ECE 445

SENIOR DESIGN LABORATORY

FINAL PAPER

BEACON

Shining Light on Glioblastoma

Team No. 33

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Abstract

This paper serves as the final documentation for our ECE 445 project. The original title of our project was “Autologous Transcranial Implant for the Delivery of Photodynamic Therapy for Intracranial Brain Tumors”. Our team changed the title of the project to “Beacon” later on to give the device a modern feel while giving a more colloquially descriptive name. In this paper, we will break down each individual component of the project, how they work together, and how we feel the overall device operates.

1 Introduction

1.1 Problem

Glioblastoma has a very poor prognosis of 12-15 months post-operation [1]. The current standard of treatment is surgical resection, radiation therapy, and chemotherapy [1]. One FDA-approved device on the market exists that attempts to solve a similar problem - Optune [2]. Other alternatives exist as well but they have low efficacy overall. In recent trials, photodynamic therapy (PDT) has proven effective in treating cancerous cells though currently it can only be administered mid-surgery while the brain is exposed [3].

1.2 Solution

To allow for photodynamic therapy (PDT) to be administered postoperatively, we propose developing a small transcranial implant that would provide the light source for this therapy. Our objective is to create a programmable device that can be implanted through the skull which will provide control over PDT delivery chronically, allowing patients with GBM to be photo-irradiated without re-entering the operating room after their resection is completed. Components of this transcranial implant would include the appropriate light source, a light diffuser, battery, and an on/off mechanism.

1.3 High-Level Requirements and Functionality

High-Level Requirement 1:

The device will produce **200J/cm^2 of 635nm wavelength hitting the 5-ALA affected cells** in the brain. This dose of light has been clinically proven to deliver a lethal dose to the photosensitized tumor cells [3]. Hitting this requirement means our device will be effective at delivering photodynamic therapy.

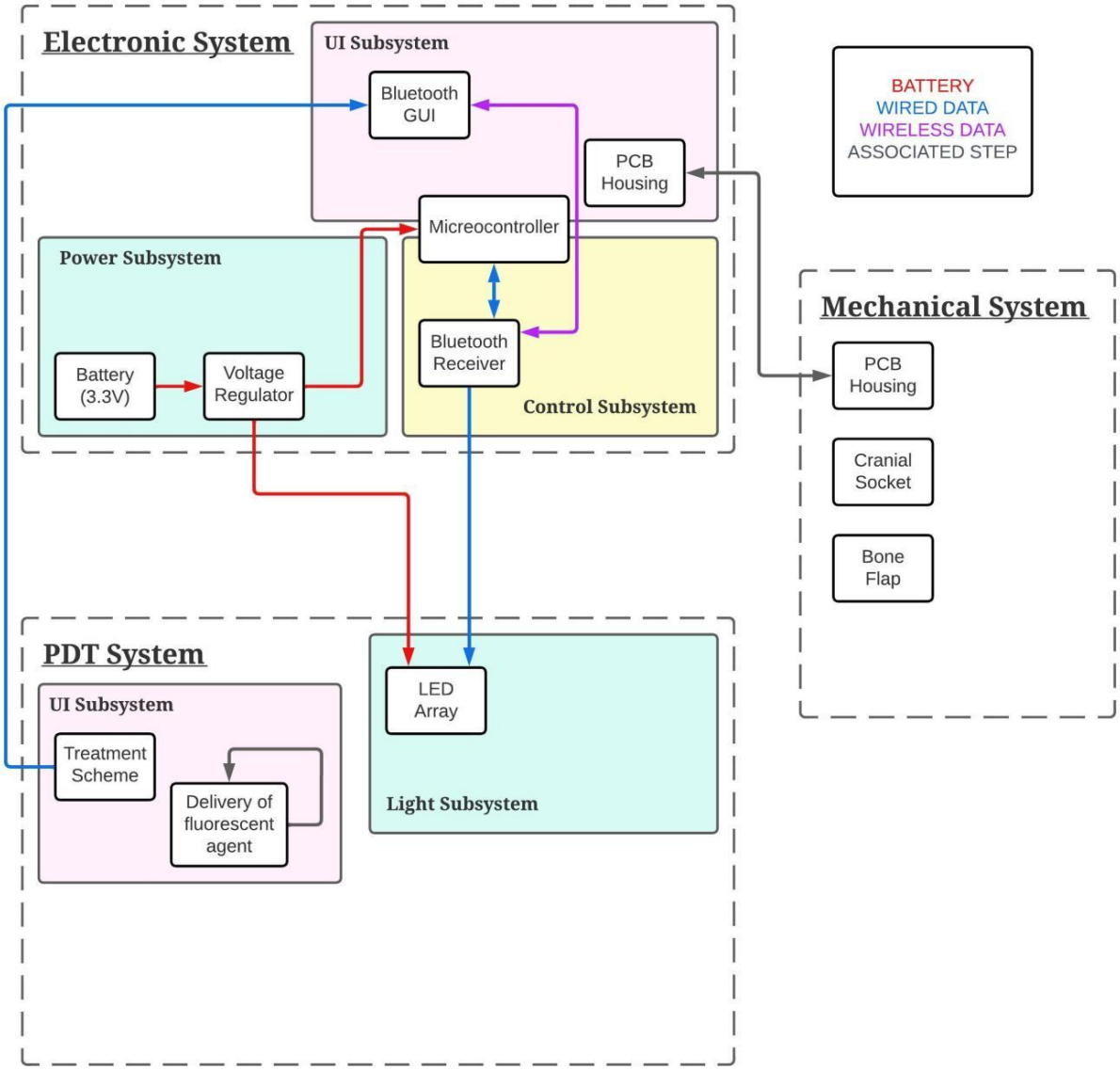
High-Level Requirement 2:

While the PDT is being administered, the **temperature around the targeted area remains lower than 39º C**. [6] Studies have shown that raised brain temperature for long periods of time results in significant cognitive impairments. To ensure patient safety we want to make sure our device does not cause clinically significant brain heating.

High-Level Requirement 3:

The overall power consumption of the device is low enough to last up to **5 years on a single battery charge**. Surgery poses a significant risk to the patient. We would like to minimize the patient danger and maximize the effectiveness of this device by making it last as long as possible

1.4 Block Diagram



1.5 Subsystem Overview

Our solution is broken down into three distinct systems: the electronic system, the PDT system, and the mechanical system. Each of those systems is further broken down into subsystems, discussed below.

1.5.1 Electronic System

1.5.1.1 Power Subsystem

The power subsystem is relatively straightforward. It is in charge of providing power to the microcontroller, LED array, and photodetector. The power from the battery will be run through a voltage regulator into the powered components after installation and for the useful life of the device.

1.5.1.2 Control Subsystem

The control subsystem consists of two parts; the microcontroller and the Bluetooth receiver. The microcontroller will act as the brains of our operation. It will store the intensities, times, and intervals that the LED array will be administering the PDT. The Bluetooth receiver will allow the doctor to prescribe an assortment of different parameters and transmit that data to the device via an external application.

1.5.1.3 UI Subsystem

The UI subsystem also contains the Bluetooth external application, responsible for sending parameters to the implant, and the battery enclosure, built into the device itself.

1.5.2 PDT System

1.5.2.1 UI Subsystem

The UI subsystem pertaining to the PDT system contains an important, though ancillary, step. The patient must ingest a fluorescent agent in order for the PDT to be successful. In the case of our study, we are using 5-ALA. It is a crucial part of our proposed project's functionality, even though it is not a process we directly control. We are also sending the overall treatment scheme to the device via the Bluetooth external application.

1.5.2.2 Light Subsystem

The light subsystem is the "business end" of our proposed project. It contains the LED array responsible for the administration of the PDT. The entire light subsystem is powered through the same energy source as the microcontroller.

1.5.3 Mechanical System

Our mechanical system acts both as a higher-level system and a lower-level subsystem. It contains the socket that is attached to the skull, the internal housing to protect the battery and electronics, and the bone flap - a piece of skull removed for surgery, that the implant will directly interact with. It also contains within it the electronics of the device.

2 Design

2.1 Equations & Simulations

Energy Dose

We use the following assumptions to determine the optical power of our LED and the energy dose it can deliver to a cranial cavity.

From the datasheet we know our red LED emits a wavelength of 630 nm at a luminous intensity, I_v, between 450 and 1800 mcd, controllable by forward current.

Assuming a sufficiently narrow emission wavelength we can say the relationship between photometric units, related to perceived eyeball sensitivity, and radiant units, related to arbitrary photon energy, can be calculated with one conversion factor: luminous efficacy, K. We find this luminous efficacy as a function of luminous efficiency, V, provided by the RCA Electro-Optics Handbook [4].

Therefore we can say radiant intensity $I_e = \frac{I_v}{V(\lambda=630)*673} = \frac{I_v}{178.345}$ [W/sr]

For the ease of calculation we will assume the tumor cavity is a spherical cap, with a surface area of 50cm^2 at a distance of 1 cm from a lambertian light source. We will also assume all of the light emitted by the diode is captured by this spherical cap. The radius of this spherical cap is related to the distance of the source by $A = 2\pi rh$, where h is the distance from the source. And the 2D angle is related to the radius by $A = 2\pi r^2(1 - cos(\theta))$. Solving for the interested quantities we find:

$$r = \frac{A}{2\pi h} = \frac{50}{2\pi(1)} = 7.95cm$$

Plugging r into the second area formula:

$$A = 2\pi r^2(1 - cos(\theta))$$

$$\theta = cos^{-1}(1 - \frac{A}{2\pi r^2}) = 29.0°$$

We can now use this 2D angle to find the solid angle Ω, that contains the 3D portion of light that will reach the tumor cavity.

$$\Omega = 2\pi(1 - cos(\theta) = 0.787\ sr$$

Using the solid angle we can relate radiant intensity to radiant flux in terms of watts, and to irradiance in terms of W/m^2.

Radiant flux, $\Phi_e = I_e \Omega$ [W] (~2-8mW)

Irradiance, $E_e = \frac{I_e \Omega}{A}$ [W/m^2]

Using the optical intensity from the datasheet we can thus say our tumor cavity can receive **39.35 to 158.8 uW/cm^2** from our LED. We can use this quantity to determine the fluence, or dose delivered to the cavity from the relating watts to joules per second. We stated that our dose should be 200 J/cm^2. Thus, our device must deliver the stated irradiance for 350 to 1400 hours to

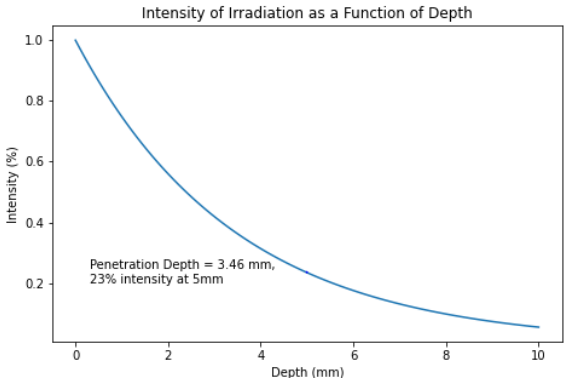
deliver the required effective photodynamic therapy dose. Further calculations will complicate the LED as a light source and the tumor cavity as a surface.

Penetration Depth

Another value of concern was the penetration depth of the light. Since much of the immediate tumor regrowth happens within 5 mm of the tumor resection cavity we wanted to know how much light would penetrate to that depth and thus how deep into the surface of the brain the device remains effective. Assuming absorption and scattering coefficients of 0.2 cm^{-1} and 20 cm^{-1}, respectively, we can calculate the penetration depth.

$$\delta = \frac{1}{\sqrt{\mu_a(\mu_a + 3\mu'_s)}} = 3.45\ cm$$

Using Beer's Law we know this means we retain 1/e or 37% of the original intensity at a distance of 3.45 cm into the brain. We can also plot the intensity of this light as a function of depth.



Light intensity (%) as a function of depth in the brain

This reveals we have 23% of the light penetrating to this 5 mm depth, meaning that we retain some amount of photodynamic therapy effect well into the surrounding cavity region.

Battery Life

Given our battery has 450mAh we can calculate the battery life of our device when operated on battery power. We found a draw of <1mAh when the device is on in ultra-low power mode, a draw of 40mAh when the device is on at low LED intensity, and a draw of 120mAh when the device is on at a high LED intensity. This means our battery will be drained in 11.25 hours at low intensity, and 3.75 hours at high intensity. These results indicate that our battery will not support a full-length PDT session.

2.2 Design Alternatives

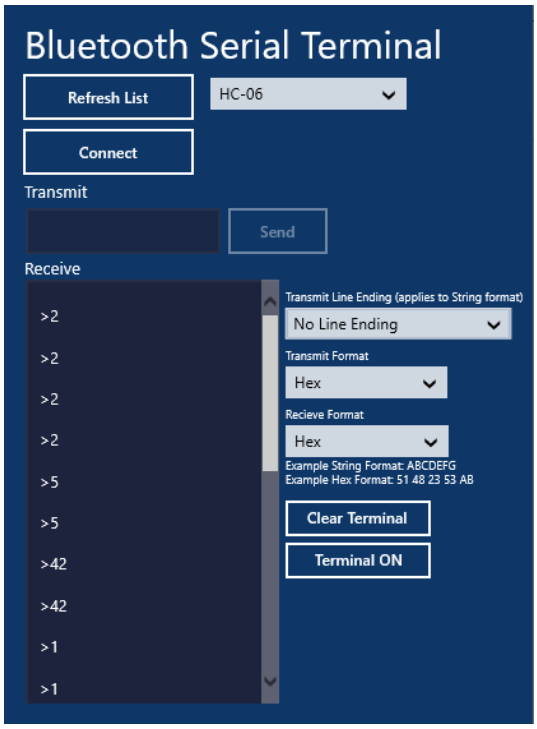
We discovered a few problems with our first PCB design that we fixed in a second revision. These include:

- Not grounding the Boot pin. (Left floating)
- Fixing the LED driver circuit

Early battery life calculations indicated that we would not be able to support a full PDT session on one lithium-ion coin cell battery so we switched to a larger, but higher charge, lithium-polymer battery. Due to the nature of our device, this second battery was still not good enough. We then determined buying a battery that would support the device for the required 350+ hours was an unnecessary purchase for this class. A new battery or charging system will have to be devised to make this device operate without a cable.

2.3 Design Description & Justification

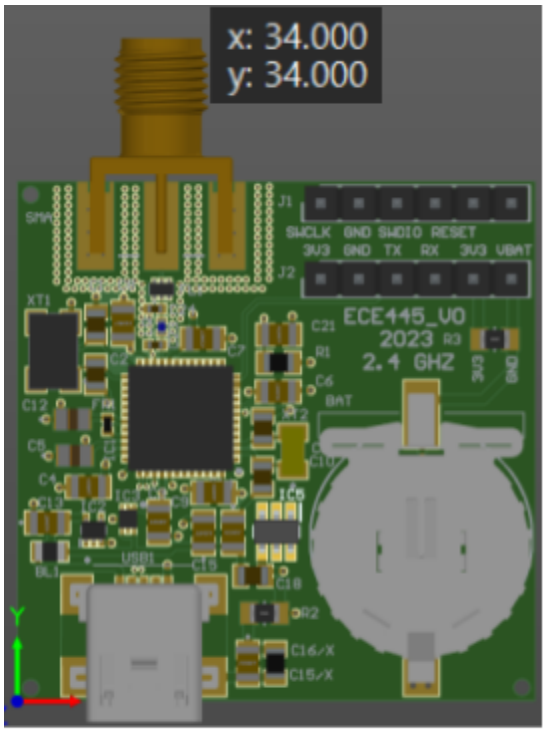
Throughout this semester we have gone through 2 PCB designs revisions. Both PCBs ended up working. The only reason why we came up with a second design was to reduce the dimensions of our PCB, which we were successful in doing so. The first PCB was 34x34mm and the second revision was 24x24mm. We will go more in depth about the design choices we made for the schematics in the next section. To control the board remotely we ended up moving away from RFID to Bluetooth for multiple reasons such as reliability, security, and safety which are crucial parameters within the medical field. We were successful in integrating the Blutooth module (HC-06) in our design as we were able to send commands from a Serial Blutooth Terminal to our PCB.



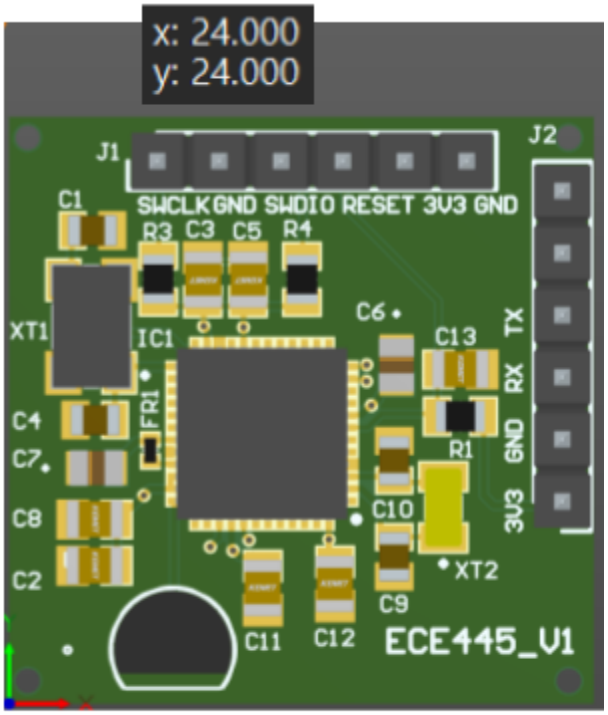
This is the GUI that we have used to control the PCB. We have installed this app from AppStore.

2.4 Subsystem Diagrams & Schematics

2.4.1 PCB Diagrams

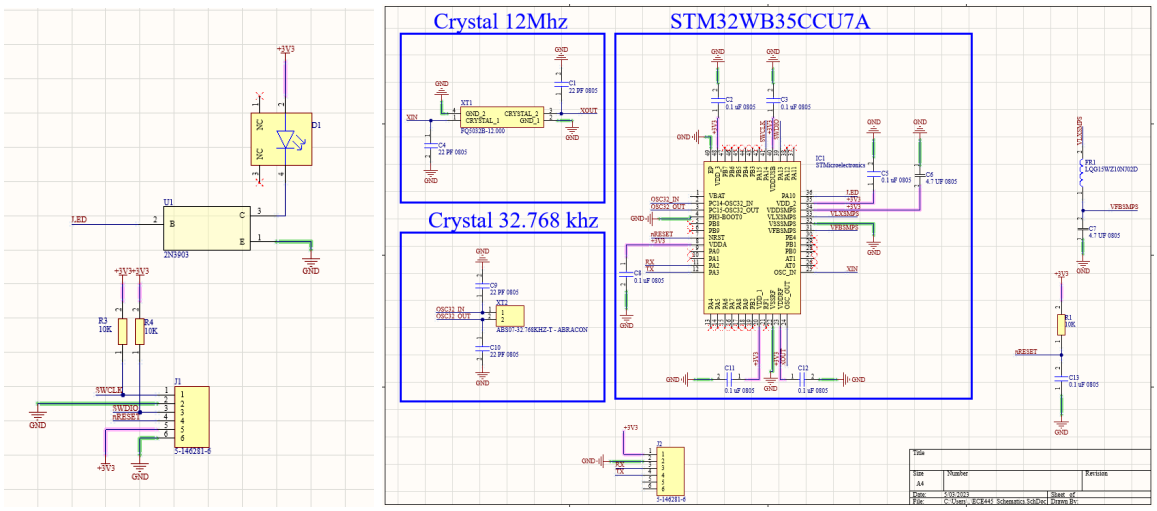


First PCB Design (Development Board)



Second PCB Design

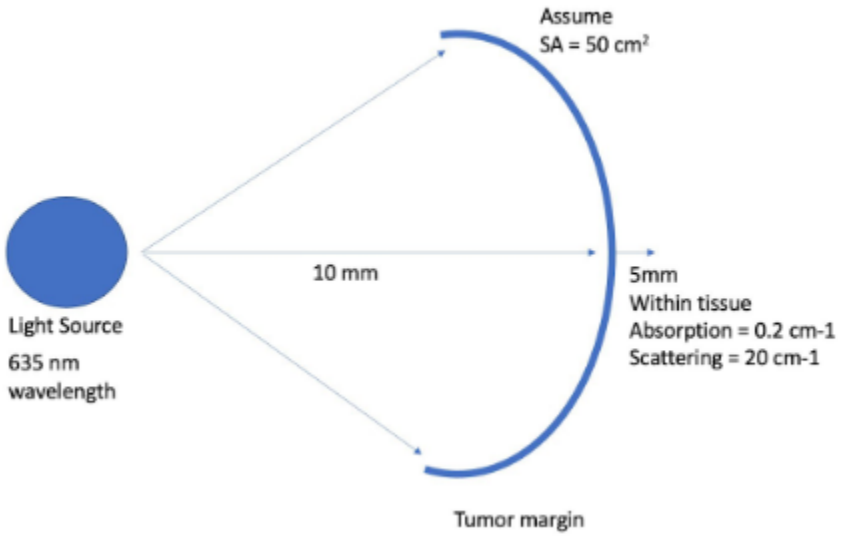
2.4.2 Electronic System Schematics



I like using the term engineering revision or Dev-board for our first revision, because it included alot of components. The reason behind this revision was to insure what we were looking for from

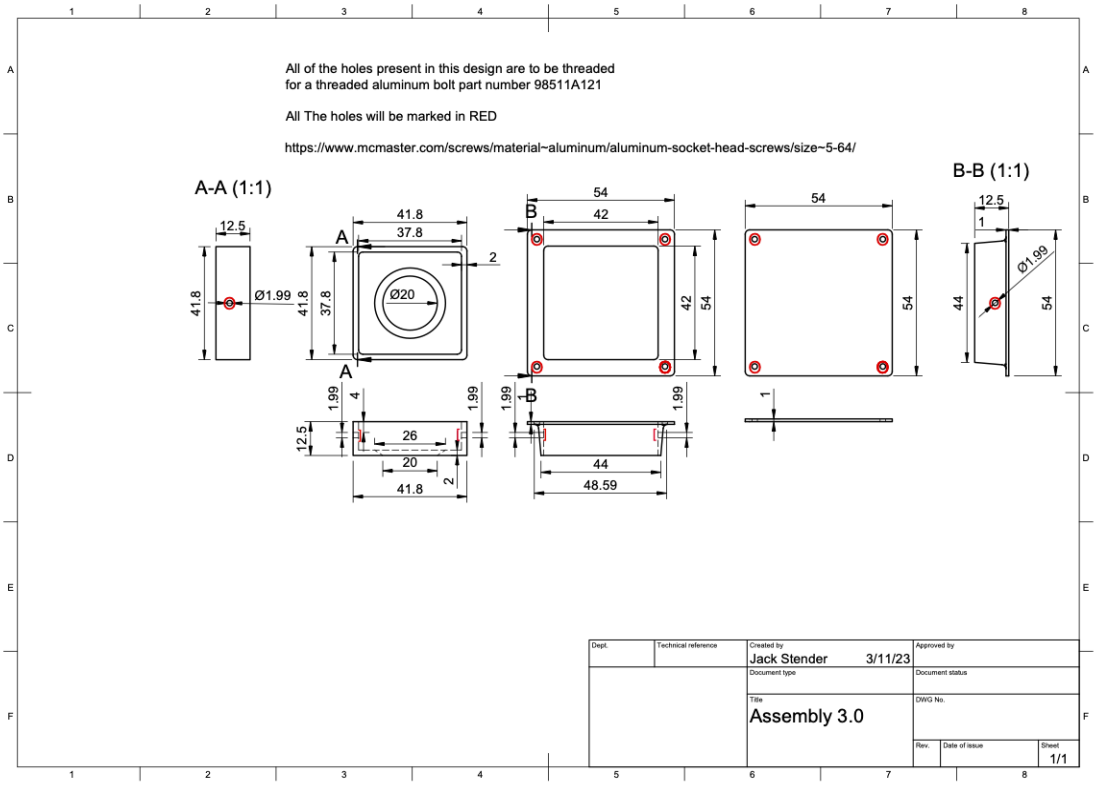
the design, what worked and what didn't, and what can be most useful to us. After troubleshooting and playing around with the first PCB, we came to a final design which is presented by the two pictures above. In the second revision we did not include a Coin-cell battery holder as we moved away from using a coin cell to a LIPO for battery efficiency purposes. We ended up not needing the USB, and the SMA bluetooth connector. These changes allowed us to reduce the dimensions of our board from 34x34mm to 24x24mm.
To deliver more power to the tissue we needed to drive more current through the LED. To do so, we ended up connecting the LED to a LED driver. The signal received from the MCU will control the Transistor inside the driver. Depending on the signal received from the MCU The transistor will either let the current flow through the LED.

2.4.3 PDT System Schematics



a drawn representation of the light source and tumor cavity problem

2.4.4 Mechanical System Schematics



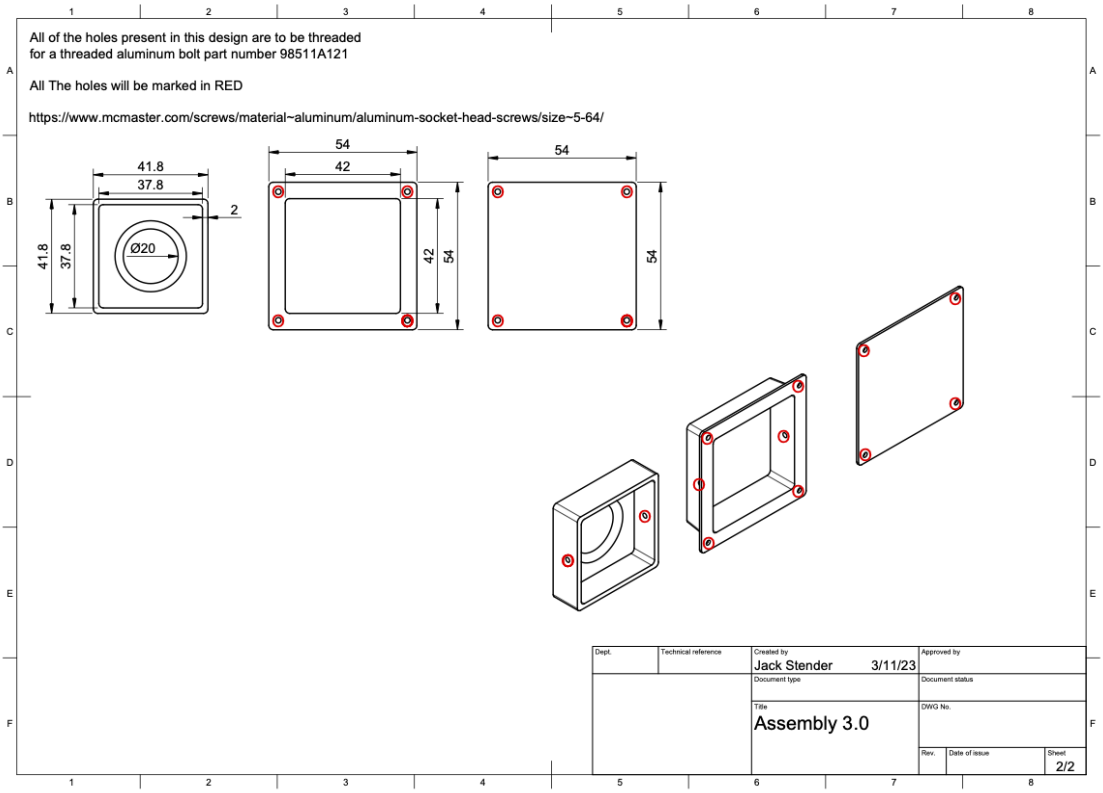


Figure: Several views of the assembly drawing for the device housing

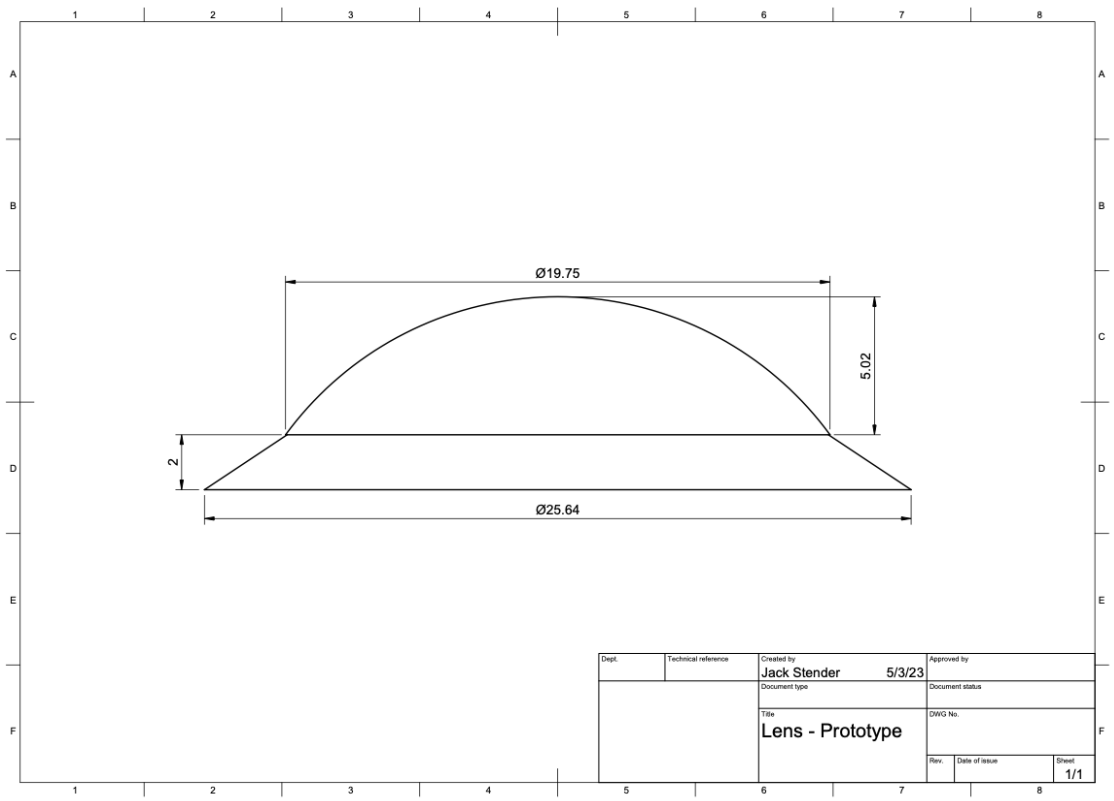


Figure: Lens design parameters (mm)

3 Cost & Schedule

3.1 Cost Analysis

Due to the generosity of our sponsors we were able to order a second revision of the board with spares, the cost is shown below. Additionally, the ECE 445 staff provided us with PCBs and stencils to make soldering faster. These helped with development tremendously.

The first revision including test batteries, components including spares, and an ST-Link programmer, totaled $294.62. The second PCB revision cost $145.06. We are very grateful to our sponsors for funding these engineering costs.

3.1.1 Part & Materials

Description	Quantity	Unit Price	Ext Price
6 hole header conn	10	$1.12	$11.20
ultra low power stm	5	$7.42	$37.10
.1uf cap	28	$0.37	$10.36
4.7uf 0805	10	$0.14	$1.40
10kohm	15	$0.10	$1.50
12MHz crystal oscillator	5	$1.16	$5.80
32.768KHz crystal oscillator	5	$0.69	$3.45
22pf cap	20	$0.17	$3.38
LED	5	$0.25	$1.25
FR1 10nH	5	$0.13	$0.65
3.7V 450 mAh LiPo battery	5	$8.99	$44.95
Npn transistor	5	$0.87	$4.35
TOTAL			**$125.39**

3.1.2 Hours of Development

All of the members of this group are Electrical Engineering students. According to the Illini Success Report from the 2020-2021 school year, the average starting salary for an Electrical Engineering major is $80,296 per year, which equates to $38.60 per hour working 40 hours a week 52 weeks a year.

Category	Hours Jack	Hours Brian	Hours Mohamed
Circuit Design	0	0	110
Housing Design	15	0	0
Breadboard Layout	10	10	30
Soldering	15	20	20
Debugging and Testing	90	80	10
Documentation and Logistic	70	90	30
TOTAL HOURS	200	200	200

Using the hourly estimates above, we calculated our labor costs for the project to be:
$38.60 (Hourly Rate) * (Total Hours) = $23,160

3.1.3 External Materials and Resources

ECE Resources

We spent a total machine shop time of approximately **10 hours**. We were able to get our final housing designs to them in a reasonable timeframe and they delivered the aluminum housing no more than two days later. We also took full advantage of the soldering stations as well as the knowledge and experience of the TAs that hold office hours in the Senior Design Lab this semester. They were instrumental in debugging, polishing, and delivering our final product

UIUC Medical School Resources

We were fortunate to be supported by the University of Illinois at Urbana Champaign Medical School. With that support came access to additional funding, access to a cadaver if we so chose, and the mentorship and understanding of professors and students at the top of their fields. Though we did not end up using the cadaver, we took full advantage of the wealth of knowledge and resources our project coordinators provided.

Development Resources

In order to effectively design, build, and implement our final designs we utilized a development board alongside the above bill of materials. The board in question allowed us to test and verify the software side of our project in tandem with the hardware development. In our final demonstration, we were able to demonstrate our Bluetooth connection on said development board, given we did not have the time to integrate it into the device itself.

3.1.4 Total Estimated Cost

After evaluating materials, labor, and development costs we have determined that the overall expenditure for our ECE445 project was **$23,725.07**

3.2 Schedule

4 Requirements & Verification

4.1 Completeness of Requirements

4.1.1 Electronic System

Requirement	Completeness
Power Subsystem	
The battery provides 3.7V to the processor, LED array, and all other powered systems and supports at least a 50 mA draw.	We were able to complete this requirement.
Depending on the PDT delivery schedule, the device can function for 5 years without battery replacement.	This requirement was outside the scope of our abilities for this class. Though the battery technology exists, it was far too expensive and difficult to acquire for this project.
Control Subsystem	
The system must be programmed with at least three unique treatment schemas.	We were able to complete this requirement.
The end user must be able to select the duration of the treatment as well as the frequency at which the treatment is administered.	We were able to complete this requirement.
UI Subsystem	
The end user must be able to select the duration of the treatment as well as the frequency at which the treatment is administered.	We were able to complete this requirement.
The implant itself must be designed to minimize any risk of postoperative complications.	The housing itself was designed with this in mind, though that material it is made of is far outside the accepted biocompatibility. We would have to re-machine the housing out of a proper biocompatible material, which was outside the scope for this class.

4.1.2 PDT System

Requirement	Completeness
UI Subsystem	
The 5-ALA fluorescent marker, which allows for the PDT to effectively target malignant cells, must not be toxic to patients.	We were able to complete this requirement. (more medical testing needed)
The 5-ALA fluorescent marker must absorb into malignant cells at an exponential rate in comparison to their healthy counterparts as it's designed.	We were able to complete this requirement. (more medical testing needed)
Light Subsystem	
The LED array must provide 200 J/cm^2 optical doses at 635 nm wavelength.	We were able to complete this requirement.
The photodetector must detect the LED array's functionality to allow the system to operate effectively.	We were able to complete this requirement in an external capacity, though the PCB itself lacks proper feedback.

4.1.3 Mechanical System

Requirement	Completeness
Cranial Implant	
The final implant must be made of a material conditioned to limit foreign body reaction. This includes medical-grade titanium as well as other materials coated in an antibacterial compound.	This requirement was outside the scope of this class. Though the housing is designed with biocompatibility in mind, we were not able to purchase a block of titanium big enough to get machined down to our housing dimensions without significant cost.
The final implant must fit within the cranial window with proper positioning inside the resection cavity to ensure PDT administration.	We were able to complete this requirement.

4.2 Verification Procedures

4.2.1 Electronic System

4.2.1.1 Power System

Using a multimeter and oscilloscope, we tested the input pins of our MCU for power and ground and output pins for a PWM signal that was being generated. We then tested the LED driver to ensure the PWM signal was making it all the way to the LED. We finally tested for continuity across all components and determined the overall current draw of the device. We then used the current to determine the power draw over time to evaluate our battery choice against our 5 year time frame.

4.2.1.2 Control Subsystem

After verifying that the proper signals were making it to each of the required pins and the continuity was correct, we flashed our control code to the MCU. This allowed us to select from three predetermined patterns, signed off on by our sponsors. The sample PDT sessions were: 1 minute on 1 minute off for 5 cycles, 30 seconds on 30 seconds off for 10 cycles, and 10 seconds on 50 seconds off for 30 cycles. We were able to, via Bluetooth, select the desired treatment scheme and observe it on the device itself.

4.2.1.3 UI Subsystem

Using Bluetooth and a serial terminal, we were able to send a string of hexadecimal codes to the device. Each of the codes was assigned to a different treatment scheme, allowing us to select the appropriate PDT procedure at will. This, in turn, would allow anyone familiar with the device and its operation to program the device as they see fit.

4.2.2 PDT System

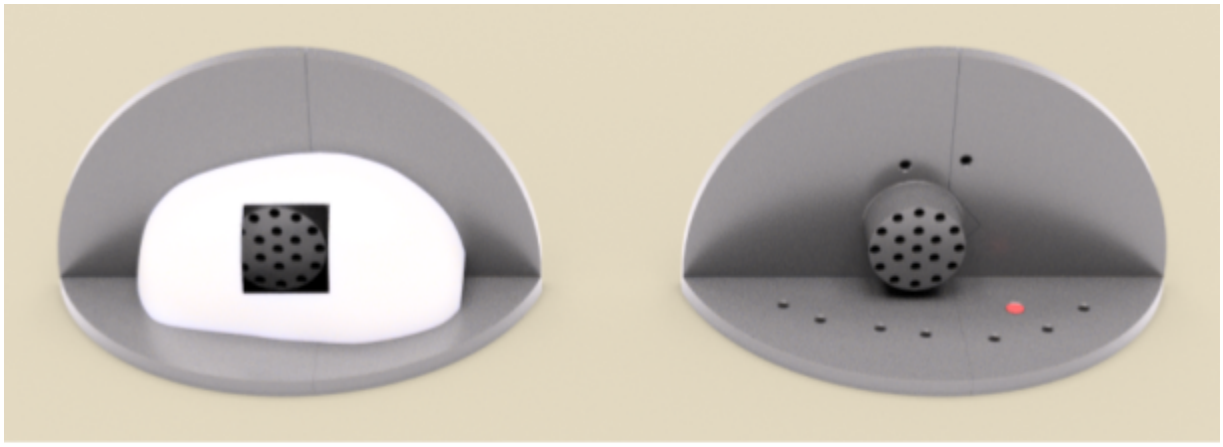
4.2.2.1 UI Subsystem

The 5-ALA fluorescent contrast dye must be ingested prior to the PDT being administered. The initial dose would be done in the presence of a healthcare professional to ensure there are no ancillary complications. Further doses would be taken on a regular schedule in tandem with our PDT system to ensure continuous saturation in the brain.

4.2.2.2 Light Subsystem

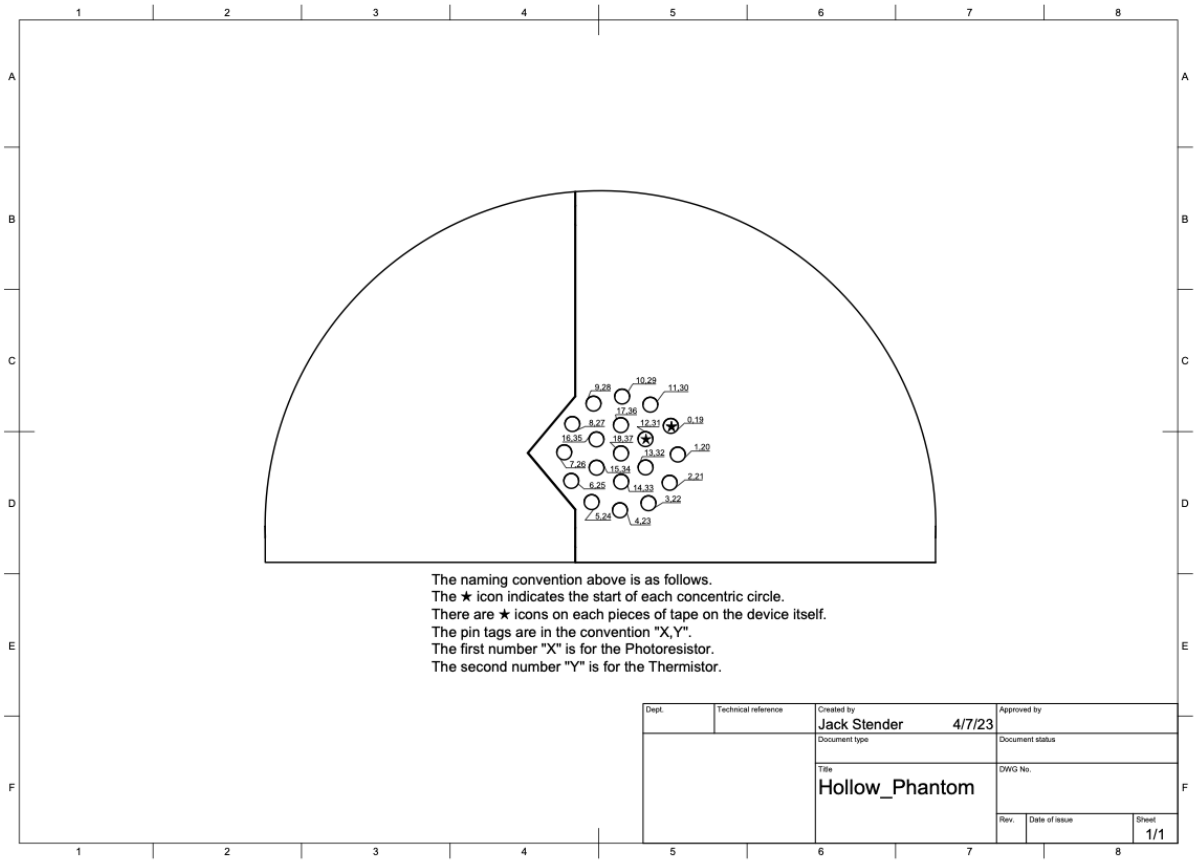
Using the testing apparatus below, we were able to test with certainty that our device meets our threshold for standard of care. We were able to put our device into the window cut into the skull shown below and turn it on for a considerable amount of time, checking for temperature increase

as well as photodetection. The array of sensors allowed us to visualize in 3D space how the light penetration and temperature falls off as we move away from the light source.



Testing Apparatus with Skull Appliance

Testing Apparatus without Skull Appliance

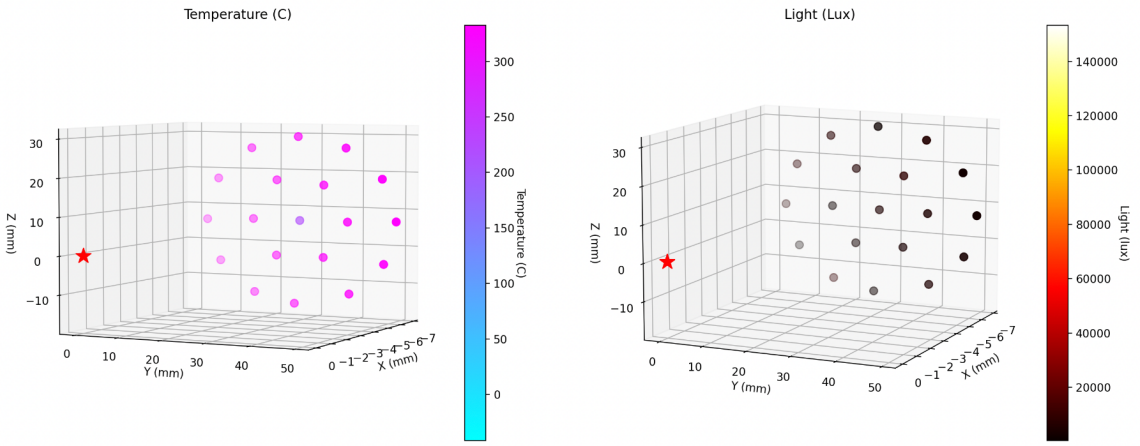


4.2.3 Mechanical System

Verification of our mechanical system will take place during final assembly of the final prototype. Before the device is used in a medical setting, it will be recreated out of a medical grade biocompatible material, sanitized, and implanted by a healthcare professional in a proper surgical setting. This verification will determine the success of the overall housing design. That being said, we were able to verify that the prototype housing is able to be screwed into the mock skull in our testing apparatus. A proper cranial window is slightly smaller than the one we are operating with currently, though with the rate at which the PCB is shrinking, that should not be a problem in the long term.

4.3 Quantitative Results

Using the skull apparatus we were able to do some preliminary testing on temperature and light received by our device. We wired 19 thermistors and 19 photoresistors into three arduino boards and parsed the data in python. It would've provided real time data about the temperature which could have been used to test PDT effectiveness in different materials that have optical penetration values similar to a human brain. Due to time constraints we were not able to come up with a fully working testing device. We did however run the device and determine no change in temperature while the LED was on.



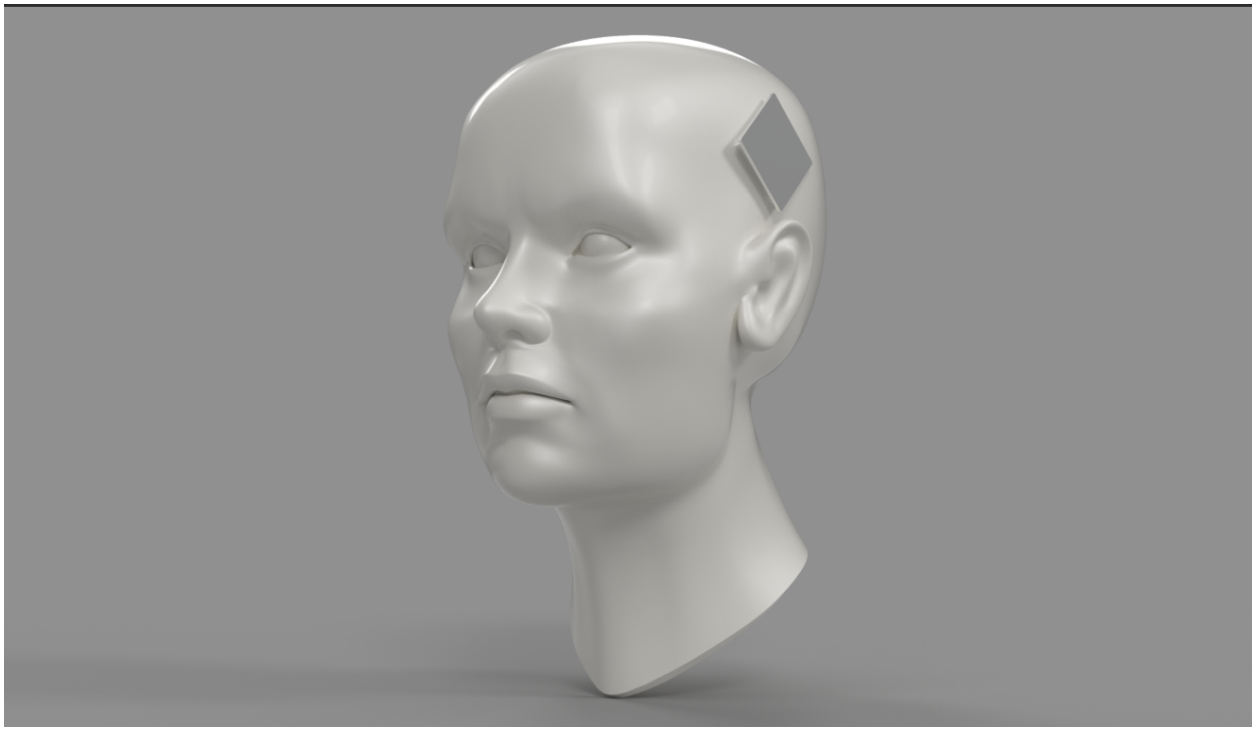
Simulated plot of temperature and light data received by the sensors

5 Conclusion

5.1 Accomplishments

We were able to accomplish the goals we set out for ourselves readily. Though there were some roadblocks to our success, we see the issues we ran into as learning opportunities on our way to

our finished project. The device, at the end of the project, did have full functionality and met all of our operational parameters. We were very pleased overall with the performance of our device.



Render of the device as it may sit on patient skull

5.2 Uncertainties

As quantified in section 2.1-Battery Life we were unable to come up with a battery supported device that will last 5 years. Due to size and battery limitations the best battery we purchased would support the most intense illumination for less than four hours. This means the device as it is currently constructed will not be able to support photodynamic therapy.
The main power sink is the LED so any efficiency gains we get with the control electronics will not mean much. Lasers have better electrical to optical power efficiencies than LED's but they are larger and require more sophisticated design to focus the beam. We think battery life is a solvable engineering problem but it will require a creative solution. There are simply no commercial batteries with the kind of charge we need. Therefore, a rechargeable system, or a near field controlled system may make more sense in future commercializable designs.

5.3 Future Work

We have spoken at length with our mentors and peers that worked with us on our capstone and have agreed that this project not only is viable but has the potential to give people their lives back. We want to continue on with the project and see it all the way through. We have a list of improvements that need to be made initially. This includes increasing the number of LEDs,

changing out the battery, integrating our custom GUI, and shrinking the overall footprint of the device. We have already started the discussion about the next iteration of the device, what we definitely, want to change, and how we can better formulate our testing apparatus to serve our needs. A discussion has been started to build a separate PCB just to operate the testing apparatus, which would allow us to use higher-quality components and get better readings. We have also spoken a little about a flexible PCB that would aid in our space constraints as well as allow us to spread the PDT into the entire resection cavity more effectively.

5.4 Ethics & Safety

5.4.1 Ethical Considerations

When developing a biomedical device, there are several places where one could violate the IEEE Code of Ethics. When meeting with our project team at the University of Illinois School of Medicine, there were three points where the ethical implications were of the utmost importance.

When developing and administering a biomedical device of such delicacy as a transcranial implant, there is a concern for patient autonomy. Patients that could otherwise be perfect candidates for PTD, and this device, in particular, might not be able to make a fully informed decision due to a misunderstanding stemming from a misunderstanding of the foundational technology. Our hope is, that with the proper literature, education, and transparency, we will be able to ensure patient understanding. In doing so, we can make sure everyone that gets the implant is both a good candidate and willing to have our device implanted.

There is a serious potential for side effects after device implantation. We have to consider the possibility that that patient might want the device removed if the implant causes a drastic drop in quality of life. Other transcranial devices, such as the Responsive Neurostimulation (RNS) system have already faced a similar ethical conundrum and workshopped explantation protocols that can be adapted to our situation.

When the unfortunate circumstance of a terminal diagnosis has to be given, some patients might take it upon themselves to seek out unproven technologies, procedures, or drugs that have the potential to improve their chances. A concern of developing a device like this is that vulnerable parties might be swayed to forgo medical warnings to access a clinical trial. We hope that carefully vetting patients for an over-inflated perspective of the theoretical positives will protect both the patient's safety and the integrity of the project overall.

5.4.2 Safety Considerations

When administering a transcranial implant, the doctor and patient are both agreeing to put an electronic circuit and battery dangerously close to the most important organ in the body. A decision like that, as researched and studied as it can be, will always come with its share of safety concerns.

With a battery-powered system powering an incredibly strong LED array very close to the surface of the brain, there is a high potential for the device to overheat inside the skull. The temperature at which healthy brain cells begin to experience damage is between 39º and 40º C (between 102º and 104º F) [6]. Our goal is to engineer and insulate the device well enough to ensure that those temperatures are never reached. Extensive bench testing will be required to reach this goal.

Like with any medical implant, whether it is an organ transplant or a device implant, the risk of a foreign body reaction is always there. Once the prototype is proven, our goal would be to implement the final device in materials designed to limit that reaction. There are antibiotic coatings that exist as well as medical-grade resins and titanium.

6 References

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