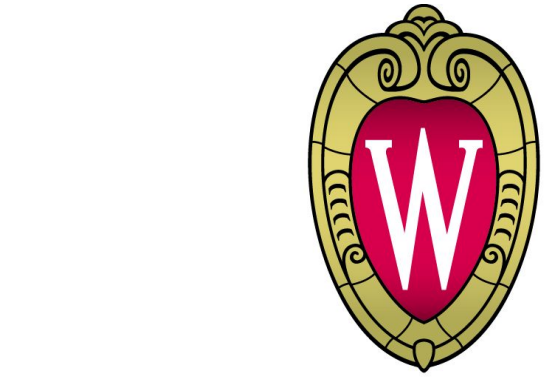

WISCONSIN

UNIVERSITY OF WISCONSIN–MADISON

Radiometric quantification of intramuscular pH to diagnose acute compartment syndrome (ACS)

Biomedical Engineering Design: 400

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October 10th, 2018

Client: Christopher Doro, MD

Advisor: Jeremy Rogers, P.h.D.

Abstract

Acute compartment syndrome (ACS) is a condition in which the pressure of the muscle compartment is increased significantly due to a traumatic event, most commonly a bone fracture. The consequences are a decrease in the pressure gradient of blood flow which prevents blood from entering the injured muscle, leading to cell anoxia, muscle ischemia and muscle death. Diagnosing ACS is problematic as current methods rely on the subjective assessments of clinical examinations and/or inaccurate intracompartmental pressure readings. These deliver unusually high false-positive diagnoses in trauma patients and often lead to the unnecessary and invasive surgical treatment of a fasciotomy. Recently however, it has been shown that alternative biochemical markers such as glucose and pH may lead to more a more accurate and concrete quantification of this condition. The aim of this project is to design a probe quantifies intracompartmental pH to diagnose ACS in humans by using optical fiber sensors. To accomplish this, we have developed and compared three potential prototypes that may exist within our design constraints. Our final design is an optically based pH probe that is biocompatible, accurate over a pH range of 6 to 7.5, able to continuously collect samples every 15 minutes, and insertable up to 5 cm into tissue. In creating a comprehensive diagnostic technology, we hope to eschew trauma patients from undergoing harmful and unnecessary surgery.

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Introduction

A. Motivation

Diagnosing acute compartment syndrome (ACS) traditionally utilizes subjective clinical examinations of trauma patients [1]. In recent years, an effort has been made to replace such qualitative measures with a method that's both accurate and reproducible. Intracompartmental pressure readings have shown some promise; however, quantifications may vary within the patients' compartments and a pressure threshold that defines ACS is not well defined [2,3]. Most alarmingly, these readings may falsely diagnose patients 35% of the time, thus a number of patients will undergo an unnecessary fasciotomy to treat their perceived ailment [4]. It is clear that a more accurate and definitive diagnosis for ACS must be explored to prevent needless and intensely invasive surgeries.

A. Current Methods

Currently, clinical examinations in combination with a pressure reading taken from the compartment are the standard for diagnosing patients with compartment syndrome (Fig. 1). This method is flawed as it has an unclear diagnosis threshold and is ultimately a subjective assessment performed by the medical professional. While this method displays 100% sensitivity, it produces false-positive diagnoses 35% of the time [4]. Experimental methods are being tested in the areas of near infrared oximetry, pH, glucose, and partial oxygen pressure measurements, some with more success than others [6]. One of the more promising alternatives for ACS diagnosis is interstitial pH quantification. The Orion™ 8133BNWP ROSS™ Combination Spear Tip pH Electrode, a Fisher Scientific product, has been utilized to diagnose adult beagles with intentionally onset compartment syndrome. The probe's tip is 3 mm wide, 40 mm long, and detects pH 0 - 14 ∓ 0.01, and is therefore not directly applicable in the human medicine setting [7]. Furthermore, Dr. Doro has shown that continuous glucose monitoring may unveil compartment syndrome in adult beagles [8]. A REAL-Time Guardian Continuous Glucose Monitoring System, Medtronic, (U.S. Patent No. 6,809,653) in conjunction with an Enlite™ Sensor, Medtronic, showed a significant difference in glucose levels between control and injured compartments. The sensor was 10 mm in length and must be calibrated for 90 minutes prior to use [9].

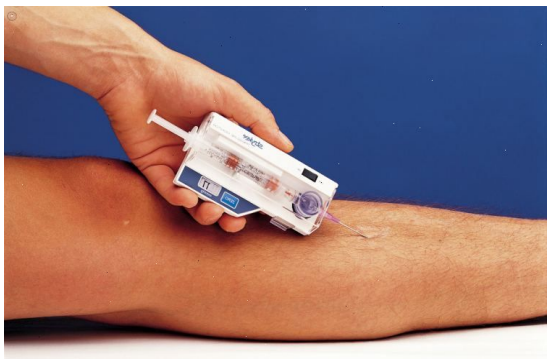

Fig. 1: Stryker pressure gauge for diagnosis of ACS. Pressure measurements are the current standard for diagnosing ACS, however, there is little consensus on the proper thresholds [5].

B. Problem Statement

Healthy patients diagnosed with ACS currently stand a 35% chance of undergoing an unnecessary fasciotomy. However, if an inflicted patient is left untreated, they stand a near certain chance of their inflicted muscle dying within eight hours. Due to the inaccuracy of diagnostic methods, surgeons frequently and wrongly attempt to save dying limbs by performing highly invasive surgeries. It is therefore imperative an more accurate, reliable, and novel diagnostic tool be developed to quantitatively and definitely decide the state of ACS in trauma patients.

Background

A. Preliminary Research

A compartment is a section within the body that includes a group of muscles and their nerves surrounded by a layer of inelastic fascia. These compartments are found all over the body, and there are multiple in each extremity (Fig. 2). Capillary beds across the compartment create a perfusion gradient, allowing blood to flow from high pressure to low pressure. This blood flow provides the muscles in the compartment with the nutrients they need to remain functioning. ACS is created when a serious injury, commonly a bone fracture or deep bruising, causes the inside of the nearby muscle compartment to swell. Since the fascia is unable to stretch, the pressure inside of the compartment rises and eliminates the perfusion gradient. Blood is no longer able to flow into the muscle because the pressure inside the compartment is no longer lower than the arterial pressure. This syndrome leads to cell anoxia, muscle ischemia, and eventually muscle death if not treated. A fasciotomy is performed to decompress the compartment, and if this is not performed in time, the patient will have permanent damage from Volkmann's Muscle Ischemia, which is death of the muscles within the compartment [11].

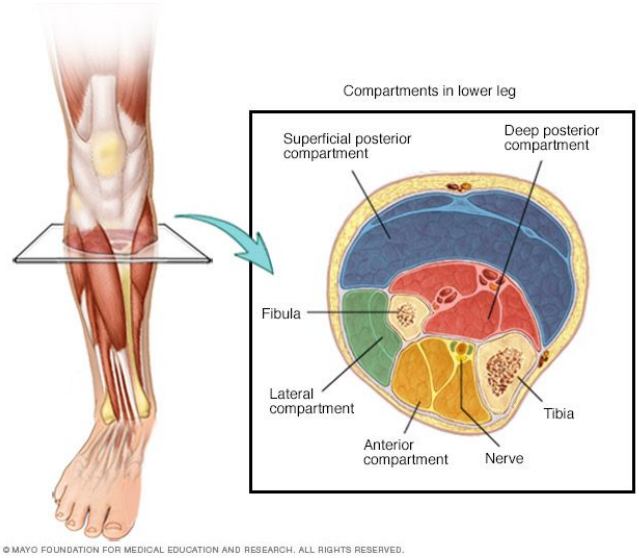

Fig. 2: The muscle compartments of the lower leg. Each muscle compartment consists of a group of muscles and the nerves and capillaries necessary to the muscles' function, surrounded by an inelastic fascia [10].

B. Design Research

Our client, Dr. Doro, has performed studies showing pH and glucose are effective biochemical markers for accurately diagnosing ACS. In Dr. Doro's experiments, a crude meat and cheese probe measured the intracompartmental pH in beagles with compartment syndrome. He found that the pH in an injured muscle can drop well below 7.1, a pH that would be fatal to a human [6, 12]. In a separate experiment, he used a Medtronic Enlite™ Sensor to measure the glucose of the canines. He concluded that the glucose level in the compartment essentially goes to zero [8]. Therefore, he highly encouraged that we try to build our probe measuring one of these biochemical markers. However, beyond Dr. Doro's initial research, he later informed us that potassium ions are a strong indicator of an increase in conductivity in the compartment. This is because dying muscle cells release potassium in mass quantities, which causes a major increase in conductivity. Therefore, potassium ions are also a potential biomarker to diagnose compartment syndrome.

In the spring semester of 2018, a previous team of BMEs working on this project decided to pursue the pH biomarker. Their literature searches showed that a glucose probe would have to be calibrated to each patient, which would increase both the length of the diagnostic procedure and leave more room for error. Unlike glucose, physiological pH is consistently 7.4 across all humans [12]. Therefore, a pH probe could easily be calibrated in a standard buffer solution.

The previous team also steered us towards the use of optical fibers as a potential light source and collection method. In terms of invasiveness, optical fiber diameters are on the scale of microns. This means there would be no issue inserting several of them, if necessary, through the 16 gauge needle. In theory, only two fibers would be needed. One would act as a light source and another would measure the amount of light transmitted.

C. Client Information

Our client, Dr. Christopher Doro, is an Orthopedic Surgeon at the UW Hospital. He has conducted his own research on compartment syndrome, mainly including the experimentation on dogs to test the effectiveness of biochemical markers, pH and glucose, as standards to diagnose compartment syndrome. He has concluded that these biochemical markers work well and has asked us to create a probe that effectively measures them in humans.

D. Design Specifications

The most important requirement for our design is that our probe is able to improve the current false positive rate of 35% for compartment syndrome by monitoring pH continuously and directly with readings being taken at least once every 10 minutes. The pH range of interest is 6 - 7.5. Additionally, the probe must be long and rigid enough to reach the muscle tissue (~1-5 cm) within a compartment in order to take measurements that are representative of the acidity in said compartment. The probe should also not create more discomfort for the patient nor a greater risk of infection, therefore the probe should be no larger than a 16 gauge needle. Medical staff must be able to use this device quickly, easily, and safely while in the chaotic environment of an emergency room. Finally, the device should ideally consist of two different parts: a disposable part that is cheap and readily available, and a reusable data collection component that is reasonably affordable. The total budget for this project is $10,000. Additional and more specific design requirements can be found under the Product Design Specifications in Appendix A.

Preliminary Designs

We developed the following designs as possible diagnostic probes. All of the designs involve a component that punctures the muscle compartment, and will be applicable to any given compartment. Depending on the location requiring diagnosis, the probe will penetrate where the black lines in Fig. 3 are drawn.

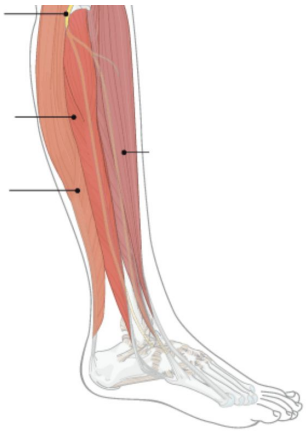

Fig. 3: Surgical reference of where the diagnostic device will be inserted into the patient. [13]

A. Hydrogel-Dye Microenvironment:

This design is composed of 7 major components: the optical fibers, the epoxy glue, the hydrogel, the pH indicator, the hydrogen-permeable membrane, the control circuit, and the outer casing. First, there are the two optical fibers that will extend into the compartment in a highly confined space. One optical fiber will be designated as the output optical fiber and shine light onto the pH indicator. The other optical fiber will be designated as the input optical fiber and will receive the light that is either reflected off or emitted from the pH indicator, depending on the exact indicator chemistry. Second, there is the epoxy glue that will serve to hold the optical fibers in place and maintain their structural stability. Third, there is the hydrogel that will be located at the end of the optical fibers. The hydrogel will serve two purposes: to allow light from the output optical fiber to pass through it relatively unimpeded and to immobilize the pH indicator. Fourth, there is the pH indicator. This indicator will change the intensity of light reaching the input optical fiber depending on the pH of the compartment that it is placed inside. Fifth, there is the hydrogen-permeable membrane that will allow for the passage of protons from the body to the pH indicator dye. This membrane will also serve as a biocompatible interface between the body and the indicator dye. Sixth, there is the control circuit. This will regulate the light being emitted from the output optical fiber, record the intensity of light from the input optical fiber, and perform calculations to correlate input light intensity to pH data. Finally, there is the outer casing. This casing will serve as a biocompatible barrier between the body and the contents of the probe, and it will also serve to hold the contents of the probe together. A complete diagram showing how all these components will be configured is shown below in Fig. 4.

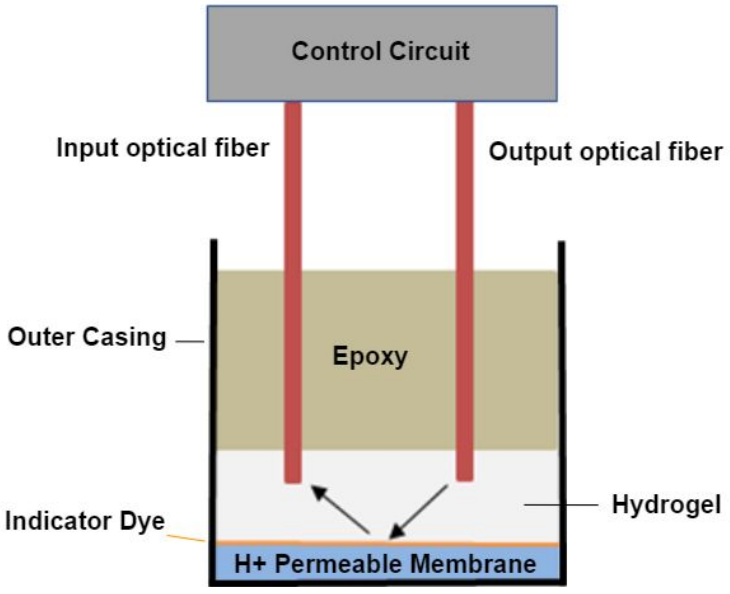

Fig. 4: Hydrogel-dye microenvironment design configuration

Overall this design will allow for safe and easy measurements of pH to be conducted by utilizing a compact design. One potential drawback of this design could be immobilizing the pH indicator dye on a hydrogel, as this could prove to be quite difficult chemistry for us to perform with our resources.

B. Reflective pH-Reactive Tape:

Using a theory congruent to the optical fiber measurement in the hydrogel microenvironment design, this design would also measure the change in intensity of reflected light coming from an output optical fiber. Additionally a similar control circuit to the hydrogel microenvironment design would be utilized since the same functions are desired from the control circuit in this design. The main difference between these two designs is the way in which the optical probes and the indicator dye are connected to each other and the way in which the pH indicator dye is immobilized. For instance, instead of a hydrogel-dye microenvironment, the indicator dye will be immobilized on a reflective, adhesive surface that is secured directly to the end of the optical fiber probe. This means that the pH-reactive tape could be tested with a commercially available probe since it is independent of the probe.

Additionally, the pH-reactive tape will consist of four layers as outlined in Fig. 5 shown below. The top and bottom layers are both securing adhesive layers that accomplish two functions. The first function, specific to the bottom layer, is to adhere the pH-reactive tape to the probe, and the second function is to hold all four layers together. The second layer from the top is the gold reflective mesh layer. This layer acts as a biocompatible intermediary between the body and the pH indicator dye since this mesh allows diffusion of protons through it, yet it is completely inert. Finally, the third layer from the top is the pH indicator dye. This dye will alter the intensity of the light reaching the input optical probe depending on the pH of the body.

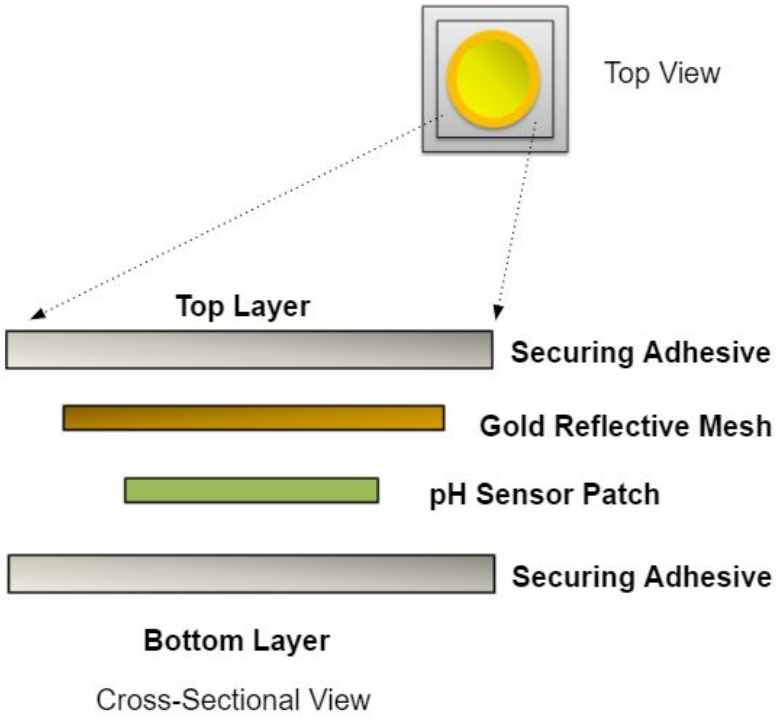

Fig. 5: Configuration of reflective, pH-reactive tape. The yellow circle represents a top view of the design. The four individual layers composing the tape can be seen in the cross-sectional view [14].

This design was based off of a current design utilized by Ocean Optics; however, their pH-reactive tape measures 0.50 inches in diameter making it far too large for our purposes [14]. Having said this, we can look to modify and miniaturize this design for our purposes. The greatest advantages to this design is that it allows for truly independent testing of the optical fiber portion and the biochemical portion of the design.

C. Microdialysis Chamber

This design is similar to the other two in that it relies on a pH indicator dye and spectrometry to determine pH; however, it differs from the other two in that the pH measurement will take place *ex vivo*. For this design, a minimally-invasive microdialysis probe will be inserted into the compartment of the patient. This microdialysis probe consists of three main parts: an inflow tube containing perfusate, a semipermeable membrane that allows for protons to be freely exchanged across it, and an outlet tube containing dialysate and the analyte. This configuration can be seen in Fig. 6 below. First, the inflow tube continually provides, which is a solution that closely mimics the composition of healthy surrounding tissue fluid. Second, a semipermeable membrane within the microdialysis probe allows for the constant exchange of protons, so that a pseudo-equilibrium can be achieved. Third, the outlet tube carries the pseudo-equilibrium solution out of the body and into a microdialysis chamber containing a known quantity of pH

indicator dye. From here, standard absorbance spectrometry can be performed using any number of commercially available spectrometry devices.

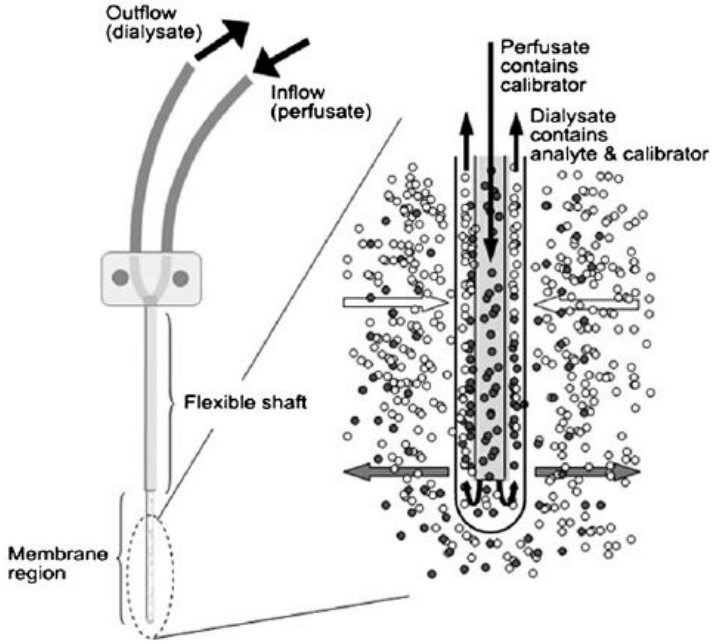

Fig. 6: Depiction of the microdialysis probe configuration as well as the microdialysis process [15].

This design is attractive because *ex vivo* measurement of pH would simplify the spectroscopy portion of the project greatly by removing the size limitations that come with *in vivo* measurement. Additionally, there would be no concerns of toxic pH indicator dyes interacting with the body. Conversely, calibration of this design could be quite difficult as a total equilibrium of protons is never reached within the body due to constant perfusate inflow. It also isn't known whether the microenvironment within the compartment affects the pH drastically, thus measuring pH *ex vivo* could result in incorrect data.

Preliminary Design Evaluation

A. Design Matrix Criteria (See Table 1 below)

Accuracy and Precision:

This ranking carries the most weight because of the current limitations of compartment syndrome diagnosis, which has a 35% false positive rate. Our new device must replace this current standard of diagnosis while still being 100% sensitive to true positives. The Hydrogel Microenvironment scored highest because the hydrogen-permeable barrier would expose the indicator to the pH within the compartment without influencing acidity.

Biocompatibility:

Biocompatibility refers to the inertness of the probe inside the body. It is ranked second-highest because the probe should not damage the surrounding tissues beyond the initial insertion. The Microdialysis Chamber scored the highest because the indicator would be outside the body, and it would involve simply removing fluid using an FDA-approved hypodermic needle.

Invasiveness:

Invasiveness refers to the degree of interaction between the probe and the inner body. Ideally, invasiveness would be minimized to decrease the amount of damage done to the patient's tissues. The nature of acute compartment syndrome and its diagnosis require an invasive procedure, so the device with the least invasiveness would score highest. All three probes, however, scored 9/15. Both the Hydrogel Microenvironment and the Reflective pH Tape would involve the insertion of an up to 16-gauge needle and an indicator container, a substance foreign to the body. The Microdialysis Chamber would not involve the insertion of an indicator, however, this method would require that fluid be removed from the body, which if done over a prolonged period could also injure the patient.

Ease of Reuse:

Ease of Reuse refers to how easy it is to prepare the device for reuse. This category encompasses either the ease of sterilization for designs that don't have replaceable parts or the ease of replacement for designs that have replaceable parts. The Reflective pH Tape and Microdialysis Chamber tied for the highest score in this category. The Reflective pH Tape would simply need to be disposed of and then another pre-made piece of tape adhered to the end of the probe. For the Microdialysis Chamber the entire analysis chamber could be reused, and only new dialysate solution and new needles would be needed for reuse.

Measurement Continuity:

Measurement continuity refers to how continuously we can receive pH measurements. The Hydrogel Microenvironment and Reflective pH Tape designs both received full marks in this category since they can be altered by the controlling circuit to be as continuous as we need.

Cost:

Cost refers to our ability to test and fabricate the probe within a reasonable budget. The disposable piece should be less than $100 to purchase, and the reusable part of the design should be less than $2000. This project is funded by a grant through the surgery department at UW-Health, therefore the budget is large, but does not have an official ceiling. The Reflective pH Tape scored highest because its parts (optical fibers, reflective tape, etc.) would be the cheapest to purchase and assemble.

Table 1: Evaluation of Proposed Designs

Criteria (Weight)	Hydrogel Microenvironment		Reflective pH Tape		Microdialysis chamber	
Accuracy and precision (35)	5	35	4	28	3	21
Biocompatibility (25)	4	20	4	20	5	25
Invasiveness (15)	3	9	3	9	3	9
Ease of Reuse(10)	2	6	4	8	4	8
Measurement Continuity (10)	5	10	5	10	3	6
Cost (5)	3	3	4	4	3	3
Total	83/100		79/100		72/100	

Table 1*:* Design matrix comparing potential devices including Hydrogel-Dye Microenvironment, Reflective pH-Reactive Tape, and the Microdialysis Chamber. Criteria are listed on the left next to their assigned weight. The total scores are out of 100, and the highest score represents the most feasible option with regards to the criteria.

A. Proposed Final Design

Based on our design matrix, we will move forward with the Hydrogel Microenvironment design for the remainder of the project. The Hydrogel Microenvironment design stands out for having superior accuracy and precision compared to the other designs. Additionally, it scored very well in biocompatibility and measurement continuity. The biggest knock on this design is its low reusability score, as continuously replacing a dye-filled hydrogel could be cumbersome. Despite this, the Hydrogel Microenvironment design accomplishes all the criteria outlined by our client, thus it should serve as an excellent blueprint to begin prototyping a probe.

Future Work

We will divide our future work into two phases based on the two-semester schedule of the class. Phase 1 (Fall Semester) will involve two separate project streams focusing separately on chemistry and physics. Phase 2 (Spring Semester) will integrate the two streams.

A. Phase I

Chemistry: The Hydrogel Microenvironment

We have selected 2',7'-Bis-(2-Carboxyethyl)-5-(and-6-)-Carboxyfluorescein (BCECF) as our pH indicator. BCECF is a synthetic, fluorescent pH indicator commonly used in physiological pH studies [16]. BCECF diffuses through extracellular fluid, and therefore will have to be immobilized within the probe to facilitate fluorescence measurement. As of right now, we are unaware of a protocol for immobilizing BCECF. We will continue our research by searching the literature and consulting with hydrogel and immobilization experts at ThermoFisher Scientific and the Beebe Lab at the University of Wisconsin-Madison. If we are unable to find a proper method for immobilization, we will look for another pH indicator.

Instrumentation: Data Collection and Processing

Once placed *in vivo*, the dye will change color based on the pH of the compartmental environment. Using optical fibers, we will expose the hydrogel and dye to a couplet of monochromatic "blinks" of light. Based on the pH, the dye will emit a certain amount of light. This will allow us to obtain a ratio of the amount of light received during each blink, from which we can calculate the absolute pH of the compartment. To obtain these readings, we will develop circuitry involving a photodiode and a bandpass filter to ensure that we get a clean signal. We will also write an Arduino code to process the signal and provide a pH measurement as an output.

B. Phase II

Assuming both project streams are successful during Phase I, in Phase II we will integrate the hydrogel microenvironment with the optical fibers and analytical circuit. Phase II will mainly consist of testing the results of this integration. Tests will include ensuring the microenvironment and optical fibers are sufficiently bonded to prevent breakage within the body, optimizing signal collection from the fluorescent dye, and calibrating and comparing the probe to other pH probes on the market.

Conclusions

The goal of this project is to develop a probe that monitors the intracompartmental levels of a biomarker to diagnose acute compartment syndrome. We have decided to use pH as the biomarker because of its consistency across humans and its ease of *ex vivo* calibration. Our proposed design is the Hydrogel Microenvironment. For the rest of the semester, we will develop the microenvironment and the instrumentation necessary to collect data from it.

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Appendix A: Product Design Specifications

Function:

Acute compartment syndrome (ACS), a dangerous condition in which the increased intracompartmental pressure (ICP) of a muscle prevents blood flow to the region, impacts many trauma patients and presents medical providers with perplexing dilemmas regarding the diagnosis and treatment of this condition. ACS diagnosis is most frequently based on clinical examination findings, but traditional measurements of intracompartmental pressure are unreliable and therefore commonly lead to misdiagnosis and unnecessarily invasive procedures. The goal of this project is to create a diagnostic tool that accurately, continuously, and easily quantifies biochemical marker associated with ACS. These markers – pH, glucose, or pyruvate – may expedite ACS diagnosis and prevent patients from receiving a false diagnosis and undergoing the trauma of a fasciotomy, the standard treatment for compartment syndrome.

Client Requirements:

- Design a probe to that can continuously measure and quantify specific biomarkers associated with acute compartment syndrome.
- The probe must be long enough to invade various muscular depths (1 in - 5 in)
- Probe must be cheap and preferably autoclavable before use (<$100 final prototype)
- The probe should be continuously analyzed by a main analyzer (8 hours of readings)
- The probe must be ergonomic for clinicians to operate (setup time 5 minutes)

Physical and Operational Characteristics:

a. Performance Requirements:

- The probe must be able to measure pH that directly relates to the presence of compartment syndrome in a patient (pH 6-7)
- The probe must be able to continuously monitor the biomarker (1 sample/15 minutes, 8 hours in total)
- The probe must be precise, so that there is a lower incidence of false positives (<34% of diagnoses) than the currently used pressure gauge detector while still ensuring that no cases of ACS are missed.

b. Safety:

- In order for the probe to be up to the current standard of care for detecting compartment syndrome, the probe, if being inserted to the patient, must be smaller than an eighteen gauge needle.
- Cannot cause an increase in discomfort for the patient.
- Cannot increase the risk of infection in the already wounded limb of the patient.

c. Accuracy and Reliability:

- The detector must accurately measure the specified biomarker/signal to avoid falsely diagnosing the patient. (pH 6-7, high sensitivity +/ - .01 pH)

d. Life in Service:

- The disposable probe should be used once per patient. This means from the time the patient enters the hospital until the patient is discharged.
- The main analyzer should be able to be reused for many patients, lasting six months.

e. Shelf Life:

- The main analyzer should have a shelf life of approximately 3 years
- The disposable probe should have a shelf life of 1 year.

f. Operating Environment:

- The probe should be continually monitoring the compartment in all situations.
    - The ER immediately following the patient's arrival into the hospital.
    - The second is the patient' hospital room.
    - Another possibility is into an operating room for possible surgery.

g. Ergonomics:

- Physicians must easily probe the patient with one hand while securing their limb with the other. Will be similar to administering a shot.

h. Size:

- The probe to detect compartment syndrome has to be small enough so a nurse can bring it into the ER and collect a reading efficiently within a crowded area surrounding a patient.
- Also, our client does not want it to "scare" the patient as the probe is getting data.
- Must be able to reach at least 4-5 inches into the body
- Must fit within an 18-gauge needle.

i. Power Source:

- The main analyzer will utilize standard wall outlets as a power source.

j. Weight:

- The probe will be roughly 5 ounces. The main analyzer will be roughly 1 pound, subject to change.

k. Materials:

- Invasive probe, pH meter, optical fibers, plastic box to house analyzer equipment, hydrogel, chlorophenol red indicator, indicator immobilization substrate

l. Aesthetics, Appearance, and Finish:

- The overall finish of the probe should not include any abrasive edges or jagged surfaces, which could injure the patient or doctor.
- The probe color will likely consist of neutral colors such as white, black, or grey.

Product Characteristics:

a. Quantity:

- One main analyzer compartment and many (20) reproducible probes to test on various subjects.

b. Target Product Cost:

- We have not been given a strict budget, the technology will be paid for through grants from the client. Final prototype should be $100.

Miscellaneous:

Standards and Specification:

- The probe will be invasive, and will therefore require FDA approval to be used in the United States.
- Before the device can be tested *in vivo* on animal models, the study will have to be approved by an internal review board (IRB).

Patient-Related Concerns:

- The patient does not want a large needle or series of tubes coming from their injured limb.
- The probe itself should also not be large or complex enough to frighten the injured patient.
- The patient may not be under anesthesia so the insertion of the probe should be as quick as possible.

Competition:

- Currently the only way to detect compartment syndrome is by pressure. There is little agreement in the literature and amongst surgeons on the proper pressure threshold for diagnosing ACS; therefore, this is very inaccurate and has led to a lot of unneeded fasciotomies.

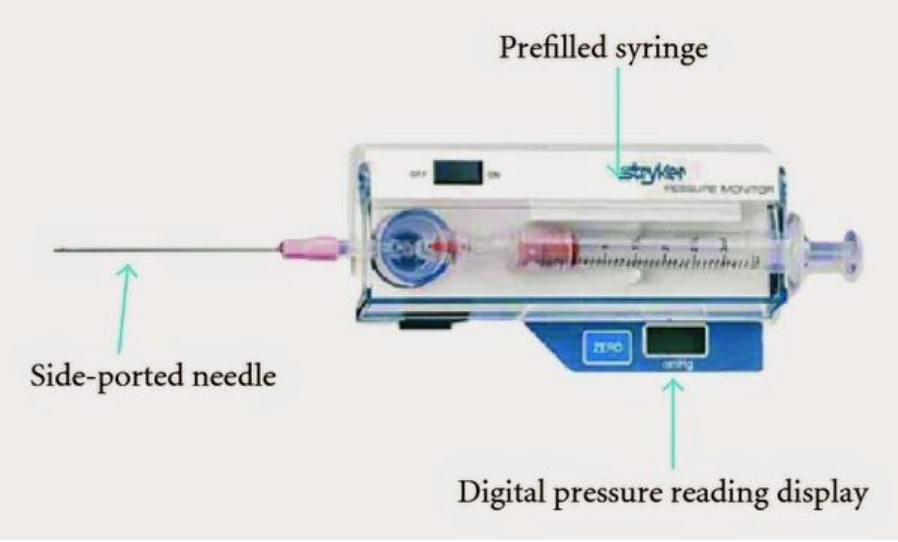

Figure 1: A Stryker Needle, a common instrument for monitoring pressure in a muscle compartment. The side-ported needle is inserted into the affected compartment, leading to a digital pressure reading that the clinician then compares to established threshold values for diagnosis.

- There is also research surrounding the use of near-infrared (NIR) spectroscopy to detect oxygen levels. While accurate in a lab setting, it has been difficult to adapt to a clinical setting.

Customer:

- Dr. Doro is an orthopedic surgeon at the UW Health Orthopedics and Rehabilitation center in Madison, Wisconsin. His research primarily focuses on diagnosing trauma patients with acute compartment syndrome.