MRI-Compatible Skull-Embedded Implant for Direct Medicine Delivery

Checkpoint Presentation: March 16, 2021

EN.601.456 Computer Integrated Surgery II

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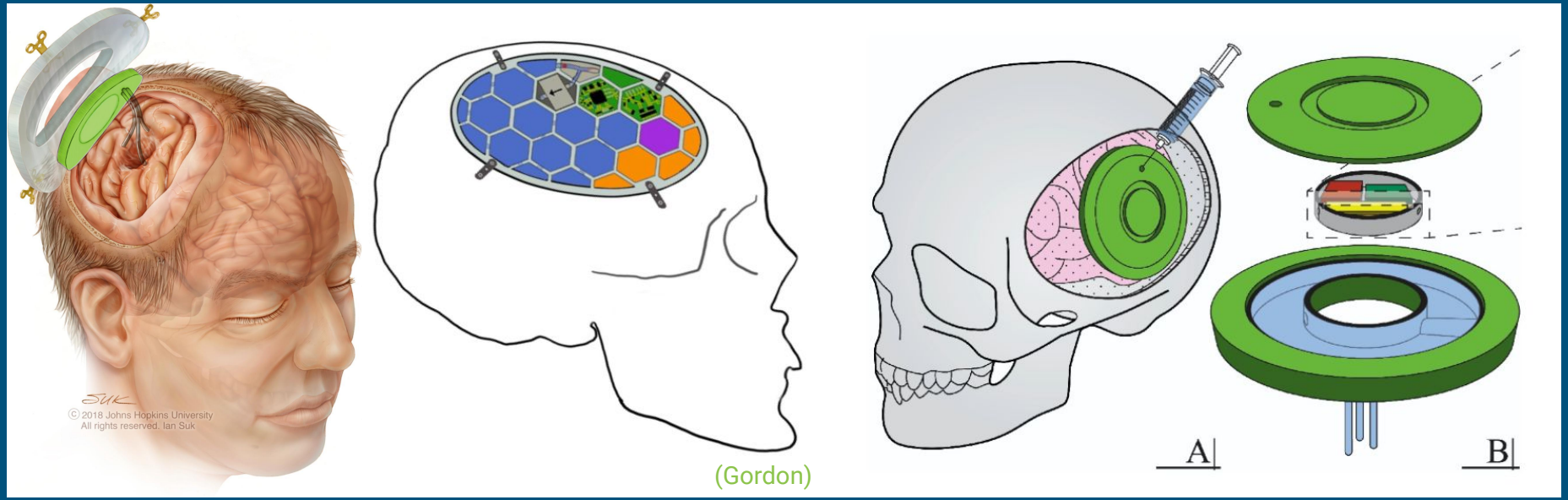
Goal: Integrate bluetooth with current implant prototype, allowing clinicians to access medicine infusion data and alter delivery settings.

Prior Work

A skull-embedded implant with the

first chronic infusion of medicine directly into the brain

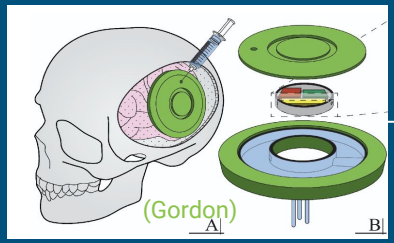


(Gordon)

Patent-pending: “Magnetic resonance imaging compatible, convection-enhanced delivery cranial implant devices and related methods” Gordon et al. 2019. Assigned to JHU.

Our Goal

1. Implement code to use information from sensing pins to perform flow rate calculations every minute
2. Implement code to use bluetooth to: (1) transmit flow rate estimates to clinicians and (2) allow implant to receive signals to turn itself on and off



Medicine Delivery Device with Bluetooth connectivity

Bluetooth

Cellular Device of patients, family, and/or healthcare provider

Cellular/ Wifi

Monitoring Network of Physician/ Patient

Select data for patient/ family viewing

Control drug delivery rate

Report:
- battery life
- power transfer status
- drug delivery rate
- low drug reservoir
- reservoir status

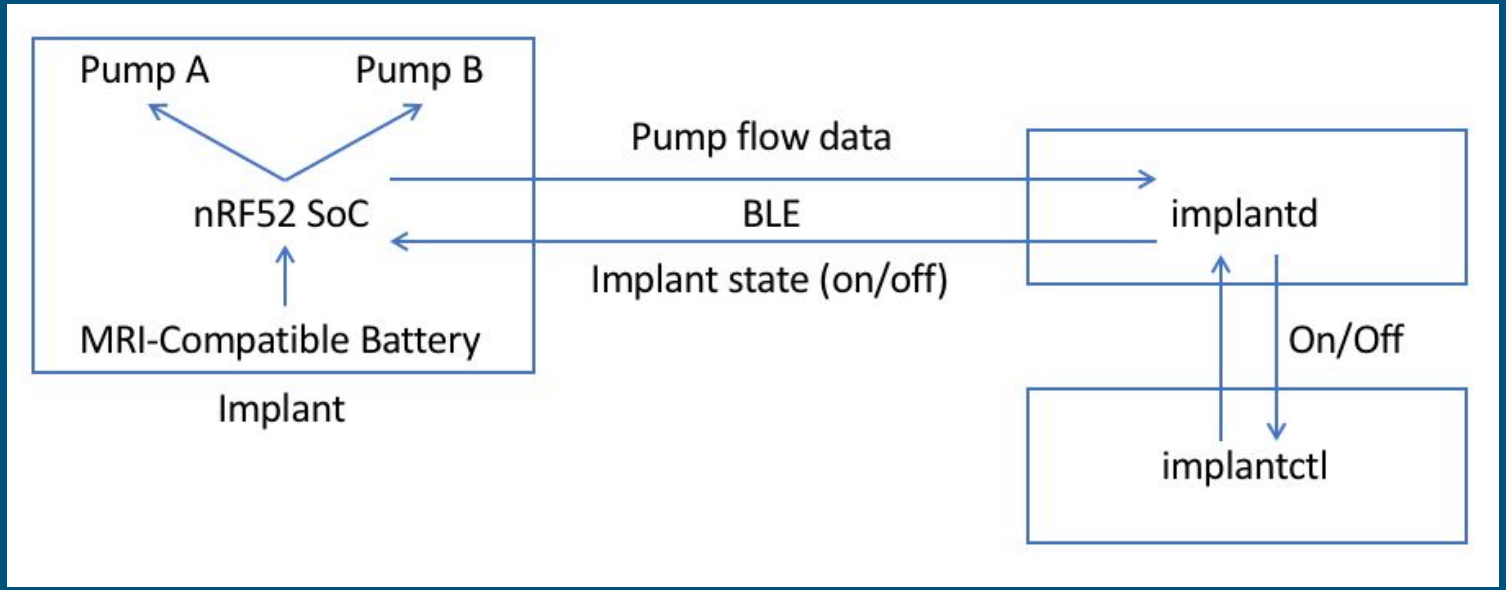
Dependencies

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	Complete	2/26
Multiple nRF52 development kits	Robust testing	Continue with testing with the current board	Pending	4/21

Deliverables

	Activity	Deliverable	Completion 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

Technical Approach Overview Recap



Design Requirements Recap

Phase 1

- Pulse-width modulation (PWM) on two output pins, PWM-L and PWM-R.
- Two analog input pins for sensing empty state of pump, SEN-L and SEN-R.
- Stop PWM operation when SEN detects empty signal, then switch PWM.
- Check for signal on sensing pin every 10 seconds.
- Implement above on *two* separate implant pumps.

Progress So Far

- All team members have login access to the remote computer connected to the board (set up by Tushar).
- Arduino has been set up and has been successfully accessed through the remote log-in.
- Have implemented code so that two pumps can be run simultaneously, which is phase 1 of the design requirements.
- To do: Debugging and testing.

Key elements of the code

```
typedef struct pump_t {
  int direction_left;
  int direction_right;
  int sensor_left;
  int sensor_right;
} pump;

/* Pins for setup: digital direction, analog sensing */
pump* pump_a = new pump{3, 5, A0, A1};
pump* pump_b = new pump{6, 9, A2, A3};
```

Single pump has:

- Two possible directions to pump
- Two sensors (one for each direction)

Note: Pumps initially hardcorded with Arduino pins that are compatible with PWM.

Key elements of the code (continued)

```
void run_pump(int direction, int sensor) {
  Serial.print("Starting on direction pin ");
  Serial.println(direction);
  digitalWrite(direction, HIGH);

  for (int i = 0; i < NUM_INTERVALS; i++) {
    Serial.print("\tRunning iteration ");
    Serial.println(i + 1);

    int reading = analogRead(sensor);
    Serial.print("\t\tSensor pin ");
    Serial.print(sensor);
    Serial.print(" detected ");
    Serial.print(reading);

    /* End this direction if we detect on the sensing wire */
    if (THRESHOLD <= reading) {
      Serial.print(", STOP");
      break;
    }

    /* Otherwise, wait another interval */
    Serial.print(", delaying for ");
    Serial.println(CHECK_INTERVAL);
    delay(CHECK_INTERVAL * TIME_MS);
  }

  Serial.println("Completed direction\n");
  digitalWrite(direction, LOW);
}
```

- Function run_pump sends PWM through specified pump direction pin.
- Collects a sensor reading every 10 seconds.
  - If senses empty state, break out of loop to stop pumping and switch directions
  - Max 10 readings per call (100 seconds) before switching directions
- Serial print statements incorporated for testing capabilities.

Problem encountered

- We want to be able to run two pumps simultaneously.
  - However this presents a challenge because one pump may become empty and need to switch directions before the other.
- We used `thread` to call run_pump function on two pumps simultaneously.
  - This is currently causing a runtime error which we are having a bit of trouble debugging
  - Should be resolved at our weekly meeting with Tushar tomorrow.

Design Requirements - Next Steps

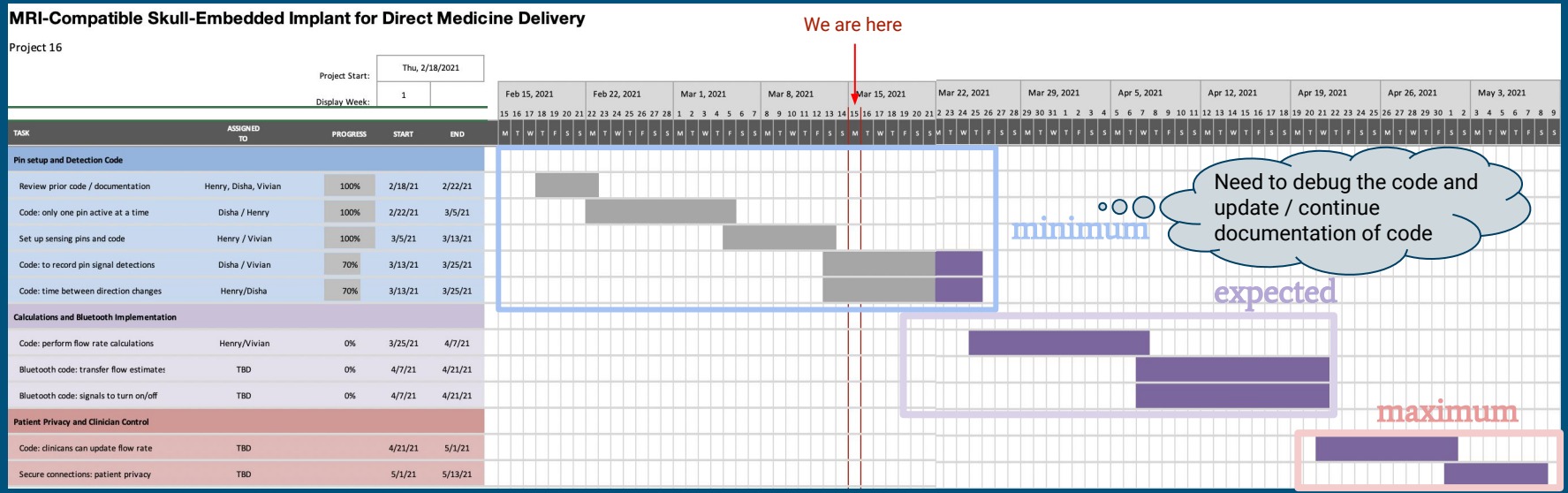
Phase 2

- Use returned sensing data to calculate the estimated flow rate.
- Record estimated flow rates and time between reversals in an internal queue buffer.
- Generate flow rate reading every 1 minute.
- Transmit over BLE the contents of estimated flow rate internal buffer every 10 min.
- Receive BLE signal to turn implant 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.

Updated Timeline



Thank you! Questions?

Appendix

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.

Chen PY, Ozawa T, Drummond DC, Kalra A, Fitzgerald JB, Kirpotin DB, Wei KC, Butowski N, Prados MD, Berger MS, Forsayeth JR, Bankiewicz K, James CD. Comparing routes of delivery for nanoliposomal irinotecan shows superior anti-tumor activity of local administration in treating intracranial glioblastoma xenografts. Neuro Oncol. 2013 Feb;15(2):189-97. doi: 10.1093/neuonc/nos305. Epub 2012 Dec 21. PMID: 23262509; PMCID: PMC3548589.

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.

Reference List

[1] 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.

[2] 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

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

Weekly Meetings and 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