Non-Invasive Monitoring Device for Early Detection of Breast Cancer Related Lymphedema

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Non-Invasive Monitoring Device for Early Detection of Breast Cancer Related Lymphedema
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Executive Summary

Breast Cancer Related Lymphedema (BCRL) is a common co-morbidity in cancer survivors following neoadjuvant therapies such as chemotherapy, radiation, and surgery. In fact, the NIH has reported that upwards of 23.8% of breast cancer survivors will develop this condition by the patient’s two-year mark of remission [1]. Lymphedema is brought about by the disruption in the lymphatic system (for example, lymph nodal biopsy) that leads to a buildup of lymphatic fluid. Current diagnostic strategies for this condition are merely retroactive and fairly limited in the parameters that are examined to reduce residual cancer burden. These parameters include patient reported symptoms and/or circumferential measurements of the upper arm ([2], [3]). In this senior design project, we developed and analyzed an experimental bioimpedance spectroscopy device that would provide clinical support to better determine early stages of lymphedema. Using a Howland Voltage Controlled Current source and an Arduino UNO, bioimpedance measurements were taken across an abridged Hodgkin-Huxley tissue impedance model to validate sensor calibration [4]. An expected range of measurements was calculated within the bounds of safe electrical stimulation limits and the supply from the device [5].

![Voltage Output vs. Input Frequency](image)

**Figure I. Voltage Measurements vs. Input Frequency**

Our design yields consistent measurements to that of the expected theoretical calculations. This calibration of the sensor response is promising as early treatment intervention may prevent long term side-effects due to delayed lymphedema treatment.
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Introduction

Background

The lymphatic system transports immune cells throughout the body through lymph fluid, and “filters” this fluid at “epicenters” throughout the body called lymph nodes. This system may also transport metastatic cancer cells throughout the body. Therefore, when diagnosing breast cancer, medical doctors look for enlarged lymph nodes in the armpit (the axillary node site) when performing diagnostic tests [1]. Radiation therapy, general infection, or injury/trauma to the lymph node (such as through a biopsy) disrupts lymphatic fluid flow and can all cause a build-up of lymphatic fluid under the skin; diagnosed as lymphedema. With damage to the node, fluid will build up in the fatty tissues just under the skin of the upper arm of these patients. This fluid build-up may cause swelling, discomfort, aching, tingling, numbness, redness of skin, an increase in skin temperature and increase the risk of post-operative infections such as cellulitis [6]. Lymphedema can sometimes cause serious problems and is often a long-term or chronic condition. This is why early detection and careful management is needed to help reduce symptoms and prevent disease progression. When diagnosing this condition, it is classified in four stages: Stage 0 through Stage 3; with Stage 3 being the most severe. A simple graphic is shown in Figure 1 of lymphedema staging for the leg.
Figure 1. Lymphedema Staging

Stage 0 presents with minimal swelling and a patient description of “overall heaviness” of the limb. Stage 1 presents with more present swelling and skin tightness that can often be relieved with compression sleeves or elevation of the limb. Stage 2 is defined by more severe swelling that does not respond to typical treatment techniques such as compression or elevation. And Stage 3 is the most severe, in which patients experience immobility due to the weight of the limb and possible lymphatic fluid drainage out of blisters or pustules on the skin. Out of the 4 stages, stages 2 and 3 are currently non-reversible. And if left untreated, stages 0 and 1 may progress to later stages [1].
Current Diagnostics

According to the American Cancer Society, in the year of 2023, an estimated 297,792 women will be diagnosed with breast cancer in the United States [1]. Major leaps and bounds have been made through fundraising and scientific discovery to support breast cancer patients, increase survival rates, and reduce residual cancer burden. However, co-morbidities with cancer are often overlooked when it comes to supporting cancer patients both in and out of remission. In breast cancer patients specifically, a common co-morbidity is secondary lymphedema caused by a lymph node biopsy. For these patients, this condition is called Breast Cancer Related Lymphedema or BCRL [6]. The NIH found that 23.8% of breast cancer survivors will develop BCRL by the two-year mark of remission [1].

Unfortunately, BCRL treatment is currently reactive as opposed to proactive. Often times, actions such as lymphatic massage, compression sleeves, rest, and elevation are not taken until a patient endures painful symptoms ([6], [7]). Additionally, it is challenging for patients to communicate the symptoms of lymphedema with their physicians as at early stages, the disease presents through “heaviness” and slight swelling which may be misread as post-operative healing. Currently, the only metric that has been widely accepted as a means of diagnosing BCRL is arm circumference; which does not entail a wholistic approach. Overall, BCRL and the necessary treatments inhibit patients’ quality of life, and early diagnosis may prevent a chronic diagnosis.
Proposed Solution

Therefore, we proposed and implemented a non-invasive monitoring system to track the development of fluid build-up under the skin of the upper arm for the purpose of early lymphedema diagnosis. This device, through a few electrode patches and bioimpedance spectroscopy, will provide early detection and patient support for BCRL in real time ([8], [9], [10]). With the help of Prof. Mahmud’s Remote Sensing Laboratory, the goal of this project was to develop a clinical support tool that eases communication between patients and doctors when it comes to developing sustainable treatment regimens. It will also provide an avenue for patients to fulfill their responsibility of personal care in lymphedema regulation as the bioimpedance readings will indicate the need of treatment intervention.

Bioimpedance spectroscopy is a simple, yet effective, way of differentiating body tissue and body fluid by examining the way current travels through the mediums of the body. To determine lymphatic fluid buildup, frequencies around 1kHz are used.

Though bioimpedance spectroscopy is not the standard treatment/diagnostic regimen for BCRL, it is evident that medical technologies are moving towards these approaches in the near future. For example, a handheld bioimpedance analysis device exists to determine body mass composition, distinguishing between non-fat and fat masses (shown in Figure 2) [11].
Figure 2. Handheld BIA Device

An example of a bioimpedance spectroscopy device for the purposes of diagnosing BCRL is the SOZO Digital Health Platform by ImpediMed [12]. This device is a large, full-body scale scan to be conducted at a physician’s office. The device is shown in Figure 3.

Figure 3. SOZO Digital Health Platform by ImpediMed
In both of the clinical support tools above, the devices conduct a one-time measurement to differentiate tissue (or tissue from lymphatic fluid) and determine whether the patient requires further treatment. The problems with these devices are the cost of the equipment (and the cost of the test on the patient’s end) and the lack of early detection. Because each test is a one-time scan, it is possible that BCRL could have developed prior to or will develop after the test is taken.

A graduate research team at Johns Hopkins has since developed their prototype “LymphaSense”, a longer term bioimpedance spectroscopy scan to determine early stages of BCRL. However, this team is looking to send this device to market, so there is limited publications regarding the workings of this device.

Figure 4. LymphaSense by Graduate Students at Johns Hopkins
There is limited data available concerning the efficacy of these devices as only basic prototypes have been developed. Therefore, an examination of a similar device to that which has been developed by the Johns Hopkins team (with adjustments for real-time, long term monitoring) will prove beneficial to managing the co-morbidity at the clinical level.

This project will greatly benefit those suffering from lymphedema. I focused primarily on BCRL because my mom struggled with the condition following her treatment from breast cancer. I’d like to think that with this device, people like her would be able to address fluid build-up as early as possible and communicate effectively with their treatment team. Ultimately, this technology will be used in conjunction with other treatment methods (compression, elevation, rest, lymphatic massage, acupuncture, etc.), but it provides a clinical support tool to physicians and patients alike in providing data points on how to best address patient-specific lymphedema. With a proactive approach, this device will aid in post-operative care, empower patients to take steps on their own to maintain their well-being, and with real-time data acquisition, improve communication between doctors and their patients after they leave the hospital/office.

Methods & Procedures

Technical Specifications

When developing this design, there were a series of technical specifications to be achieved. Firstly, the device must be precise, thus making tissue differentiation and fluid build-up apparent at early stages. Secondly, the device must not be burdensome to the patient. If this
device were to be implemented as a clinical support tool under the intention of real time monitoring, the device must be worn over an extended time period. Therefore, power considerations and placement must be optimal. Thirdly, and most importantly, the device must be safe to use. When conducting bioimpedance spectroscopy, it is imperative that the device will not go over safe current limits.

Design Constraints

There were also a few constraints to this design project. Firstly, the $100 budget greatly limits the extent to which this project can be prototyped. Secondly, due to time constraints and the medical nature of the design, testing is limited. Because it is a medical device, patients are going to want a more professional design with safety features and FDA approval, which is not attainable on this budget or time-constraints. Therefore, I see a completed device to be one that collects data to suggest that further improvements would be sufficient for a BCRL clinical support tool.

Project Design

Between September (2023) and May (2024), a non-invasive monitoring device for early detection of breast cancer related lymphedema was designed and developed. This device was designed in two stages with two subsystems. The first stage was a prototyped benchtop-reliant design, and the second stage a transition to portable device. The two subsystems include the bio-amplifier design, and the other a self-contained supply and data acquisition/analysis system.
Bio-Amplifier Design

Preliminary stages of prototyping consisted of constructing a Howland voltage-controlled current source modeled after current designs found in literature ([4], [13], [14]. It consists of an INA128 Instrumentation amplifier in which a simple $R_G$ value can adjust the gain. With an $R_G$ value of 51KΩ, the gain of this amplifier is satisfactory for the purposes of detecting small changes in lymphatic fluid buildup and tissue differentiation [11]. The design also contains a high pass filter and low pass filter with the use of LF412 operational amplifiers. The design is shown in Figure 5.

![Diagram of Howland Voltage Controlled Current Source]

**Figure 5.** Howland Voltage Controlled Current Source

The decision to use a current source as opposed to a voltage supply to the device was so that fine tuning output within safe electrical current stimulation limits could be easily conducted. Though a current source is supplied across the tissues, the output measurement taken is of the voltage difference between the electrodes on the body to determine fluid changes under the surface of the
skin. There were few changes to this amplifier between the two stages of prototypal development. During the benchtop phase, the amplifier stood alone as the entirety of the device. Supply from a function generator provided the input voltage waveform, and the DC excitation from a DC power supply. When transitioning to a portable design, an Arduino UNO R3 microcontroller (detailed below) provided the input voltage, and batteries were used for the DC supply.

*Microcontroller Supply & Data Acquisition*

The second stage of designing a portable device required the use of an Arduino UNO R3 microcontroller for the purposes of input voltage supply and remote data acquisition and analysis. All coding and uploading of code to the Arduino board was through the Arduino IDE (Integrated Development Environment) 1.8.19 platform. Utilizing the pulse-width modulated (PWM) capabilities of the Arduino UNO board, an input signal of 2.5V peak-to-peak was established on the analog pin 9 (refer for Figure 6). Each time the code was uploaded to the microcontroller device, the PWM signal was set to a specified frequency within the range of 150 to 10KHz in which the lower frequencies examine tissue mediums like muscles and bones whereas the higher frequencies distinguish others such as water retention and fat [11]. In this device, bioimpedance spectroscopy is conducted for the entire makeup of the arm, with special attention to frequencies around 1KHz for the purposes of lymphatic fluid buildup.
Real time communication from the device to a host device (iPhone 11) was established using a Bluetooth BLE module in accordance with the Arduino UNO R3 and an nRF Toolbox application. However, testing was not conducted with real-time communication due to time constraints.

**Tissue Impedance Modeling**

Due to the safety considerations regarding medical device testing, the accuracy of the developed sensor in this design was tested against an abridged Hodgkin-Huxley tissue impedance model; in which the output measurements were compared with the range of possible values depending on input frequency. The tissue impedance model used in the testing procedure is shown in *Figure 7*, below [13].
Figure 7. Abridged Hodgkin-Huxley Tissue Impedance Model

Due to the parallel capacitor, the tissue impedance model shown in Figure 7 has an impedance that is affected by frequency. In the experimental trials, RP was 21KΩ, RS was 1.5KΩ, and CP was 0.1µF.

DFX Results
The two design stages (benchtop & portable) were necessary to the proposed engineering specifications to construct a working and validated clinical support tool. Benchtop design allowed for the flexibility of troubleshooting the bio-amplifier design and establishing calibration before testing was conducted with the Arduino. Testing with the Arduino allowed for the transition into a standalone device that would relieve patient burden and ease communication with physicians and clinical staff. As a whole design, the non-invasive monitoring device proposed addresses a number of factors. This includes (but is not limited to) cost, safety,
sustainability, and impact on society. The simplicity of the design allows for a device to be constructed with a budget below $100 and the maximum current output is well below the dangerous range. It is a sustainable design as devices can be retrofitted per patient (with the only substitution being swapping the electrode pads). And overall, the device is easy to use for the patient, and provides meaningful data back to the patient’s care team.

**Test Plans & Results**

The testing process involved a calculation of the expected output voltage measurements across the electrode pads in relation to the frequency of the input supply and the range of safe electrical current stimulation values. Due to complex impedances, we know that the tissue impedance model (the abridged Hodgkin-Huxley circuit) is dependent on the frequency of the input. **Table 1** shows the calculated expected range using Ohm’s law and known complex impedances of resistors and capacitors (**Equations 1-2**). As stated above, in the experimental trials, RP was 21KΩ, RS was 1.5KΩ, and CP was 0.1µF. After measurement of the components, RP was 21.03KΩ, RS was 1.493KΩ, and CP was 0.1 µF.

\[ Z_{CP} = \frac{1}{j\omega CP} \quad (Eq 1) \]

\[ Z_{EQ} = \frac{1}{\frac{1}{RP} + \frac{1}{Z_{CP}}} + RS \quad (2) \]
<table>
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<th>Frequency (w)</th>
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<th>(Z_{RS})</th>
<th>(Z_{CP})</th>
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After determining the known impedance, Ohm’s law (V=IR) was used to find the expected range of output voltage measurements. The range was across the safe limits of current stimulation and expected output with a 2.5Vpp input supply: \(15\mu\text{A}\) to \(49\mu\text{A}\). Table 2 shows the calculation of the expected range of voltage outputs.
Finally, the device was connected to the Arduino UNO module, the benchtop supply, and the oscilloscope, to take $V_{\text{out}}$ measurements across the tissue impedance model at each of the frequencies listed. Table 3 provides the summary of these results, and is graphically shown in Figure 8.
Table 3. Measured $V_{out}$

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</table>

Figure 8. Measured $V_{out}$
Discussion

Significant results

The results shown in Figure 8 are significant as they show measured output values within the expected range as established by calculations with the complex impedances of the tissue model and the safe range of electrical stimulation. Not only are these measurements within the range, but the trend follows a similar path indicating a high level of sensitivity of the sensor. Therefore, this device should be able to detect very minute changes in the fluid makeup of the arm.

Greater Impact

From the project results, it can be concluded that bioimpedance spectroscopy can be conducted with adequate sensitivity for the purposes of early stage lymphedema diagnosis. This calibration of the sensor is encouraging as early treatment intervention may prevent long-term side effects due to delayed lymphedema treatment. Furthermore, in the course of one academic year, our team primarily consisting of one undergraduate was able to mimic a device that has been previously developed by a team of graduate student researchers at Johns Hopkins over the course of many years. This device is inexpensive, simple in application, and sensitive in measurement. Due to the simple and versatile nature of this device, it will likely have applications that extend beyond those suffering from breast cancer related lymphedema. For example, physicians might use this inexpensive bioimpedance spectroscopy device for sports medicine, addressing injury healing and inflammation; or in patients with diabetes to monitor swelling at extremities.
Recommendations for Future Effort

The simplicity in nature of this device allows for a wide range of possible applications, though it has been tailored to early stage BCRL diagnosis. Because of the wide range of possible applications, there are a variety of recommendations to be made for future effort. Firstly, a more robust remote monitoring system must be established to meet the specified goals. PWM supply and Bluetooth communication through the BLE module were achieved before the end of the semester, however, data analysis was not performed on these real-time measurements. Therefore, future work could involve finalizing the stand-alone design. This may also include a smaller printed circuit board of the current source and a 3D printed device housing for portability.

A second suggestion for future effort would be to automate testing across all frequencies for true bioimpedance spectroscopy. As detailed in the methods section, measurements were taken one at a time at a specified frequency. The code uploaded to the Arduino UNO board was manually changed per frequency for assurance in efficacy of measurement techniques. Therefore, a simple “for-loop” within the Arduino code for the PWM signal supply would be sufficient to test across the entire range of frequencies.

A final suggestion for future effort would be to examine the “uncontrolled” parameters from this design and testing procedure. Bioimpedance analysis can so easily be mismeasured due to differences in room temperature, placement of electrodes, preparation of the skin, patient hydration, etc. [11]. Therefore, a future study may include testing on a patient, and having that testing occur under a series of different configurations of the above parameters. Therefore, the device efficacy and sensitivity would be supported more fully.
Statements

Safety and Ethical Considerations

Special attention was given to safety and ethical considerations over the entire duration of this project. The design and testing plans were decided in accordance to the Code of Ethics for Engineers from NSPE (National Society of Professional Engineers), IRB (Institutional Review Board) requirements, University of New Hampshire RCR (Responsible Conduct in Research) standards, and other scientific literature indicating the grave consequences of negligence in human medical device development.

Project Timeline of Tasks & Milestones

Milestones for the completion of this project (and the duration of time each of which took to complete) are listed below.

1) The first task completed was conducting literature review on scientific resources regarding biocompatible patches, biosensors, bioimpedance analysis, bioimpedance spectroscopy, lymphedema pathology, safe levels of electrical stimulation, etc.. These sources can be found in the citations or supplemental reading of the appendix. This first task was incredibly important to developing a robust design and understanding enough background to write a thesis (as part of the honors program requirements). Conducting scientific literature review is essential to distinguish this device’s contribution to the field and to gain expertise in this area. This fits into the proposed plan as it was the first task completed and a background in scientific literature is needed for every future step.
2) The second task completed involved a written and oral proposal to be defended to peers and professors. The submissions are found in the appendix. This task was important in order to practice scientific communication, to meet deadlines in a timely manner, and to seek feedback on the original idea from peers and faculty.

3) The third task completed was conducting research on possible parts and constructing a Bill of Materials (BOM). The completed BOM can be found in Table 4. This task was important as an engineering capstone project and supplemental thesis does not rely only on scientific literature and suggested exploratory questions, but real data and experimental results brought about by testing on a prototyped design. Constructing a BOM was the first step in developing the proposed design, in which acquisition of the materials comes before construction and refinement. This fits into the overall project timeline as one of the preliminary tasks to implementation and testing.

4) The fourth task was drawing a schematic and printed circuit board (PCB) design for sensor development. Though the PCB was not used in final implementation, a great deal of learning was at the result of this stage. The design can be found in Figure 5. This is an important task to complete (and to execute well) as it is the main sensor design.

5) Concurrent with the fourth task, the fifth task involved building a breadboarded prototype of the Howland Voltage-Controlled Current source with the LF412 and INA128 integrated circuit chips. All datasheets can be found in the appendix. This was an important step in the design process as adjustment and testing is easy with a breadboard design. This fits into the proposed plan as a breadboard prototype is sufficient for proof-of-concept.
6) The sixth task was developing code in the Arduino IDE for data acquisition and analysis. This was an important task to delve into to examine the capabilities of the microcontroller to not only collect and store the bioimpedance readings, but to relay that information wirelessly (remote sensing). Furthermore, this task involved coding for the Arduino PWM supply in which frequency is manipulated, changing the current injection across the tissue impedance model. This is what differentiates bioimpedance spectroscopy from basic bioimpedance analysis. This fits into the proposed plan as a discrete wearable device entails portability and real-time data acquisition and analysis.

7) The seventh task was performing calculations (based on complex impedances from the tissue impedance model) to develop a range of expected output voltage measurements depending on the frequency of the supply voltage. This was an important task to complete regarding conducting an experiment per the scientific method as testing against a known value allows for a controlled experiment.

8) The eighth task was connecting the breadboarded prototype to the Arduino UNO microcontroller and testing against the known impedance of the tissue model. This task fit into the original proposal plan as it served to validate and verify the efficacy of the designed sensor.

9) The ninth task (though incomplete) involved connecting the Bluetooth BLE module to the Arduino UNO readings for remote sensing and communication back to the cellular device through the nRF Toolbox. This was an important task to examine as completion of this design would entail a stand-alone device without requirements of bench top connection for data analysis. Without the Bluetooth BLE module, the device must be operated locally at a laboratory bench.
10) For the tenth task, analysis of the benchtop data was conducted and written up in the form of a poster and thesis/final report. This was an important step in the project design to practice scientific communication and defending of the design.

Cost Analysis

Not only is this device moving towards reducing residual cancer burden in post-operative breast cancer patients, but it is also cost effective, minimizing the barriers that are present in the medical sector today. With simple and few integrated circuits and readily available microcontrollers and electrode pads, expense is at a minimum for patients and caregivers. Table 4 below lists the materials necessary to build this design. Upon human testing and patient implementation, though, a printed circuit board (PCB) would be optimal for device robustness, which would add to the cost.
Table 4. BOM

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<th>Vendor</th>
<th>Part Number</th>
<th>Description</th>
<th>Unit Price</th>
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<td>LF412CN Operational Amplifier</td>
<td>Digikey</td>
<td>LF412ACN/NOPB-ND</td>
<td>J-FET Amplifier 2 Circuit 8-PDIP</td>
<td>$4.93</td>
<td>$14.79</td>
</tr>
<tr>
<td>INA128P – Instrumentation Amplifier</td>
<td>Digikey</td>
<td>INA128P-ND</td>
<td>Instrumentation Amplifier 1 Circuit 8-PDIP</td>
<td>$13.62</td>
<td>$40.86</td>
</tr>
<tr>
<td>RC Components</td>
<td></td>
<td></td>
<td>Resistors, capacitors, and wires for breadboard prototyping</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Electrode Pads &amp; Lead wires</td>
<td>Amazon</td>
<td>3.5 mm, button lead wires</td>
<td>Ordered for more robust testing</td>
<td>$9.99 + $8.95</td>
<td>$18.94</td>
</tr>
<tr>
<td>In-lab equipment</td>
<td>Varies</td>
<td>Varies</td>
<td>DMM, Function Generator, Oscilloscope, etc.</td>
<td></td>
<td>*</td>
</tr>
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Acknowledgements

Amy Prendergast, as principal investigator and sole contributor, contributed to all phases of this engineering capstone project and concurrent thesis, including idea brainstorming, planning, prototyping, troubleshooting, revising, data collection, data analysis, and proceeding scientific communication. Amy started the project in mid-September and continued through mid-May under the guidance of Professor Mahmud and peer advice from participants in Dr. Mahmud’s Remote Sensing Lab. Funding for this design project came from the Department of Electrical and Computer Engineering at the University of New Hampshire.

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References

Cited

American Cancer Society, Jan. 25, 2022. [Online]. Available:
https://www.cancer.org/cancer/types/breast-cancer/about/how-common-is-breast-cancer.html


**Supplemental Reading**


Appendices

Scientific Communications

- Original Project Proposal
- Interim Report from 791H
- Annotated Bibliography
- URC Poster

Datasheets

- Arduino UNO R3
- Bluetooth BLE Module
- INA128 Instrumentation Amplifier
- LF412 Operational Amplifier

Data Collection / Analysis

- Capstone Data