Remotely controlled nanofluidic implantable platform for tunable drug delivery

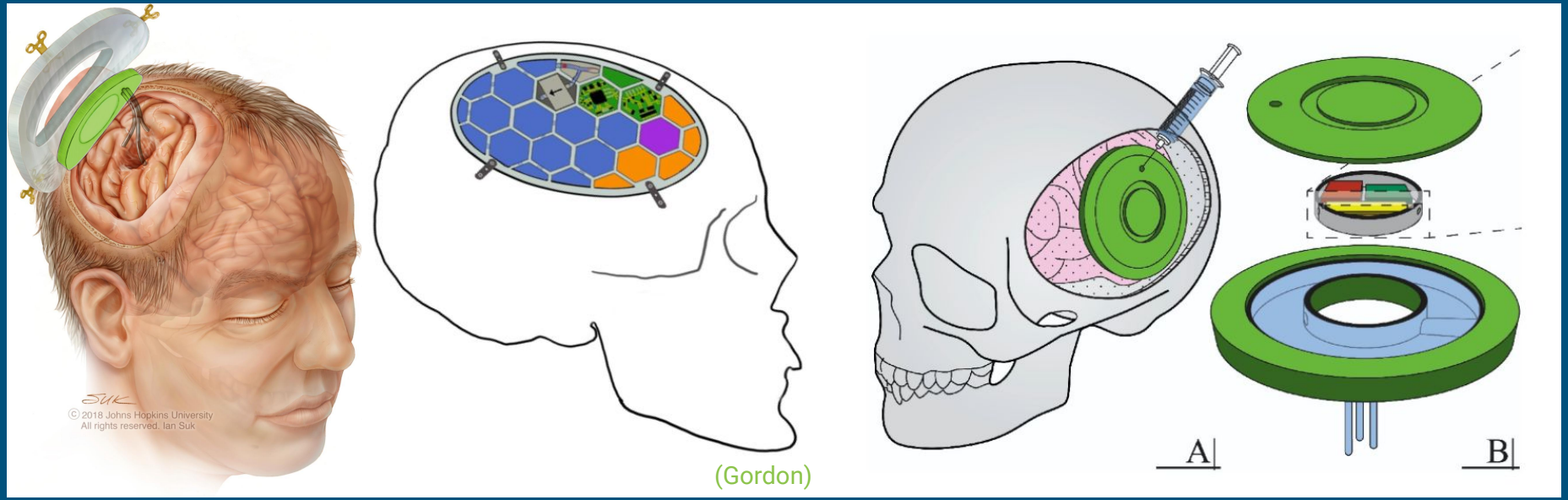
Di Trani N, Silvestri A, Bruno G, Geninatti T, Chua CYX, Gilbert A, Rizzo G, Filgueira CS, Demarchi D, Grattoni A. Remotely controlled nanofluidic implantable platform for tunable drug delivery. Lab Chip. 2019 Jun 25;19(13):2192-2204. doi: 10.1039/c9lc00394k. PMID: 31169840.

Henry Noren (Group 16)

Center for Neuroplastic Surgery Research

Project Summary

An MRI-compatible skull-embedded implant with the
first chronic infusion of medicine directly into the brain

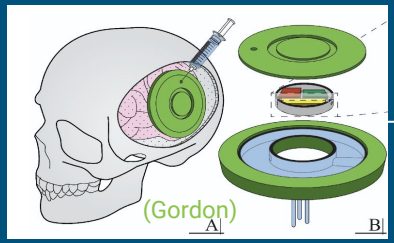


(Gordon)

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 Low Energy (BLE) to transmit flow rates to clinicians and allow them to turn the pump on an 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

Paper Selection

“Remotely controlled nanofluidic implantable platform for tunable drug delivery”

Two main reasons this paper was selected:

- It presents a solution to an unmet clinical need closely related to ours
  - Modifiable, remote-controlled, personalized drug delivery to treat chronic conditions
  - We are focused on a similar need in the cranial/neuro space for conditions such as GBM
- It leverages a similar remote communication strategy to ours
  - Uses BLE to support communication between implant and computer
  - Outlines functionality verification experiments that we can model our own tests on

Summary of Problem and Key Results

- Problem
  - Need for personalized drug delivery with dosage and time modulation capabilities
  - Not a one-size-fits all solution
  - Recent advances in implantable delivery systems are largely sustained release
  - Not all conditions benefit from constant administration
- Their solution is a subcutaneously implantable remote-controlled device that delivers drugs at adjustable rates and intervals
  - Demonstrate ability to modulate release of enalapril and methotrexate
  - **Demonstrate that device supports reliable communication via BLE, doing so with relatively low power consumption with potential for long term implant lifetime**

Some Background

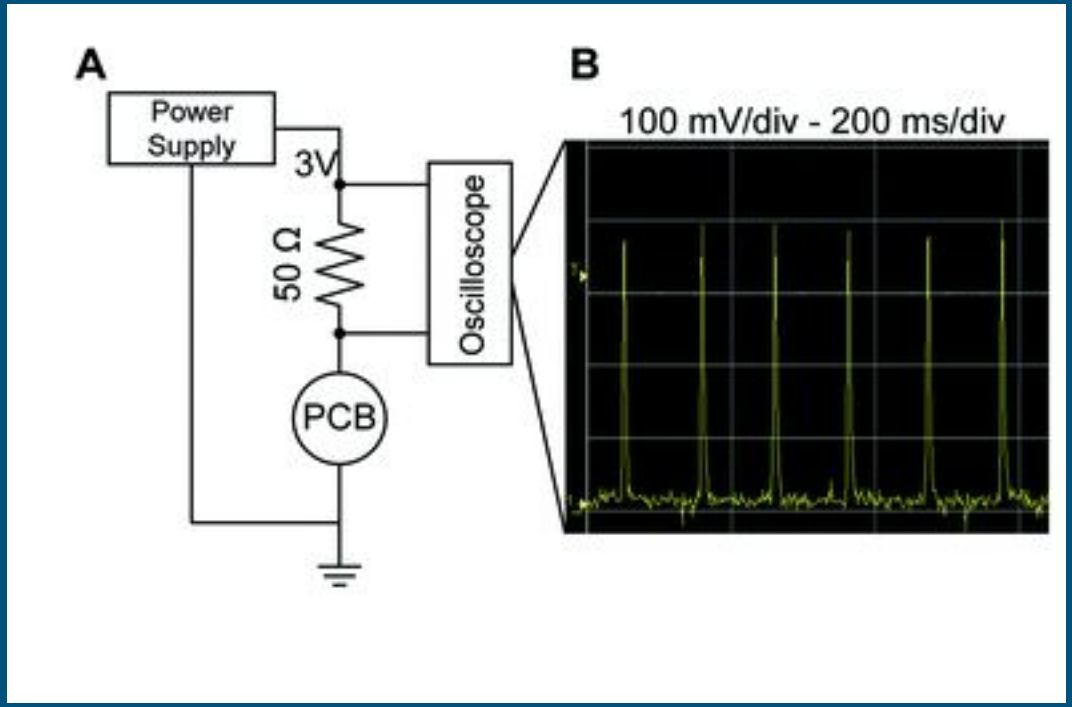
- Current implantable drug delivery systems have limitations
  - Biodegradable polymeric systems: multi-pulse release, lacking dosing control
  - Propellant infusion pumps: constant release over time, lacking dosing control
  - Synchromed Medtronic devices: dosing control, but costly and too bulky for implantation
  - Microchip and ChipRx: remote communication, but too small reservoir size for chronic scale
- Given the benefits and drawbacks of previous systems, these characteristics would make an ideal implant:
  - Modulation capabilities (dosage-on-demand, tunable dose, rate, time)
  - **Wireless/remote communication (i.e. Bluetooth)**
  - Release stoppage when not needed
  - Compact physical dimensions for discrete and comfortable implantation

BLE approach

As in our project, they use Bluetooth Low Energy (BLE).

- They use the system-on-chip CC2541 and connect to PC using a Bluetooth dongle
  - Our project uses Nordic Semiconductor nRF51 DK
- Main advantage of BLE is its low energy consumption
  - Better patient safety
  - Batteries have limited supply, need to minimize recharging and need for further intervention

Power consumption evaluation



Di Trani [4]

Background: 97.5 µW

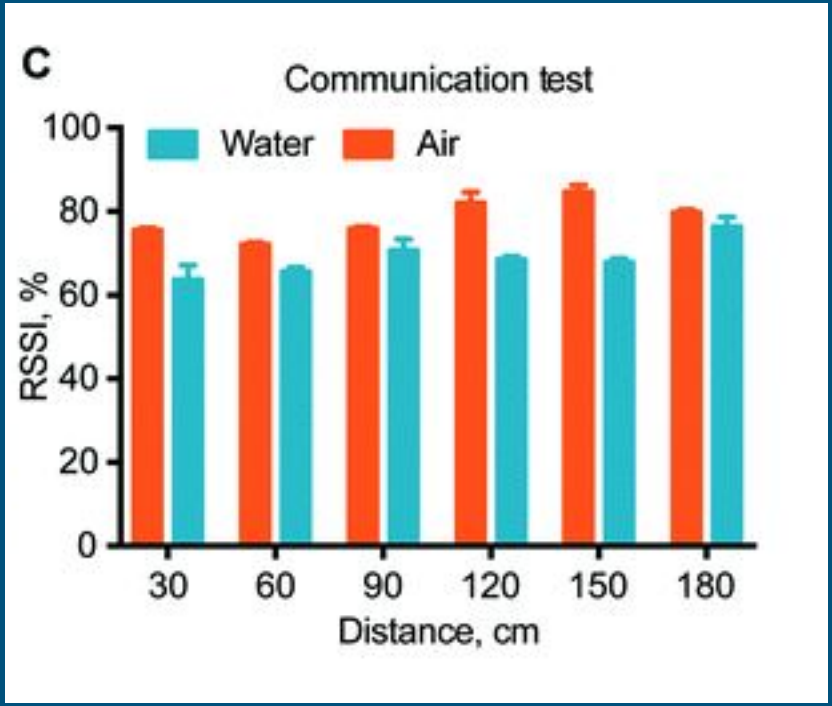
Advertising: 12.5 µW

Communication: 1.22 mW

Lifetime of 20 days

Note: Can increase lifetime by reducing advertising frequency and number of connections.

In vitro communication stability analysis



Measured received signal strength indication (RSSI) at distances 30-180cm

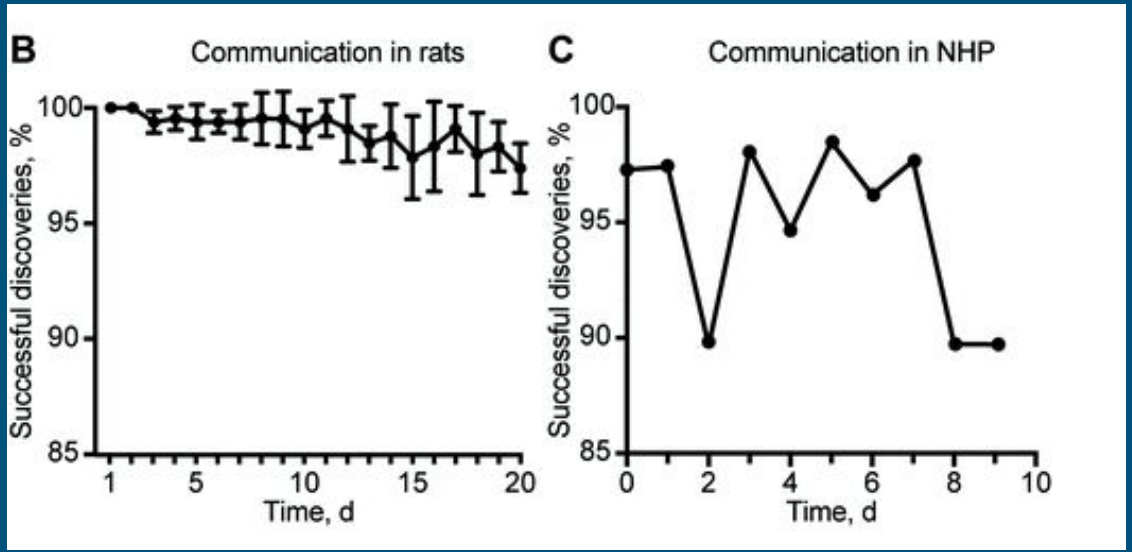
Air: Remains ~80%

Water: Remains ~70%

Only need above 15-30% to be stable, so implant passed for both conditions.

Di Trani [4]

In vivo communication assessment



Di Trani [4]

Measured percent of successful discoveries.

Rats: High ~99%, decreases after day 11

Primate (NHP): Mean 95% over 9 days, variable distance due to mobility

Assessment and Critiques

- Things that were done well:
  - Explanation of the root problem conveyed the significance of solving it
  - They clearly stated their goals within context of personalized medicine
  - The motivation behind each of the experiments testing BLE made sense
- Things could have been done better:
  - Present the power consumption evaluation data in a more meaningful way that highlights the source breakdown and reasoning
  - More thorough explanation of reduction of power consumption since that is a key next step
  - Test *in vitro* communication stability over larger range of distance than 30-180 cm to identify the maximum distance that supports stable communication
  - In *in vivo* test, report the *RSSI* score as well as % successful discoveries to match the *in vitro* test and show multiple metrics of good performance

Next steps

- Minimize power consumption, maximize implant lifespan
  - Main end goal is to effectively treat patients with chronic or even lifelong conditions
  - Allow them to conduct further *in vivo* studies over longer periods of time
- What my group gained from this paper
  - As the semester concludes and we complete our implementation of BLE communication, we are preparing to perform similar tests this summer and beyond
  - We will also eventually be assessing power consumption and communication performance *in vitro* and *in vivo* swine studies in the future

References

[1] Tamimi AF, Juweid M. Epidemiology and Outcome of Glioblastoma. In: De Vleeschouwer S, editor. Glioblastoma [Internet]. Brisbane (AU): Codon Publications; 2017 Sep 27. Chapter 8.

[2] 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.

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

[4] Di Trani N, Silvestri A, Bruno G, Geninatti T, Chua CYX, Gilbert A, Rizzo G, Filgueira CS, Demarchi D, Grattoni A. Remotely controlled nanofluidic implantable platform for tunable drug delivery. Lab Chip. 2019 Jun 25;19(13):2192-2204. doi: 10.1039/c9lc00394k. PMID: 31169840.

Questions?