# EIROF Electrode-Facilitated Solution to Compartment Syndrome Diagnosis Using pH

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## 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. 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, effective method to reduce misdiagnosis of ACS. Taking compartmental pH measurements provides an alternative, more accurate method of diagnosis. One option for pH detection is the use of iridium oxide electrodeposited on Pt-Ir electrodes. We will be implementing this technology in a 16-gauge needle for eventual use in humans after testing in animals with an 11-gauge needle.

Keywords: biomedical engineering, bioinstrumentation, acute compartment syndrome, EIROF, iridium oxide

## 1. 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 imperfect, 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.

### *1.1 Physiological Background*

 

ACS is a limb- and life-threatening condition in which blood is prevented from leaving a muscle compartment (compartments shown in figure 1). 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 hrs 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 2, is a procedure where the muscle compartment is sliced open to reduce intracompartmental pressure and allow blood flow to return to normal *[5]*.

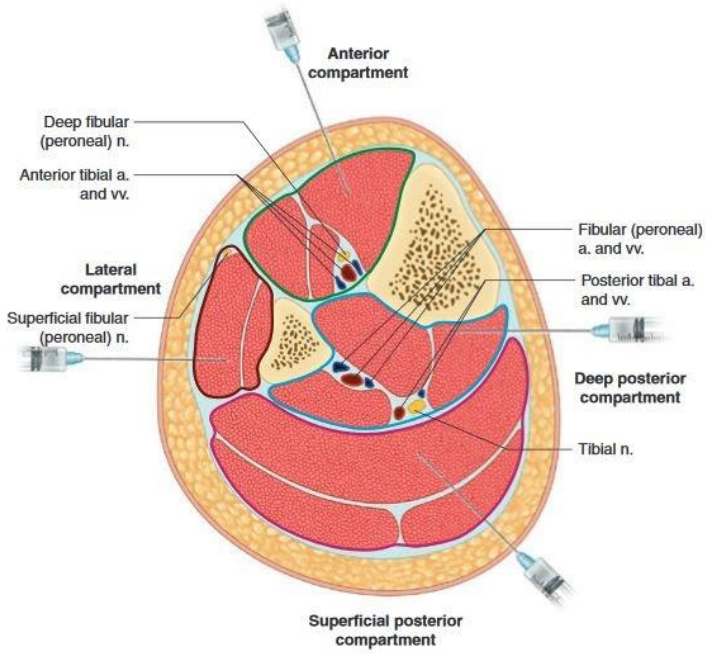


**Figure 1:** Muscle compartments in the lower left leg [5]

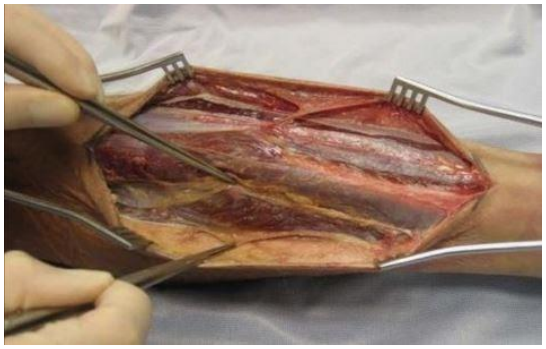

**Figure 2:** Fasciotomy of right forearm [3]

*1.2 Modern ACS Diagnostic Alternatives*

Common methods of ACS diagnosis today involve first testing compartment pressure directly using a catheter-enclosed pressure monitor; however, this is often error prone and can result in misdiagnosis *[4] [5] [6]*. More recent advancements have resulted in the development of new technologies, such as those utilizing near-infrared spectroscopy (NIRS) to detect blood oxygenation completely non-invasively *[7]*. However, NIRS has yet to demonstrate great accuracy in diagnosing ACS *[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 *[8]*.

*1.3 Current ACS Diagnostic Methods*

Currently used methods of ACS diagnosis (such as direct pressure measurement) are highly unreliable and result in a very large percentage of false positive diagnoses (35%) *[6]*. 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] [9]*. 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 *[10]*. Because pH measurement in muscle compartments requires direct contact with the extracellular fluid in each compartment, restrictions require that the pH measuring device be able to at least fit in a 16-gauge needle (the largest permitted in human patients) *[3]*, with a tip inner diameter of 1.19 mm *[11]*.

*1.4 Iridium Oxide Electrode Background*

Iridium Oxide (IrOx) electrodes can be used to detect pH *[12]*. When deposited on a substrate such as platinum (Pt) or platinum-iridium (Pt-Ir) wire, IrOx 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 Nernstian relationship with pH *[13]*. The interaction between the IrOx layer and hydrogen ions in solution can be seen in equation 1 below. As hydrogen ions adsorb to the IrOx surface film, electrons also adsorb to form a new hydrated IrOx ion and water. The electrons travel through the Pt-Ir wire and can be detected as a small voltage (on the order of millivolts) when measured with respect to the Ag/AgCl reference electrode.

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

***Equation 1:*** *Redox reaction between IrOx and solution*

*1.5 Iridium Oxide Electrode Fabrication Theory*

Repeated cycling of current can create an Electrodeposited Iridium Oxide Film (EIROF), which is far more stable than a single-layered electrode *[14]*. The number of electrons transferred for each hydrogen ion present can be used to determine pH of the solution via a voltage measurement and the Nernst equation *[13]*. 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 *[15]*. However, no commercial solutions exist for this technology, and the methods required to fabricate it are complicated *[13]*. Fortunately, we were able to procure many of the necessary materials and devices from the University of Wisconsin-Madison. We fabricated the IrOx and Ag/AgCl electrodes using a potentiostat to create layered films on each substrate for maximum electrode stability *[15] [16] [17]*.

## 2. Methods

*2.1 Preparation of Electrodepositing Solution for IrOx Electrode*

The fabrication of the IrOx electrode utilizes the electrodeposited iridium oxide films (EIROF) technique in alkaline solution. The electrodepositing solution was prepared according to methods by Yamanaka (1989), using iridium tetrachloride, oxalic acid dihydrate, hydrogen peroxide, and anhydrous potassium carbonate [14]. The oxides from iridium, which is a group VII metal, are insoluble in alkaline solution. Precipitation of iridium oxide ($IrO_2$) will occur once a strong base such as potassium carbonate is added. Therefore, oxalic acid can be used to stabilize and form an iridium oxide complex even in a basic solution [12].

*2.2 Electrodeposition of Iridium Oxide Electrode*

The three-electrode cell setup includes a thin Pt/Ir wire as the working electrode, thicker Pt/Ir wire as the counter electrode, and an Ag/AgCl as seen in figure 3 below. The electrodes were immersed in the electrodepositing solution prepared beforehand. By using a Metrohm Autolab potentiostat, potential cycling of triangular waveform was applied from 0 to 0.55 V at 50 mV/s for 50 cycles, followed by pulse of square wave at 0.5 s intervals for 1600 cycles *[18]*. The triangular waveform was used to improve the EIROF adhesion of the oxide layer on the substrate *[18]*.

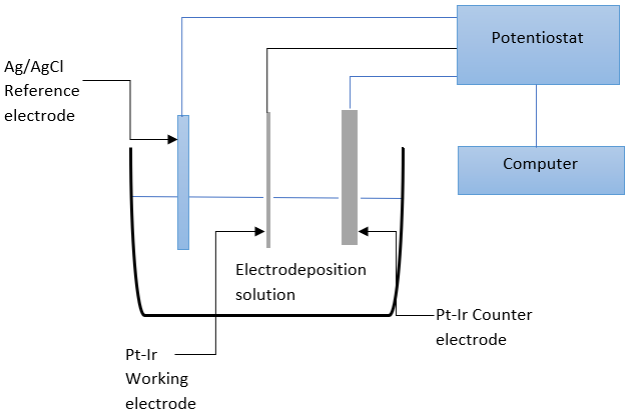


**Figure 3**: Three-electrode cell set up of IrOx electrodeposition. From the left, Ag/AgCl as the reference electrode, thinner Pt/Ir wire as the working electrode, and thicker Pt/Ir as the counter electrode.

*2.3. Electrodeposition of Layered Ag/AgCl Reference Electrode*

The Ag/AgCl reference electrode was fabricated using two Ag/AgCl wires that act as the working and counter electrode, respectively. Potential cycling of a square wave was performed to improve the layering of the Ag/AgCl film and maximize electrode operation time *[19]*.

*2.4 48-hour Drift Test*

To test the clinical scenario of diagnosing patients with compartment syndrome, 48-hour drift tests were conducted to compare the reliability and accuracy of two pH sensors: an ISFET sensor with Ag/AgCl reference, and an IrOx wire with Ag/AgCl reference. These electrodes were put inside a pH = 4 buffer solution and the voltages were recorded for 48 hours at 5-minute intervals using an Arduino in serial communication with a computer. The electrodes were considered accurate if they measure pH close to that of the buffer solution. They were considered reliable depending on the length of time during which they were able to accurately measure the solution's pH; this was effectively the time taken for the electrodeposited film to wear down. We hypothesized that the ISFET combination will maintain voltage longer than the IrOx electrode due to the lesser integrity of the IrOx electrode electrodeposited film when compared with that of the Ag/AgCl electrode.

*2.5 Equivalent Circuit for the Iridium-Oxide Electrode*

The interface between the iridium-oxide electrode and its surrounding environment can be modeled as shown in figure 4 with an electrolyte resistance in series with a parallel combination of interface resistance and capacitance. The electrolyte resistance refers to the resistance of the solution in which the electrode is placed, in our case, the resistance of the intramuscular fluid to transmit charge. The interface resistance, also called the charge transfer resistance, is the resistance associated with physical transfer of charged particles from the electrode to the muscle compartment and vice versa which takes place through oxidation-reduction reactions at the surface. The interface capacitance represents the behavior of the electrode as it theoretically behaves when there are no charged particles being physically transferred across the interface. In this case, the interface would develop a double layer of charge, one layer on the electrode side of the interface and the other on the electrolyte side. Even small perturbations of the charge on the electrolyte side of the interface, caused by biological activity, indirectly cause changes in the charges on the electrode side of the interface which are then conducted up the wire to the rest of the circuitry.

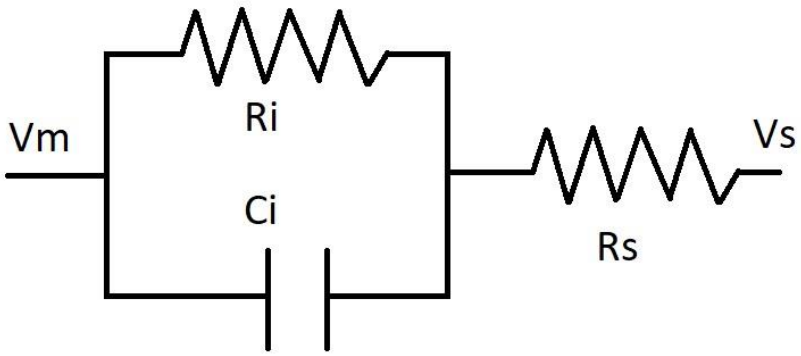


***Figure 4:*** *The equivalent circuit of the interface of a general electrode and the solution in which it is places. Vs is the end of the interface which is in the solution and Vm is the end which corresponds to the electrode and is connected to the rest of the circuitry. Rs is the electrolyte resistance, Ri and Ci are the interface's resistance and capacitance, respectively.*

The overall impedance of this equivalent circuit is especially useful when considering the input impedance of the amplifier necessary for amplifying the signal obtained from the electrode. As the electrodes decrease in size, their impedance increases, requiring a higher input impedance on the amplifier to ensure the amplifier operates as intended. While this impedance increases with decreasing size, it also increases with decreasing frequency of the signals being read by the electrode, as can be seen in figure 5 obtained from Blau et al. *[20]*.

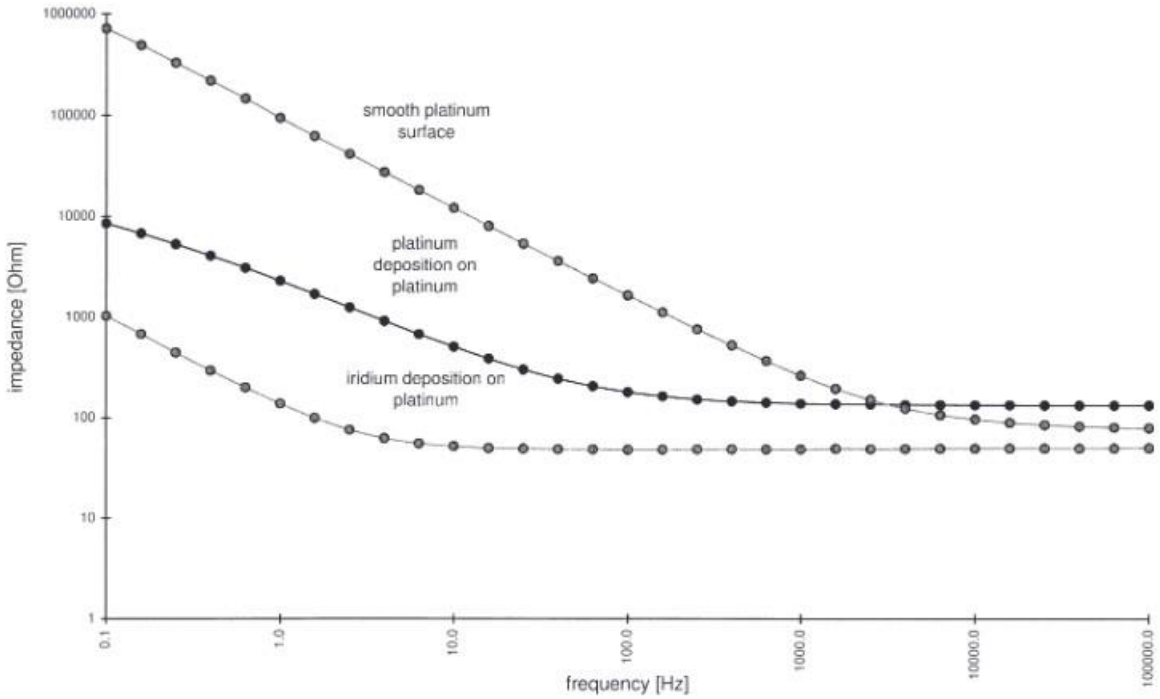


***Figure 5:*** *A plot of the total impedance of the equivalent circuit for three electrode types: (1) a smooth platinum electrode, (2) a platinum wire with coated in platinum, and (3) a platinum wire coated with iridium oxide. You can see how the impedance of the circuit increases for all three cases when frequency decreases but the platinum with iridium oxide coating consistently has the lowest impedance of the three. This plot and its data were obtained from [20].*

*2.6 Filtering and Amplification Circuit*

The pH signals we are trying to isolate should theoretically have a frequency near 0 Hz because it should remain stable and non-oscillatory. There is always ambient noise to be considered but our target frequency being 0 Hz allows us considerable freedom in the choice of a corner frequency for the low-pass filter to be implemented to eliminate this noise. We chose the corner frequency to be at 7 Hz so that 60 Hz would be well into the rejection band of the filter and 0 Hz would be well into the pass band of the filter. This means that 0 Hz is guaranteed to be unaltered by the filter while 60 Hz is guaranteed to have a very strong attenuation. This focus on 60 Hz as the representative of all noise arises solely from the knowledge that it is the most common frequency of ambient noise and is therefore most likely to be encountered. While there will also be noise from nearby nerve and muscle activity, these signals exhibit a wide range of frequencies and therefore cannot be easily removed through the application of any passive filtering technique.

The instrumentation amplifier must have an input impedance much larger than the impedance of the electrodes to ensure it works as close to ideally as possible. As you can see in figure 5 above, the impedance of the platinum electrode coated with iridium is approximately 1 kΩ when the frequency of the signal is 0.1 Hz. While this value would increase as the frequency decreases further to the theoretical 0 Hz frequency of the pH signals we attempt to measure, it would still be in the range of low kΩ, which is much lower than the typical input impedance of an instrumentation amplifier, generally on the order of GΩ. Once the electrode setup has been passed through the passive filter described above, it is then input into this amplifier to increase the magnitude of the resulting signal to the microcontroller. You can see this final setup in figure 6 below, generated in LT Spice.

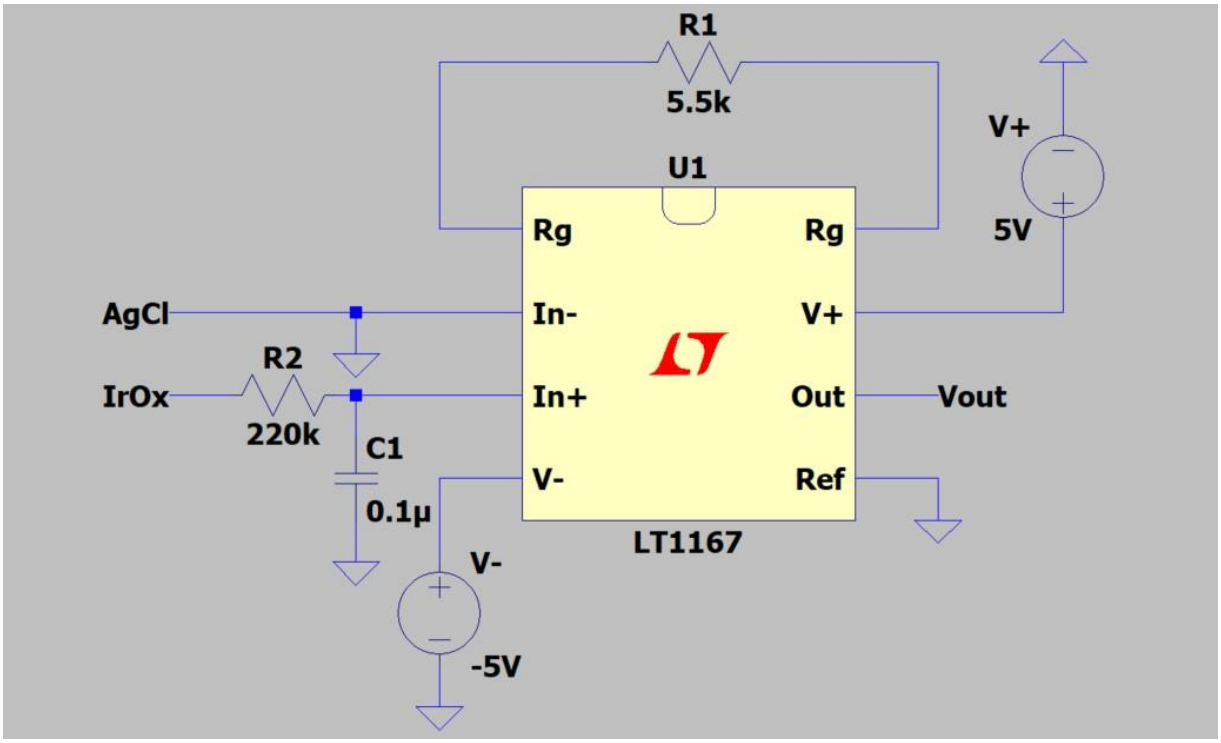


***Figure 6:*** *The filtration and amplification circuit used to refine and amplify the signal obtained from the Iridium-Oxide electrode connected at node IrOx and the Silver Silver-Chloride reference electrode connected at node AgCl. Vout is the pH-dependent voltage which is passed to the microcontroller for analysis, recording, and display.*

*2.7 Cadaver Testing*

This testing aims to observe whether our electrode can measure pH in a real muscle compartment and the value is accurate by making a comparison with a commercial probe. We hypothesized that both the IrOx electrode and commercial probe will have similar pH measurement. The IrOx electrode was inserted inside the muscle compartment of a porcine cadaver and compared the pH values obtained with Sentron pH probe. Both IrOx and Ag/AgCl electrodes were first calibrated using buffer solution with different pH. The muscle was then punctured with a stainless steel 11-gauge needle before inserting a double lumen tube containing the IrOx electrode and the Ag/AgCl reference electrode. The setup of testing

can be seen in figure 7. An incision was made for commercial probe insertion to measure the pH of the compartment. The voltage values recorded was converted into pH using the regression line equation from calibration and compared with the values obtained with the Sentron probe.

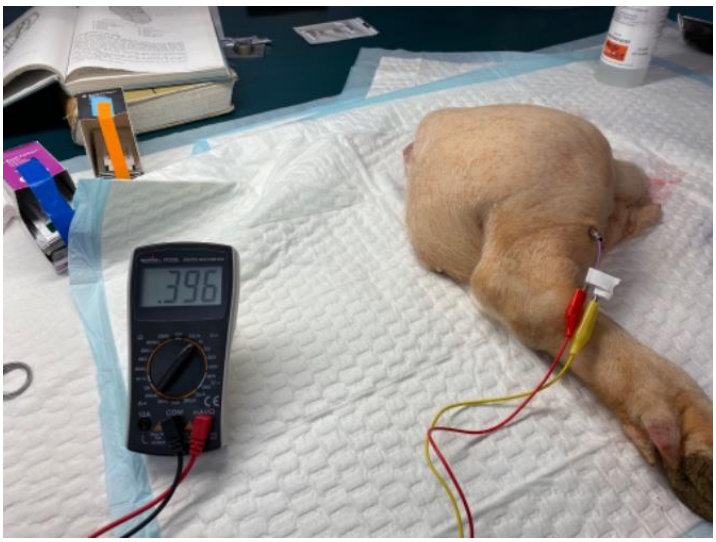


***Figure 7:*** *The setup for cadaver testing which includes a stainless-steel needle injected into the muscle compartment. A double lumen tubing containing the IrOx and Ag/AgCl electrodes was inserted through the hole of the needle. The electrodes were connected to a digital multimeter to measure the voltages.*

## 3. Results

*3.1 Drift Test of ISFET + Ag/AgCl compared with IrOx + Ag/AgCl*

The results of the drift test are shown in Figure 8. From the graph, the Ag/AgCl reference is more reliable than the IrOx electrode. It continued to measure pH until ~18 hrs into the experiment before it began to break down. The IrOx electrode only lasted ~8 hrs. However, the IrOx electrode was more accurate with a standard deviation of 0.181, while the Ag/AgCl reference had standard deviation of 0.334. Both standard deviations were calculated from the beginning of the experiment to just before the electrode began to experience breakdown.

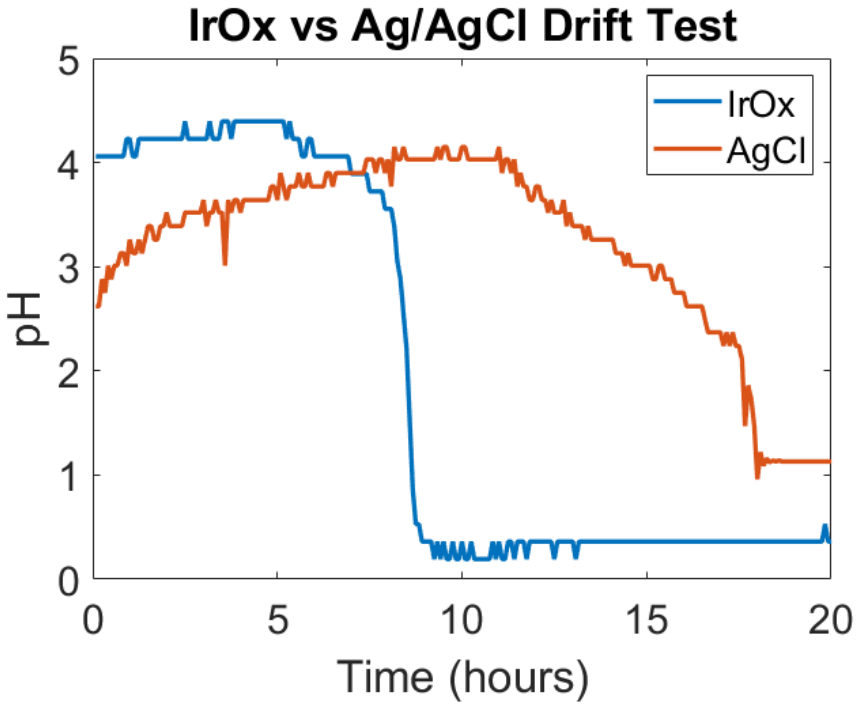

**Figure 8: Drift Test.** The pH was recorded automatically every 5 minutes for 48 hours. While the Ag/AgCl reference has greater longevity, the IrOx electrode has a lower standard deviation, indicating lower variance from its starting value during its operating time and hence greater accuracy.

*3.2 Equivalent Circuit Model Parameter Values*

From Blau et al., the values for the equivalent circuit model described in section 2.5 can be approximated as follows: Ri = 1.06 kΩ, Rs = 48 Ω, and Ci = 1.5 mF **[20]**. This source also provides us with a method of determining these values experimentally for our setup as these values are not associated with an electrode with a size and shape different from ours. Unfortunately, this procedure required the use of a potentiometer which we no longer have access to due to the COVID-19 outbreak and we were therefore unable to determine the values associated with our specific electrodes.

*3.2 Cadaver Testing*

The pH measured using the commercial probe was 5.66 pH while the IrOx and Ag/AgCl electrodes recorded pH of 2. There was a big difference between pH from the commercial probes and the electrodes. However, pH of 6 was observed when the electrodes were inserted into the compartment with the tubing, but without the stainless-steel needle. This value is closer to the pH measured with commercial probe. There were some discoloration observed at the end of the electrodes which showed a sign of flaking of the IrOx layer.

## Discussion

Previous limitations for using pH as a chemical marker for compartment syndrome have been the cumbersome size of pH probes. ISFET technology has made improvements towards miniaturizing pH detection instrumentation, but it still suffers limitations due to impurities, instability, and size. **[21]** Current ISFET chips have width of ~1mm, which is small enough to fit in a 16 gauge needle but would not leave adequate room for a reference electrode **[22]**. The proposed method for an injectable pH sensing electrode would allow for less invasive delivery and continuous monitoring. Two wires of 127-micron diameter are all that is required to sense pH in solution due to special interactions between the electrodeposited coatings and the solution. IrOx has reacts with hydrogen ions to create a surface voltage. Along with a reference electrode, this can be used to determine pH in solution

The 48-hr drift tests showed that the IrOx electrodes broke down at a faster rate than the Ag/AgCl electrodes, which made them the limiting factor in the longevity of the electrodes in solution. To reach 48-hr of continuous monitoring, Ag/AgCl electrode must gain an additional 30 hrs before breakdown, and the IrOx electrode must gain an additional 38 hrs. To achieve this, changes must be made to the deposition protocol to make a thicker IrOx layer that is more resistant to flaking. Heat treatment after electrodeposition has also been shown to prevent IrOx layer breakdown and should be explored in the future **[23]**.

The cadaver testing shows that the IrOx and Ag/AgCl electrodes were able to detect the ions inside the muscle compartment and provided a voltage value corresponding to the pH inside the compartment. However, this value was not relevant as it did not provide an accurate reading close to the pH recorded from the commercial probe. Nevertheless, the pH measured without the stainless-steel needle was closer to the actual pH of the compartment as recorded with the commercial probe. The results show that the current delivery method does not provide sufficient contact between the electrodes and the fluid of the compartment. Furthermore, the discolorations observed on the IrOx electrode indicate the flaking of the IrOx layer. The friction that occurs when inserting the electrodes into the needle might have caused the flaking issue that affected the pH reading.

The delivery method of these electrodes was feeding them through medical tubing and having them placed inside of a stainless-steel needle. The tubing prevented the needles from contacting each other or the needle. This design was limited by the fluid contact of the electrodes. As seen in cadaver testing, the pH was much different when the two electrodes were inserted with the needle compared to without the needle. The width of the tubes had to be large enough to allow solution from the compartment to enter and contact the electrodes. An improved design inspired by Park et al. **[24]** would use a catheter and adhesive to place these electrodes on the outside of catheter. An insulating coating would be placed over the wires/adhesive to prevent solution contact with a gap left at the tip to allow for direct contact with the compartment. This design would come

much closer to the minimum size required for the two wire pH electrodes making this minimally invasive and clinically practical.

## Conclusion

The current diagnostic method for ACS involves intracompartmental pressure readings, but the current accepted criteria for a diagnosis has a false positive rate of 35%. **[6]** A diagnosis of compartment syndrome requires a fasciotomy, which is an invasive procedure that has a substantially higher infection rate than patients not requiring a fasciotomy. Along with the risk of infection, a fasciotomy has a risk of non-union for the injury. **[25]** To protect patients from wasteful fasciotomies, there is a need for a new diagnostic method that has a more universal diagnostic criteria that will reduce false-positive diagnosis of ACS. Due to the physiology of muscle activity increasing carbon dioxide and lactic acid, pH has shown to have a significant decrease as a muscle approaches ischemia **[10]**.

A two-electrode system that employs a platinum and iridium alloy wire electrodeposited with Iridium Oxide as a working electrode along with a reference electrode made from silver chloride coated silver wire provides a viable replacement for the current diagnostic methods of ACS. These electrodes were able to sense pH inside a solution. To make this proposed design clinically practical, improvements must be made to the delivery method, and the electrodes must resist breakdown to allow for continuous monitoring over a 48 hr period; the 48 hr drift testing we performed confirmed our hypothesis that Ag/AgCl electrodes would not break down as quickly as IrOx electrodes due to film stability. Thus, the IrOx electrode is the limiting factor in the operating time of this device and must be improved. After improving the electrodes and delivery methods, animal testing should be completed with induced compartment syndrome to determine the design's ability to detect compartment syndrome in more realistic environment.

Additional literature searches were performed to determine the optimal IrOx electrodeposition protocol to maximize electrode longevity without any cost to sensitivity, and an outline of this research has been provided in appendix **D.** Furthermore, a new design has been proposed for the delivery method of these electrodes to increase solution contact in appendix **C.**

Future FDA approval will be required if this product is to become marketable. Based on a similar device which involves intramuscular electrical stimulation using a needle, we believe that the device be classified as a Class II device *[26]*.

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**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.

**Appendix B: Design Matrix For pH sensing**

To evaluate the three pH electrode options, ISFET, Platinum and Iridium wires, and Iridium-Coated Needle, 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. Ease of use relates to the electrode's pH sensitivity - with greater sensitivity meaning 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 it affects the sensor's fitness for our application environment. If the sensor has a low durability score, it is much more likely to fail during use, with potentially life-threatening consequences. Additionally, this criterion evaluates the expected lifetime of the device. 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 1 summarizes the scores of each design in each of these categories.

**Table 1:** Summary of the pH sensor design evaluation.

| **Criteria** | **ISFET** | **Pt-Ir** | **Ir-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) [11]. 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.

**Appendix C : Fabrication Protocol**

Ag/AgCl Layered Electrodeposition

The steps of fabricating the Ag/AgCl reference electrode through layered electrodeposition are described as below, modified from the procedure described in *Medical Instrumentation* [27]:

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. The wires are connected in a two-electrode setup to their respective terminals (Working Electrode/Sensing Electrode, Reference Electrode/Counter Electrode) on an Autolab potentiostat
5. 1.5 V is passed through the circuit using a square wave (one second on, one second off) for 1000 cycles.
6. The fabricated Ag/AgCl electrode is then wiped and stored.

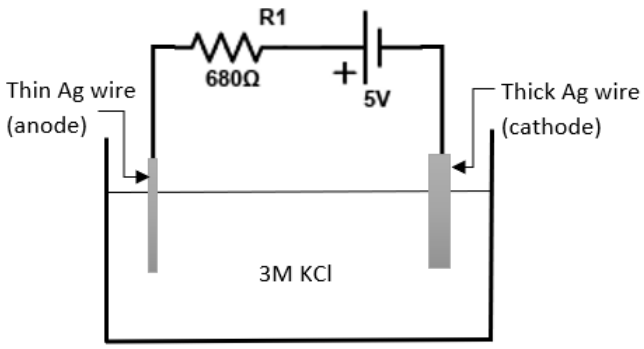


**Figure 9**: Setup of Ag/AgCl electrodeposition

IrOx Electrodeposition Solution

The fabrication protocol that we followed is as follows [15]:

1. Dissolve 75mg iridium tetrachloride in 50mL water
2. Stir 30 min
3. Add 0.5mL 30% hydrogen peroxide (aq) and stir 10 min
4. Add 250mg oxalic acid dihydrate and stir 10 min
5. Adjust pH slowly to 10.5 by adding small portions of anhydrous potassium carbonate
6. Leave at room temperature for 2 days to stabilize

The solution turns from greenish-yellow to blue-black after 48 hours.

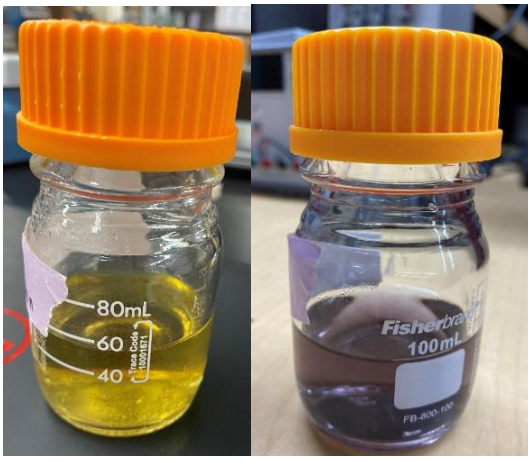


**Figure 10:** Electrodeposition solution before (left) and after (right) two days

IrOx Layered Electrodeposition

The steps for the electrodeposition of IrOx electrode are as follows [18]:

1. Set up Pt-Ir working electrode with Pt-Ir counter electrode and Ag/AgCl reference electrode in electrodeposition solution
2. Acquire wave generator and oscilloscope
3. Vary triangular waveform from 0 to 0.55V at 50mV/s for 50 cycles
    a. This is to improve EIROF adhesion to substrate
4. Pulse 0 to 0.55V square wave at 0.5s intervals for up to 1600 cycles

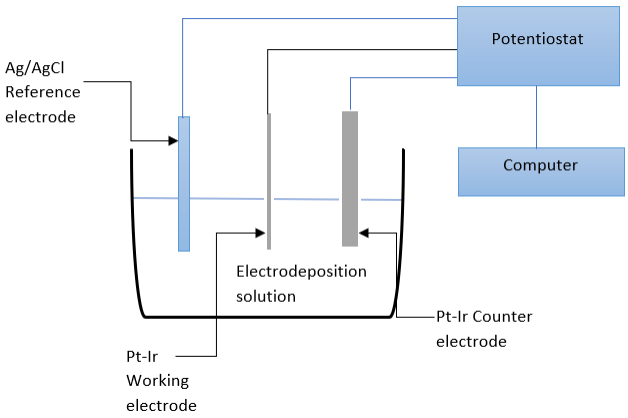


**Figure 11:** Three-electrode cell setup for IrOx electrodeposition

**Appendix B: Design Matrix For pH delivery method**

To evaluate the four designs for delivery method we generated 5 criteria: ease of calibration, fluid contact, fabrication complexity, ease of insertion, and biocompatibility. Fluid contact is the most important criteria because this is critical for the function of the electrodes. Without adequate fluid contact the readings will be unstable. Ease of calibration, ease of insertion, and biocompatibility are tied for second most importance because these will determine the usability for this product in an operating room. If the design does not receive adequate score in these three categories, then it is not feasible for use in a clinical setting, Fabrication complexity is the least important due to this not affecting how effective the electrode is, but it is still a category because it will affect the cost of a commercially available electrode. Table 1 summarizes the scores of each design in each of these categories.

**Table 1:** Summary of the delivery method design evaluations

| Criteria | Two-Lumen Catheter | Electrodes on outside | KCL + ion exchange | IrOx electrodeposited |
|---|---|---|---|---|

| | w/ micro electrode Array | of catheter | membrane | on needle |
|---|---|---|---|---|
| Ease of Calibration (20) | 20 | 20 | 18 | 20 |
| Fluid Contact (30) | 25 | 30 | 25 | 30 |
| Fabrication Complexity (10) | 3 | 8 | 3 | 5 |
| Ease of insertion (20) | 18 | 20 | 18 | 20 |
| Biocompatibility (20) | 20 | 17 | 20 | 18 |
| Total (100) | 86 | 95 | 84 | 93 |

Ease of Calibration

The only design that did not receive full marks in this category was the KCL + ion exchange membrane due to it requiring ion equilibrium to be reached with the solution. To calibrate this would require more time to reach equilibrium in each of the three buffer solutions required to calibrate. The other three designs would reach potential instantaneously.

Fluid Contact

The Electrodes on outside of Catheter and the IrOx electrodeposited needle received full marks because the contact surfaces are exterior to the catheter/needle. The other two designs have the electrodes inside a needle/catheter, which relies on width to obtain enough solution contact.

Fabrication Complexity

The Electrodes outside of the catheter design was awarded the easiest to manufacture because its protocol is similar with one used previously by the team, and the electrodeposition is the same as before. The other designs were ranked lower because their fabrication requires expensive equipment and new electrodeposition techniques.

Ease of Insertion

This requirement is determined by the width of the insertion device and the lubriciousness of the material. The electrodes outside of catheter and the IrOx on the outside of the needle were ranked highest because the width of the insertion can be small due to the electrodes not relaying on the width of the needle for fluid contact. Likewise, this is a downfall for the others.

Biocompatibility

The Two-Lumen design ranks high because it does not use any materials that are not well documented as biocompatible. The KCL + ion exchange membrane prevents ion leaking from the silver chloride electrode, which is the most toxic portion of the design. The electrodes on the outside of the catheter design introduces an adhesive and an insulator to the design, which adds more concern for toxicity. The IrOx electrodeposited needle has concern for extra flaking from IrOx due to the unnecessary surface area of the IrOx layer.

Total

The Electrodes on outside of a catheter ranked the highest because it ranked highly in the three categories related to ease of use, which makes it clinically practical. The fabrication is simple, so this would be cheap to manufacture; therefore, affordable to patients. This design ranked low in biocompatibility but using a proper adhesive and insulating layer can mitigate these concerns.

**Appendix C:** Final design for new proposed delivery method.

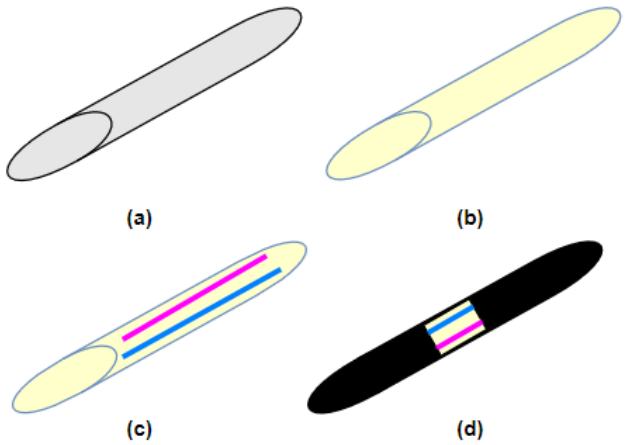


**Figure 12:** Layering procedure for a delivery method for two pH sensing electrodes. a) a catheter as the base material. b) a layer of adhesive to attach the electrodes. c) adhere the electrodes to the outside of the catheter. d) coat the apparatus with a lubricious, biocompatible insulator.

**Appendix D: IrOx electrode operation and fabrication equations**

From Equation 1 in Section 1.4, we have:

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

Simplified, we have:

$$2IrO(OH) + 2H^+ + 2e^- \leftrightarrows Ir_2O(OH)_2 + H_2O$$

**Equation 2:** simplified redox reaction of IrOx and H+ in solution

This equation governs the reaction occurring between the IrOx film and hydrogen ions in solution. As shown by Martinez et al. (2009), the relative abundance of the chemical species in this equation can be used in the Nernst equation to directly calculate the potential of the IrOx electrode [28]. Doing so, we arrive at:

$$E = E^{\circ\prime} - 0.059 * pH$$

**Equation 3:** IrOx electrode potential given redox potential and expected pH

Where $E$ is the potential of the IrOx electrode, $E^{\circ\prime}$ is the IrOx redox potential at pH = 7.0, and $pH$ is simply the pH value expected. From here, it is easy to see how the solution pH can be calculated from the instantaneous IrOx potential and redox potential at pH = 7. This could be an alternative to electrode calibration using a linear regression.

Additional IrOx fabrication optimization has been pursued by Saied et al. (2014) [29]. Electrodeposition can be accomplished using Cyclic Voltammetry (CV), just as we did during our IrOx fabrication steps. Saied et al. found that IrOx pH probe sensitivity does not depend on electrodeposited layer thickness, but layer thickness can influence the longevity of the probe in solution. To optimize layer thickness, this equation can be followed:

$$H = 931.20 - (511.59A) + (386.71B) + (403.76C) - (433.62AC)$$

**Equation 4:** IrOx electrodeposited film height calculation

Where $A$ is scan rate, $B$ is temperature, $C$ is number of cycles, and $H$ is film thickness (nm). Greater layer thickness can increase the IrOx probe's operational lifetime in solution.

Heat can also be used to maximize electrode lifetime. Yamanakaha (1991) found that, at temperatures below 100°C, heat treatment could be applied without a reduction in sensitivity [30]. At 100°C, water is evaporated and the electrodeposited

IrOx films become hard and difficult to remove by physical or chemical means; this makes heat treatment an excellent option for maximizing electrode operation time [30].