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Detection of Acute Biomarkers to Optimize Target Engagement in Bioelectronic Medicine

by

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Chapter 6: Thesis Chapter for the Public

Precise Targeting of Bioelectronic Medicine

Purpose of this chapter

I wrote this chapter to share the joy I find in science. Science is a journey of discovery to learn more about ourselves and the world we live in. Science is a shared journey – with experts also in our field, with future experts (who may be in middle school right now), and with those outside the field (including the public). The Ludwig lab is committed to research that furthers humanity and I am thankful for this opportunity to share our work. I would like to thank the Wisconsin Initiative for Science Literacy (WISL) for their support in putting together this chapter. In particular, I thank Elizabeth Reynolds for her feedback on drafts of this chapter.

Portions of this chapter were presented at the UW-Madison 3-minute thesis (3MT) competition 2022:

https://www.youtube.com/watch?v=xFAa44zQmAI

6.1 Analogy of the nervous system

We are a little bit like computers! A computer has wires connecting its mother board to its speakers and microphones, which is how it 'speaks' and 'listens'. Similarly, we have nerves connecting our brains to organs throughout our body. Organs include our heart, lungs, and stomach. The difference between nerves and wires is that our nerves can regrow. They are alive! Like an electrical wire, our nerves carry electrical signals, which our brain uses to communicate with our organs and our organs use to send signals back to the brain. We know how to tap into wires to edit the signals travelling on them – we call this hacking. Similarly, we can use electrical stimulation to edit the signals travelling on our nerves. By 'hacking' the electrical signals on nerves, we can change organ function for therapeutic reasons. This is the premise of bioelectronic medicine.

6.2 Example of a bioelectronic medicine therapy

The carotid sinus nerve is a small nerve in our neck that connects blood pressure sensors in the carotid artery, a major blood vessel in our neck, to our brain. This nerve conveys critical information on blood pressure in the carotid artery to the brain, which then uses it to adjust blood pressure throughout the body.

In a clinically utilized therapy, a metal stimulation electrode is implanted next to the carotid sinus nerve during a surgical procedure. Electrical stimulation is then delivered through the metal electrode and additional electrical signals are introduced on the carotid sinus nerve. The brain receives these additional signals via the carotid sinus nerve and, concerned blood pressure is too high in the carotid artery, sends signals to lower blood pressure throughout the body.

The response can be miraculous! A patient with chronic high blood pressure can have this device turned on, and within minutes their blood pressure returns to a healthy normal level.

6.3 The problem of imprecise stimulation in bioelectronic medicine

Unfortunately, this miraculous response is only the case for the minority of patients. In the majority, the stimulation dose, or electrical current, that can be delivered is limited by off-target nerve activation. And there are many off-target nerves in the region of the neck. These off-target nerves can be activated by the electrical stimulation before the on-target carotid sinus nerve and lead to painful side effects, for example, unintended muscle contractions.

To move bioelectronic medicine forward, we need ways to stimulate nerves that are more precise. This has been the subject of my PhD thesis!

6.4 Improving target engagement in bioelectronic medicine

With the goal of improving the precision of electrical stimulation in bioelectronic medicine therapies, I have been running computer models to develop the Injectrode. The Injectrode is an injectable stimulation electrode that is delivered to the target nerve under ultrasound imaging guidance. The Injectrode is soft and fits snugly around the target nerve (Figure 6.1). This snug fit allows isolation of the target nerve and more precision stimulation. Further, the metal Injectrode 'attracts' electric current to it, routing current towards the target nerve. I have shown that when the Injectrode is used in addition to standard noninvasive electrical stimulation, it lowers the stimulation dose required to activate the target nerve by more than 10 times!

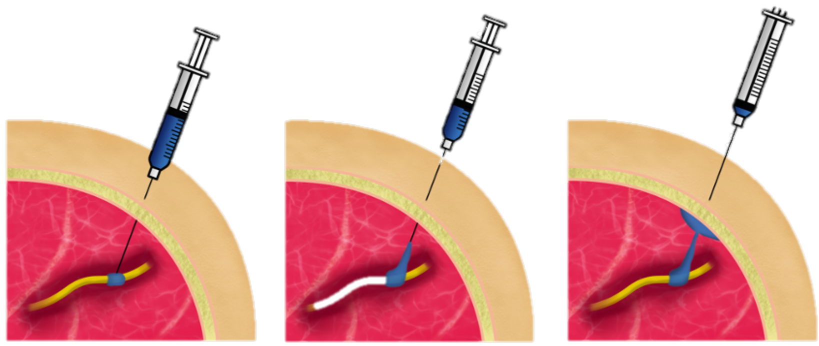

Figure 6.1: Injectrode delivery to the target nerve. Figure from Verma et al., 2021.

I then developed a way to directly measure nerve target engagement, which could be used in a human patient. I did this for two reasons. Firstly, we need to be able to measure target engagement to improve it. Secondly, I wanted to show that the Injectrode I developed using computer models would work in real human patients too.

When looking for methods to directly measure nerve target engagement, I was inspired by a paper from Ottaviani and his colleagues (2020). They introduced a very thin insulated metal wire with an exposed tip, called a microneurography electrode, into the target nerve and showed they could record neural activity from the nerve (Figure 6.2). Because the wire was so thin, it was barely felt as it entered flesh! I built on their work by investigating if the microneurography electrode could measure evoked electrical signals on the nerve following therapeutic electrical stimulation. I tested the microneurography electrode from Ottaviani's study alongside traditional recording electrodes used in the bioelectronic medicine fields. I did the experiments in living pigs. We needed to use pigs because they have similar size nerves to humans. The pigs were under anesthesia during the experiment. My experiments showed that the microneurography electrode could accurately measure electrical signals on the nerve following therapeutic electrical stimulation. My work suggests that microneurography of the target nerve, as demonstrated by Ottaviani and his colleagues (2020) in humans, could be used in patients to measure and improve nerve target engagement during bioelectronic medicine therapies.

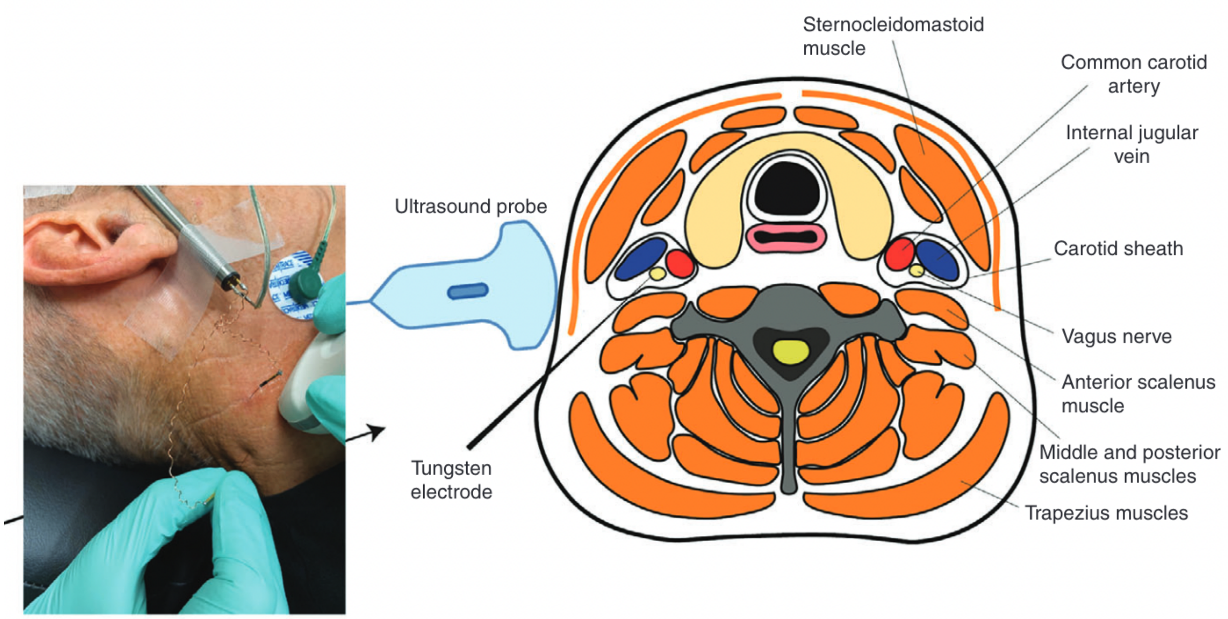

Figure 6.2: Ottaviani and his colleagues inserted a very thin metal wire through the skin and into the target nerve. They were able to record electrical activity from the nerve. Figure from Ottaviani et al., 2020.

6.5 How I used the Injectrode and microneurography electrode to improve electronic bone growth stimulators

While working on my PhD, I came across noninvasive electronic bone growth stimulators. These devices are applied to the skin and deliver electric currents to the underlying bone, which helps accelerate bone growth. Bone growth stimulators are prescribed by physicians for fractures that have not healed by themselves even after several weeks to months. I learnt several things about noninvasive electronic bone growth stimulators that led me to believe the therapy might be facing a target engagement problem. First, invasive electronic bone growth stimulators were shown to work better than noninvasive stimulators. Invasive stimulators are positioned closer to the bone and able to deliver a stronger electrical stimulation to the bone. Secondly, studies in small animals, where the fractured bone is closer to the noninvasive stimulation electrode and more electrical stimulation reaches the bone, showed that the therapy worked well. These excellent results were not always seen in humans. Thirdly, no one had yet measured the electrical current reaching the bone during noninvasive electronic bone growth stimulation. I decided to do just that!

I used the same microneurography electrodes from the previous study in pigs to measure the electrical stimulation reaching the bone during noninvasive electronic bone growth stimulation. I did these experiments in cadaver human legs that people had selflessly donated after their death. I found that very little of the applied noninvasive electrical stimulation was reaching the target bone! These results suggested that noninvasive electronic bone growth stimulation might have a target engagement problem.

In an effort to improve the electrical stimulation reaching the bone during noninvasive electronic bone growth stimulation, I believed the Injectrode could help – just as it had with noninvasive nerve stimulation. To test the idea, I compared the measurements taken in the human cadaver legs during noninvasive electronic bone growth stimulation to measurements taken with Injectrode-augmented (Injectrode filled into the bone fracture) electronic bone growth stimulation. I measured an increase in electric stimulation reaching the bone with the Injectrode-augmented stimulation. I repeated the experiments in sheep, a large animal model commonly used to test fracture healing therapies, and came to the same conclusions.

This study in cadavers laid the groundwork for a future study where we will test Injectrode-augmented electronic bone growth stimulation versus traditional noninvasive electronic bone growth stimulation. We believe the Injectrode-augmented electronic bone growth stimulation will result in faster fracture healing.

6.6 What I am doing now

I am now using the target engagement framework and additional disease-relevant measurements to develop a new bioelectronic medicine therapy to tackle Alzheimer's disease. I look forward to sharing more about that work in the coming years!

6.7 My journey to bioelectronic medicine

It took me several years of describing my interests to discover the field of bioelectronic medicine. In middle school and high school, thanks to some particularly inspirational and supportive physics teachers, I loved physics! Thank you Ms Chee Hwai Mei, Mr Terrence Chiew, Mr Bernard Taylor, and Mr Jason Chan. In particular, I enjoyed the physics on electricity and magnetism. At the same time, biology was a subject I found fascinating but scored poorly in, particularly due to the need to memorize heavily to do well in the examinations. I wanted to use the conceptual lens of physics to study and understand biology. It took me several years of describing this, talking to people, and internships to land upon the field of 'bioelectronic medicine'. It was perfect – applying electricity to the body to excite neural activity and alter physiology for therapeutic purposes. Since then, I have worked in several university labs and companies in the field and been guided by incredible mentors.

6.8 My future

In the long-term, my goal is to translate bioelectronic medicine advances from university labs to therapies that benefit patients. The last few years in graduate school have given me insights into the scientific methods, practices, and thought processes. Next, I plan to join a growing company in the field of bioelectronic medicine to contribute and understand what it takes to translate a proof of concept in animal studies to a clinically useful therapy.