Project Proposal

MRI-COMPATIBLE SKULL-EMBEDDED IMPLANT FOR DIRECT MEDICINE DELIVERY

EN.601.456 Computer Integrated Surgery II

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Clinical Motivation

Glioblastoma Multiforme (GBM) is one of the most aggressive types of brain cancer. Currently, the diagnosis of GBM is somewhat of a death sentence for patients because of its malignancy – the median survival time is 14.6 months [1]. There are more than 18,000 new cases in the U.S. per year [2] and the recurrence rate is over 90% [3]. When a GBM is diagnosed, the patient first receives a surgery to remove as much of the tumor as possible. However, total removal is impossible, hence radiotherapy and chemotherapy are often administered to eliminate any potential remaining tumor cells [4]. Unfortunately, over 99% of promising therapies [5] are unable to reach the tumor and be effective due to the blood-brain barrier, which is a barrier that mediates communication between the peripheral and central nervous system.

Patient survival and the standard of care for GBM has been stagnant for the last three decades. Thus, getting past the blood-brain barrier has become one of the most active areas of research, and intersects with the field of neuroplastic surgery: for a skull reconstruction surgery, the collapsed part of the skull is replaced with a 3D-printed, plastic cranial implant that emulates the strength and biocompatibility of the human skull bone. There is a hollow thickness in the cranial implant very close to the brain. Hence, the idea of embedding a cranial implant in this space with functional technology to deliver therapeutics across the blood-brain barrier is of great interest. Once this platform technology is developed, this implant device can be filled with any liquid therapeutics. The target users of this implant device are currently patients with GBM, but eventually it will be applicable to patients with all kinds of neurological diseases such as Alzheimer's and Parkinson's.

Prior Work

This project has been ongoing for several years in the Center for Neuroplastic Surgery Research. Significant progress has been made in the hardware components for the implant device, such as manufacturing all parts of the device with MRI-compatible material, developing the mechanisms for the pump that delivers drugs from the reservoir through the catheters, and designing the mechanism of power supply for the pumps. A sketch of one of the prototype designs is shown below in Figure 1. Now that a prototype has been developed, it will be implanted in a swine study in March 2021. The pump will not be turned on because the purpose of this initial study is to evaluate the structural integrity (i.e. no leakages) and compatibility of the device in an animal model.
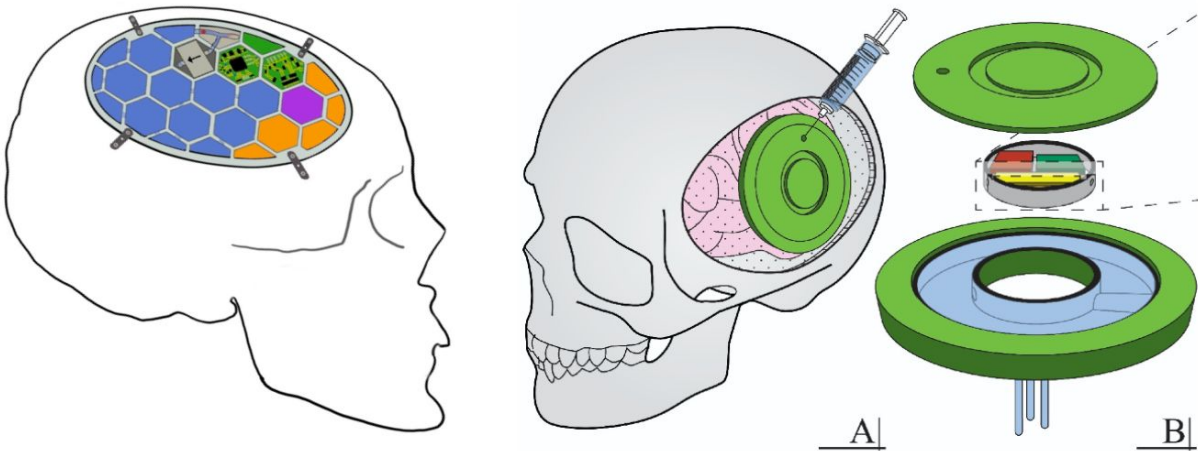
Figure 1: A preliminary prototype of the implant device.

Goals

As seen in the previous section, there is a need to further develop the software component of the device in order to provide a means of communication between the device and the clinicians. Our ultimate goal is to implement real-time Bluetooth connectivity in the device which would allow the device to report its battery life, power transfer status, drug delivery rate, and reservoir status, as well as allow its delivery rate to be controlled through Bluetooth connectivity by clinicians. However, due to time constraints imposed by the semester-long CIS II class, we have identified specific aims to be completed by the end of this class that would set up the foundation for the communication between the device and clinicians using its Bluetooth connectivity. Our specific aims are to

1. Implement code to use information from sensing pins to perform flow rate calculations every minute, and
2. Implement code to use Bluetooth to
    a. transmit flow rate estimates to clinicians,
    b. allow the implant to receive signals to turn itself on and off

The completion of the two aims above would be a principal milestone for the software development of the device. Being able to calculate the flow rate of the therapeutics being delivered using information from sensing pins in the implant device allows clinicians to better understand the current medicine delivery status. In addition, when the implant device would be able to report its flow rate to clinicians, as well as receive signals to turn itself on and off, the efficiency and convenience for real-time control of the device will be significantly enhanced. Ultimately, implementing these two aims could improve the quality of treatment delivered by this implant device.

Technical Approach

Figure 2 shows a high level overview of our technical approach. The skull-embedded implant will contain an MRI-compatible battery, which will power the nRF52 SoC, which will support Bluetooth Low Energy connection. The nRF52 will communicate with two pumps, left and right, which correspond to their respective pumping direction. Over BLE, the implant driver implantd will receive pump flow data, including estimates of the flow rate and time between pumping direction reversals, and be able to turn pumping action on and off. The master implant controller implantctl will communicate with implantd to turn the implant power on and off, so that both pumping and power can be turned off during frequent MRI scans.
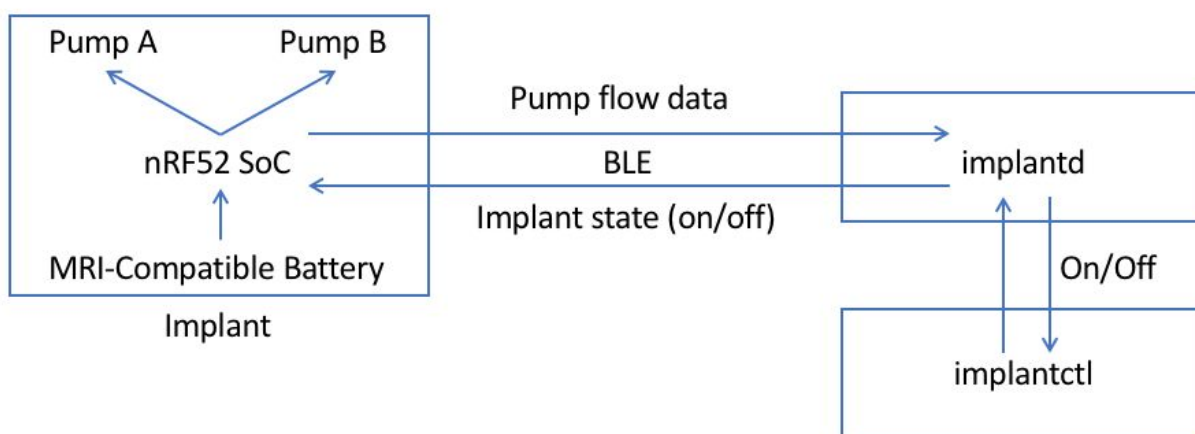

Figure 2: Technical Approach Overview.

The design requirements of our technical approach are split into three phases as shown in more detail below. Our expected deliverables are completed in Phase 1 and 2, maximum in phase 3.

Phase 1

- Pulse-width modulation (PWM) on two output pins, PWM-L and PWM-R, corresponding to their pumping direction (right and left).
    - Only one of the PWMs is actively pumping at any given time.
- Two analog input pins for sensing empty state of pump, SEN-L and SEN-R, which correspond to PWM-L and PWM-R.
- Stop PWM operation when the respective SEN detects signal that pump is empty, then switch PWM to the other direction.
- Check for signal on the sensing pins every 1 minute.
- Use info from SEN-L and SEN-R to calculate estimated flow rate.

Phase 2

- Record estimated flow rates and time between direction reversals in an internal queue buffer.
- Generate flow rate reading every 1 minute.
- Over BLE, transmit the contents of the flow rate internal buffer every 10 minutes.
- Receive BLE signal to turn implant pumping action on and off.
- Run with as little power draw as possible.

Phase 3

- Over BLE, receive new target flow rate and update original to newly received rate.
- Employ LE Secure Connections for BLE Communications.

Key Activities and Deliverables

	Activity	Deliverable	Target Date
Minimum	Implement code that only allows one pin to be active at one time in Runtime	-Documentation of code and test results demonstrating performance	3/3
	Set-up two analog "sensing" pins and supporting code to sense empty state of the pump	-Secured pins on the implant -Documentation of code and performance results	3/11
	Implement code to record signal detections from pins and time between direction reversals	-Documentation of code and performance -Accuracy tests and test results	3/25
Expected	Implement code to use information from sensing pins, to perform flow rate calculations every minute	-Documentation of implementation and math used for flow rate calculations -Testing procedures for accuracy. Results of testing	4/07
	Implement code to use bluetooth to: 1) transmit flow rate estimates to clinicians, 2) allow implant to receive signals to turn itself on and off	- Working bluetooth implementation - Code documentation. -Testing procedures and testing results.	4/21
Maximum	Implement code that allows implant to receive and update to new target flow rate numbers given by clinician	- Code documentation. - Testing for signal reception and flow rate updating accuracy. Testing results	5/01
	Employ low energy secure connections: patient privacy	- Documentation of code	5/13

Table 1: Minimum, expected, and maximum key activities along with their corresponding deliverables.

Table 1 lists the key activities and their respective deliverables. The deliverables are classified as either minimum, expected, and maximum deliverables. Minimum deliverables are associated with activities to be completed in Phase 1, expected deliverables correspond to activities in Phase 2, and maximum deliverables correspond to activities in Phase 3. The phases of the project were previously outlined in Section 4: Technical Approach.

Broadly, the minimum activities include set up of the pins and gaining basic signals from the sensing pins. The deliverables associated are documentation of the code, creating tests, and obtaining testing results. The expected activities build on the minimum by using the obtained signals to compute flow rate calculations and transmit those calculations via bluetooth to the clinicians. Associated deliverables here will be documentation of code, utilized math, testing, and testing results. Finally, the maximum activities are allowing the implant to receive clinician feedback and update flow rate accordingly, as well as implementing low energy secure connections. Deliverables will once again be documentation of code, testing, and testing results.

Dependencies

Table 2 shown below outlines our significant dependencies. Our team will be focussed on the implementation of software components remotely connecting to hardware components. Our supervisor Tushar and other members of the NPS lab will be completing all hardware aspects of prototyping and testing our implementation. Should there be an extreme circumstance in which a team member has to go to the lab in person to interact with the hardware, Henry will be in Baltimore for the rest of the spring semester and will be able to do so.

Dependency	Need	Contingency	Status	Deadline
nRF52 development kit	Need Bluetooth low energy board for pins	Could start some code with existing pins	Complete	2/22
Remote virtual machine	Connect to the implant and test pins	Code on GitHub, have Tushar test in person	Almost Complete	2/26
Compatibility of sensing pins	New pins on implant must be compatible with existing hardware and software	New pins	Not complete, based on prior work should be compatible	3/01

Table 2: Outline of dependencies.

Timeline

A preliminary timeline for completing the minimum, expected, and maximum outcomes is shown below in Figure 3. Currently the team is reviewing prior code and documentation, and will start with Phase 1 (minimum) coding and documentation after background information is properly gathered.

The timeline is currently outlined with strict dates, with an attempt to fit in the maximum activities, but based on progress made with minimum and expected activities, the timeline will be altered. The current aim is to complete pin set-up and obtain signals from the pins by mid-March. We will then move on to performing flow rate calculations and bluetooth initialization, which we aim to complete by mid-April. Once these steps are complete, the maximum activities will be started. The goal for the maximum activities is to finish the coding implementation such that clinician's can give feedback and update flow rate through bluetooth. If this is completed by the end of April as shown in the timeline, the rest of the semester will be spent implementing low energy secure connections for patient privacy.
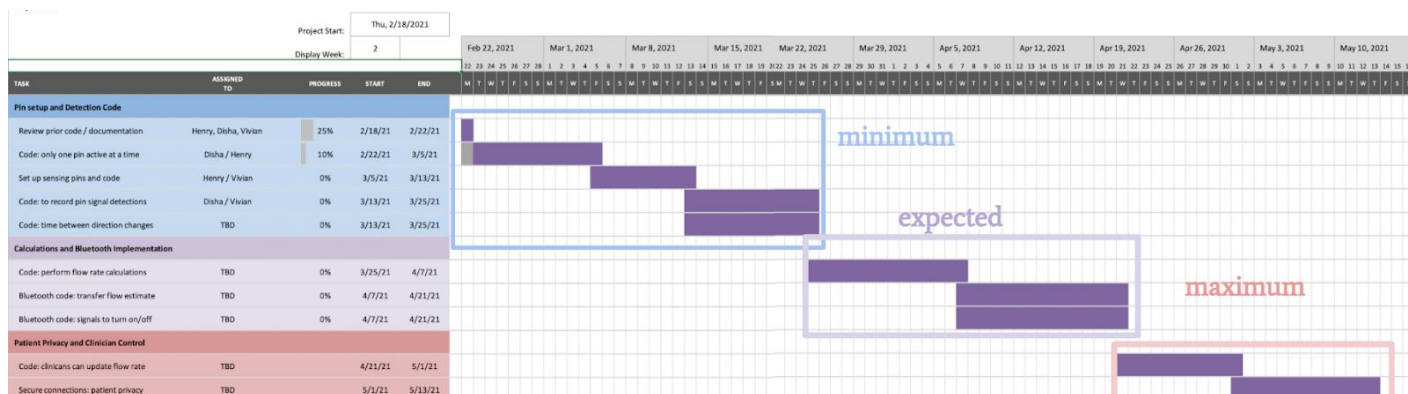

Figure 3: Project Timeline.

Team Members / Mentors and Roles

Team Members

- Disha Mishra (dmishra4@jhu.edu): 3rd Year BS/MSE Candidate, Biomedical Engineering
- Henry Noren (hnoren1@jhu.edu): 3rd Year BS/MSE Candidate, Biomedical Engineering
- Vivian Looi (nlooi1@jhu.edu): 2nd Year BS Candidate, Computer Science

All tasks are currently divided equally. All team members are working on understanding background information and prior work. Different activities of the minimum requirements will then be split up equally once everyone has been caught up with background information. The current

plan is that Henry and Disha will work on implementing code such that only one pin is active at a time, while Vivian works on implementing the signal detection of the sensor pins.

Team Mentors

- Dr. Chad Gordon: Director, JHU Neuroplastic & Reconstructive Surgery
- Dr. Avi Rubin: Technical Director, JHU Information Security Institute
- Dr. Nathan Scott: Senior Design Professor, JHU Mechanical Engineering
- Dr. Mehran Armand: Principal Faculty, JHU Applied Physics Laboratory

Primary Project Supervisor

- Tushar Jois: 3rd Year PhD student, Computer Security

Management Plan

Meetings:

- Weekly Neuroplastic Surgery Laboratory meetings on Monday 10AM
- Weekly meetings with Tushar: TBD, likely Wednesday 10AM
- Biweekly meetings for group: Monday 9PM, Thursday 10AM

Programs Used:

- Communication using Email and Slack
- Sharing code using GitHub
- Writing Reports and Documentation and Uploading onto CIS Wiki

Reading List

Oh S, Odland R, Wilson SR, Kroeger KM, Liu C, Lowenstein PR, Castro MG, Hall WA, Ohlfest JR. Improved distribution of small molecules and viral vectors in the murine brain using a hollow fiber catheter. J Neurosurg. 2007 Sep;107(3):568-77. doi: 10.3171/JNS-07/09/0568. PMID: 17886557; PMCID: PMC2615393.

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Zhou Z, Singh R, Souweidane MM. Convection-Enhanced Delivery for Diffuse Intrinsic Pontine Glioma Treatment. Curr Neuropharmacol. 2017;15(1):116-128. doi: 10.2174/1570159x14666160614093615. PMID: 27306036; PMCID: PMC5327456.

Vogelbaum MA, Aghi MK. Convection-enhanced delivery for the treatment of glioblastoma. Neuro Oncol. 2015 Mar;17 Suppl 2(Suppl 2):ii3-ii8. doi: 10.1093/neuonc/nou354. PMID: 25746090; PMCID: PMC4483037.

Mehta AM, Sonabend AM, Bruce JN. Convection-Enhanced Delivery. Neurotherapeutics. 2017 Apr;14(2):358-371. doi: 10.1007/s13311-017-0520-4. PMID: 28299724; PMCID: PMC5398992.

Davis ME. Glioblastoma: Overview of Disease and Treatment. Clin J Oncol Nurs. 2016 Oct 1;20(5 Suppl):S2-8. doi: 10.1188/16.CJON.S1.2-8. PMID: 27668386; PMCID: PMC5123811.

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[2] Ostrom, Q.T., et al., CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro Oncol, 2013. 15 Suppl 2: p. Ii1-56.

[3] Central Brain Tumor Registry of the United StatesCBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2004–2007 www.cbtrus.org. Accessed June 28, 2012

[4] Hottinger AF, Stupp R, Homicsko K. Standards of care and novel approaches in the management of glioblastoma multiforme. Chin J Cancer. 2014 Jan;33(1):32-9. doi: 10.5732/cjc.013.10207. PMID: 24384238; PMCID: PMC3905088.

[5] Solid lipid nanoparticles for skin and drug delivery: Methods of preparation and characterization techniques and applications - ScienceDirect: https://www.sciencedirect.com/science/article/pii/B9780128162002000153

[6] Gordon, Chad. Magnetic Resonance Imaging Compatible, Convection-Enhanced Delivery Cranial Implant Devices and Related Methods. CraniUS®, 2020.