Paper Review

# Remotely controlled nanofluidic implantable platform for tunable drug delivery

EN.601.456 Computer Integrated Surgery II

Henry Noren

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# Project Summary

The focus of our project is the integration of bluetooth connectivity with the current prototype for an MRI-compatible skull-embedded implant for direct and chronic medicine delivery to the brain in collaboration with the Center for Neuroplastic Surgery Research at Johns Hopkins. The clinical motivation behind the development of this device is the unmet need for improved treatment for Glioblastoma Multiforme (GBM). GBM is one of the most aggressive types of brain cancer, with a median survival time of just 14.6 months [1]. The current standard of care for GBM is surgery, however complete removal is often impossible, and patients often undergo postoperative radiotherapy and/or chemotherapy to eliminate remaining tumor cells, however the vast majority of promising chemotherapies do not reach the tumor because of the blood-brain barrier [2]. The purpose of the implant device, shown in **Fig. 1**, is to overcome this barrier to effective treatment by enabling medicine delivery directly to the tumor resection site.

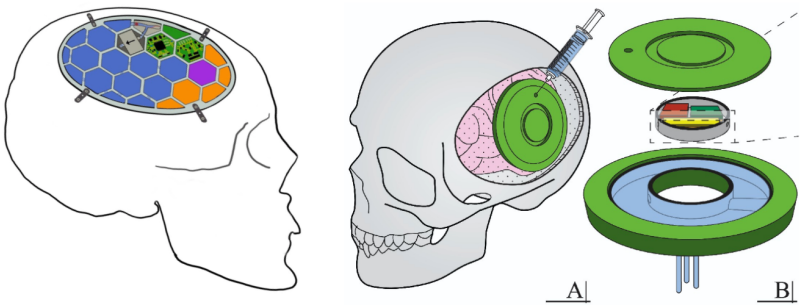


**Figure 1:** A preliminary prototype of the implant device (Gordon) [3].

Our project for CIS II is focused exclusively on software development for the current prototype, which contains two pumps for medicine delivery. Our ultimate goal is to use Bluetooth to (1) give clinicians access to a variety of information on the implant's state, including battery life, pump flow rate, and drug volume in the reservoir, and (2) enable clinicians to modify pump flow rate for personalized drug delivery. Our CIS II semester-long aim is to implement code to calculate the flow rate of the two pumps based on the sensing pin readings every minute. Additionally, we are implementing code to use Bluetooth Low Energy (BLE) to receive signals from the clinician to turn either of the pumps or entire implant state on or off and to transmit calculated flow rates back to the clinician at set intervals. Establishing this backbone of BLE communication between the implant and clinicians places the project in a good position for further swine studies which could take place in Summer 2021.

# Paper: “Remotely controlled nanofluidic implantable platform for tunable drug delivery”

**Paper Selection Reasoning**

This paper [4] was selected for two reasons. Namely, (1) it presents a solution to an unmet clinical need that is closely related to ours and (2) it leverages a similar communication strategy to ours that relies on BLE. The authors of this paper are addressing the need for modifiable, remote-controlled, and personalized drug delivery to treat chronic conditions and we are addressing the need for a MRI-compatible, remote-controlled, skull-embedded implant for direct and prolonged drug delivery to the brain to treat conditions such as GBM. Similar to our project, the authors use BLE to communicate with their implant and discuss key experiments that test BLE functionality. The verification of our own implementation can be modeled after their tests on BLE power consumption, communication stability, and signal strength. I will focus my review of the paper specifically on these sections of the paper that are relevant to our project.

**Summary of Problem and Key Results**

The clinical motivation behind the work described in this paper is the need for personalized drug delivery that allows for dosage and timing modulation to treat chronic diseases, such as hypertension and rheumatoid arthritis, that require long term care. In recent years there have been advances in implantable devices that support sustained drug release, however not all conditions benefit from the constant administration of drugs. Additionally, recent advances in precision medicine have established that the treatment of chronic diseases requires more than a one-size-fits-all approach that considers the inter- and intra-variabilities of patients. Thus the root problem the authors of this paper address is the optimization of maximal treatment efficacy and minimal side effects for patients with chronic conditions.

This paper discusses the development of a subcutaneously implantable remote-controlled nanofluidic device capable of releasing drugs over a sustained period of time at adjustable rates and intervals. These adjustments are made using BLE remote commands. They demonstrate the implant’s ability to modulate the release of two drugs, namely enalapril and methotrexate, which are commonly used therapeutics for hypertension and rheumatoid arthritis respectively. More relevant to our project, they demonstrate that the device supports reliable communication via BLE and does so with relatively low power consumption.

**Background**

The vast majority of implantable drug delivery systems developed to date provide drug administration for a defined period of time at a specific rate. These systems have been beneficial to patient treatment but do not satisfy a key unmet clinical need. For example, biodegradable polymeric systems allow for multiple-pulse drug release and propellant infusion pumps allow for constant release over time, but both lack dosing control post implantation. Delivery systems that do allow for external modifiable dosing, such as some Synchromed Medtronic devices, are costly and implantation prohibitive due to their bulkiness. Some microelectromechanical-based systems, such as Microchip and ChipRx, have demonstrated the attractive advantage of remote communication with the release mechanism, but have been limited in their efficacy due to small reservoir sizes that are not compatible with the needs of long-term disease management.

Given the successes and drawbacks of these previously developed implant systems, the authors of the paper identify the following characteristics of an ideal programmable delivery system:

1. Zero-order release kinetics, which means a constant amount of drug is eliminated per unit time but the rate is not dependent on the concentration of the drug.
2. Modulation capabilities for dosing-on-demand, tunable dose, rate, and time.
3. Wireless/remote communication (i.e. through Bluetooth).
4. Release stoppage when not needed.
5. Compact physical dimensions for discrete and comfortable implantation.

The aspect of this paper which is most relevant to our project for CIS II is their implant's remote communication capability, which is an attractive feature for convenient monitoring and telemedicine interests. They used the system-on-chip (SoC) CC2541 (Texas Instruments) for Bluetooth Low Energy (BLE) communication. The main advantage of BLE is its ulta-low energy consumption, which is advantageous in ensuring the patient's safety. BLE is also preferred for these types of implantable technologies because they are often powered by batteries and have a limited power supply before recharging/battery replacement is necessary, which could require further intervention. The implant was powered by a CR2016 (VARTA) battery and two general-purpose input-output pins were connected to electrodes for drug modulation. They performed communication over BLE with a remote PC using a USB Bluetooth dongle.

**Experiments Performed**

*Power consumption evaluation*

The power consumption of the circuit board was evaluated with an oscilloscope to monitor the voltage across a resistor of 50Ω, which models the internal load of the battery, as a supply of 3V was provided (Fig. 2A). Different sources of power consumption, including background use,

advertising (Fig. 2B), and communication, were assessed to estimate the power lifespan of the implant. Background processing consumed 97.5 µW, advertising consumed 16.5 µW, and communication consumed 1.22 mW. This significantly higher consumption associated with communication is because of the data transmission between the implant and server that requires higher energy. The battery has a capacity of 270 mWh, so the authors estimated that the power lifetime of the implant in high power consumption was about 20 days. However, upon reducing advertising frequency from 100 ms to 10 s, the lifespan was increased to 30 days without a significant decrease in connection stability. The authors also proposed that the energy consumption of the electrodes could be reduced by implementing a square or pulse wave that could increase the power lifespan up to 3 months. Lastly, they suggest that decreasing the number of connections by transmitting the implant state in regular advertisements could also reduce power consumption and extend the lifetime multiple months.

*In vitro communication stability analysis*

To evaluate the stability of BLE communication, connection between the computer and implant was established at varied distances of separation from 30 cm to 180 cm. They measured the received signal strength indication (RSSI) score to assess the quality of communication in two conditions, in air and submerged in water to model subcutaneous implantation. Each communication test lasted 60 minutes and was performed in replicates of 3 for each condition. The results show that increasing the distance between the implant and computer does not cause a significant decrease in communication stability (RSSI) between 30 cm and 180 cm (Fig. 2C). The RSSI remains at about 80% in air and 70% in water across distances. For the connection to be stable, the RSSI should be above 15-30%, so these results demonstrate the implant's ability to maintain stable connections *in vitro*.

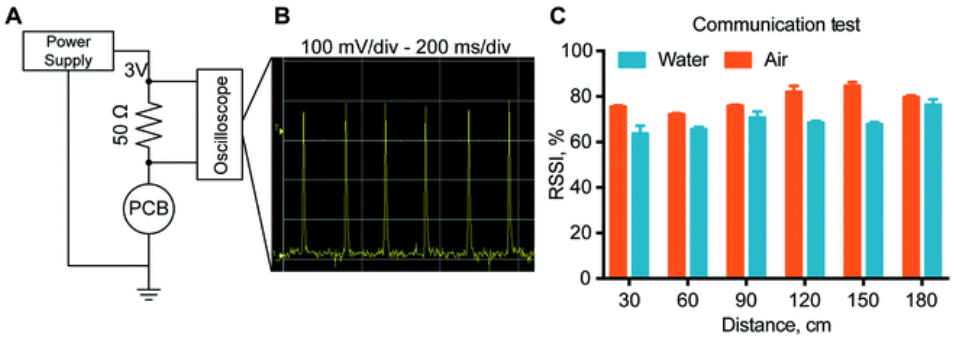


**Figure 2: Power consumption and communication stability evaluation [4].** (A) Experimental setup for power consumption analysis. (B) Oscilloscope measurements with peaks representing power required for the system to advertise via BLE. (C) Communication stability test results showing RSSI score for distances between 30-180 cm in air and submerged in water.

*In vivo remote communication assessment in rates and non-human primate*

To evaluate the safety of the implant before clinical translation, the biocompatibility of the device was tested in rats and a non-human primate (NHP) (Fig. 3A). The communication reliability of the implant was assessed by measuring the percent of lost advertisements during the discovery routine of the BLE connection. In the rats, the percent of successful discoveries remained high at 99-100% for the first 11 days, and then slightly decreased for the remaining of the 20 days (Fig. 3B). They attributed the non-successful discoveries in the rats to battery discharge which reduced power to the antenna and resulted in a shorter communication range. In the NHP, the successful discovery rate had a mean of 95% over 9 days (Fig. 3C). They attribute the loss of advertisements (non-successful discoveries) in the NHP to the animal's large confinement area which resulted in variable and sometimes considerable distance between the implant and computer.

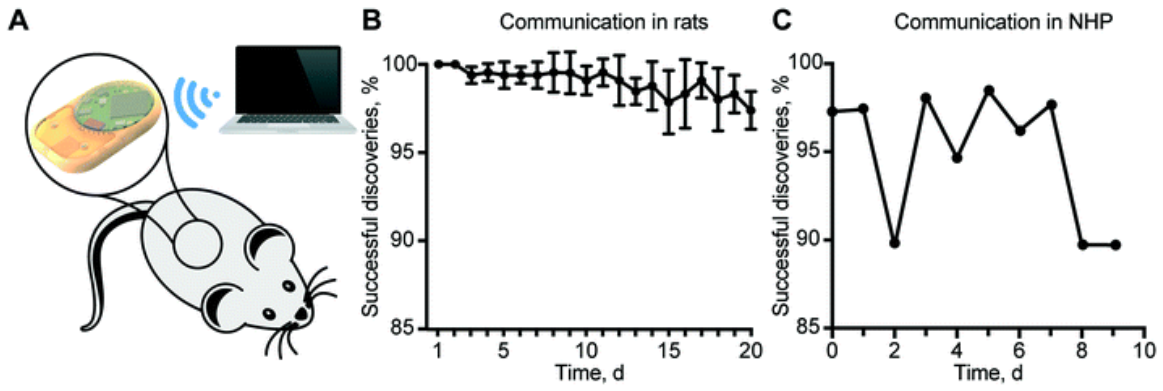


**Figure 3: In vivo communication assessment in rats and NHP [4].** (A) Illustration of computer to implant communication through BLE. (B) % successful discoveries in rats (n=6) over 20 days. (C) % successful discoveries in NHP over 9 days.

**Conclusions Made**

By making modifications to the implant system, establishing BLE connection and communication could consume power at a rate that allows the implant to function for up to several months. The implant is capable of maintaining a stable connection in both air and water, simulating subcutaneous implantation conditions. Lastly, the *in vivo* animal models verified the implants ability to perform reasonably reliable communication. Thus, the authors demonstrated the potential for BLE to be leveraged in drug delivery implants for remote communication.

**Assessment and Critiques of the Paper**

The paper did an excellent job of contextualizing the solution to the problem they are addressing and conveying the significance of the development of this implant. Their discussion of the unmet need for an adjustable drug delivery system that is optimized to the unique treatment requirements of the individual patient justifies their clinical motivations very well. Overall, their motivation behind their experiments related to the implant's remote control functionality through BLE made logical sense and supported the validity of the device. The *in vivo* evaluation of the BLE communication in rats and the NHP was particularly beneficial in establishing the legitimacy of their device and convincing the reader of the high potential for clinical translation in the future. With that said, there are some aspects of the paper that I believe could be improved.

In their discussion of the experiment in which they evaluate the power consumption of the implant system, I believe they could have presented the data in a more meaningful way. Since they evaluated three different sources of power consumption (background use, advertising, and communication), they could have better visualized the results by showing a figure that breaks down the percentage of consumption by source, such as a pie chart. Additionally, in this section they introduced multiple different strategies to decrease power consumption. Since minimizing power consumption is one of the main next steps in the development of this implant, their discussion and justification of these strategies could have been more extensive. With respect to the *in vitro* evaluation of communication stability in air and submerged in water, their results would have been more insightful if they tested communication over a larger range of distances. They only evaluated distances between 30 cm and 180 cm, which did not allow them to identify the maximum distance at which stable communication could be achieved. This is an important performance metric that they did not collect and present in the paper, but will be extremely important in clinical translation to human patients who are mobile and could benefit from longer range communication. Lastly, in the *in vivo* evaluation of communication, the percent of successful discoveries was reported as the key performance metric, while the RSSI was reported for the *in vitro* evaluation. Their verification of BLE communication could have been stronger if they reported both these metrics for the *in vivo* models.

From my point of view, the next steps in the development of this device are the minimization of power consumption and maximization of implant lifespan. Given that the end goal of this device is to improve the treatment of patients with long term or even lifelong chronic conditions, this optimization is a high priority. This would also allow them to conduct further *in vivo* animal studies over longer periods of time to gain more preclinical insights on all areas of the implant's performance. This paper proved to be quite relevant to our as the CIS II semester comes to a conclusion and we transition to performing similar tests of power consumption and communication performance *in vitro* and *in vivo* in the summer and beyond.

# References

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