DEPARTMENT OF
Biomedical Engineering
UNIVERSITY OF WISCONSIN–MADISON

Compartment Syndrome

BME 400 Final Report

December 11th, 2019

Client:

Dr. Christopher Doro

Advisor:

Dr. Amit J. Nimunkar

Team Members:

Team Leader: Jonah Mudge

Communicator: Hunter Huth

BPAG/BWIG: Lucas Ratajczyk

BSAC: Syafiqah Saidin

Abstract

Acute compartment syndrome (ACS) is a complex and difficult-to-diagnose condition in which trauma causes increased pressure in a muscle compartment, which can subsequently lead to muscle ischemia and death. Current methods of ACS diagnosis are often inaccurate, with pressure-based diagnosis reaching a rate of 35% false-positive in one study. False-positive ACS diagnosis results in unnecessary fasciotomies, which are incredibly invasive and expensive procedures that often leave the patient with permanently impaired limb function. More recent methods of ACS diagnosis continue to suffer from inaccuracy and a lack of supporting literature, indicating the necessity of a new, more effective method to reduce misdiagnosis of ACS. The previous team that worked on this project presented a solution involving Ion-Sensitive Field-Effect Transistor (ISFET) pH sensors to detect acidic intramuscular environments indicative of muscle ischemia. We will be miniaturizing and implementing this design in a 16-gauge needle for eventual use in humans after testing in animals with an 11-gauge needle . Additionally, we plan to fabricate and test iridium oxide (IrOx) electrodes as a possible miniaturized replacement for ISFETs. Furthermore, we are in the process of designing and testing a user interface to display the pH on a screen and record pH input values for a physician to use for ACS diagnosis in a clinical setting.

Table of Contents

Introduction

Acute compartment syndrome (ACS) is a difficult-to-diagnose and complex condition caused by an increase in muscle compartment pressure resulting in insufficient blood flow to the muscle tissue, causing muscle ischemia and possible tissue death [1]. ACS is uncommon, with an annual incidence of approximately 7.3 per 100,000 men and 0.7 per 100,000 women [2]. Because of this, there is limited information available from literature, and no gold standard for clinical diagnosis [3]. Furthermore, current methods of ACS diagnosis are flawed, with false-positive rates for direct pressure-based diagnosis reaching up to 35% [4]. The treatment for ACS is usually a fasciotomy of the affected muscle compartment, which can involve complications such as uncontrolled bleeding and infection [3]. Even if initially successful, subsequent operations are needed to remove dead muscle tissue and prevent sepsis, sometimes requiring limb amputation [3]. Fasciotomy survivors suffer from diminished range of motion, pain, and emotional trauma, making false-positive ACS diagnosis a serious issue, especially with the high cost of a fasciotomy operation [3]. Seeing that ACS misdiagnosis is a fixable problem in modern medicine, our client, Dr. Christopher Doro (an orthopedic surgeon with UW Health Orthopedics and Rehabilitation in Madison, WI), submitted this project to the BME department in an effort to minimize false-positives and reduce the number of ACS patients that suffer as a result.

Current methods of ACS diagnosis involve first testing compartment pressure directly using a catheter-enclosed pressure monitor [5]; however, this is often error prone and can result in misdiagnosis. More recent advancements have resulted in the formation of companies such as

Odin Technologies and their near-infrared spectroscopy (NIRS)-based Valkyrie, which estimates blood oxygenation and is completely non-invasive [6]. However, NIRS has yet to demonstrate great accuracy in diagnosing ACS, and given that the technology has been in existence for several decades, it may not be the best solution [3]. Another alternative developed by NASA looked into the possibility of using ultrasound to estimate compartmental pressure, but this also has yet to be proven effective [7].

Given the issues with current methods of ACS diagnosis, and the ineffectiveness of other existing alternative methods, the previous team selected to work on this project decided to use pH as a biomarker threshold for diagnosis [8]. They tested an Ion-Sensitive Field-Effect Transistor (ISFET) for pH measurement and saw that it was appropriate for this application. However, the ISFET sensor casing was too large to be inserted in a 16 gauge needle, the largest size allowed for use in human patients [3]. Our team aims to take this previous work and advance it to the point of laboratory animal testing and possible clinical environment testing. Our goal is to design and test a device for clinical use capable of interfacing with an ISFET probe and measuring the pH within a muscle compartment, and displaying and recording the pH so a physician can use it as a reliable indicator of whether compartment syndrome is actually occurring. Furthermore, we plan to miniaturize the previous team's ISFET concept or replace it with a smaller pH sensing device, such as an iridium oxide electrode, to facilitate insertion via a 16 gauge needle; though this size is not required for animal testing, it will allow us to more easily reach the point of human testing [9].

Background

Acute Compartment Syndrome

ACS is a limb- and life-threatening condition in which blood is prevented from leaving a muscle compartment such as those in figure 1a [5]. The most common cause of this blockage is bone fracture, which puts athletes at higher risk of developing this condition. The inability for blood to leave causes intracompartmental pressure to increase which eventually exceeds arterial pressure, preventing blood from entering the compartment. The lack of fresh blood causes buildup of tissue metabolites like CO_2 that can cause tissue death and necrosis [5]. These conditions can damage the patient's whole body but will at least cause permanent damage to the muscles in the compartment [5]. If 6 hours have passed since the injury or blockage began but the physician is unsure if the compartment has ACS, a fasciotomy is performed. A fasciotomy, as seen in figure 1b, is when a surgeon cuts open the muscle compartment to reduce intracompartmental pressure and allow blood flow to return to normal [5].

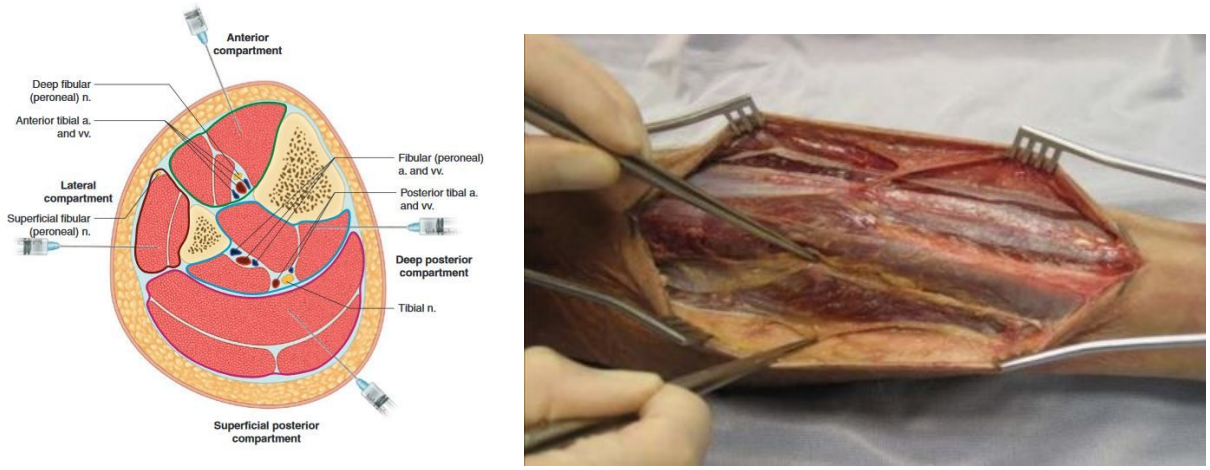

Figure 1: (a) Muscle compartments in the lower left leg [5]. (b) Fasciotomy of the right forearm [3].

Conventional methods of diagnosing ACS include measuring intracompartmental pressure for the increase that is associated with blood outflow blockage. However, this method is highly unreliable and results in a very large percentage of false positive diagnoses (35%) [4]. A more accurate diagnostic method measures the partial pressure of oxygen in the blood of the compartment to detect the decrease associated with ACS. This method, while very reliable, is also far more expensive than pressure measurements, with the cost of single-use probes reaching upwards of $2,000 on top of multiple-use equipment that is even more expensive [3, 10]. Recent research has indicated that pH is also a reliable method of diagnosing ACS and can theoretically be implemented in a more cost-effective manner than partial pressure of oxygen diagnostic methods [11]. The work of previous semesters was focused on selecting a suitable pH probe for use in humans and resulted in the selection of a solid-state pH sensor, the ISFET [8]. Restrictions require that the largest needle that can be inserted into a human patient is a 16 gauge needle, with tip inner diameter of 1.19 mm [12]. More information about the ISFET and its functioning can be found below.

ISFET pH Probes

ISFET probes are a special type of field-effect transistor (FET) which has a selectively permeable membrane that allows only H^+ ions across it [13]. This will eventually reach an equilibrium potential at which the concentration gradient caused by the lower $[H^+]$ on the FET side of the membrane (causing H^+ to enter the FET) is balanced by an electrical gradient produced by the solution's attempt to reach a concentration equilibrium (the influx of positive charge from H^+ entry repels other positively charged H^+ ions, opposing the concentration

gradient) [14]. The equilibrium potential serves as the gate voltage for the FET which regulates the current flowing from Drain to Source (see figure 3). The reference electrode is used to determine the equilibrium potential of the solution as a whole, not just of H^+, for comparison with the gate potential [13]. In this way, the ISFET accounts for any effect non-H^+ ions have on the gate potential, increasing the accuracy of the pH reading [13].

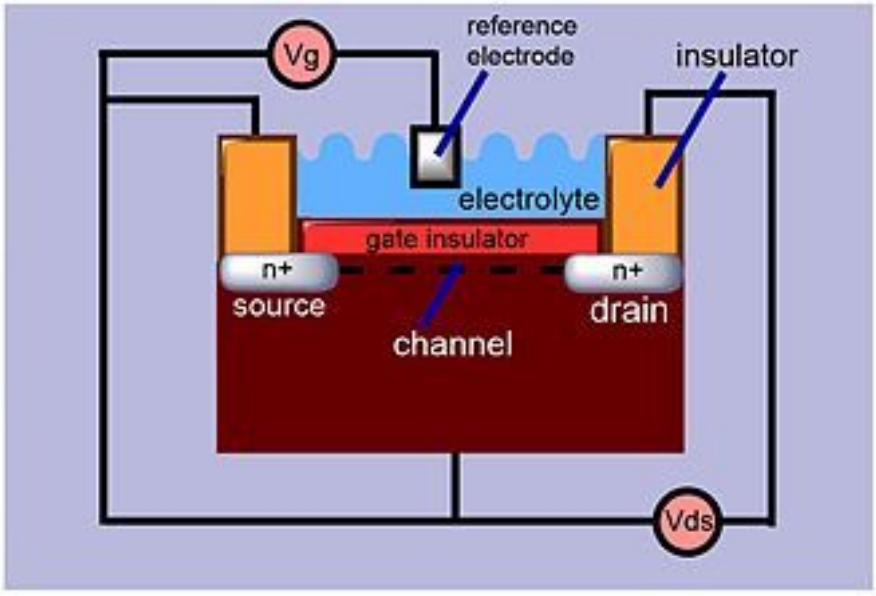

Figure 3: Structure of an ISFET pH probe [15]. The electrolyte develops the gate voltage which controls the current flowing between the drain and source terminals in a pH-dependent fashion. The reference electrode accounts for the contribution of the non-H^+ ions that may be contributing to the equilibrium potential.

Iridium Oxide pH Electrode

Iridium Oxide (IrOx) electrodes can also be used to detect pH [9]. When deposited on a substrate such as platinum (Pt) or platinum-iridium (Pt-Ir) wiring, it reacts with hydrogen ions in solution and can be used in combination with a reference electrode (such as Ag/AgCl) to get an

output voltage that has a linear relationship with pH [16]. The interaction between the IrOx layer and hydrogen ions in solution can be seen in equation 1 below.

$$2[IrO_2(OH)_2.2H_2O]^{2-} + 3H^+ + 2e^- \leftrightarrows [Ir_2O_3(OH)_3.2H_2O]^{3-} + 3H_2O$$

Equation 1: *Redox reaction between IrOx and solution*

This chemical equation governs the redox reaction occurring between the IrOx layer and hydrogen in solution. The number of electrons transferred for each hydrogen ion present can be used to determine the pH solution via a voltage measurement and the Nernst equation [16]. Consisting of merely two wires (the IrOx pH sensing electrode and the Ag/AgCl reference electrode), this pH sensing solution is extremely small in diameter and would fit easily within a 16 gauge needle for use in testing. However, no commercial solutions exist for this technology, and the methods required to fabricate it are complicated [16]. In order to pursue IrOx as a solution, fabrication must be undertaken by our group.

Preliminary Designs: User Interface

Initially, we believed the pH sensor from previous semesters would work and be used in the final prototype, meaning the majority of our design contribution would be integrating the ISFET into a device and begin testing. Thus, our preliminary designs focused on this aspect with the primary consideration being the user interface. The three candidates for this aspect were a touch screen, an LCD, and direct-to-cloud interfaces.

Design 1: Touchscreen Interface

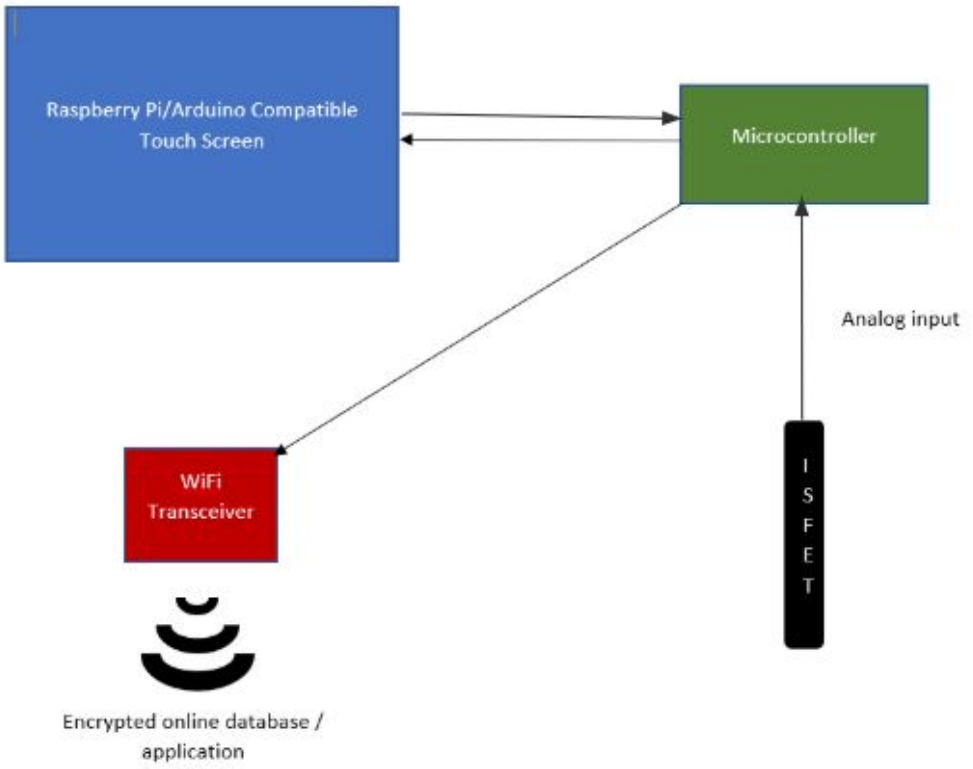

Figure 4: The first proposed design with a microcontroller which interfaces with the user through a touch screen display, and is capable of sending data over a Wi-Fi transceiver.

The first design is the "TouchScreen" Design, and uses a touch screen to interact with the user. A microcontroller determines the pH from the ISFET sensor and displays the signal on the touch screen user interface. The user can also set up a Wi-Fi connection which can upload the data to a cloud-based location, so it is viewable from multiple devices in real time. This would allow the user to monitor multiple probes simultaneously, and can determine the status of a case

from any location. This design emphasizes the value of a clinician having access to the data at all times, so a closer eye can be kept on a patient.

Design 2: LCD-screen Display

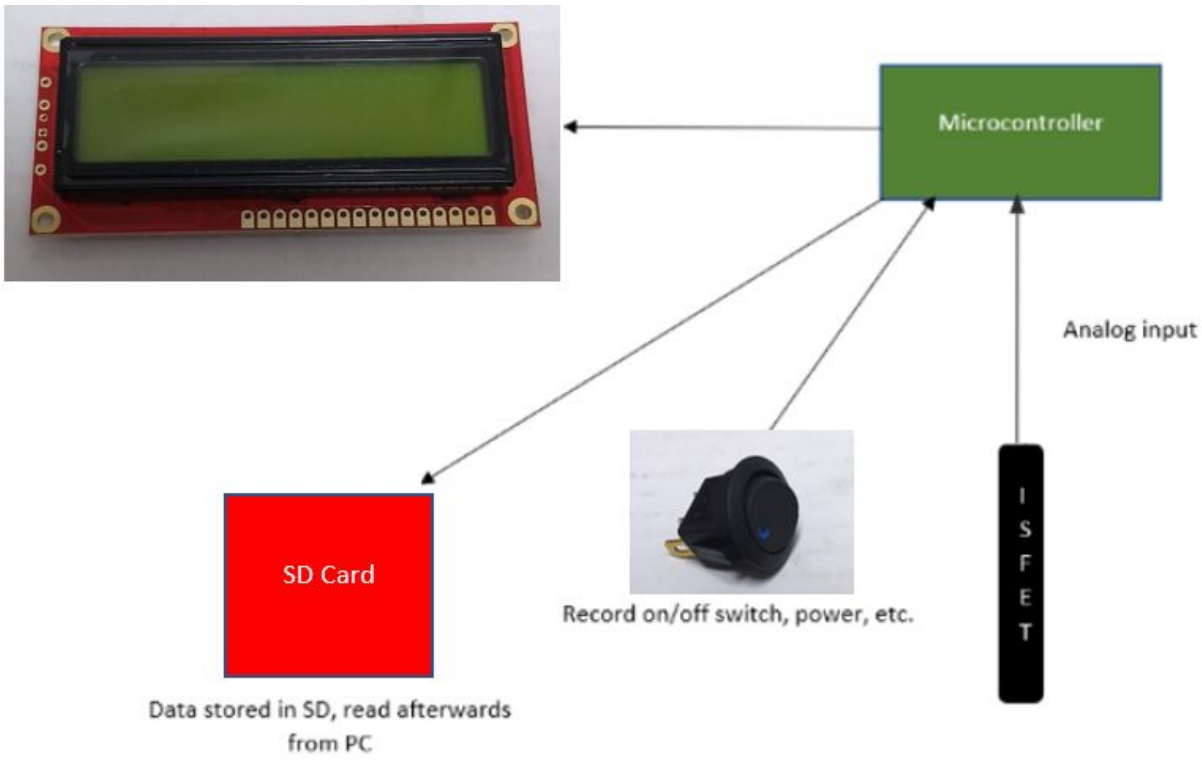

Figure 5: The layout of the LCD design which involves a microcontroller connected to the ISFET sensor, SD card Hub, LCD display, and power switch

The second proposed design uses a microcontroller to receive and interpret the signal from the ISFET sensor and displays the data in real time on an LCD display while saving the data simultaneously to an SD card, which can be reviewed later for clinical evidence. The entire circuit is controlled by a power on/off switch. The SD card will create folders to hold the data of each case and will be capable of recording data for at least 48 contiguous hours. The LCD design

aims to stress reliability and resilience by having simpler components, which can withstand more extraneous conditions while being less prone to failure. The drawback to this design is having a lack of accessibility to this information from multiple locations.

Design 3: Phone/Computer Interface

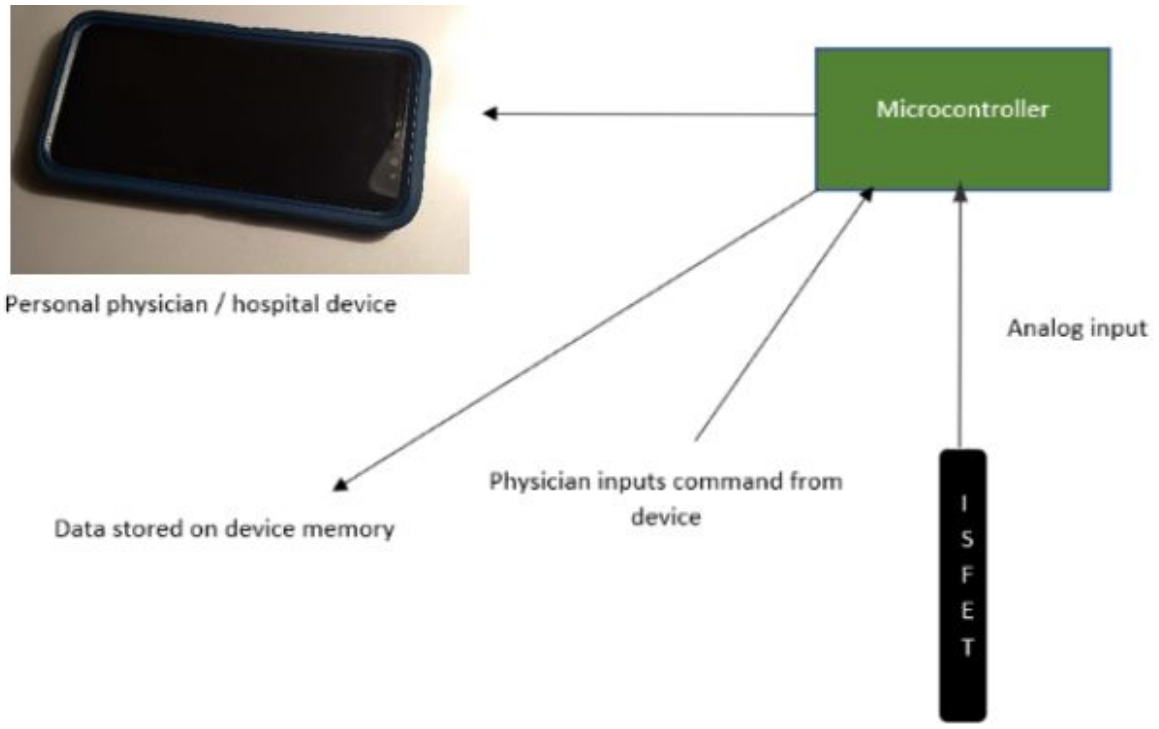

Figure 6: The third interface design that interfaces the user through the microcontroller with phone/computer.

The third interface design requires an application installed in the phone or computer that can either be personal physicians' or hospital devices. The physicians can use the application to start, view, save, and edit the pH recordings up to 48 hours. Once the ISFET is inserted into the muscle compartment, the physicians can input their command to start recording. The analog input from the ISFET sensor will be sent to the microcontroller which will display the digital

output on the devices. The pH recordings of the muscle compartment will be stored in the device memory thus giving an easy access for the physicians. This design aims to make it easier for physicians to obtain and view the data as needed. However, there is a concern about the patients' medical information security as these devices have the potential to be hacked.

Preliminary Design Evaluation: User Interface

Of the design criteria, reliability and safety merit the highest priority due to the nature of the device's intended use in humans. The device must generate values that are accurate and precise as a failure in this respect would endanger the health of the patient from false positives and false negatives. The device's reliability also takes into account the likelihood of unintentional data loss. The safety of the device was considered based on information security because the information being handled is medical in nature and thus, its transmission and storage has strict legal regulations. Resilience is the next highest priority since the device is intended for use in the high-stress environment of a hospital operating room and may be treated roughly by users under pressure. The portability criterion focused on the accessibility of the data for the physician and is also vital for use in an operating room setting. The ease of use criterion evaluates each design's ability to be used by someone without advance knowledge of the device's workings. The cost criterion was lowest priority due to the accessibility of funding from the client and the high cost of competing devices. While this is a high-priority consideration relative to other ACS diagnosis methods, the differences between the three designs are less of a concern.

Table 1: The design matrix of three preliminary designs of user interface with ratings for each category

Criteria	Touch	LCD	Phone/Computer
Reliability (25)	20	25	20
Safety (25)	20	25	15
Resilience (20)	13	20	15
Portability (15)	15	8	12
Ease of Use (10)	6	9	7
Cost (5)	3	5	4
Total (100)	77	92	73

The second design was our leading design and led every category except for portability. The LCD display is more reliable because it does not depend on wireless connectivity for operation, which reduces risk of data loss. The LCD is safer because it would have less user interaction, and it would require less sterilizing of the display. The Touch and Phone/Computer designs would get blood and other fluids on them from being used during procedures; furthermore, the Phone/Computer design would be carried with the doctor out of the hospital requiring extra precautions. Resilience is referring to the designs' ability to withstand normal operating stress, which includes wear/tear and dropping. The LCD has much simpler components, and the display has reduced risk of breaking compared to a touch screen. Portability, which was dominated by the touch screen followed by the phone/ computer, refers to how accessible this data is from multiple locations. The touch screen would use Wi-Fi to upload

this data and have it be accessible from any location while simultaneously displaying in real-time next to the patient. The Phone/Computer design uses bluetooth to send the data to an associated electronic device, so this can be moved throughout the operating room, but is still limited to within the necessary range of the bluetooth transceiver. The LCD data is displayed in real time by a wired connection to the arduino and can only be transferred by SD card, which gives it the lowest score in this category. The LCD is the easiest design to use because it requires minimal interaction from the user after being powered on. The Touch Screen and Phone/Computer would require the user to setup the proper connections prior to use. Finally, The LCD has the cheapest components, so it received a perfect score in the cost category.

Proposed Final Design: User Interface

The LCD interface design was chosen as the proposed final design due to its reliability, safety, resilience, ease of use, and low cost. This design has less complicated components which includes switches for record, and on and off, an LCD screen, an SD card, microcontroller, and the ISFET sensor. The sensor will record the pH readings in the muscle and send the analog input to the microcontroller and display the numbers on the LCD screen. At the same time, the pH values will be recorded in the SD card for up to 48 hours of recording. This interface design is simple and easy to use for clinicians, providing the important information at all times.

Preliminary Designs: pH Electrodes

The prototype will also focus on miniaturizing the previous prototype to match the requirement of being no larger than an 11 gauge needle for canine testing. The previous sensor was 3 mm in diameter, but the inside diameter of an 11 gauge needle is 2.388 mm [12]. Several pH electrode options were researched and their basic technologies adapted to suit our application best. This section discusses the advantages and disadvantages of each design and selects an optimal pH electrode setup to proceed with.

ISFET

The ISFET from previous semesters was too large for the maximum needle size, even without a reference electrode, and proved nonfunctional after multiple attempts to repair it. A smaller, functional ISFET probe was found which may be usable in the final design. The mechanism of ISFET functioning was discussed in the background section under "ISFET pH probes." The ISFET design uses an Ag/AgCl reference electrode made from the electrodeposition of chloride onto silver wire. The Ag/AgCl electrode is then attached to the backside of a Bare Die ISFET chip. The entire ISFET/reference assembly is placed near the tip of a stainless steel needle. The final prototype for this design can be found in figure 12. Figure 8 below is a microscopic image of the ISFET sensor used in the previous prototype without its housing.

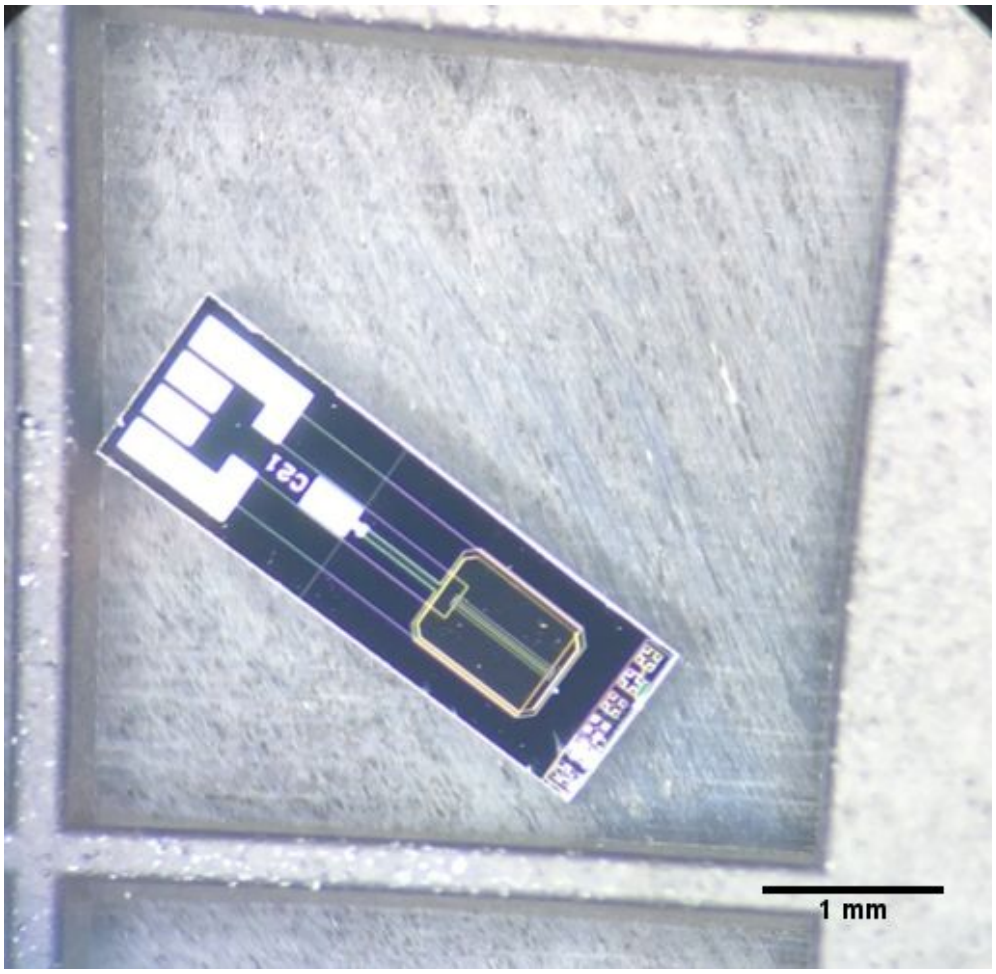

Figure 8: The micro ISFET bare die chip. This sensor is approximately 1mm in width and ~3mm in length. [17]

Winsense is a manufacturer from Thailand that makes a slightly bigger sensor that is 1.44 mm in width and 3.5 mm in length. [18] This would only provide .948 mm of additional room inside an 11 gauge needle (2.388 mm inner diameter) [12]. Next semester's research will be focused on creating an ISFET/reference configuration that will fit inside an 11 gauge needle for canine testing.

Platinum-Iridium

Using a Pt-Ir alloy wire with Iridium Oxide electrodeposited on it in conjunction with an Ag/AgCl reference electrode manufactured from an electroplated Ag wire, creates a potential between the two electrodes.[19] These two electrodes would be fed through a 16 gauge needle for insertion into the muscle compartment as seen in figure 9. The IrOx would be deposited on the Pt-Ir alloy wire by placing two Pt-Ir wires in a 4 mM aqueous $IrCl_4$ solution and cycling a voltage of 0 V and .55 V followed by pulsing between 0 V and .55 V for 1600 pulses at .5 seconds per pulse [19].

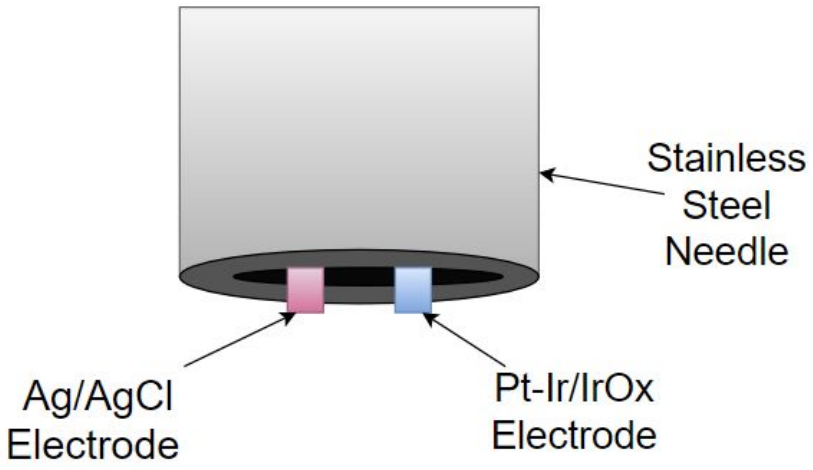

Figure 9: Design for a pH sensor that uses a Pt-Ir/IrOx pH electrode with a Ag/AgCl reference electrode inside a stainless steel needle

Iridium Coated Needle

To miniaturize the design of an iridium working electrode with an Ag/AgCl reference electrode, this design electroplates the stainless steel needed used for insertion and runs an

Ag/AgCl reference electrode through the needle as shown in figure 10. The needle would be plated using the same procedure used to coat the Pt-Ir wire, and Stainless Steel has been shown to be a suitable material for depositing IrOx [19].

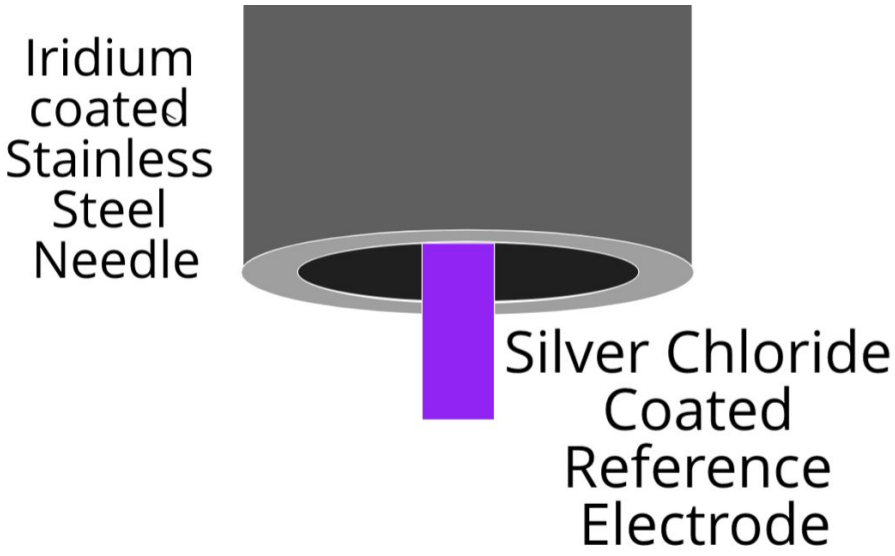

Figure 10: Design for a pH sensing needle that uses uses the needle as a working electrode with Ag/AgCl reference electrode.

Design Evaluation: pH Electrodes

To evaluate these three pH electrode options, we generated 5 criteria: size, fabrication complexity, ease of use, durability, and cost. Size and fabrication complexity are tied for the greatest importance given that a low score in either of these categories severely limits our ability to make a working prototype. Next is ease of use, which relates to the sensitivity of the electrode to pH - with greater sensitivity meaning that a larger voltage change is produced from the same change in pH - and the difficulty of integrating it into our prototype's circuitry. This criterion also heavily impacts the likelihood that we can make a working prototype. Durability is an

important consideration as this affects how well-suited the sensor is to our particular application. If the sensor has a low durability score, it is much more likely to fail during use, possibly with life-threatening results. Additionally, this criterion accounts for the device no longer works properly. In the case of the two options manufactured by us, this relates to the time before the electrolyte buffer begins to flake off the sensor or to become depleted. Last is cost, which, while important in all design situations, is less of a consideration for this project due to the low cost of the sensor and materials relative to our budget. Table 2 summarizes the scores of each design in each of these categories.

Table 2: Summary of the process by which the pH sensor designs were evaluated.

Criteria	**ISFET**	**Platinum-Iridium**	**Iridium-Coated Needle**
Size (25)	15	20	25
Fabrication Complexity (25)	10	20	20
Ease of Use (20)	20	15	15
Durability (20)	5	20	15
Cost (10)	10	5	7
Total (100)	60	80	82

Size

The ISFET design ranked lowest in this category due to the fact that the bare die's width of 1.44 mm has a small margin of fit within the inner diameter of a 11-gauge needle (2.388 mm)

[12]. The iridium-platinum wire design was ranked lower than the iridium-coated needle because it requires a second wire to be inserted into the needle where the iridium-coated needle does not.

Fabrication Complexity

The iridium-platinum wire and the iridium-coated needle both follow the same fabrication protocol and thus, were ranked equally in this category. They also ranked higher than the ISFET because fabrication of the ISFET design requires the use of a cleanroom to handle circuitry on such a small scale, making the process much more difficult.

Ease of Use

Here, the ISFET proved better than the other two designs because the fact that it is purchased means that it also comes with an analog front-end system that greatly eases the integration of the ISFET into any prototype circuitry. In this category again, the platinum-iridium wire is not significantly different from the iridium-coated needle. Both acquire their pH-dependent in the same way and thus, require the same noise reduction and signal amplification prior to integration with the prototype circuitry.

Durability

The ISFET also ranked lowest in this category due to the delicate nature of the electrical connections formed at the micro-scale in the cleanroom. The iridium-coated needle was lower in rank than the platinum-iridium wire because the iridium-coated needle has less protection from the shear stresses on the exterior of the needle during injection and removal. However, since the coating of iridium is chemically bonded to the needle, this is much less likely to impact the sensor performance than the weak electrical connections in the ISFET design.

Cost

The materials prices for the two iridium-based design options were all very similar, hence their very similar scores. The iridium-coated needle design is cheaper than the platinum-iridium wire design because it doesn't require a platinum-iridium wire. However, the ISFET design would actually be cheaper than either of the iridium-based designs, hence its high score in this category.

Total

The ISFET's low ranking in almost every category leads to the unsurprising conclusion that it is the worst of the three designs. However, the similarities in design and ranking of the other two designs led to a correspondingly close score gap between the iridium-coated needle and the platinum-iridium wire. The iridium-coated needle's advantages in size and cost overcame the platinum-iridium wire's minor advantage in durability, resulting in the proposal that the final prototype follow the iridium-coated needle design.

Fabrication/Development Process

Due to extended lead times on shipping components for the fabrication of the IrOx electrodes, we opted to test different Ag/AgCl reference electrode options. This way, we ensured that one reference electrode could be used as a definitive benchmark against which the sensing electrode voltage will be tested in the future. We fabricated an Ag/AgCl reference electrode using electrodeposition method and compared with the ones obtained from the Winsense kit and the 450μm-diameter from the World Precision Instruments[20]. A list of materials can be found in table 1 of Appendix C.

Methods

The steps of fabricating the Ag/AgCl reference electrode through electrodeposition are described as below [21]:

1. A thin and thick Ag wire are prepared and rinsed with ethanol to remove finger oils
2. 3M of KCl (22.3 g) solution is prepared with 100 ml of deionized water and stirred until dissolved.
3. Both wires are immersed in the KCl solution. The thin Ag wire is connected to 680 Ω resistor and the positive terminal (act as anode) and the thick Ag wire is connected to the negative terminal (act as cathode).
4. 1.5 V is passed through the circuit for 10 minutes until the thin Ag wire changed to purple-black color.
5. The fabricated Ag/AgCl electrode is then wiped and stored.

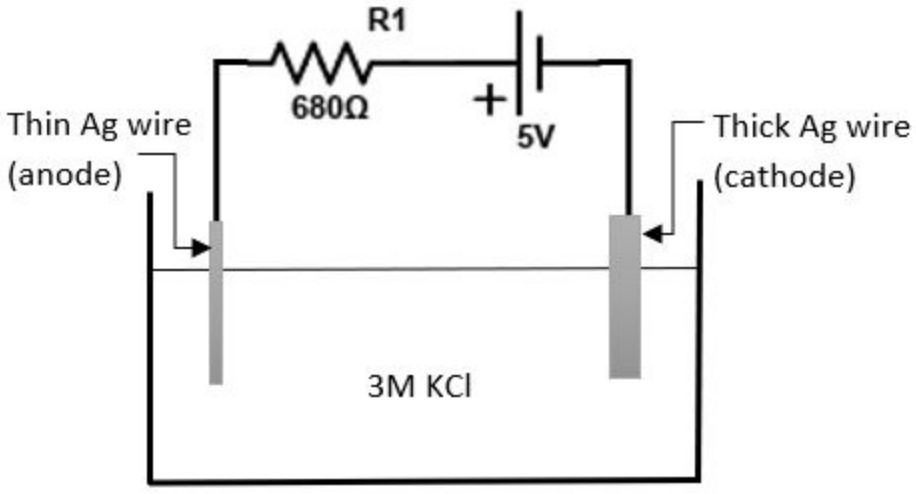

Figure 10: Setup of Ag/AgCl electrodeposition.

Figure 11: Electrodeposited Ag/AgCl reference electrode alongside a human hair.

Two wires are then soldered on the PCB with the Winsense ISFET chip specifically with the drain and source connections. The electrodeposited Ag/AgCl reference electrode is attached to the ISFET with heat shrink. Other than to secure the reference electrode in place, the heat shrink is also used to protect the solder part and to minimize the drain and source corrosion. The ISFET sensor and the reference electrode are then connected to the analog front end which functions to measure the voltage.

Final Prototype

The final setup of the ISFET apparatus includes the Winsense ISFET sensor and the electrodeposited Ag/AgCl reference electrode attached with heat shrink, a multimeter, and an analog front end. There are five pin connections on the analog front end which include: +V, the output voltage terminal; D, the drain input terminal; S, source input terminal; G, the reference electrode terminal; and GND, the ground terminal. The +V and GND terminals are connected to the multimeter to read the voltage, the G terminal to the reference electrode and the D and S

terminals to the drain and source wires of the ISFET respectively.

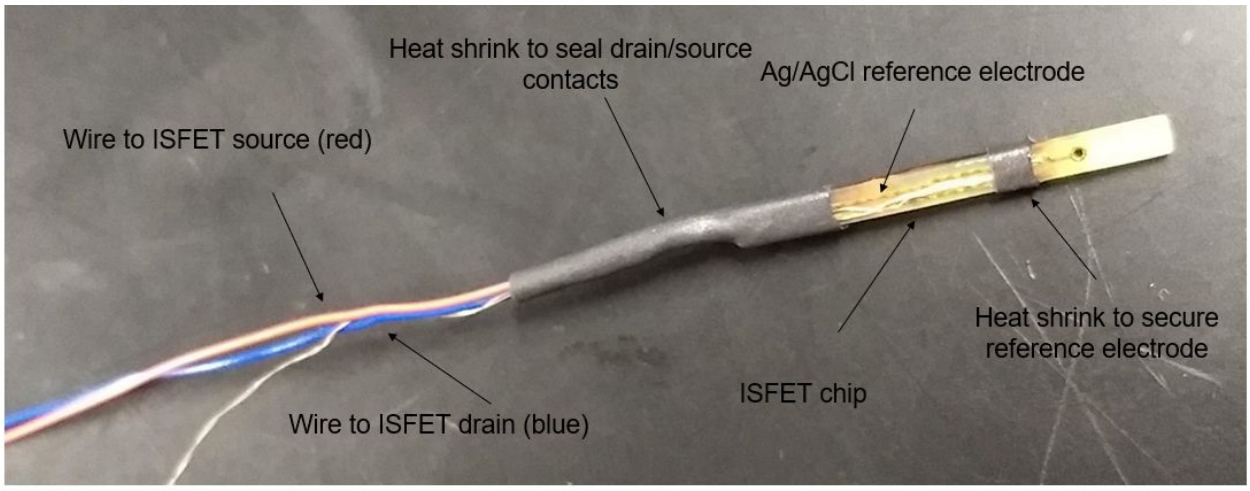

Figure 12: ISFET probe attached with the electrodeposited Ag/AgCl reference electrode. Both are sealed with heat shrink to secure the reference electrode in place and protect the source and drain connections.

The ISFET sensor and the electrodeposited Ag/AgCl reference electrode need to be calibrated before using. The whole ISFET apparatus was first rinsed in deionized water and wiped dry. It was then put into buffer solutions with pH of 4,7, and 10. The voltage readings were obtained from each solution and plotted the regression line. The pH equation can then be obtained from the linear regression equation (Appendix B).

Testing

The main challenge of this design is to find the smallest and reliable reference electrode for the ISFET sensor. The reference electrode is important to complete the electrical circuit and provide a stable reference potential. Therefore, an ISFET sensor drift test is conducted with three different Ag/AgCl reference electrodes (see Appendix B for data).

- ISFET sensor drift test

The goal of this test to determine which reference electrode provide stable and accurate reading of voltage/pH when immersed in pH 7 buffer solution for 1 hour. The Ag/AgCl reference electrodes used include the ones obtained from Winsense kit, the 450μm-diameter, and the electrodeposited electrode. Each reference electrode is first cleaned with deionized water and calibrated as described in the *Final Prototype* section. The reference electrode was then left in the pH 7 buffer solution and recorded the voltage reading using the multimeter for every 10 minutes (1 hour duration). Based on the voltage measured, the drift from the neutral pH reading was observed. If big drift is observed, the reference electrode might not be reliable to record accurate pH readings for a long period. Specifically because, one of the requirements of this design is to measure the pH for 48 hours. Therefore, this design will evaluate the reliability of the sensor for a longer application. In the future, we will leave the sensor in the buffer solution for 48 hours to observe any voltage drift.

Results

The Ag/AgCl reference electrode testing revealed that most of the electrode types tested had very little drift over the course of an hour (Appendix B, Figure 2). To ensure that we were selecting the best electrode, however, we calculated the standard deviations of each electrode's drift data and determined that the Winsense kit electrode and the electrodeposited electrode had similar values of 0.04 and 0.07 respectively, compared to a standard deviation of 0.2 for the 450 μm electrode (Appendix B, Table 4). Though the kit electrode had a lower standard deviation, the electrodeposited electrode is much thinner and can be made much longer than the kit

electrode, so it has been selected as our best option moving forward. Additionally, the kit and electrodeposited electrodes had a negligible difference in standard deviation, lending further support to the decision to select the electrodeposited electrode.

Discussion

As can be seen in Appendix B, the electrodeposited Ag/AgCl reference electrode is more accurate and has greater precision over time than the 450 µm Ag/AgCl reference electrode, the smallest commercially available electrode of its kind. When combined with a pH-sensing electrode of similarly miniscule proportions, it forms the smallest pH measuring device on the market.

The information obtained from this device may be used unethically or the research conducted with this device may be performed unethically. While we cannot control the actions of researchers using our device, we intend to seek IRB approval for the testing of the device in dogs and humans to ensure the research process is as ethical as possible.

The PCB-mounted ISFET used in the final prototype proved too large for the 11-gauge needle for animal testing, let alone the 16-guage needle required for use in humans. While the PCB-mounted version of the ISFET was much easier to implement in the prototype, it does not meet the design requirements and thus, an alternative solution needs to be developed. Next steps include the development of the iridium-coated needle design which scored highest in the evaluation of pH-sensing electrode designs. This was delayed beyond the scope of this semester due to shipping issues but will be done immediately at the beginning of next semester.

Some sources of error in the testing of the pH probes include the waterproofing of the final prototype, and the thoroughness of ethanol washing of the silver wires prior to electrodeposition. If the device's waterproofing was not thorough enough, it could result in electrical faults that damage the internal circuitry of the analog front-end system. The external signs of this damage could have presented themselves in an unobtrusive manner, allowing them to compromise the accuracy and safety of the device without being noticed. The possibility of incomplete ethanol cleansing of the silver wire prior to electrodeposition would at worst result in premature flaking of silver chloride from the Ag/AgCl electrode. This premature flaking would make the drift of the electrodeposited wire greater than anticipated. However, since the drift of this electrode was already very low relative to the other electrodes tested, rectifying this hypothetical mistake would only afford a minor improvement.

The final source of error comes from the fact that the pH drift testing lasted only one hour due to time constraints. The final product will ideally be capable of continuous pH monitoring for up to 48 hours, meaning this one hour of drift testing is very unlikely to be representative of the drift over the course of 48 hours. Conducting a full 48 hour drift test is another part of the plans for next semester which will address this concern.

Conclusions

Acute compartment syndrome occurs when the pressure within the closed compartment increases which will impair local circulation and eventually lead to muscle ischemia and death [1]. Current methods used to diagnose this condition, such as pressure and oxygen, can be inaccurate and expensive [5][6]. Based on the research by our client and past design teams, pH

diagnosis has been shown to be more accurate, reliable and can likely be implemented with less cost. Therefore, the main goal of our design to develop a device that is capable of measuring the intramuscular pH of the muscle compartment that relate to ACS, which is between pH of 5 to 7. The device should also fit inside a 16 and 11 gauge needle for testing with humans and dogs, respectively. Following the past design team, we used the ISFET sensor and the electrodeposited Ag/AgCl electrode as our proposed final design. However, the size of the whole ISFET apparatus is still too big to fit inside the 11-gauge needle due to thickness of the heat shrink.

Our team did consider other non-ISFET design that is smaller in size, but due to time constraint, we decided to use the ISFET sensor we currently have for testing with multiple reference electrodes. Therefore, for our future work, we will further minimize the current design to fit 16-gauge needle by fabricating a non-ISFET design incorporating IrOx. This design coats the stainless steel needle with IrOx to act as a pH sensor and inserts the electrodeposited Ag/AgCl reference electrode inside it. This design will surely minimize the size of the sensor and fulfill the design requirements. However, due to the flaking of the current electrodeposited reference over time, we will need to coat a thicker AgCl around the Ag wire for longer application. The pH sensor device will then undergo a 48-hour drift test to ensure its reliability and stability to maintain a constant pH/voltage in neutral buffer solution. We will also fabricate the proposed LCD interface design to display, manipulate, and store the pH readings. Finally, we will test the pH sensor inside the muscle compartment of a dog.

References

[1] Olson, Steven & Glasgow, Robert. “Acute compartment syndrome in lower extremity musculoskeletal trauma*,” J Am Acad Orthop Surg*. 13: 436-444. The Journal of the American Academy of Orthopaedic Surgeons. 13. 436-44, 2005.

[2] M.M. McQueen, P. Gaston and C.M. Court-Brown. “Acute Compartment Syndrome,” *The Journal of Bone and Joint Surgery,* vol. 82, no. 2, 200-203, March 2000.

[3] C. Doro, private communication, Sep 2019.

[4] A. Whitney, R. V. O’Toole, E. Hui, M. F. Sciadini, A. N. Pollak, T. T. Manson, W. A. Eglseder, R. C. Andersen, C. Lebrun, C. Doro, and J. W. Nascone, “Do one-time intracompartmental pressure measurements have a high false-positive rate in diagnosing compartment syndrome?,” *Journal of Trauma and Acute Care Surgery*, vol. 76, no. 2, pp. 479–483, Feb. 2014.

[5] D. Purcell, B. A. Terry, and B. R. Sharp, “Acute Compartment Syndrome,” in *Emergency Orthopedics Handbook*, D. Purcell, S. A. Chinai, B. R. Allen, and M. Davenport, Eds. Cham: Springer International Publishing, 2019, pp. 79–85.

[6] Odin Technologies, “The Valkyrie: A non-invasive diagnostic device for monitoring blood flow in trauma patients.” Electronically accessed from https://www.odinhealthtech.com Oct 8, 2019

[7] T. Ueno, A. R. Hargens, and W. T. Yost, “Method and apparatus to assess compartment

syndrome," US7381186B2, 03-Jun-2008.

[8] W. Bacon, M. Austin, K. Murphy, and A. Goodman, "Improving Acute Compartment Syndrome Diagnostic Technology with an Ion-Sensitive Field Effect Transistor," in *Sensors*, 2019

[9] S. A. M. Marzouk, S. Ufer, R. P. Buck, T. A. Johnson, L. A. Dunlap, and W. E. Cascio, "Electrodeposited Iridium Oxide pH Electrode for Measurement of Extracellular Myocardial Acidosis during Acute Ischemia," *Analytical Chemistry*, vol. 70, no. 23, pp. 5054–5061, Dec. 1998.

[10] J. W. Weick et al., "Direct Measurement of Tissue Oxygenation as a Method of Diagnosis of Acute Compartment Syndrome," Nov-2016. [Online]. Available: https://www.ingentaconnect.com/content/wk/jot/2016/00000030/00000011/art00008. [Accessed: 08-Oct-2019].

[11] S. T. B. Challa, A. R. Hargens, A. Uzosike, and B. R. Macias, "Muscle Microvascular Blood Flow, Oxygenation, pH, and Perfusion Pressure Decrease in Simulated Acute Compartment Syndrome," Journal of Bone, vol. 99, no. 17, pp. 1453–1459, Sep. 2017.

[12] "Syringe Needle Gauge Chart," Sigma-Aldrich. [Online]. Available: https://www.sigmaaldrich.com/chemistry/stockroom-reagents/learning-center/technical-library/needle-gauge-chart.html. [Accessed: 11-Dec-2019].

[13] C.-S. Lee, S. K. Kim, and M. Kim, "Ion-Sensitive Field-Effect Transistor for Biological Sensing," Sensors, vol. 9, no. 9, pp. 7111–7131, Sep. 2009.

[14] E. Widmaier, H. Raff and K. Strang, Vander's Human Physiology: The Mechanisms

of Body Function, 14th ed. New York City: McGraw-Hill Education, 2016, pp. 516-517.

[15] Grour T., Najari M., Mehdi A., and Lassaad El Mir Mabrouk (2018). Graphene field-effect transistor for pH sensing application: Compact modelling and simulation study. [online[Research Gate. Available at: https://www.researchgate.net/figure/Structure-of-the-Gr-ISFET-with-Aluminum-oxide-Al2O3-sensing-film_fig1_325804457/ [Accessed 2 Oct. 2019].

[16] M. Khalil, S. Wang, J. Yu, R. L. Lee, and N. Liu, "Electrodeposition of Iridium Oxide Nanoparticles for pH Sensing Electrodes," *Journal of The Electrochemical Society*, vol. 163, no. 9, Jun. 2016.

[17] Sentron.nl. (n.d.). *ISFET pH-sensor kit*. [online] Available at: https://www.sentron.nl/files/9014/9441/6231/pH-kit_leaflet_rev03.pdf [Accessed 9 Oct. 2019].

[18] Winsense.co.th. (2019). *Winsense ISFET pH Sensor (WIPS) Product Datasheet*. [online] Available at: http://www.winsense.co.th/item/item_image/winsense_isfet_ph_sensor_wips_datasheet.pdf [Accessed 9 Oct. 2019]

[19]R. D. Meyer, S. F. Cogan, T. H. Nguyen, and R. D. Rauh, "Electrodeposited iridium oxide for neural stimulation and recording electrodes," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 9, no. 1, pp. 2–11, Mar. 2001.

[20] World Precision Systems. “Micro Dri-Ref Reference Electrode.” [Online]. Available: https://www.wpiinc.com/driref-450-micro-dri-ref-reference-electrode

[21] Clark, J., Neuman, M., Olson, W. and Webster, J. (2010). *Medical instrumentation*. 4th ed. New York, N.Y.: Wiley, pp.7-10.

Appendix A:

Product Design Specification

pH Probes to Diagnose Compartment Syndrome

Date: 26 September 2019
Team Members: Jonah Mudge, Lucas Ratajczyk, Hunter Huth, Nur Saidin
Advisor: Dr. Amit Nimunkar
Client: Dr. Christopher Doro

Function:

The pH probe interface must reliably display the pH level read by an ISFET sensor, and record it on a screen that is easily usable by a surgeon. It must be capable of recording pH data for a clinically relevant time period, while ensuring that no data or timestamps are lost. The device must also feature buttons (on a touch screen or otherwise) that are simple and reliable for a surgeon to interact with quickly, especially in high-stress situations in an OR. Along with probe interface is the ISFET probe casing, which must be able to fit into a 16 gauge needle while allowing accurate pH readings.

Problem Statement:

Compartment syndrome is a difficult-to-diagnose condition that occurs when tissue pressure in a muscle compartment rises enough to cause ischemia and possible muscle death. False-positive diagnosis of compartment syndrome can lead to expensive, invasive surgeries, and unnecessary surgeries. Our goal is to design and test a device for clinical use capable interfacing with an ISFET probe and measuring the pH within a muscle compartment, and using the pH as a reliable indicator of whether compartment syndrome is actually occurring.

Client requirements:

- Create a device capable of measuring intramuscular pH *in vivo*

- The device must be able to record at least 48 hours of pH measurements
- The device should be minimally invasive

Design requirements:

1. Physical and Operational Characteristics

a. Performance requirements:

- The probe should accurately measure the pH that relates to compartment syndrome that is within the range of 5 to 7.
- The probe must continuously record the pH inside the compartment up to 48 hours.

b. Safety:

- The electronics should not cause electrical shock to the user or patient.
- The device should not cause any infection to the muscle compartment.
- The device should not dissociate or fragment during compartmental insertion.
- The device must not release toxic materials into the patient.
- The device must be sanitizable to prevent transfer of infectious material.

c. Accuracy and Reliability:

- The device must be able to acquire the signal from the ISFET probe without noise
- pH read from the probe must be accurate within a range of 5 - 7
- Accuracy must be within 0.5 to ensure accurate readings and diagnosis

d. Life in Service:

- The probe must maintain its structure and function over many daily uses.
- The probe is disposable for a single use but the electronics of the pH sensor should last at least 5 years.
- The electronic systems must be resilient for repeated use without breakdown.

e. Operating Environment:

- The probe must survive insertion into a muscle compartment without shattering
- The probe casing must not degrade or otherwise allow any leakage into the muscle compartment during insertion and monitoring
- The main analyzer/probe interface must be able to survive falls in the case of an accidental drop
- The main analyzer/probe interface must be able to weather small spills of bodily fluids or chemicals that might occur during an OR situation

f. Ergonomics:

- The handheld probe interface should be shaped in a form that is easy to hold and does not pose any risks of injury from dropping

g. Size:

- The probe must fit through the hole of a 16 gauge needle and 11 gauge needle for human application and canine testing, respectively.
- The handheld portion of the device must not exceed a prism of the size 8”x8”x3”

h. Weight:

- The probe must not exceed 2 ounces in weight
- The handheld portion of the device must not weigh more than 16 ounces

i. Materials:

- Semiconductor for the probe
- Metal for the wiring to and within the handheld device
- Hard plastic for the housing of the handheld portion of the device

j. Aesthetics, Appearance, and Finish:

- Skin safe coating and material for use inside the body (muscle compartment)
- The device should be intuitive and simple to understand and operate
- The coating of the handheld portion of the device should have a rough texture to allow for better grip in time-sensitive situations

2. Production Characteristics

a. Quantity: 1 (prototype)

b. The budget is dependent upon grants received by the client with minimum immediately available funds exceeding $1,000

3. Miscellaneous

a. Standards and Specifications:

- The size of the needle is limited to a 16-Gauge needle to align with standards for use in trauma patients.

b. Customer:

- Customers (practicing trauma doctors) would desire a pH sensor that is placed inside a 16-gauge needle, which can read the real-time pH inside the muscle

compartment of a patient who is at risk for compartment syndrome.

c. Patient-related concerns:

- The device must have a detachable and replaceable needle/sensor. The display and electronics casing should be sterilizable with an alcohol.
- Material of the device doesn't cause an inflammatory response, which could further increase pressure in the limb.

d. Competition:

- The Valkyrie by Odin Technologies uses Near-infrared spectroscopy to estimate the blood oxygenation. This device has a benefit of being completely non-invasive, but this technology has been around for decades without success in accurately diagnosing compartment syndrome.
- Patent (US7381186B2) by NASA is a system which uses the reflections of ultrasonic waves emitted into the compartment to estimate compartmental pressure.

Appendix B: Testing

Example linear regression for calibration

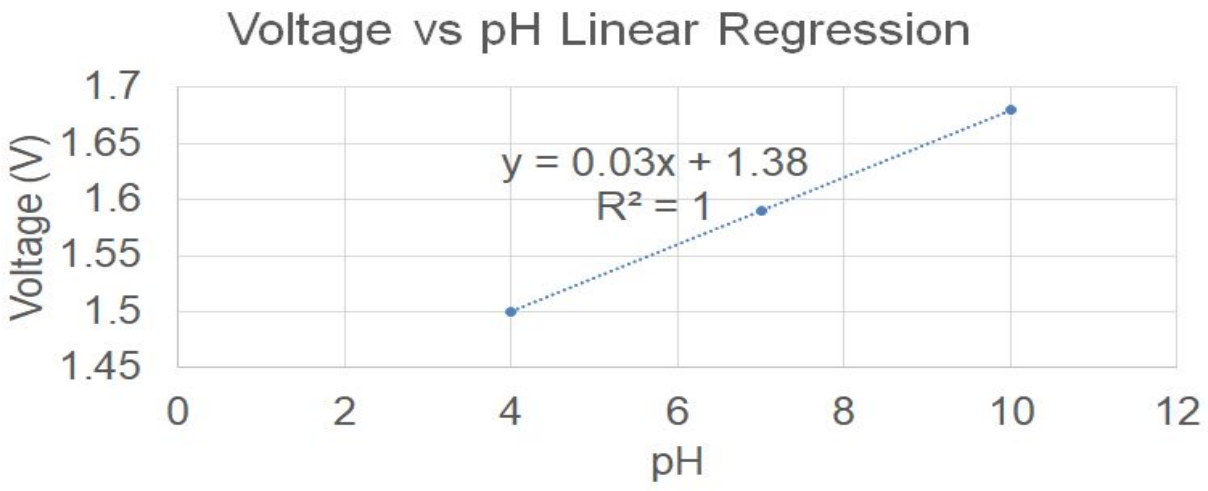

Figure 1: The linear regression plot of voltage vs. pH obtained when immersing the ISFET sensor and electrodeposited Ag/AgCl electrode in buffer solutions with pHs of 4, 7, and 10, once each.

Winsense kit electrode

Table 1: Data acquired from 1 hour drift test on kit electrode at 10 minute intervals. See Combined Data section for trendline.

Kit electrode 1 hr drift test (pH = 7)		
Time (min)	Voltage	Kit electrode
0	1.383	6.96699
10	1.38	6.908738
20	1.378	6.869903
30	1.378	6.869903
40	1.382	6.947573
50	1.382	6.947573
60	1.382	6.947573
pH = (voltage - 1.0242) / 0.0515		

Electrodeposited electrode

Table 2: Data acquired from 1 hour drift test on electrodeposited electrode at 10 minute intervals. See Combined Data section for trendline.

Electrodeposited electrode 1 hr drift test (pH = 7)		
Time (min)	Voltage	Electrodeposited electrode
0	1.59	7
10	1.593	7.1
20	1.594	7.133333333
30	1.595	7.166666667
40	1.596	7.2
50	1.596	7.2
60	1.595	7.166666667
pH = (voltage - 1.38) / 0.03		

450 Micron electrode

Table 3: Data acquired from 1 hour drift test on 450 micron electrode at 10 minute intervals. See

450 micron electrode 1 hr drift test (pH = 7)		
Time (min)	Voltage	450-micron electrode
0	1.364	7.160877514
10	1.373	7.325411335
20	1.38	7.453382084
30	1.384	7.526508227
40	1.387	7.581352834
50	1.391	7.654478976
60	1.395	7.727605119
pH = (voltage - 0.9723) / 0.0547		

Combined Data

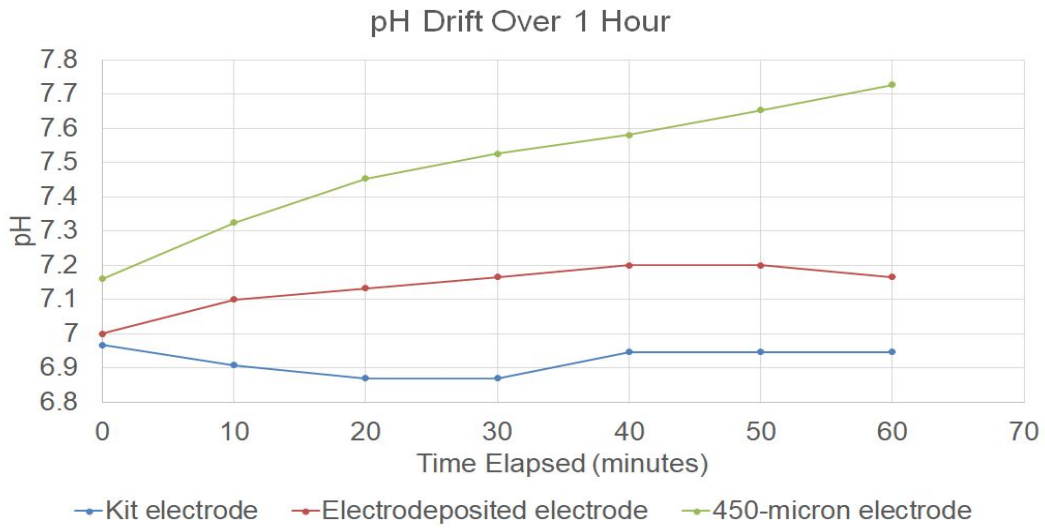

Figure 2: pH drift of each reference electrode in combination with the ISFET over one hour. The 450 micron electrode (green) displays a much higher standard deviation and variance than the other two electrodes.

Table 4: Standard deviations of each electrode acquired from the drift tests. The 450 micron electrode displays a much higher variation than the other two electrodes.

Reference Electrode	Calculated Std Dev
Kit	0.04
Electrodeposited	0.07
450 micron	0.20

Appendix C: Materials

Table 1: List of cost and quantities of the materials ordered. N/A denotes that a material was not ordered but was already possessed. The total cost was $769.85.

Purpose	Item	Quantity	Cost	Source
ISFET operation	ISFET complete Kit	1	$90.00	Winsense
	PCB mounted Bare die	1	$41.00	Winsense
	Bare die chip	1	$21.00	Winsense
Electrodeposition of IrOx on Pt-Ir wire	127 micron Pt-Ir wire	10 ft	$194.00	A-M Systems
	Iridium Tetrachloride	1g	$103.00	AmBeed
	30% Hydrogen Peroxide	1 L	$27.00	Lab Alley
	Oxalic Acid Dihydrate	100g	$26.50	Sigma-Aldrich

Electrodeposition of AgCl on Ag wire	127 micron Ag wire	10 ft	$48.00	A-M Systems
	Ethanol	N/A	N/A	N/A
	680 Ω resistor	N/A	N/A	N/A
	KCl	N/A	N/A	N/A
Testing of reference electrodes	Dri-Ref 450 Micron Ag/AgCl reference electrode	1	$206.00	World Precision Instruments (WPI)
Fabrication of user interface	LCD Screen	1	$16.95	Sparkfun
	Toggle Switch	1	$1.50	Sparkfun
	Record Button	1	$3.95	Sparkfun
	Arduino Nano	1	$14.95	Sparkfun