Improving Acute Compartment Syndrome diagnostic technology by measuring intramuscular pH with an Ion-Sensitive Field Effect Transistor

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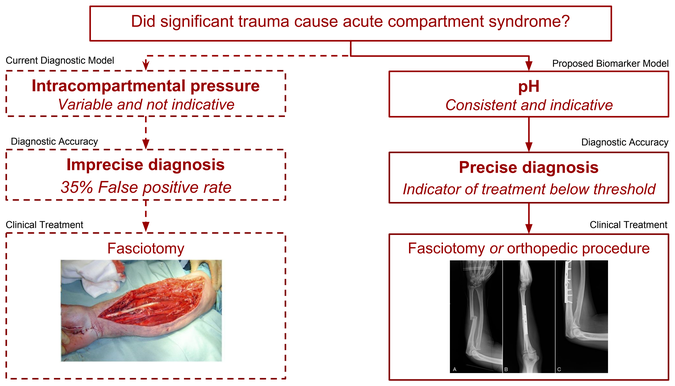
UW BME Design

Abstract

Acute compartment syndrome (ACS) is a condition in which a traumatic injury causes the tissue pressure in a muscle compartment to increase. As a result, tissue pressure exceeds the blood perfusion pressure, leading to cell anoxia, muscle ischemia and muscle death. Current ACS diagnosis methods rely on subjective assessments such as clinical examinations and intracompartmental pressure readings that return a false-positive diagnosis in 35% of cases, resulting in unnecessary, invasive surgery. Research has shown that pH is a more indicative biomarker of ACS than pressure. Our goal is to develop an invasive probe that accurately measures physiological pH in humans. Researchers will be able to use this probe to set a pH threshold below which doctors can diagnose ACS.

Critical Emergency Room Question



Intracompartmental pressure readings are too variable between patients for precise ACS diagnosis. A definitive measure is critical so patients avoid unnecessary and invasive surgeries [1], [2].

Acute Compartment Syndrome

- Result of trauma and impeded blood flow to muscles
- pH shown to decrease in canines with ACS [3]
- Translating results to emergency room device requires:
  1. **Rapid device calibration (< 2min)**
  2. **Bioelectrochemical sensor**
  3. **Deep tissue penetration (2-8 cm)**

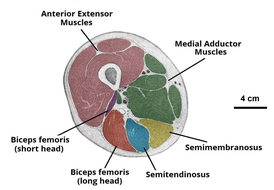


Figure 1: ACS probe will enter physical environments such as the anterior muscle compartments of the thigh [4].

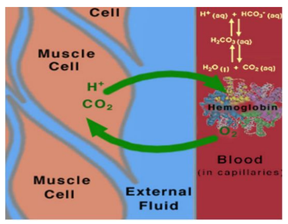


Figure 2: In a healthy person, blood carries CO2 away from cells, thus stabilizing their pH. ACS impedes blood flow, so CO2 remains in the muscles and decreases pH [5].

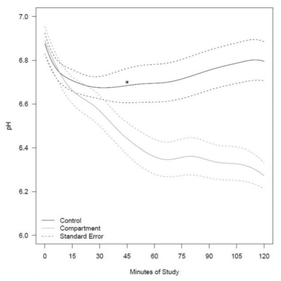


Figure 3: Correlation of muscular pH and ACS in canines. The longer ACS lasts, the lower the pH [6].

Fabrication Scheme

Proof of Concept → **ISFET Design** → **ISFET Manufacturing**

ISFET Technology

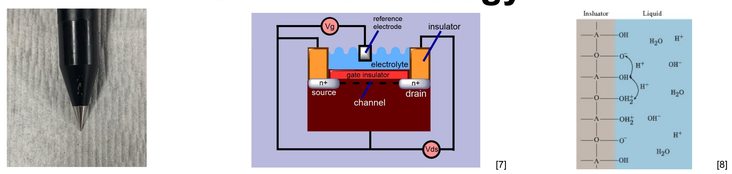


Figure 4: Left to right: Purchased DeltaTrak ISFET probe; Cross-sectional diagram of ISFET technology; Molecular interaction of pH on insulated surface

Field-Effect Transistor (FET):

- Current between source and drain regulated by voltage at gate insulator [9]
- Gate insulator: Voltage produced by hydroxide layer that reacts with protons in solution [8]

Ion Selectivity:

- DeltaTrak probe: SiOH gate insulation
- Threshold voltage dependent on the pH of its environment [9]

Gate Reaction:

$SiOH + H_2O \leftrightarrow SiO^- + H_3O^+$

Signal Processing

Patient › Signals › Processing › Diagnosis

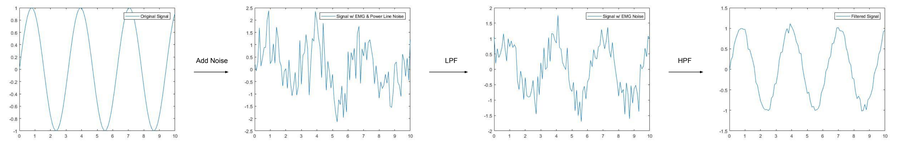


Figure 5: Signal filtering progression. Original signal had potential electromyographic and power line noise components added and then filtered out to demonstrate the potential filtering that would take place on the anticipated signal to be acquired.

- Signal will likely contain:
  - Electromyographic noise
  - Power line noise
- Bandpass filter (BPF) prepared to attenuate signals with frequency components outside of the desired range

Proof of Concept: ISFET vs. Glass Bulb Sensor

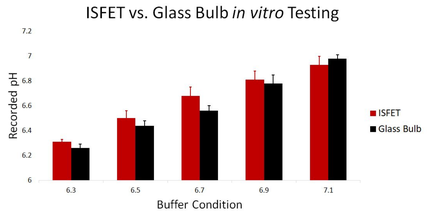


Figure 6: Record pH of ISFET and glass bulb vs. pH of buffer.

Key Points

- No significant pH difference between ISFET and glass bulb measurements
- Meat pH converged to buffer pH
- ISFET is highly durable and rigid, which allows it to pierce sample

Figure 7: ISFET pH probe insertion in meat sample

✓	Accurate and Precise	✗
✓	Sterilizable	✓
✓	Miniaturizable	✗
✓	Durable	✗
✓	Affordable	✓

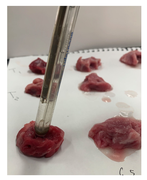


Figure 8: Glass bulb pH probe insertion in meat sample

Influence of K^+ Concentration on pH

[10]

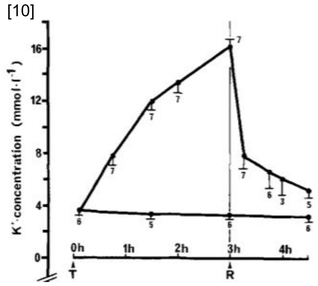


Figure 9: K^+ concentration during muscle ischemia. Ischemia was induced in a rabbit model for first three hours before flow was restored [10].

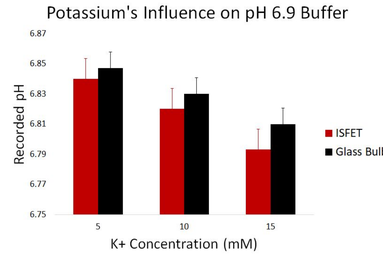


Figure 10: ISFET and glass bulb pH measurements recorded as a function of K^+ concentration.

Key Points

- K^+ concentration rises during muscle ischemia [10]
- K^+ concentration plateaus around 15 mM in interstitial fluid [10]
- Increasing K^+ concentration within ischemic range doesn't significantly impact pH
- No difference between probes

Discussion and Implications for Design

ISFET vs Glass Bulb Sensor

- Takeaway: ISFET is comparable to the standard glass bulb sensor
- Diagnostic accuracy: Is error attributable to instrumentation or samples?

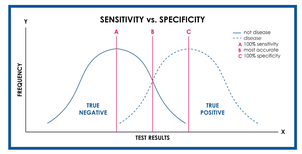


Figure 11: Example Receiver Operating Characteristic (ROC) curve for analysis of sensitivity and specificity of a diagnostic test [11].

Influence of Potassium on pH

- Takeaway: Physiological potassium concentrations do not significantly affect pH
- Gate insulator: SiOH will not provide false diagnosis because of K^+

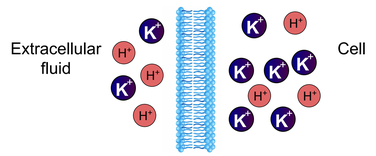


Figure 12: Schematic of hyperkalemia at the level of the cellular membrane.

Future Work

1. Future Tests:
   - Sensitivity/Specificity - is measurement error caused by instrumentation?
   - Drift test - does the ISFET's accuracy change over time?
   - *In vivo* study - does an ISFET accurately report pH in a canine model?
2. Miniaturize design to fit in an 18-gauge needle (CAD model and circuit)
3. New material selection: Replace ABS with non-cytotoxic material
4. Outsource fabrication to company with clean room

Acknowledgements

- Dr. Christopher Doro, Client
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- Professor David Beebe, BME 550
- Professor Justin Williams, BME 550

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