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EPIC: Examining Patch Impedance Characteristics

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Date: June 13, 2019

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EPIC: Examining Patch Impedance Characteristics

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EXAMINING PATCH IMPEDANCE CHARACTERISTICS

By

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THESIS

Submitted in Partial Fulfillment of the Requirements for the

Bachelor of Science Degree in

Electrical Engineering and Bioengineering in the School of Engineering

Santa Clara University, June 7, 2019

Santa Clara, California

ABSTRACT

In the United States, approximately one in 4 adults have at least one chronic illness, making up approximately 84% of US Healthcare Spending. Unfortunately, 50% of patients with chronic diseases do not take their medication properly and as such spend more money trying to get better – approximately $100 billion in annual preventable costs. One solution to this issue is digital medicine as it allows for the monitoring of patient medicine consumption.

Our industry partner has developed a three-part digital medicine system with the aim of allowing patients with chronic health issues to better reach their health goals through monitoring of medication consumption. About one-third of clinical trials exhibit erroneous data, showing intermittent malfunction of the patch in the system. The focus of this senior design project is decoding these erroneous readings due to the patch and proposing possible solutions.

This senior design project took the form of a design of diagnostic experiments, culminating in a mathematical model that synthesized all of the phenomena we uncovered through experimentation.

ACKNOWLEDGEMENTS

Many people have contributed to the success of this project. We would like to acknowledge and thank them in this section of our thesis.

We would firstly like to thank our industry partners for giving us the opportunity to work with their product for our Senior Design project, and to the team members for their guidance and partnership on this project.

We would like to thank our advisors, Dr. Shoba Krishnan of the Department of Electrical and Computer Engineering and Dr. Prashanth Asuri of the Department of Bioengineering. We'd also like to thank Santa Clara University's Bioinnovation Design Lab for its support of this project.

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1. PROJECT INTRODUCTION

1.1 Project Rationale

In the United States, eighty-four percent of healthcare spending is on chronic illness, with an approximate one in four American adults suffering from at least one chronic illness (Anderson, 2010). Fifty percent of these patients do not take their medications correctly (Sabaté, 2003), and as a result, get further from their health goals and spend more money trying to get better. In fact, studies show that approximately $100 billion in annual costs are due to this issue and are totally preventable if only patients took their medications as instructed (Osterberg & Blaschke, 2005).

1.1.1 Digital Health as a Solution

Digital medicine is a possible solution to this problem. Digital medicine is defined as the technology that integrates sensors and transmitters with pharmaceuticals to create a system individualized to the patient, with the added benefit of allowing for the monitoring of medication consumption (Steinhubl & Topol, 2018). Digital medicine has the potential to create a new form of healthcare where patients are more engage with their health goals. Our corporate project sponsor is one such company developing a digital healthcare system.

1.1.2 Our Project Sponsor's System

Our industry partner's system has three parts. The first part is pill with an integrated circuit, subject to its own FDA regulatory pathways, which transmits its unique ID once digested by the patient's stomach acid. The second is a patch with a data pod that is set to read a variety of physiological signals, one of which is the "Ingestible Event Marker" (IEM), which is the signal sent by the pill upon its digestion. The IEM, which is about the size of a grain of sand and is included in the patient's medication, notifies the patch and datapod with a unique identifier indicating that the patient has consumed the pill. The last part of the systems is an app that allows the data gathered by the data pod to be made more accessible to the patient and their healthcare provider to allow for better monitoring of the patient's medication consumption.

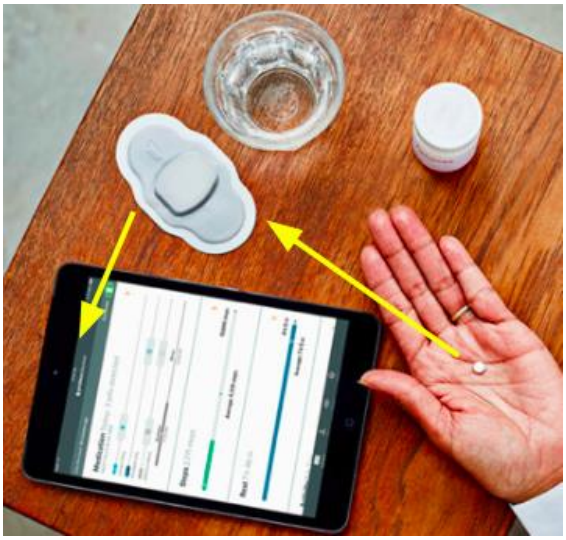


Figure 1.1: Our Project Sponsor's 3 Part System

As aforementioned, the datapod measures a handful of physiological signals, one of which is skin impedance. Skin impedance, or the effective resistance of the skin, is the primary mechanism informing whether or not the patch is still on the body.

1.2 Discussion of Results of Clinical Trials

The physiological range for skin impedance is ranges from 1000 to 2500 Ω. Thus, the expected skin impedance versus time reading would look like this (without ingesting any pills):

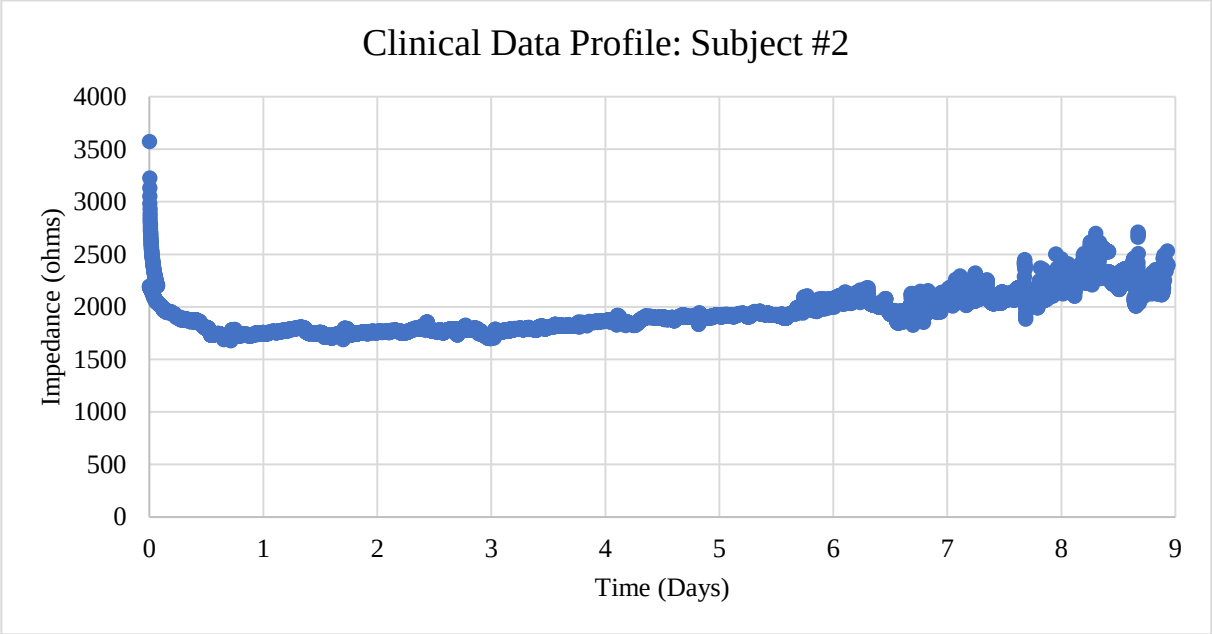


Figure 1.2: Expected Skin Impedance vs Time results (without IEM)

In this graph, a number of things should be noted. Firstly, there is a small portion of time at the beginning of the graph wherein the system reads higher impedance values (ca. 3500 Ω) then stabilizes into physiological range (1000 to 2500 Ω). Our team named this portion of the graph the "bonding period" signifying the time it takes for the patch to establish good connection with the skin of the patient. It was seen in the results of every experiment completed. Secondly, there is

little to no variation within the normal physiological range once the connection is established – this means that the patch is well connected to the skin and remains well connected for a week, just as intended.

There are, of course, situations in which the patch comes off the body, which is called a "lead-off" condition. The system's lead-off condition is programmed to 20 kΩ. This mechanism is meant for when the lead is taken off the body purposefully or has fallen off the patient and comes into contact with a non-conductive material (namely, air). If this impedance value is registered, the data pod will stop taking readings and thus might miss when the patient takes their medication (the IEM). However, in about one third of trials, the industry sponsor witnesses 20 kΩ values being registered whilst still on the patient's body visibly in contact with the skin, regardless of whether a patient has taken their pills or not. Below is an example of such data (without ingesting any pills):

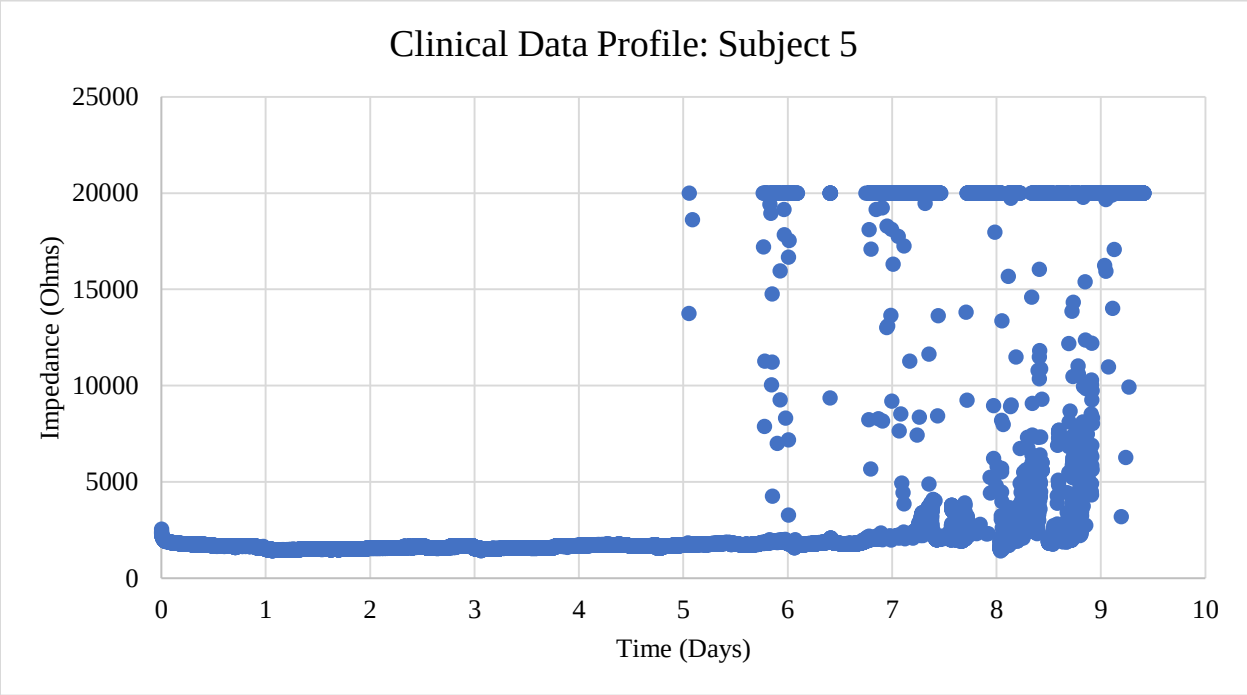


Figure 1.3: Erroneous Skin Impedance vs Time results (without IEM)

What is seen in the data is a period of oscillatory readings from physiological range up to 20 kΩ and back down to physiological range. As was noted before, a bonding period is seen at the beginning of the graph. However, the most interesting aspect of this erroneous data is that the oscillatory readings do not begin until after a few days of wear and are intermittent in nature, jumping between high and low impedance values in the span of minutes. Furthermore, there is a cyclic nature to this behavior – periods of high impedance can be tracked to happening during the daytime and better connections are seen during the night-time (which can be attributed to resting on the patch thus establishing a better connection).

The team was first tasked with replicating the data seen in the clinical trials. Subject A and B both were moderately active in their patch wear, lighter skin pigment, and male. Subject A was in their early 20's while Subject B was in their early 30's. Subject C was in her early 20's with dark skin pigment, low body fat content, and a highly active lifestyle.

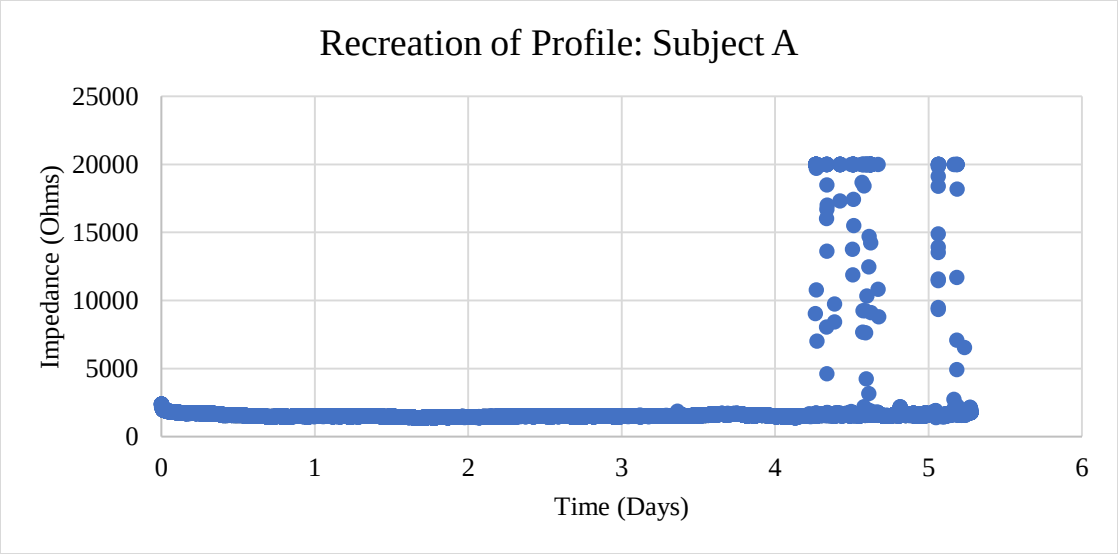


Figure 1.4: Subject A - Impedance vs Time without IEM

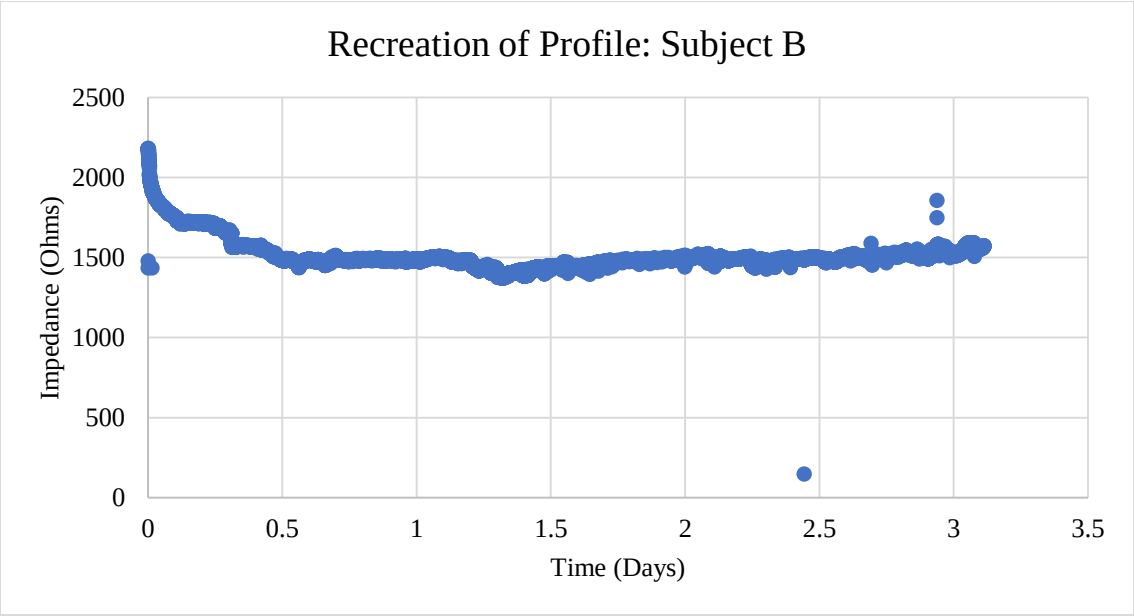


Figure 1.5: Subject B - Impedance vs Time without IEM

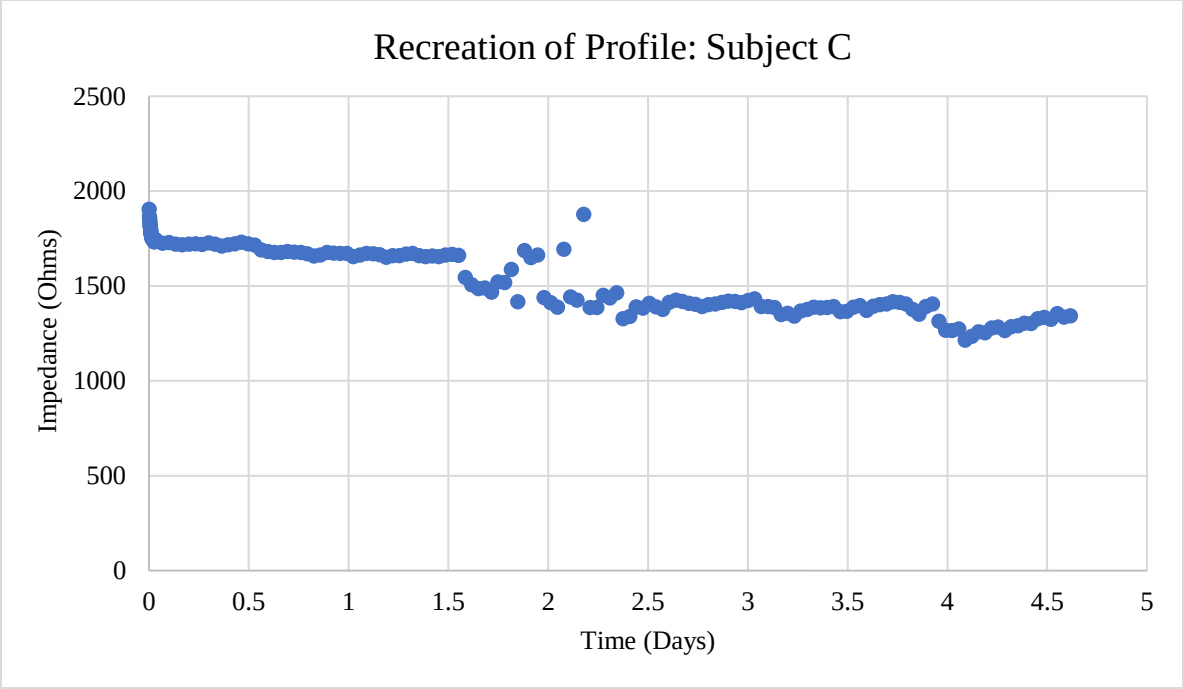


Figure 1.6: Subject C - Impedance vs Time without IEM

Subject A's data shows the random oscillation between high and low impedance (Figure 1.4: Subject A - Impedance vs Time without IEM) while the patch is still on the body, while the other two subjects showed data within physiological range throughout the duration of wear. This corroborates how the system only shows erroneous readings for1 in every 3 patients.

Since both the pill and the app were taken out of the equation when this data was recorded, they clearly do not contribute to this erroneous lead-off behavior. This means that within the system, the patch is the source of this false lead-off condition. Our corporate project sponsor tasked this student team with troubleshooting the possible mechanisms within the patch that could be creating these false positives.

1.3 System Sketch

After preliminary experimentation, the team determined three possible interfaces wherein high impedance mechanisms could be born (Figure 1.7). In essence, it was determined that the 20 kΩ impedance values could be a function of one of the 3 issues: the hardware is malfunctioning, the contact between the hydrogel leads and the electrodes becomes weak, or skin chemistry is contributing to a loss in conductivity over time.

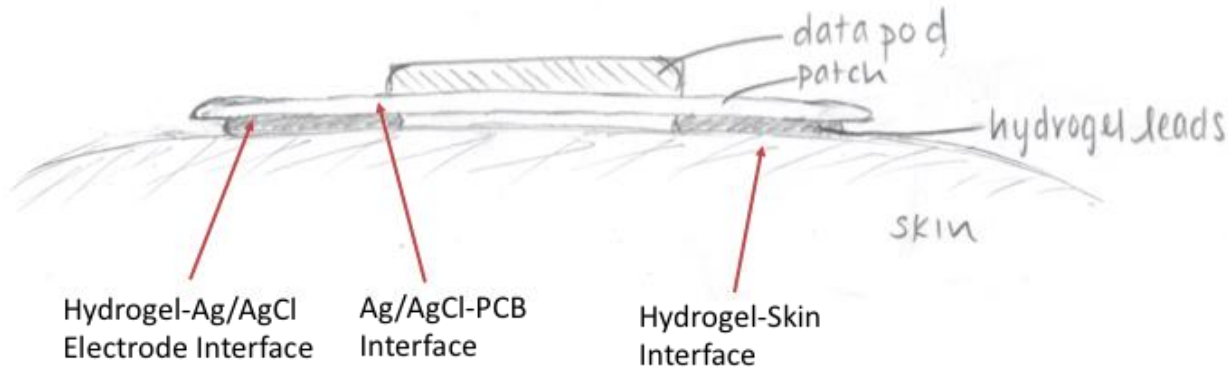


Figure 1.7: System Sketch with Interfaces of Concern

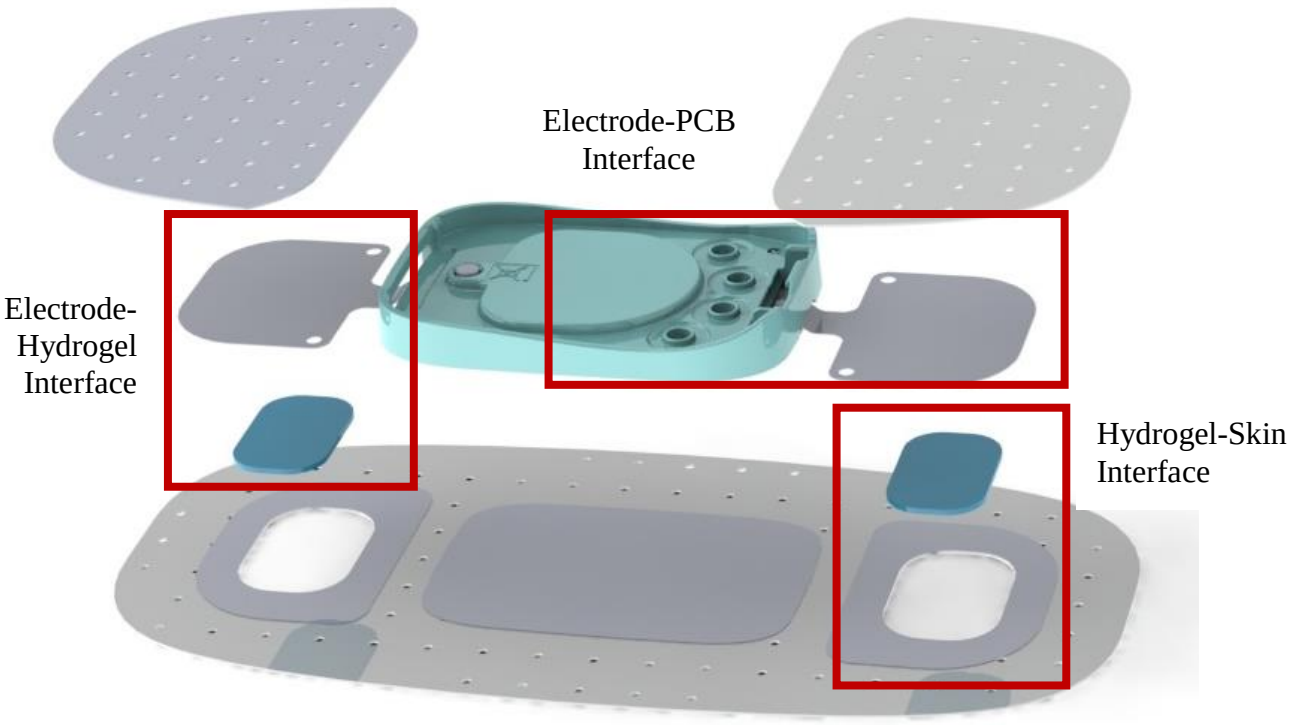


Figure 1.8: System Sketch in Exploded View with Interfaces of Concern

Our group set out to create experiments surrounding these three interfaces of concern seen in Figures 1.7 and 1.8 in hopes to eliminate possible hypothesized lead-off pathways. Therefore, our senior design project took the form of a design of diagnostic experiments. Our thesis is organized into a comprehensive list of all of the experiments we designed and ran for each interface, and the useful conclusions drawn from each.

2. ELECTRODE-PCB INTERFACE

The electrode-PCB interface encompasses the Ag-AgCl traces, carbon ink, brass pogo pins, 3V battery, and the PCB inside the data pod. Experiments were performed to investigate the impact of these electrical components on how the data pod measures impedance. The experiments performed included fixed impedance measurements with and without the patch, comparing behavior with low battery voltage and new battery, and effects of damaging the carbon ink and Ag-AgCl. This interface is important to study because discovery of a mechanism at this interface that results in rapid changes in impedance would provide great insight into how to prevent the behavior.

2.1 Fixed Impedance Measurements (Data Pod Only)

Our industry partner has built a device called a strip saver, which is ideal for measuring impedance on the bench. The data pod connects to the strip saver the same way as it connects to a patch, except that it can be powered externally with a micro USB or three AA batteries. A 1.8 kΩ resistor was measured using the strip saver as shown in Figure 2.1.

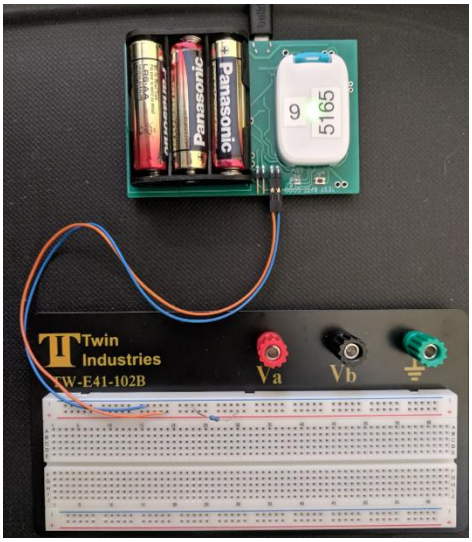


Figure 2.1: Strip saver with data pod inserted measuring 1.8 kΩ resistor

Measured impedance never exceeded expected value during the 14-day trial period as Figure 2.2 shows. This indicates that the high impedance measurements seen in clinical trials are not a result of anything occurring within the data pod alone.

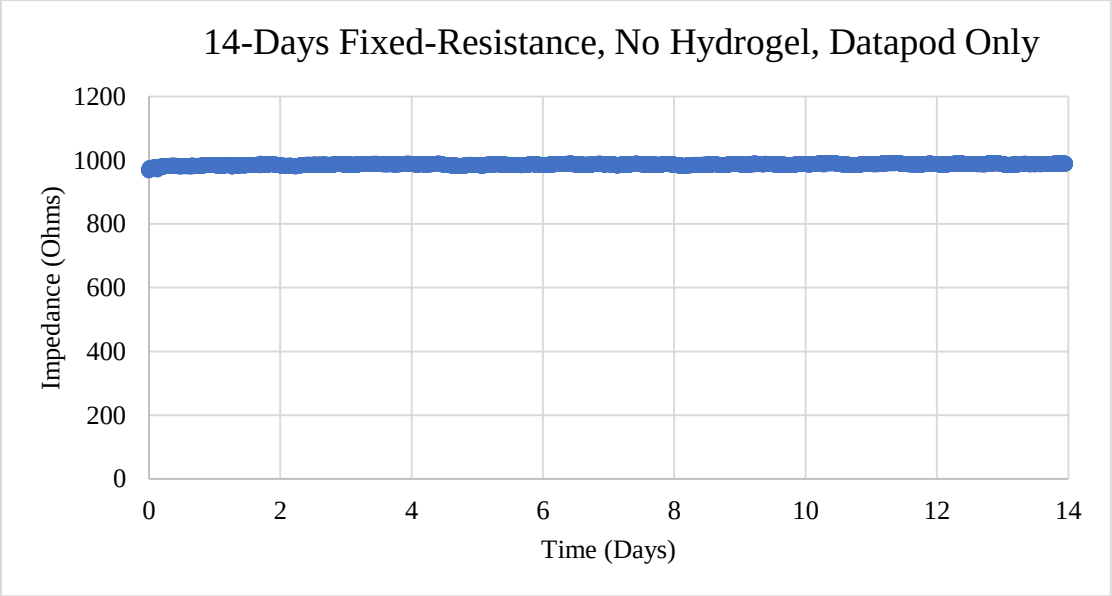


Figure 2.2: Impedance measurements showing no variation

2.2 Fixed Impedance Measurements (Data Pod and Patch)

Additional experiments were performed to determine the impact of measuring the same 1.8 kΩ using the data pod and patch together as shown below in Figure 2.3. The hydrogel was removed from the patch to eliminate variables associated with hydrogel. The programmable parameters of the data pod were set so that all unnecessary sensors were turned off during the experiment to extend the life of the battery.

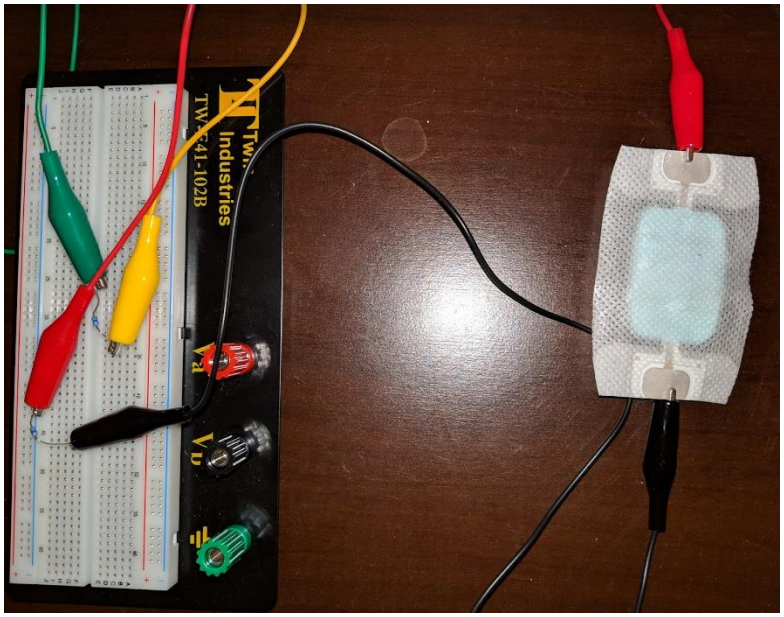


Figure 2.3: Data Pod and Patch Measuring 1.8 kΩ resistor

The battery in the patch lasted nearly 14 days and as before there were no variation in measured impedance. This experiment along with the previous one demonstrates that the high impedance measurements seen in clinical trials are the result of processes and interactions associated with the human body. Figure 2.4 shows that the measured impedance did not change.

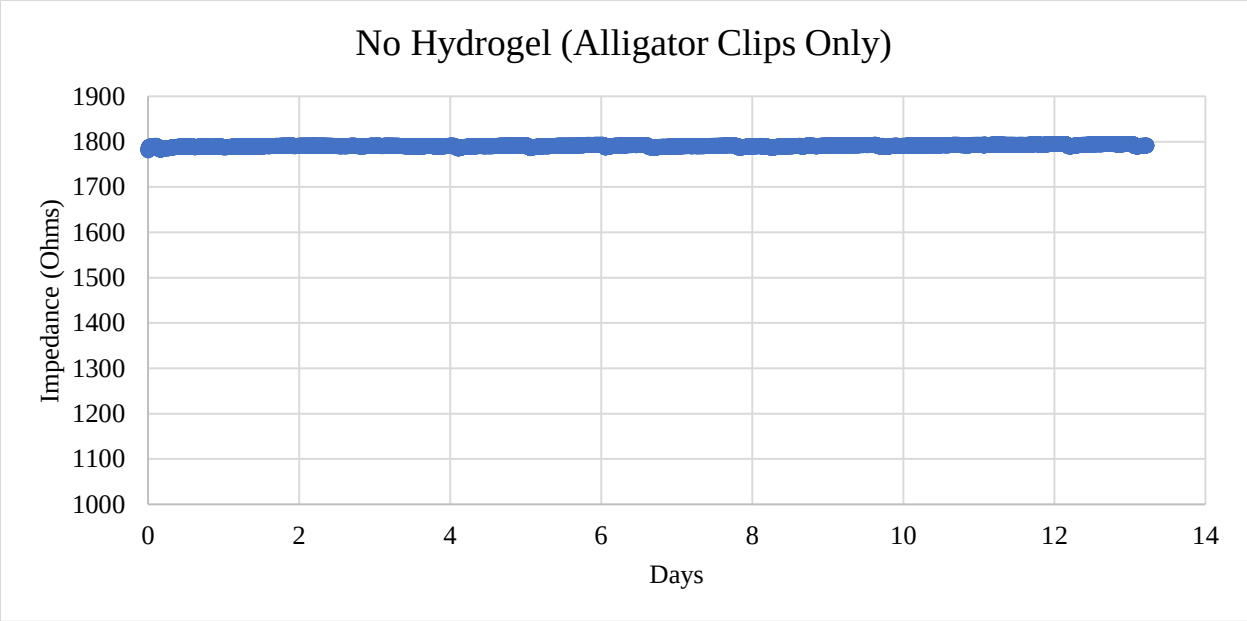


Figure 2.4: Impedance Measurements showing no Variation

2.3 Damaged Carbon Ink and Ag-AgCl

During manufacture of each patch, the flexible circuit assembly is coated with Ag-AgCl and carbon ink. The flexible circuit assembly is fixed to a rigid plastic backing and sealed shut. It was observed that during normal use the brass pogo pins would wear the carbon ink and Ag-AgCl. Figure 2.5 shows an example of such damage. The cause of the damage to the carbon ink and Ag-AgCl is likely caused by the user sleeping on the patch, where their weight pushes on the data pod and causes the pogo pins to bottom out against the hard plastic.

Figure 2.5: Damaged Carbon Ink and Ag-AgCl

Experiments were performed to investigate the impact that this wear has on measured impedance. Each flexible circuit assembly was pre-damaged using the tip of a probe and then worn on the body. If the impedance behavior seen in clinical trials was the result of damage at this interface, then a pre-damaged flexible circuit assembly should result in high impedance erratic impedance readings immediately. However, the data in Figure 2.6 show that while damage of the

flexible circuit assembly does cause an overall minor increase in measured impedance, it does not cause the rapid changes in impedance seen in clinical data.

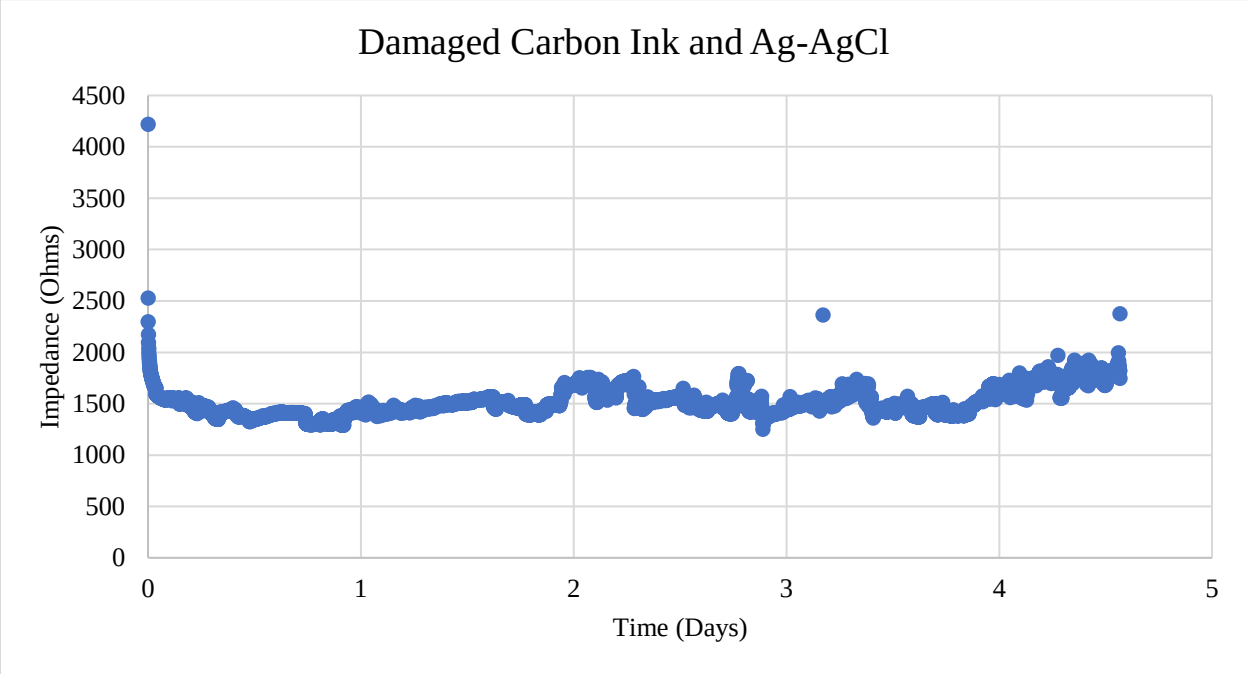


Figure 2.6: Measured Impedance with Pre-damaged Carbon Ink and Ag-AgCl

2.4 Battery Voltage: Aged Battery, New Patch

The high impedance readings tend to show up after 3-4 days of wearing the patch. The battery voltage of a normal patch begins at 3 to 3.1 V and is depleted at approximately 2.7 V. Experiments were conducted to characterize the impact of battery voltage on measured impedance.

The data pod was placed in a new patch and placed in a sealed container. This allows the battery to drain as the device takes measurements, but the patch is not exposed to motion, sweat, mechanical stresses, etc. Next, the patch was worn as normal and allowed to take impedance measurements of skin. The results in Figure 2.7 show that the data pod recorded no high impedance, demonstrating that the high measurements were not a result of aged battery voltage.

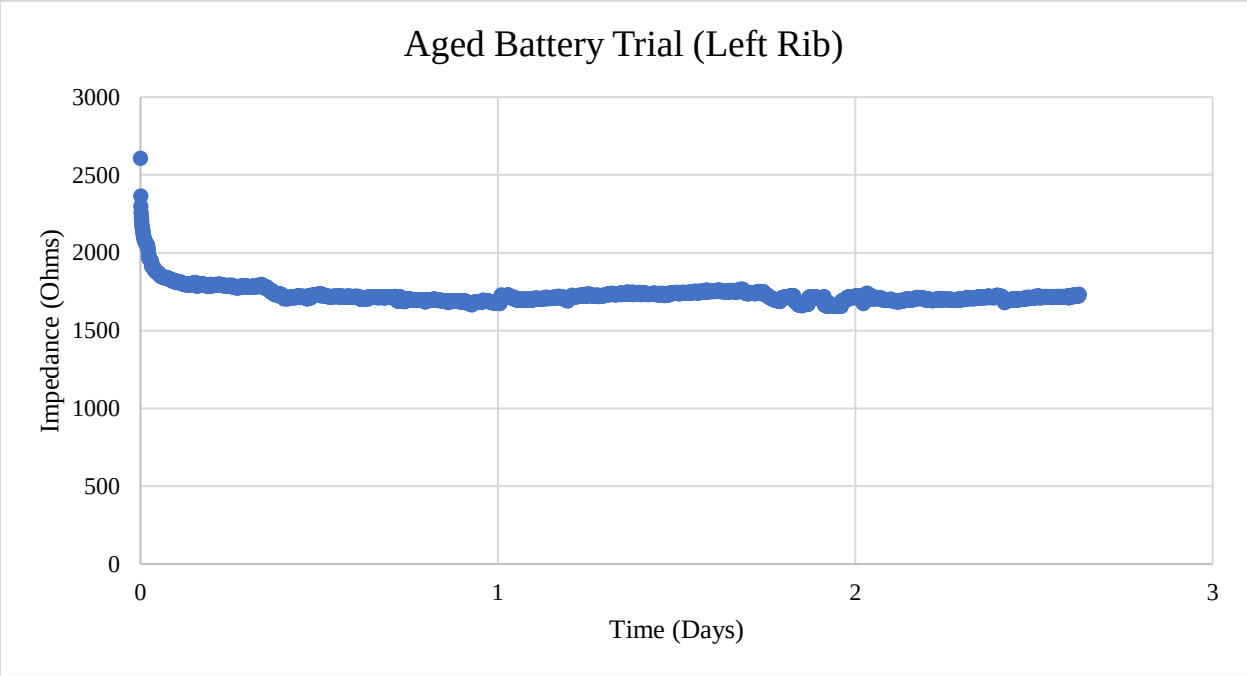


Figure 2.7: Aged battery, new strip for left rib shows no high impedance readings

2.5 Conclusions

The experiments performed at the Electrode-PCB interface could not recreate the rapidly changing high impedance readings seen in clinical trials. This is vital in understanding that the high impedance readings must be occurring as a result of interactions between the patch and the human body through motion, sweating, and mechanical stresses.

3. HYDROGEL-SKIN INTERFACE

The Hydrogel-Skin Interface contains the hydrogel leads found on the patch as well as the patient's skin and all of its chemical components. This interface was important for exploration because it was hypothesized early on in the project that skin chemistry was a likely factor for the false-positive lead off behaviors seen in the clinical data from our corporate project partners.

The hydrogel is sourced from Axelgaard (Axelgaard Manufacturing Co, LTD, 2018). The hydrogel is the means by which the patch is able to stick to the patient's skin for long periods of wear. Unfortunately, very little information was provided on the chemical composition of the hydrogel, but it is known that the hydrogel contains two conductive polymer layers separated by a nylon mesh. Through experimentation, it was found that the hydrogel was incredibly hydrophilic and when introduced to any volume of liquid, could not retain its shape. Thus, it was concluded that the polymers used in the hydrogel were likely not highly cross-linked.

The skin is a rather physiologically complex organ, which was increasingly apparent with each experiment conducted. In order to accurately diagnose the mechanisms leading to false-positive lead-off within the patch, the team focused on three main areas of how skin physiology might affect the hydrogel leads: hydration of the leads, occlusion of the leads, and normal wear.

3.1 Hydration of the Leads

This area of investigation was created to explore the effect of physiological analogues to sweat on the patch both *ex vivo* and *in vivo*. Since sweat contains salt, the experimentation included observing how salt content affects the rehydration of hydrogels.

3.1.1 Hydration-Dehydration Testing

Experiments were performed by placing the patch inside an air-tight container with a desiccant. A penetration in the side of the container allowed for wires to connect to the hydrogel. The wires were connected to a 1.8 kΩ resistor outside of the box. A data logger was included in the box to record temperature and humidity during the experiment. Figure 3.1 shows the wires connected to the patch atop the desiccant and Figure 3.2 shows the entire setup.

Figure 3.1: Close-up of patch, wires, and data logger

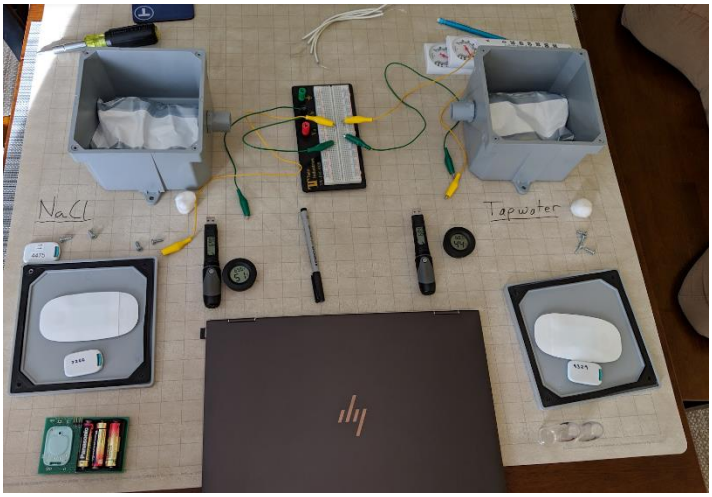


Figure 3.2: Wide angle view of test setup

In the first experiment, both patches were hydrated approximately once per eight hours. The result was a gradual climb in impedance followed by a rapid drop in impedance when hydration was administered. The tap water and sweat hydration showed very little difference in the way that impedance climbed. Figure 3.3 shows an example of the hydration-dehydration cycle.

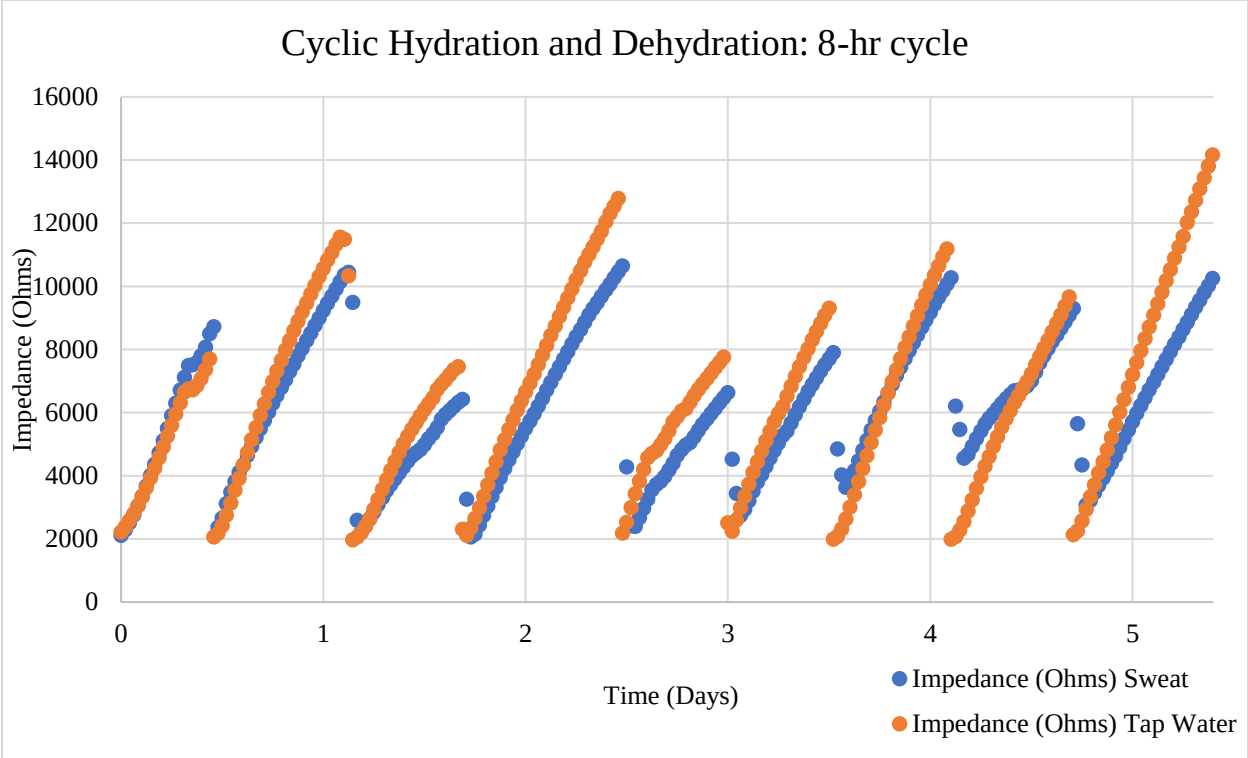


Figure 3.3: 8-hour cycle rehydration/dehydration

The second experiment involved similar conditions but a longer dehydration period. Figure 3.4 shows impedance climbed to 20 kΩ very quickly for the first few days, but afterwards would not exceed the 15,000 Ω mark. This could be due to the desiccant becoming saturated with moisture. The hydrogel seemed to form around the wires with each hydration-dehydration cycle, which could also account for the decrease in impedance because the wires were making better connection as the hydrogel and wires bonded. At the end, the hydrogel was allowed to dry out for days until the battery depleted.

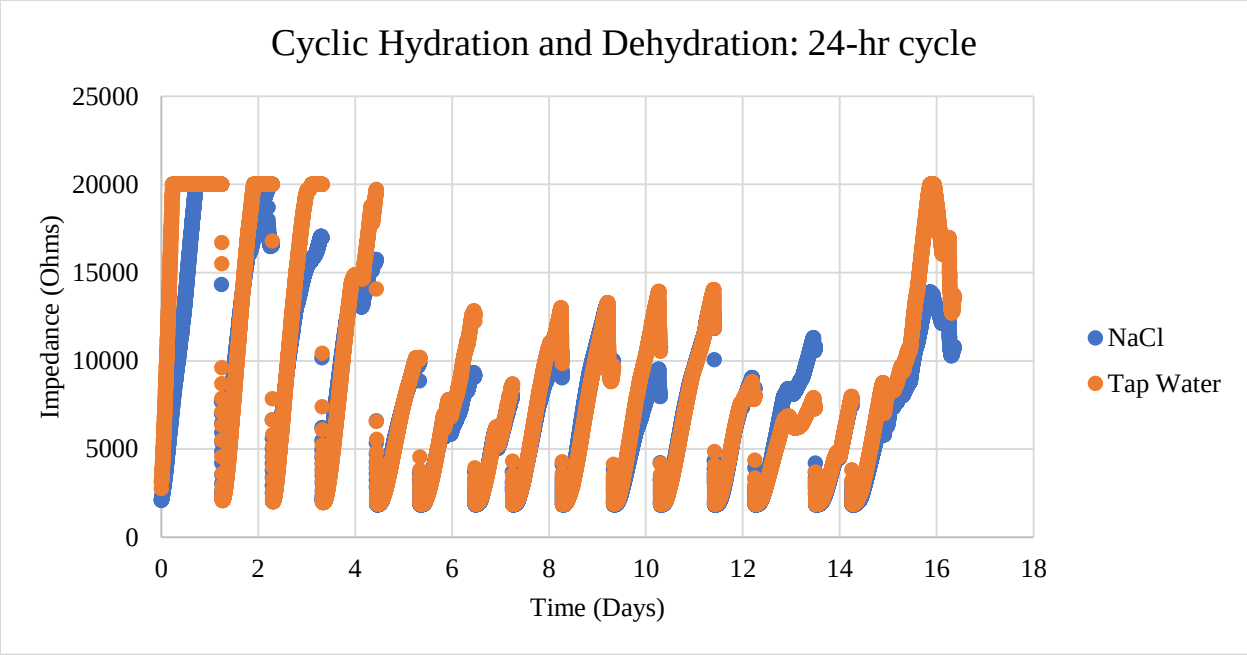


Figure 3.4: 24-hour cycle rehydration/dehydration

The hydration-dehydration cycles experiments showed that although hydration has an enormous impact on impedance, it does not demonstrate rapid changes in impedance that were seen in clinical data. It also showed that the hydrogel does not tend to degrade following multiple hydration-dehydration cycles, in that the data pod can continue to read normal impedance levels once rehydrated.

3.1.2 Skin Phantom

The previous experiment involved looking at the effects of cyclic rehydration on the patch without a substrate. In reality, the patch is placed on the patient's skin, which is a physiological substrate that is responsible for the cyclic hydration and dehydration of the leads. As such, it became pertinent to develop some form of *ex vivo* experimentation that would allow for the

recreation of perspiration and dehydration; that is, without having to wear the patch. As a result, methods for creating phantom skins were explored.

Skin phantoms serve to closely mimic the physical and chemical properties of human tissues for a variety of applications besides just this line of inquiry (Lazebnik, Madsen, Frank, & Hagness, 2005). A variety of polymers can be used to create phantom skins, but agarose was chosen as the medium for the creation of the following skin phantoms for its ease of use and its availability. Varying concentrations were explored, with 0.5% and 1.0% agarose proving to be the most similar to the physical properties of skin. In order to simulate perspiration, 0.1 M NaCl was introduced to the skin phantom via soaking the skin phantom for varying lengths of time in the “sweat” solution, and by dissolving the gels in the “sweat” solution. It should be noted that this concentration of sweat is somewhat greater than physiological conditions, but it serves as a good indicator of the effects of ions on the system (Montain, Cheuvront, & Lukaski, 2007).
The skin phantom was employed at first to simulate sweating. Swelling to as much as 0.7 mm of height was seen in the hydrogel leads (Figure 3.6) and impedance values much lower than the physiological range (300-500 Ω) were collected by the data pod after a short bonding period (Figure 3.5). This led to the conclusion that the phantom skins were over-transpiring causing the hydrogel leads to lose their structural integrity and delivering too many ions to the leads thereby decreasing the measured impedance values.

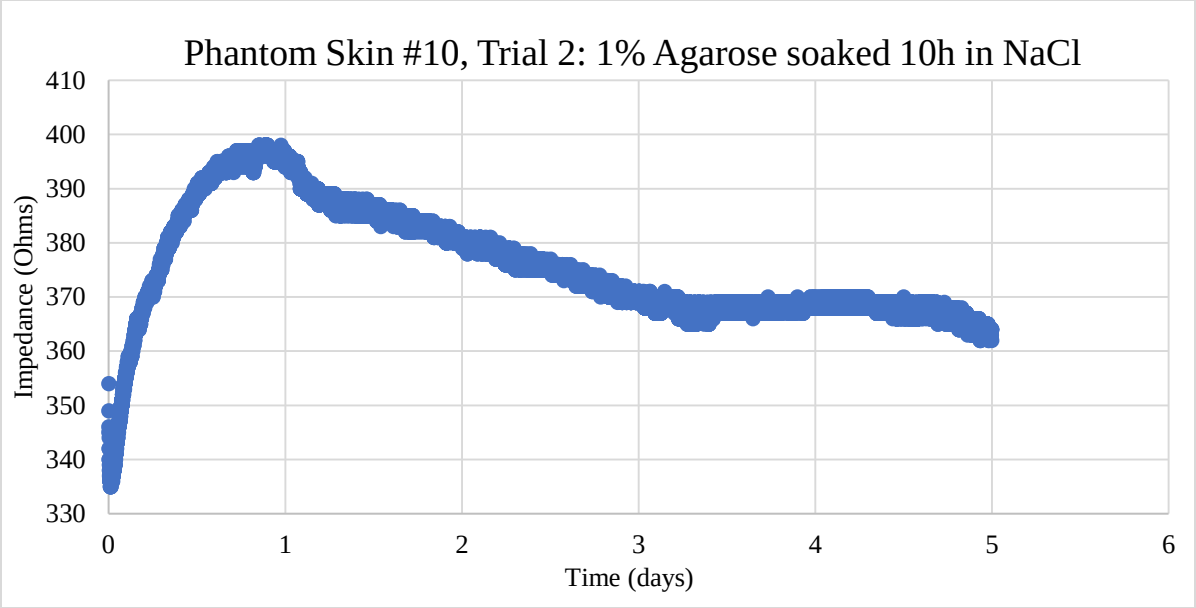


Figure 3.5: Phantom Skin Results showing low impedance values and bonding period

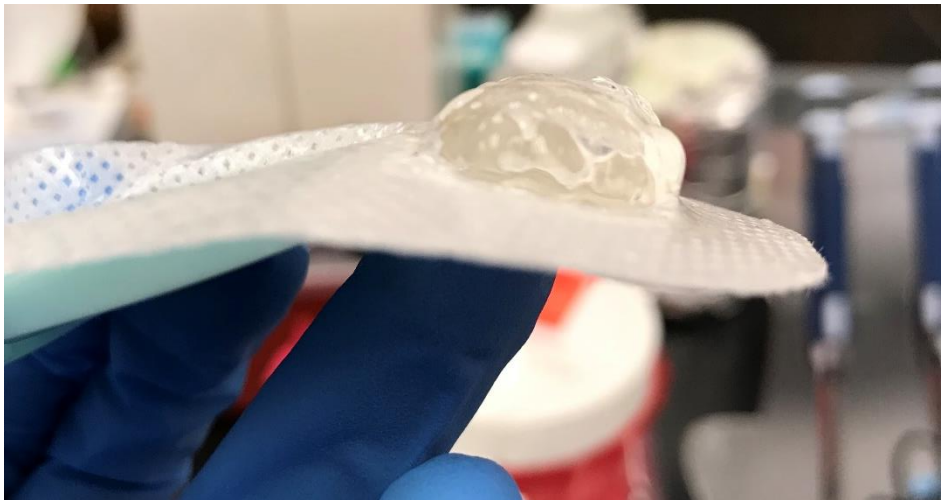


Figure 3.6: Swelling of leads due to transpiration from agarose phantom skins

As a result of this finding, various protocols were tried to attempt to recreate a drying effect on the patch, but no successful method was found. One such method was placing a thin layer of PDMS on top of 1% agarose gel (Figure 3.7), and then placing the patch on top of the PDMS to

collect data for an extended period of time. The immediate result was 20 kΩ values as the PDMS proved impermeable to the transpiration from the agarose.

Figure 3.7: Thin Layer PDMS 1% Agarose 'Dry" Skin Phantom

The lack of success in creating a physiologically accurate skin phantom that would properly mimic the drying and hydrating properties of the skin resulted in the abandoning of this line of experimentation. This has become future work for next year's team. The eventual goal of this experimentation is to not only create a phantom that sweats and dries, but one that would produce sebum (oil produced by the sebaceous glands in the skin) as well as mimic the physical properties of skin such as surface roughness and rheological properties.

3.2 Occlusion of Leads

After discussion with our corporate partners about trends in the clinical data, it was hypothesized that buildup of oils on the skin beneath the leads could lead to occlusion, thus a loss in connection and a possible cause for high impedance. Oil produced by the skin, or sebum, are intermittently reabsorbed after production, and are found in higher concentrations in certain parts of the body and in certain age ranges, including the age range of the patients used in the clinical trial (Picardo, 2009).

To test this hypothesis, a 0.5 cm layer of Vaseline was applied directly onto a new patch and worn for twenty-five minutes (Figure 3.8) – 20 kΩ readings were noticed right away and stayed constant until the removal of the patch.

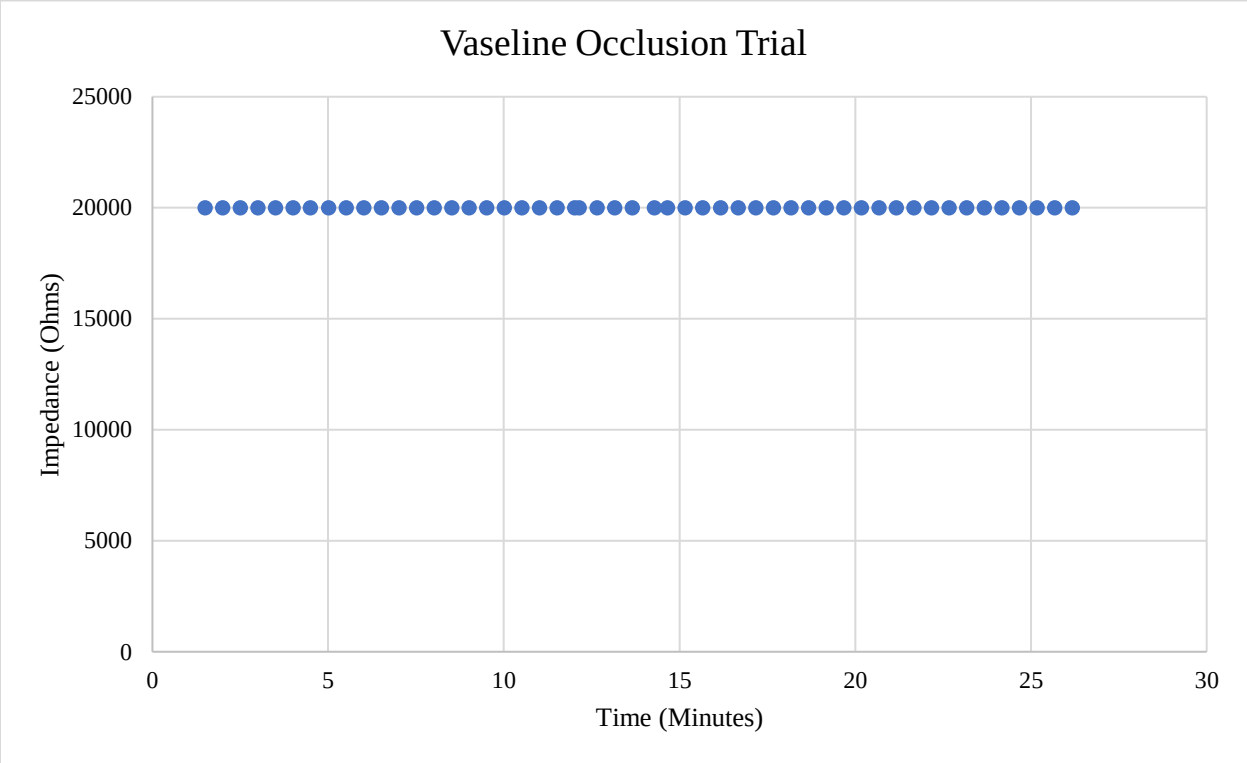


Figure 3.8: Vaseline Experiment

This confirmed the conclusion that occluding the leads with a naturally produced non-conductive material is a possible source of the behaviors seen in the clinical data. The results of this experiment opened a line of inquiry about the degree of occlusion necessary to create the oscillatory readings seen in the clinical data, and experiments were created around testing the percentage of skin contact necessary to cause a false positive lead off condition.

3.2.1 Oil Experiments

Experiments were conducted to test the impact of skin oil or sebum on measured impedance. Olive oil was chosen as an analogue for sebum and was applied to the hydrogel prior to wear. Figure 3.9 shows how olive oil was applied to the patch.

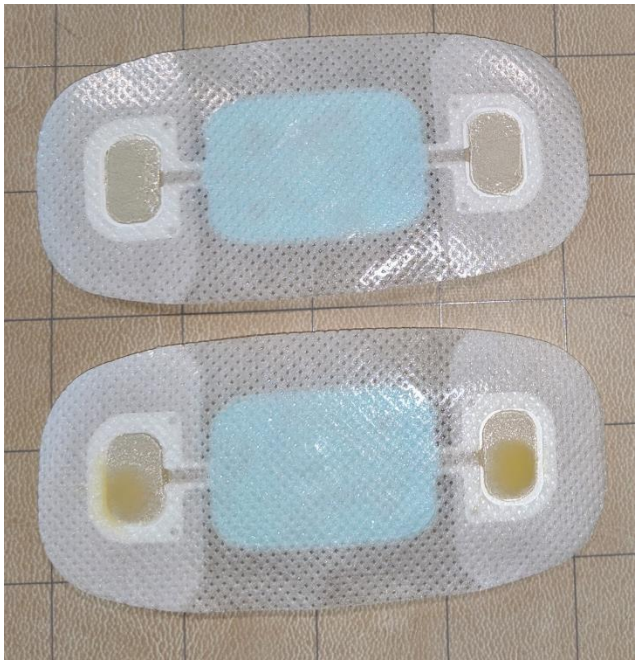


Figure 3.9: Untreated patch vs. patch treated with olive oil

The patch treated with a small amount of olive oil shows a typical bonding period followed by normal impedance readings. The skin and patch have absorbed most of the olive oil within five

hours. Patches treated with a larger amount of olive oil could not bond successfully and would slip off the body. Figure 3.10 shows the bonding period of a treated patch is very similar to a typical bonding period, which means that oil on the surface of the skin is not causing high impedance readings.

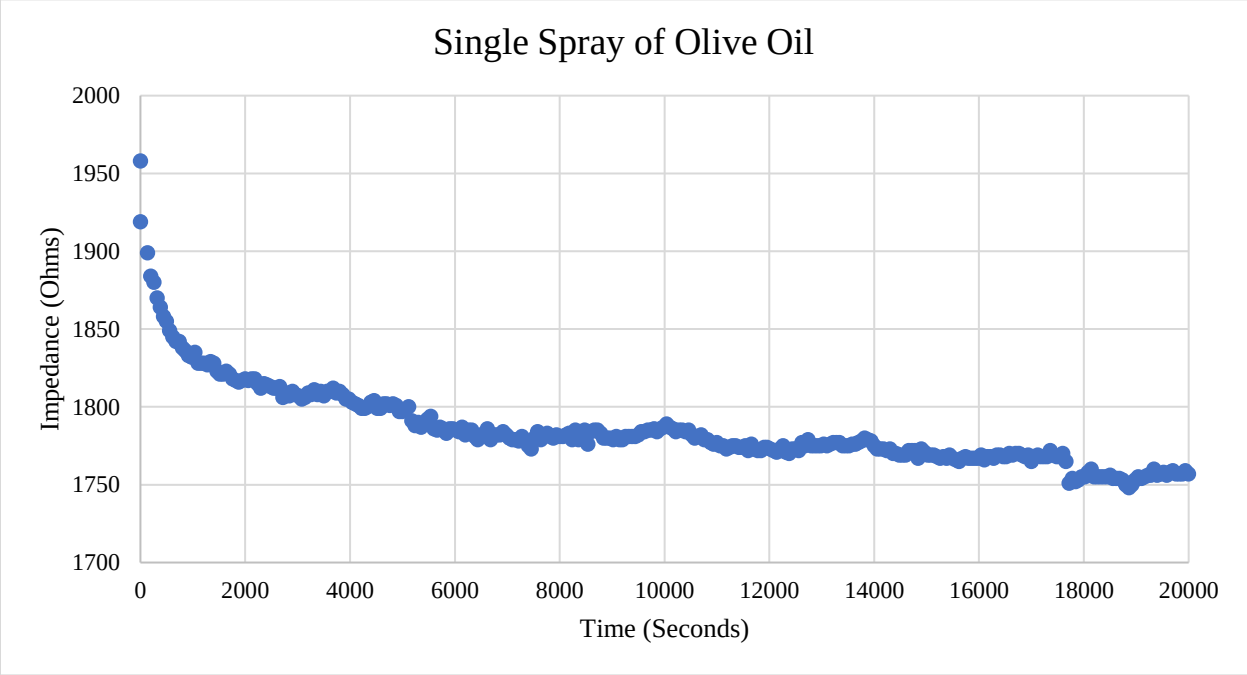


Figure 3.10: Bonding period with olive oil is very similar to a typical bonding period

3.2.2 Skin Contact Area Experiment

Each hydrogel on the patch is approximately 160 mm^2. Under ideal conditions, both patches are 100% in contact with the skin. However, as resistance is the inverse of surface area in a conductor, it follows that the skin contact surface area is an important component in measuring skin impedance. Experiments were conducted to characterize the impact of skin contact surface area on measured impedance by using the data pod and a strip which

has been modified to allow for smaller contact surface area with plastic packing material as shown in Figure 3.11.

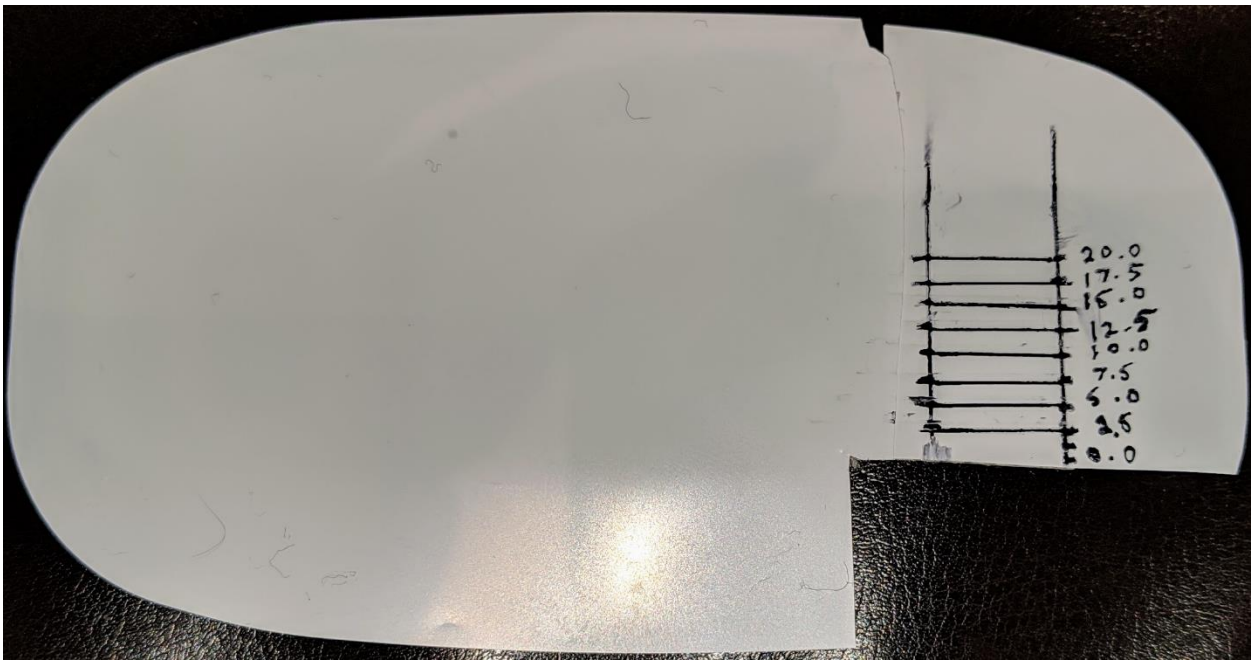


Figure 3.11: Patch modified for skin contact surface area experiments

As expected, as skin contact surface area decreased, measured impedance increased significantly, but only once a critical point was reached. Figure 3.12 shows that measured impedance remains below 5000 Ω until as little as 12% of the hydrogel is in contact with the skin, at which point measured impedance jumps rapidly.

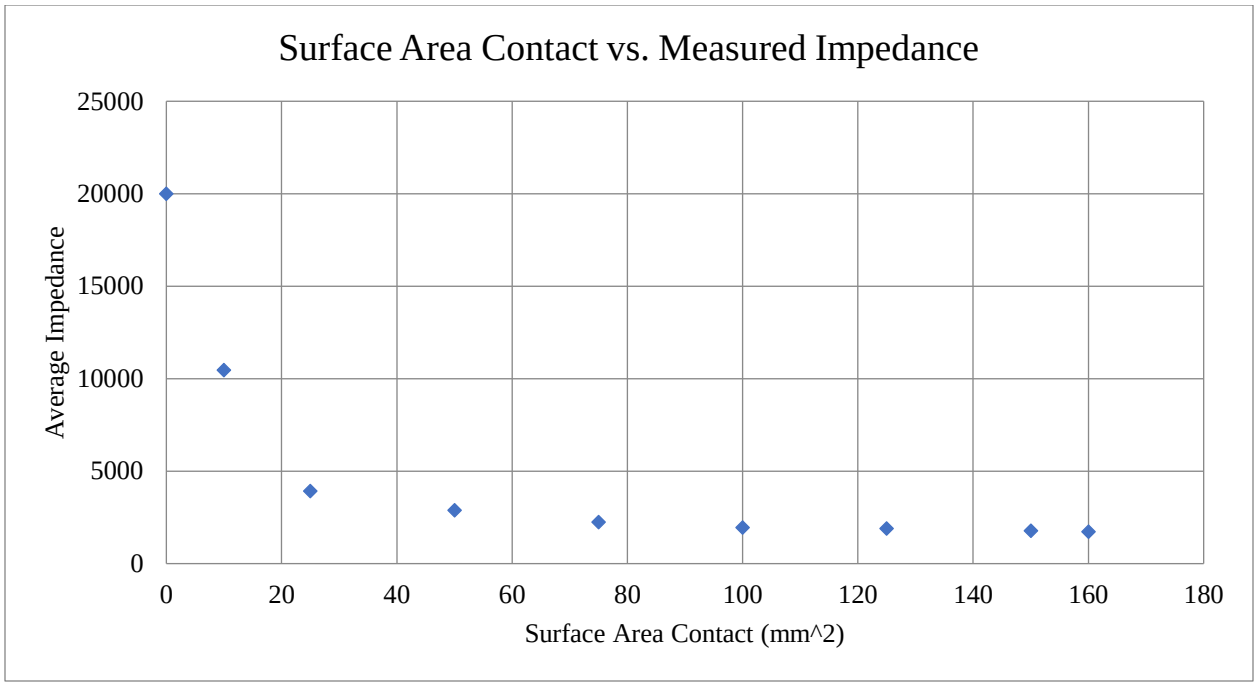


Figure 3.12: Impedance increases rapidly as contact surface are decreases below 20mm^2

3.3 Normal Wear

This product is marketed towards the everyday person and tracking their medication consumption. Thus, the patch should be able to withstand the wear and tear that comes with everyday activity. Such activities would expose the patch to aging, heat, sweat, and movement.

3.3.1 Aging the Patch

To further understand the impact of aging on measured impedance, experiments were conducted that perform the opposite of the *2.4 Battery Voltage: Aged Battery, New Patch* experiment. First, the patch was "aged", or worn for five days without a data pod installed, thus keeping the battery full. Next, the data pod was installed and began measuring impedance for the remainder of the battery's capacity. The behaviors seen in the erroneous clinical data, characteristic oscillations between lead-off impedance values and those within the physiological range, were immediately present despite the brand-new battery (Figure 3.13).

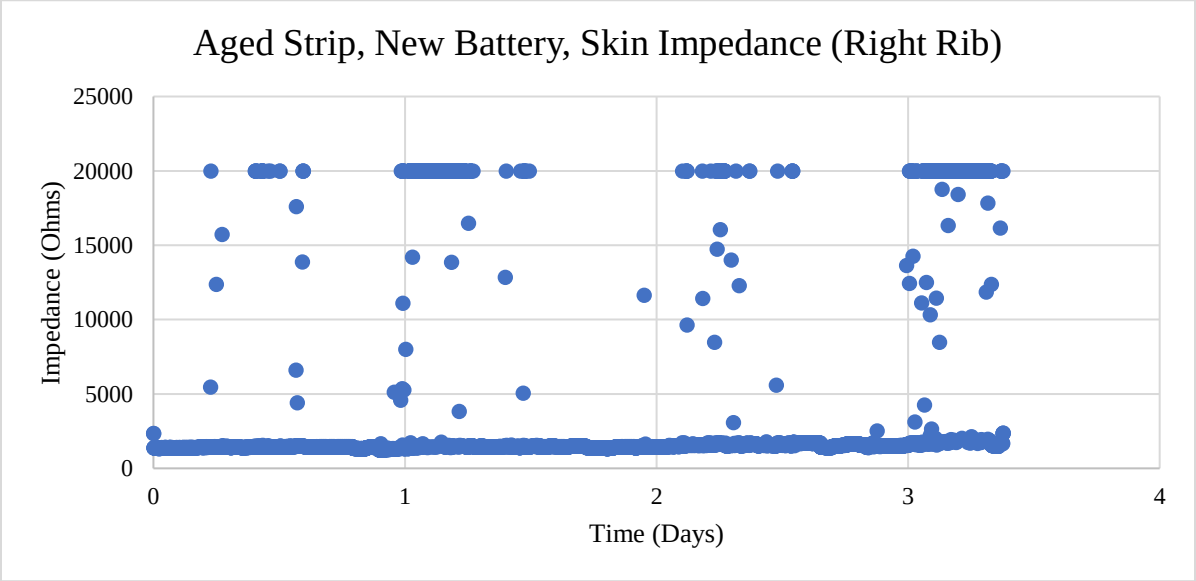


Figure 3.13: Aged patch, new battery shows immediate high impedance readings

3.3.2 Thermal Conductivity Testing

One problem with validating a good connection is that looking under the patch will impact the connection, making observations invalid. The assumption was made that thermal conductivity is reduced for a poor connection, so it would result in a higher differential temperature between the skin and the top of the patch. Infrared imaging was used to measure ΔT over the course of a normal week of wear (Figure 3.14).

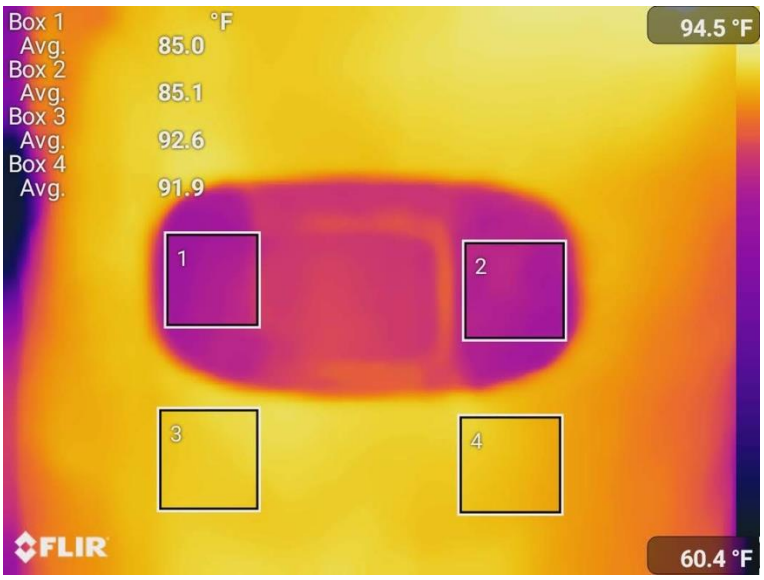


Figure 3.14: Example of infrared image of patch and skin

An increase in ΔT between the skin and the top of the patch can be attributed to a decrease in thermal conductivity and therefore a decrease in adequate connection. This can be from loss of contact or other poorly conductive material introduced between the hydrogel and the skin. Controls were put in place to ensure that thermal images were taken in the same outfit, during the same time every day following one hour of light office work to limit variation in skin temperature shows that

the temperature difference is increasing over time by about 0.5°F, meaning the connection is possibly weakening (Figure 3.15).

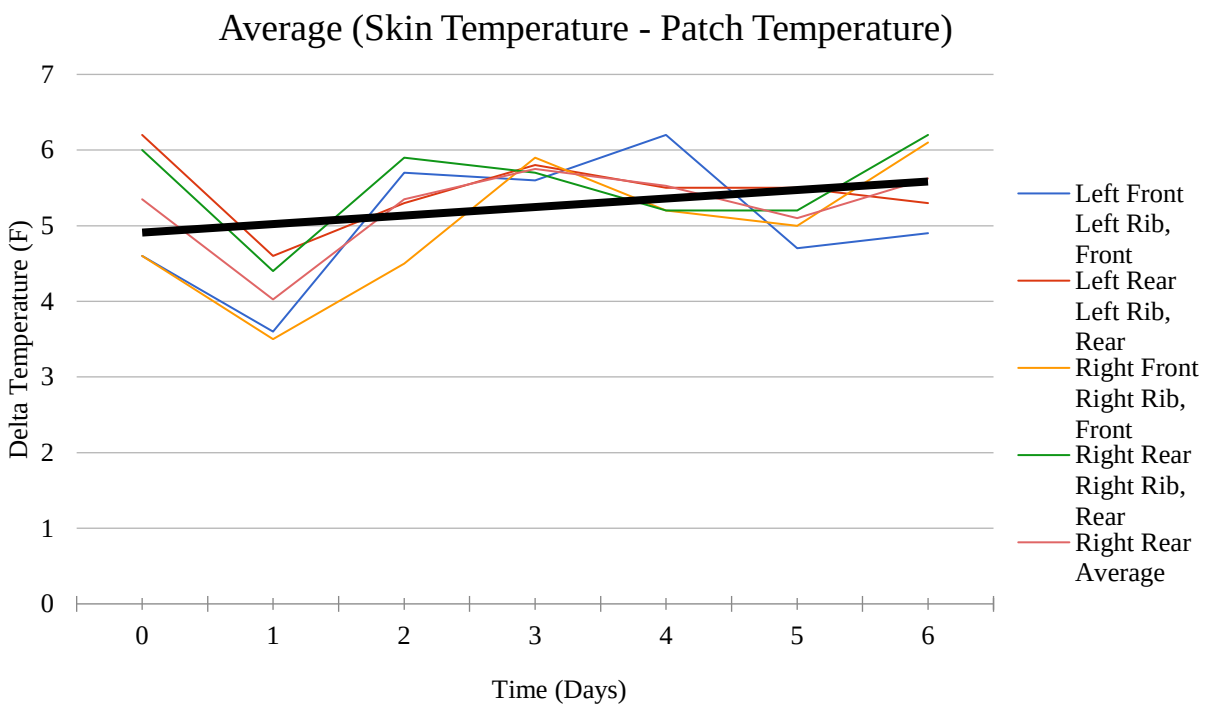


Figure 3.15: ΔT increase shows connection is slowly weakening over time

3.3.3 Flex Test

This experiment was created in order to see how purposeful movement might affect skin impedance. A series of leans and stretches were carried out by the subject for five minutes each. These included a stationary upright position to establish a baseline, then a forward lean, a backward lean, and a bend to either side. This same test was conducted a second time with an aged patch. What was seen was a fluctuation in impedance due to the induced shear stress, with the impedance readings of the test with the aged patch being 100 Ω apart as seen in Figure 3.16.

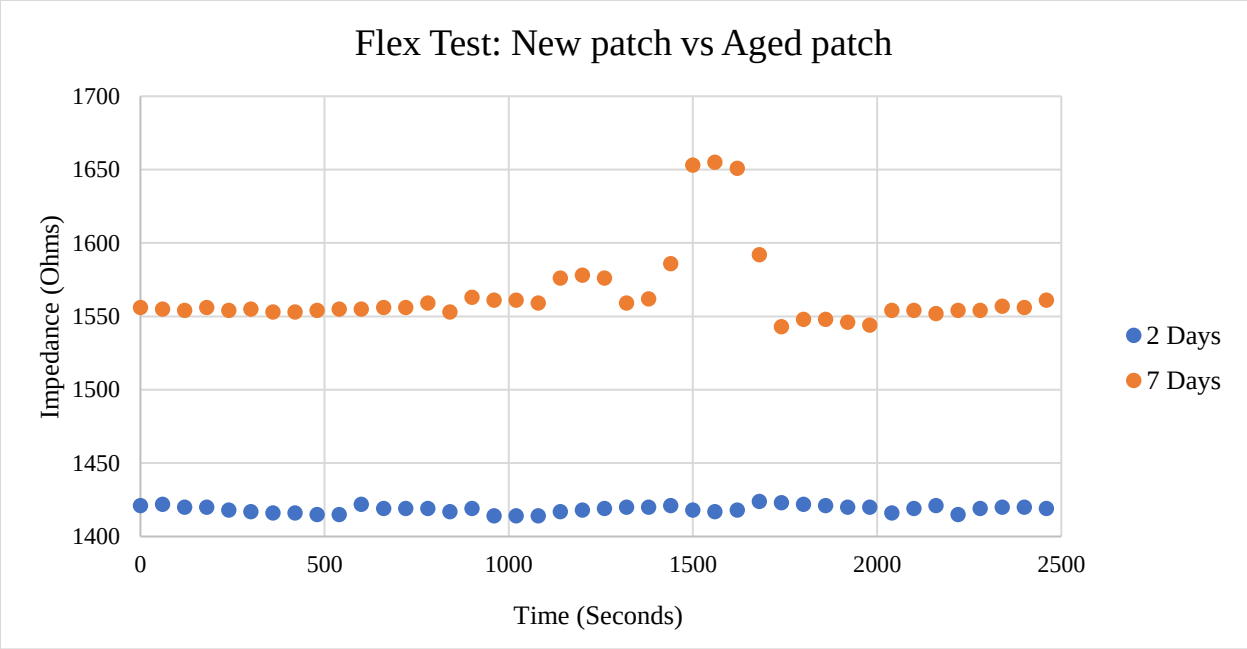


Figure 3.16: Impedance measurements while flexing, new vs. worn patch

3.3.4 Extreme *in vivo* Testing

A normal aspect of human behavior is exercise. High intensity exercise causes movement, sweat, and elevated skin temperatures. It was explored how all three of these might contribute to *in vivo* results. One patch on either ribcage was worn for 48 hours and put through two rigorous two-hour periods of exercise. What was seen was a small but noteworthy overall decrease in measured skin impedance within physiological range as shown in Figure 3.17. One 20 kΩ impedance reading was noted on the right side of the subject's body, which can be traced back to while the subject was sleeping (Figure 3.18Figure 3.18). It was confirmed that sweat increases the amount of hydration and the concentration of conductive ions at the leads, thus decreasing overall impedance.

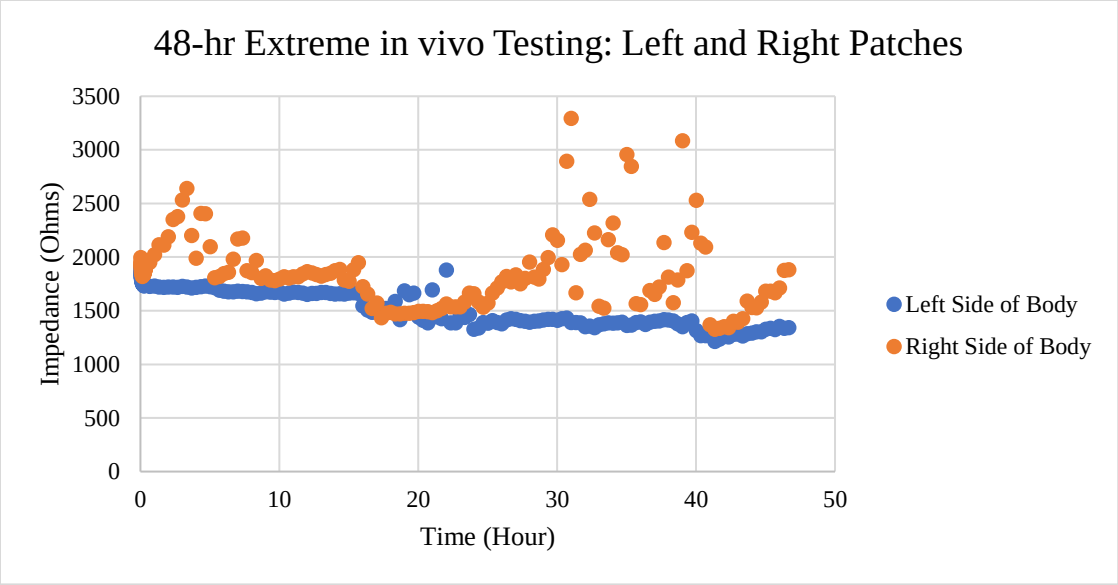


Figure 3.17: 48-hr Extreme in vivo test (excluding 20 kΩ reading)

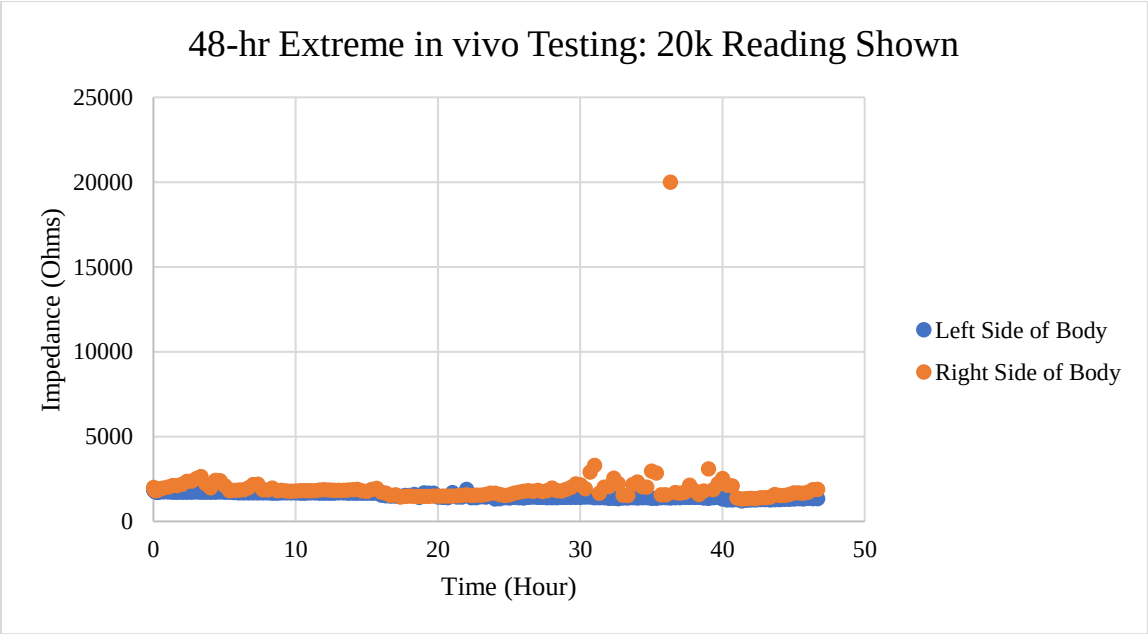


Figure 3.18: 48-hr Extreme in vivo test (showing 20 kΩ reading)

3.4 Conclusions

The experiments run at this interface yielded results that indicated the mechanisms causing false positive lead off conditions are likely at this interface. While movement, heat, and sweat all seem to cause changes in impedance when varied, the results that most closely matched the behavior in the clinical data profile closest. The experiments at this interface definitively proved that the erroneous data is a function of how the patch ages with time. These results are applied within a mathematical model which will be shared in Chapter 5: Project Contributions.

4. ELECTRODE-HYDROGEL INTERFACE

The final subsystem of interest was the Electrode-Hydrogel interface. This interface included everything from the Ag-AgCl electrode through the hydrogel and was of great importance because it involved a hydrogel of unknown composition. The hydrogel plays the role of connecting the Ag-AgCl electrode to the skin, therefore, being a critical component of this subsystem. The experiments analyzed the effect of environmental and chemical stresses on measured impedance. It was hypothesized that the hydrogel was a large contributor to the erroneous lead off exhibited in the clinical data. As such, alternate gels were examined to see if high impedance readings could be eradicated through the replacement of the hydrogel.

4.1 Humid and Dry Box Experiment

This experiment was run to explore how humid and dry conditions alter measured impedance. In these experiments a patch was connected to a data pod that was placed in one of two sealed boxes: one simulating humidity (Figure 4.2), and one simulating dry conditions (Figure 4.1). The patch was then connected via wires and alligator clips to a 1.8 kΩ resistor. A piece of aluminum was placed between the pre-existing plastic and the hydrogel to act as an attachment for the alligator clips. Cotton balls acted as a desiccant within the sealed dry box and a damp sponge acted as the source of humidity within the humid box. The patches were connected to the data pod, placed in their respective chambers, and connected to the 1.8 kΩ resistor. The chambers were sealed for three days.

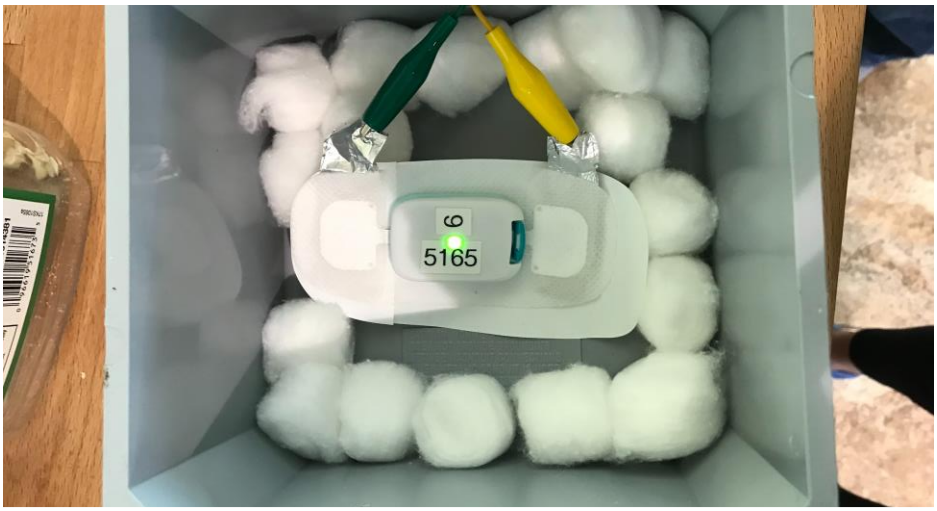


Figure 4.1: Dry box set-up

Figure 4.2: Humid box set-up

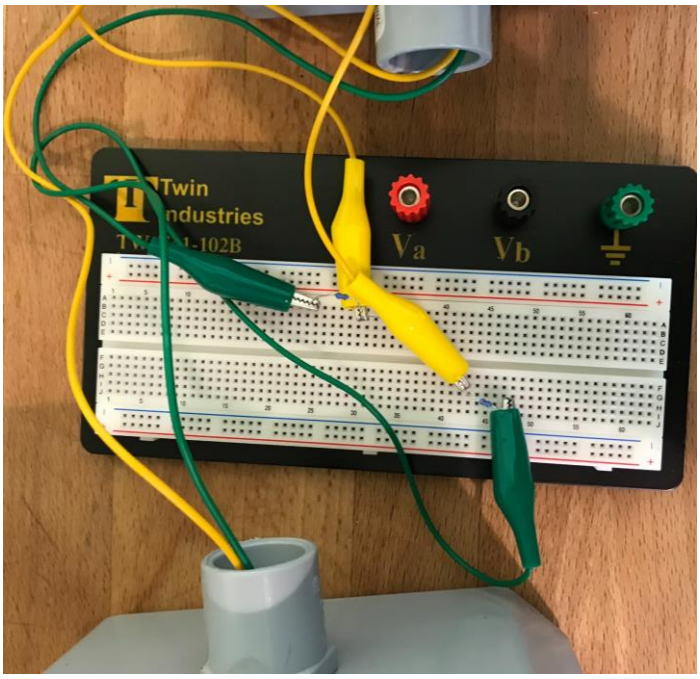


Figure 4.3: Electrical Setup of Experiment

The measured impedance for the dry box followed a clear cycle of high to low impedance (Figure 4.4). Our team assumed that it correlated varying ambient temperature with colder temperatures being exhibited at night and hotter during the day. The humid box exhibited a pattern a similar cycle with slight increases of impedance measured at day 1 and 2 (Figure 4.5). Overall, dry and humid conditions can lead to changes in impedances, but not to the extent of erroneous lead off exhibited in one-third of the clinical data.

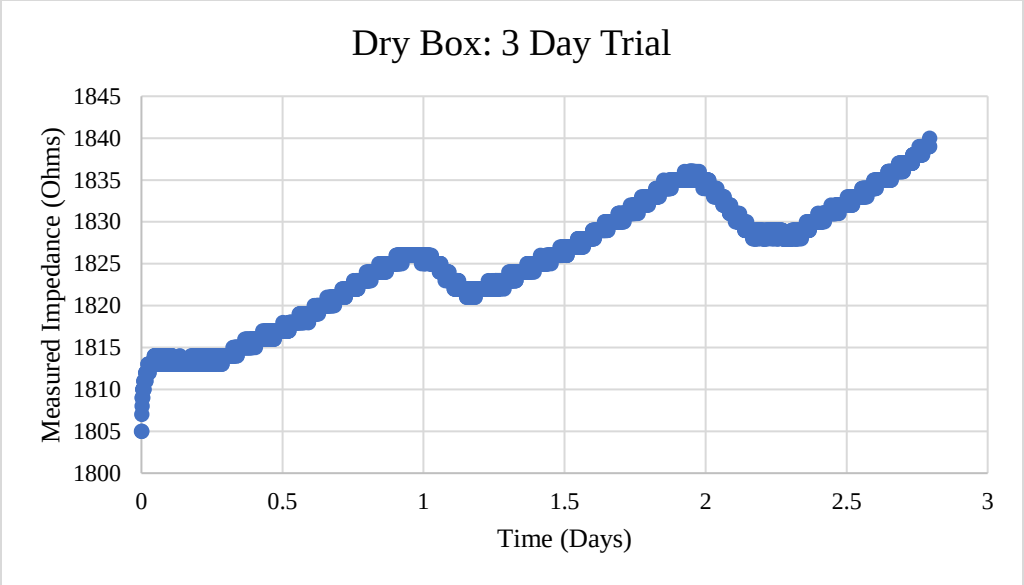


Figure 4.4: Dry box experiment results

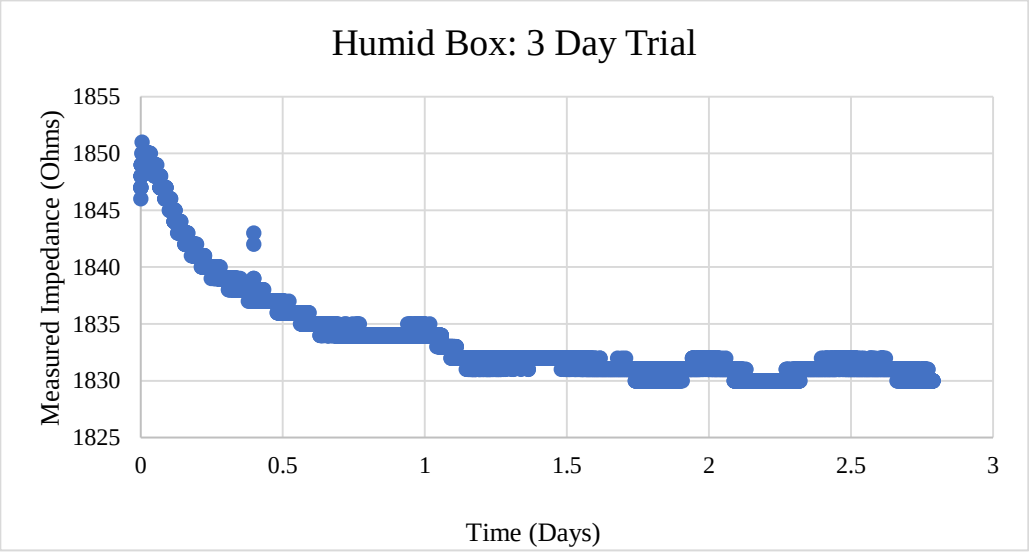


Figure 4.5: Humid box experiment results

4.2 Rehydration and Dehydration (Hydrogel Only)

To examine how salt might affect the hydrogel exclusively, a data pod was connected to the strip saver, and the strip saver was connected via female ends of electrical wires and conductive wires to both ends of the hydrogel (Figure 4.6). The hydrogel rested on top of a 3D printed well and inside the well was desiccant. The hydrogel was then exposed to small volumes of varying concentrations of NaCl (0.1 M, 0.5 M, and 1 M NaCl) periodically.

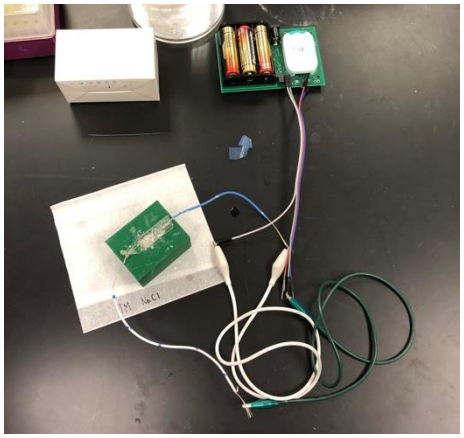


Figure 4.6: Hydrogel only rehydration-dehydration experimental set-up

Figure 4.7: Well with hydrogel and 0.1 M NaCl

As concentrations of NaCl increased, measured impedance increased as seen in Figure 4.8. This was to be expected as higher concentrations of salt result in higher amounts of salt accumulation that could potentially occlude the lead. Although this positive correlation was exhibited, high 20 kΩ impedance was not measured at 1 M NaCl eliminating salt accumulation as a possible factor leading to erroneous lead off.

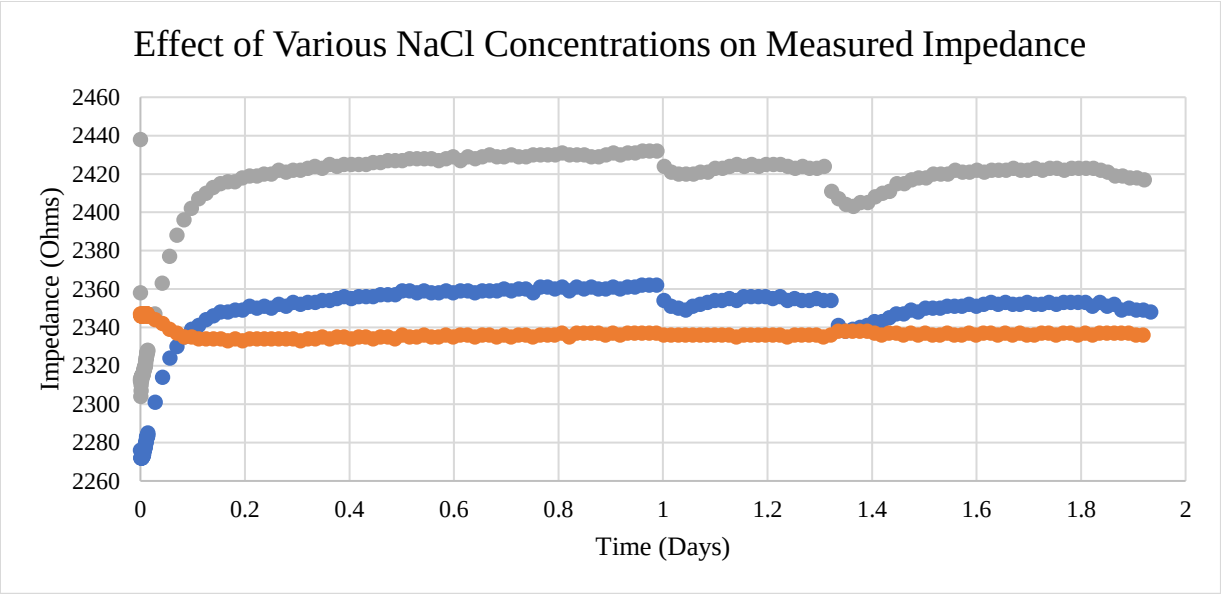


Figure 4.8: Results from varying concentrations of NaCl rehydration-dehydration

4.3 Alternate Gel Test

When conducting the alternate gel test it was assumed that the current hydrogel was the reason for the erroneous lead-off exhibited in a third of our project sponsor's clinical data. The purpose of the test was to find a suitable replacement for the hydrogel that would eradicate high measured impedance readings. Two gels were examined, Spectra 360 electrode gel (Parker Laboratories, 2015) and the Signa electrode gel (Parker Laboratories, 2015). The Signa electrode gel was conductive, but not well suited for long term applications because it could not retain its structure for a week. While the Spectra 360 electrode gel was also conductive and water soluble, its structure was maintained for the duration of a week in an open setting.

The next step was to remove the hydrogel without damaging the Ag-AgCl electrode. Freezing the patch was observed to be the most efficient method for removing the hydrogel and introducing a new gel on top of the electrode. The patch was then placed inside a similar chamber to that in Figure 4.1 and hydrated every 8 hours with small volumes of 0.1 M NaCl.

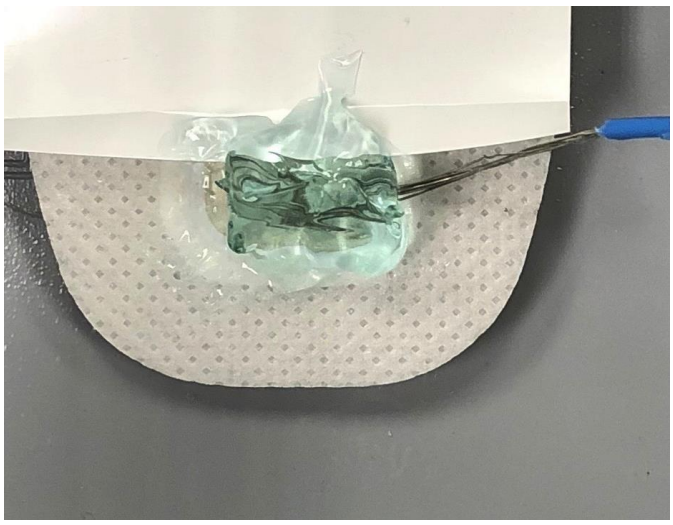


Figure 4.9: Spectra 360 electrode gel experimental set-up

The immediate 20 kΩ data suggests that there was a poor connection initially that eventually became a more established connection. While the Spectra 360 gel experienced both dehydration and rehydration, its measured impedance did not change like was the case with the current hydrogel in use. The main issue with the Spectra 360 gel is that it was not sheet based. This led to movement of wires during experimentation which could contribute to the high average impedance and abnormal behavior seen in the data. A suitable alternate gel should be sheet based, conductive, and well suited for long term application is necessary.

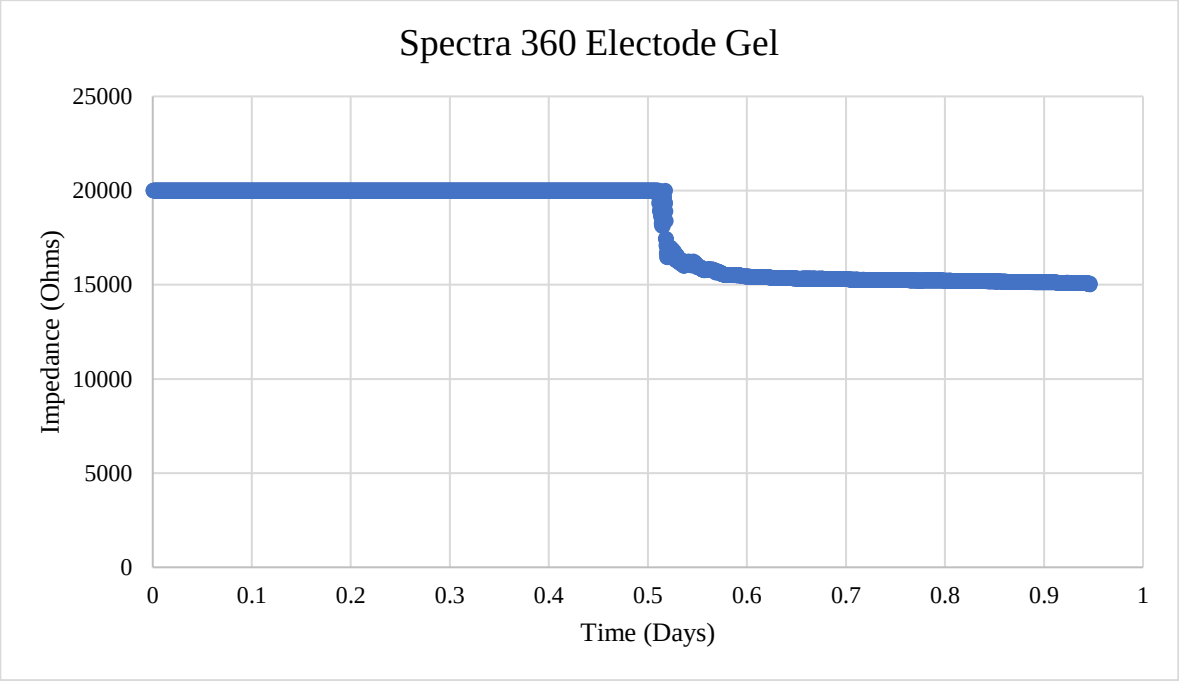


Figure 4.10: Spectra 360 electrode gel rehydration-dehydration experiment results

4.4 Conclusions

The environmental and mechanical stresses applied to the hydrogel (changes in humidity and salt exposure) showed changes in impedance, but did not mimic the behavior seen in the clinical data. While it has not yet been proven that the hydrogel is the main source leading to high impedance, alternate gels fitting the descriptions in *4.3 Alternate Gel Test* should continue to be explored.

5. PROJECT CONTRIBUTIONS

The purpose of this project was to identify the cause of the sporadic high impedance measurements and to determine a solution to prevent it from happening. Initially it was assumed that the measurements were erroneous, but the results of the skin contact surface area experiments demonstrate that the impedance can change rapidly at low surface area. If contact surface area is the cause of high impedance measurements, then the solution is to improve skin adhesion or find another way to determine lead-off condition. This chapter discusses two contributions provided to our industry sponsor. First, the voting table, which seeks to provide an alternative method for determining lead-off condition, will be discussed. Next, the mathematical model will be shared, which seeks to provide further evidence that low contact surface area is the cause of the rapid jumps in impedance seen in the clinical data.

5.1 Voting Table

The data pod is capable of monitoring temperature, motion and ECG in addition to skin impedance. While the device was originally planned to use skin impedance to determine lead-off condition, it could be modified to make decisions based on information from all four sensors via a voting table. Figure 5.1 shows an example of a voting table that could be used to utilize all four sensors to determine lead-off. Under this scheme, two sensors would be required to vote for lead off before it is flagged, which means that if temperature, ECG, and accelerometer all vote for lead on, then a high impedance reading cannot flag lead off by itself.

Sensor	Data	Vote
Impedance	<10000 Ohms	Lead On
	>10000 Ohms	**Lead Off**
Temperature	>85F	Lead On
	<85F	**Lead Off**
ECG	Normal	Lead On
	Abnormal	**Lead Off**
Accelerometer	Movement	Lead On
	No Movement	**Lead Off**

Figure 5.1: Example of a voting table and setpoints

5.2 Mathematical Model

The mathematical model uses data gathered from the skin contact surface area experiments to provide a projected measured impedance for a given surface area, following the equation: $R=l/A$, where R is resistance, ρ is conductivity, l is length, and A is contact area. A random walk is used to test the assumption that surface area is the cause of rapid changes in impedance. Holding ρ and l constant, the script varies area and outputs the result.

The starting point of surface area is ideally approximately 160 mm^2, which is full contact. However, examination of clinical data shows that there is a bonding period that must be accounted for, so for the first few hours of wear, the script simulates the bonding period so that the starting point is typically between 140-160 mm^2. From there, the surface area has a 50% chance of increasing or decreasing. The step size by which it can move is called the delta area. Delta area increases over time, simulating the loss of adhesive capability and aging of the patch. The rate of aging is how quickly the step size can increase and is determined by k.

Finally, clinical trials demonstrated that there was a tendency for high impedance readings to occur during the day, and less likely to occur at night. This is attributed to the fact that the patient is lying down on the data pod, increasing the contact surface area. The tabular representation of these parameters can be found in Figure 5.2.

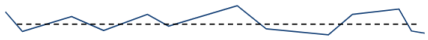
Patch Behavior	Model	Visual Description
Skin Impedance	R = ρl/A	
Contact Area	A = 160 mm^2 (Ideal)	
Poor Connection	Random Walk of Surface Area	
Aging	Increasing Step Size (aging factor)	
Periodic Impedance Jump	Day/Night Cycle	

Figure 5.2: Tabular representation of Mathematical Model Parameters

Figure 5.3 shows an example of the resulting impedance output of a random walk of surface contact area. The resulting impedance from the random walk of surface area closely mimics the measured impedance shown in clinical trials (which can be seen in Figure 1.3). Moreover, because of the random component, there were many cases where the model did not yield any high impedance readings, also mimicking clinical trials. It was observed that there is critical point in surface area below which impedance tends to rise quickly, lending to the idea that low contact surface area is ultimately the cause of the high impedance jumps. Note that the bonding period is also coded into the mathematical model, or the period where impedance starts high then the patch makes better contact with the patient's skin. Another aspect of the mathematical model is sampling rate. A low sample rate appears to have a low-pass filtering effect on the readings (Figure 5.4, bottom graph). It is suggested that the software be altered to measures more frequently once the data pod reads high impedance so that a more accurate sense of the impedance behavior is gathered.

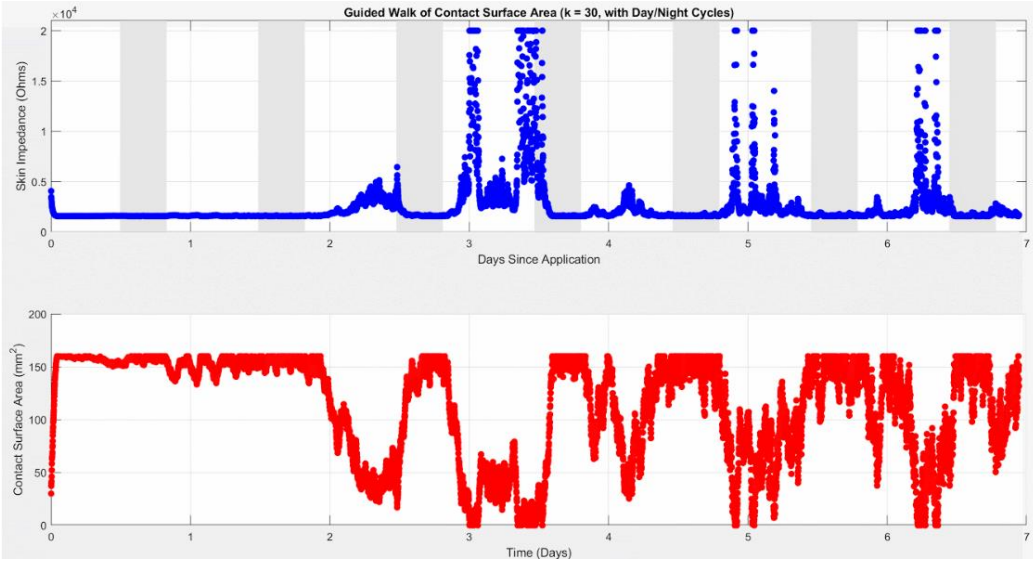


Figure 5.3: Projected Impedance and the Random walk of Contact Surface Area

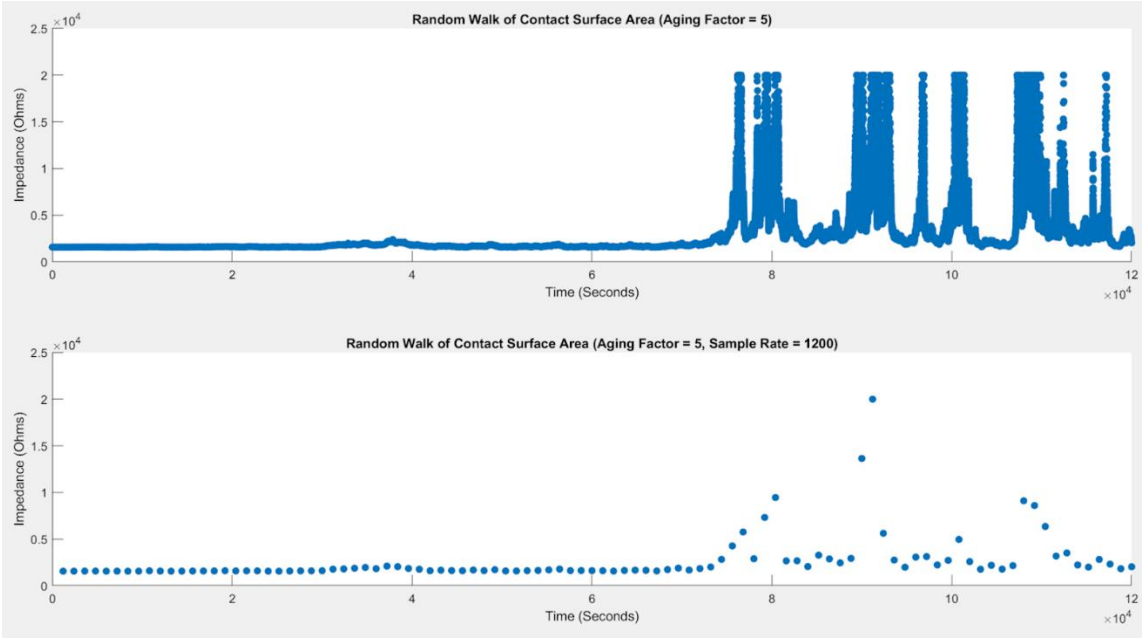


Figure 5.4: Sampling Rate in Mathematical Model (top graph has a higher sampling rate)

6. ETHICAL DIMENSIONS

6.1 Sustainability Considerations

The datapod is powered by a small 3V CR2016 coin cell (Li / MnO_2) located in the patch behind a water-proof seal. It is rated for 90 mAh and has a very low self-discharge rate, which makes it an ideal source for the low-power sensors, lasting approximately one week under normal use. Lithium and Manganese Dioxide batteries are non-rechargeable, so while the datapod is reusable, the patch is single-use. The state of California requires all batteries to be recycled or taken to an appropriate waste management facility, so it is important that patients be made aware of the disposal requirements associated with the patch.

The majority of the patch is made up of plastics and other long-lived components. It can reasonably be expected that one of these patches will be disposed of each week and thousands over the course of a lifetime. One potential solution is to make the 3V cell with rechargeable battery technology and place it in the datapod along with the PCB. This solution would also reduce plastic waste, because there would be no need for a second water-sealed container to house the battery, only one for the datapod and battery combination.

6.2 Ethics of Informed Consent and Privacy

The ethical definition of safety (Martin & Schinzinger, 2010) is "if, were its risks fully known, those risks would be judged acceptable by reasonable persons in light of settled value principles." In other words, for a consumer to use any product, they must first understand the risks associated with each decision made, be it medical, technological, or personal. Furthermore, the public has a right to understand and be aware of those risks and should have the right to assess their safety, as they are primary stakeholders in the situation. This is the ethical concept of Informed Consent. To this end, the public should be required to consent to any informed risks – such an action avoids any deception or fraud in seeking solutions to the problem at hand. This theory emphasizes the need to deliver power to stakeholders so that they not only understand the various sides to technology in their daily lives, but that they realize they have the right to NOT use technology just as much as they have a right to partake in the fruits of technological advancement.

Our industry project sponsor has created a device in a new market of "digital medicine" – a drug that not only ameliorates medical problems, but one that can track often the patient takes it. It can then send that information to their doctor or their insurance company. At the core of this invention is the sharing of a patient's personal medical data with a third party. Furthermore, given that the information is shared via Bluetooth, a protocol with dubious security, any individual with a Bluetooth dongle and appropriate software can access and download a patient's information without their consent. This technology is improving the health of patient, but it just as equally endangers them through not protecting their privacy. If standard patient medical records are kept private, then so too should this digital health system. Therefore, by the ethical principle of informed

consent, such risks must be made aware to the patient so that they are aware of the risks associated with the technology and can come to a decision in light of their value principles and the fully known risks.

7. TEAM AND PROJECT MANAGEMENT

7.1 Cost Analysis

The bulk of the materials used in this project were provided by our project sponsor. The most common of these materials was the patch component of their system, which they provided to us free of charge. They also provided us with data pods upon request, and a ream of the sheet gel used for the hydrogel leads. All other materials were purchased using funds from the Bioinnovation Design Lab. These include two plastic airtight boxes used as environmental chambers, humidity loggers, electrical equipment (breadboards, wires, alligator clips), and Bluetooth dongles.

7.2 Project Timeline

The following timeline describes the action items completed during each chronological phase of our project. This timeline changed with our biweekly discussions with the corporate team.

May 2018 to August 2018

- Literature search to understand the extent of how wearable devices interact with skin chemistry of the user/patient
- Replicate the behaviors and patterns seen in project sponsor's clinical data
- Understand how to use the project sponsor's system for future experimentation

September 2018 to December 2018

- Creation of system sketch broken down into three interfaces
- Experimentation: humidity chamber experiments, skin phantom development, electrical subsystem testing, preliminary dehydration/rehydration testing

January 2019 to March 2019

- Abandoned Skin Phantom experiments – left to future work
- Began searching for alternate gels for leads – unfinished, left to future work
- Experimentation: hydrogel characterization, flex testing, saltwater dehydration/rehydration testing, thermal conductivity testing

April 2019 to June 2019

- Development/sophistication of MATLAB mathematical model and voting table
- Final presentation at industry partner HQ (5/3/19) and Senior Design Conference (5/9/19)
- Completion of thesis

7.3 Team Management

The team was managed by one of the three engineering students on the team. The team manager served as the first point of contact with the industry project sponsor, coordinating the schedules of the team and synthesizing all data for progress reports, as well as organizing and writing the majority of the thesis. Meetings with the corporate sponsor were held twice a month to discuss the results of experimentation and receive feedback on how to best proceed with our diagnostic experimentation.

Each team member worked on a variety of experiments in all three interfaces. The most experimentation occurred at the Hydrogel-Skin Interface, with two students sharing the responsibility of experimentation at this interface. The least explored interface was the Electrode-Hydrogel Interface, with a handful of experiments left unfinished and thus became future work.

8. CONCLUSIONS AND NEXT STEPS

8.1 Summary of Accomplishments

In the following section, we will discuss our project outcomes by discussing our accomplishments and contributions as well as sharing the feedback received from our project sponsor when we presented our work to them. From our experimentation at each interface, it was proven that the source of the erroneous impedance behavior was not a function of the electrical subsystem, but rather a function of aging. Aging occurs due to how the patch interacts with the patient's skin over time, and therefore the mechanism likely contributing to the erroneous impedance readings in the clinical data lies at the Hydrogel-Skin Interface. This, however, does not rule out the Electrode-Hydrogel Interface as a possible source of erroneous lead-off. The interface was not explored thoroughly enough to determine if it is a likely cause or not.

8.1.1 Review of Project Contributions

Our project contributions are the proposed voting table and the mathematical model developed in MATLAB. Our learnings thus far indicate that one should not simply rely on impedance to determine lead off, but rather include other parameters for reliable and accurate measurement. The voting table employs all four sensors on board to determine a true positive lead off condition. For example – if the skin impedance sensor reads 20 kΩ, but the accelerometer, PCB temperature, and ECG all point towards the patch still being on the patient's body, the skin impedance data would be overruled. The mathematical model was a culmination of all of the phenomena witnessed during our experimentation. By introducing a random walk of surface area, with skin contact area being able to increase with time to simulate aging, as well as day/night

cycles to recreate the better contact during nighttime, we were able to produce data that very closely mimicked what our project sponsor saw in one-third of their clinical trials.

8.1.2 Feedback from our Project Sponsor

A final project presentation was given at our industry partner's headquarters a week before the Senior Design Conference. The feedback we received was very positive. They were very pleased that we were able to independently corroborate the physiological trends they had seen in their erroneous clinical trials. Furthermore, they were impressed that we were able to so closely model the clinical trial data in the mathematical model, and gave us some areas to improve upon to provide greater sophistication of the model. One such area is to build into the model the capacitive nature of human skin to more accurately recreate the skin's interaction with the patch. Additionally, The Company is currently employing a similar voting table to that which we proposed, but are limited by the data storage capabilities of the data pod used on the patch.

8.2 Project Shortcomings

Some work was left unfinished during the course of the project, especially at the Electrode-Hydrogel Interface. One such example was the inability to find a viable alternative to the current hydrogel being used in the system. Many gels were tested, but none were conducive to maintaining their structural integrity during wear. As such, this has been left to future work.

It was determined that the source of the behavior seen in the clinical trials was a function of aging of the patch but the exact mechanisms contributing to the behavior remains unknown. Nonetheless, there is a significant foundation for future teams to allow further discovery of the possible mechanisms informing the clinical data behavior.

8.3 Future Work

A significant amount of time and resources were spent on developing a physiologically accurate skin phantom that would allow for repeatable, *ex vivo* bench testing. The aim of this was to allow for ease of experimentation in determining possible mechanisms leading to high impedance readings. A variety of polymers and protocols were explored to allow for simulated "sweating" of the skin phantom, but none were successful. It was determined that creating a physiologically accurate skin phantom was a project in and of itself and thus would become future work that would fall to our successors.

The mathematical model developed on MATLAB has opportunity for further sophistication. One such improvement would be to build in the capacitive nature of skin into the existing program. Such an addition would allow for a more realistic model of how the skin would respond to varying contact area as a function of aging over time of wear.

8.4 Lessons Learned

Throughout this process, our team has learned many valuable lessons. One lesson is to have patience working on a project where data is generated rather slowly. Since the bulk of our experimentation was focused on the mechanisms leading to aging, experiments would range up to two weeks at a time – it was disappointing when the data gathered ran counter to our hypotheses and it felt as if two weeks of precious time was wasted. Another valuable lesson learned was how to apply the lessons learned in the classroom to a corporate setting. Working on a corporate-sponsored project was fast-paced and required constant communication and careful planning, which is very different to our university setting.

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