELD (function generator for RF stimulation)	29.95
Arduino Pro Mini 328 (logic board)	9.95
SunFounder IIC I2C TWI (LCD display)	12.99
Arduino TEMPERATURE & HUMIDITY SENSOR PRO	17.50
Bioresorbable Nerve Inhibitor	0.00
Coil of Wire	1.00

High level schematics of The Bifrost

The Bifrost device (i.e. chosen solution of an RF-based wireless stimulator for powering of a bioresorbable nerve blocker) will engage with the local nerve as seen in Figure 5. The Bifrost will send an RF signal transcutaneously through the skin inhibiting the nerve near the operation site.

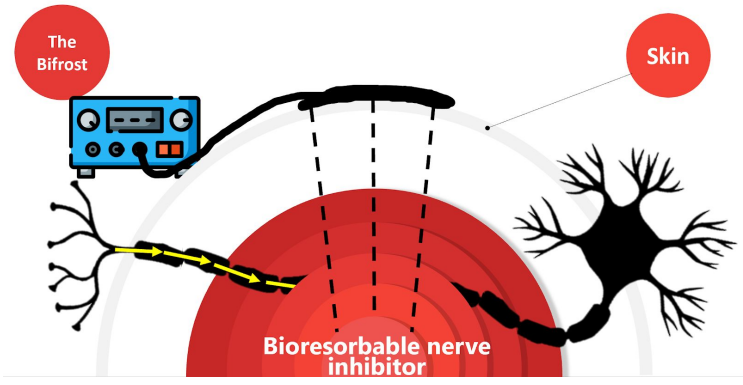

Figure 5: A high-level depiction of the engagement Bifrost will have with the implanted nerve inhibitor.

The key components of the device can be seen in Figure 6. As seen in Figure 6, the core of the device will be a logic processor which will take information from the user

controls and accordingly send activation/deactivation signals to the function generator. Due to the low efficiency of RF transmission, the generated AC voltage signal will be sent through an amplifier which will finally be passed through the transmitting coil. The receiving coil of the bioresorbable nerve inhibitor will convert this magnetic signal into electric inhibition of the nerve (Figure 6).

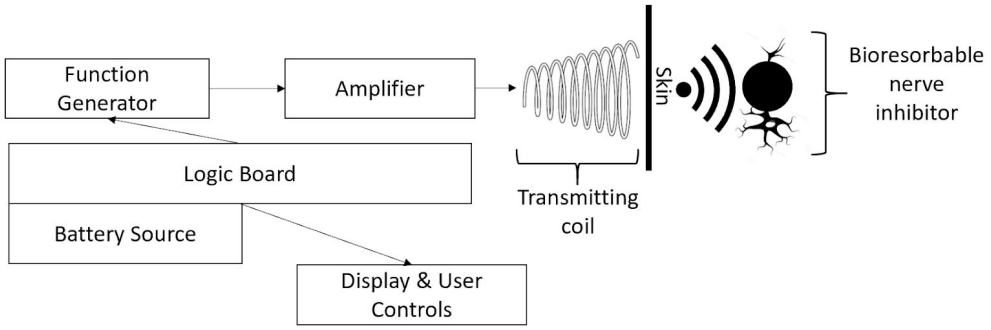

Figure 6: A schematic depicting key component of the Bifrost that will work to transmit the appropriate message to the inhibitor.

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