Improving acute compartment syndrome diagnostic technology by measuring intramuscular pH with an Ion-Sensitive Field Effect Transistor

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Abstract

Acute compartment syndrome (ACS) is a condition in which a traumatic injury causes the pressure in a muscle compartment to increase. As a result, intracompartmental 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

Did significant trauma cause acute compartment syndrome?

Current Diagnostic Model

Intracompartmental pressure
Variable and not indicative

Diagnostic Accuracy

Imprecise diagnosis
35% False positive rate

Clinical Treatment

Fasciotomy

Proposed Biomarker Model

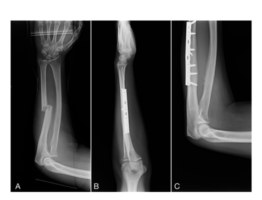
pH
Consistent and indicative

Diagnostic Accuracy

Precise diagnosis
Indicator of treatment below threshold

Clinical Treatment

Fasciotomy *or* orthopedic procedure



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)**

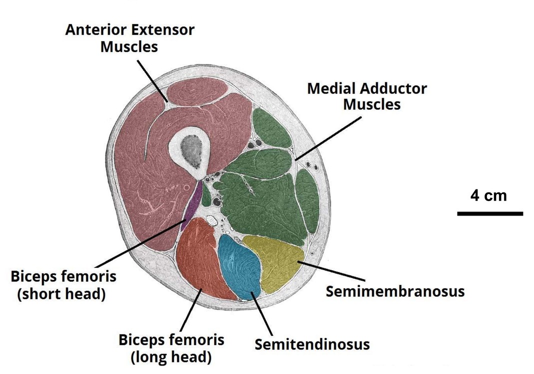


Figure 1: ACS probe will enter physical environments such as the anterior muscle compartments of the thigh [4].

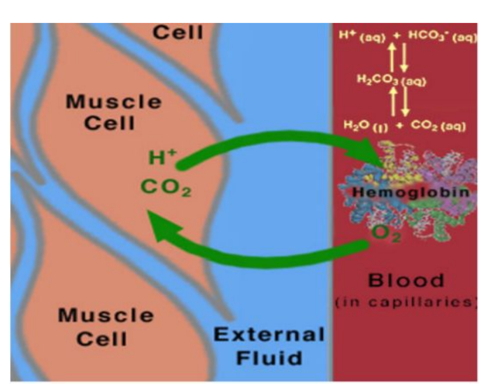


Figure 2: In a healthy person, blood carries CO2 away from cells, thus stabilizing their pH. ACS impedes blood flow, so CO2 remains in the muscles and decreases pH [5].

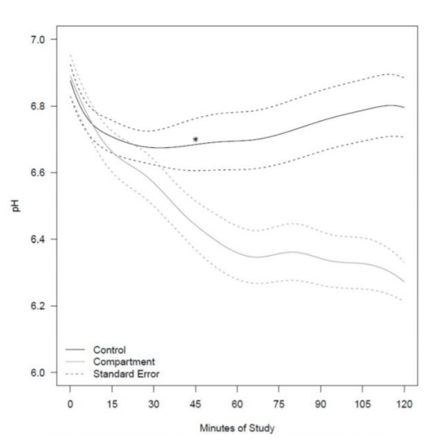


Figure 3: Correlation of muscular pH and ACS in canines. The longer ACS lasts, the lower the pH [6].

Fabrication Scheme

Proof of Concept → ISFET Design → ISFET Manufacturing

ISFET Technology

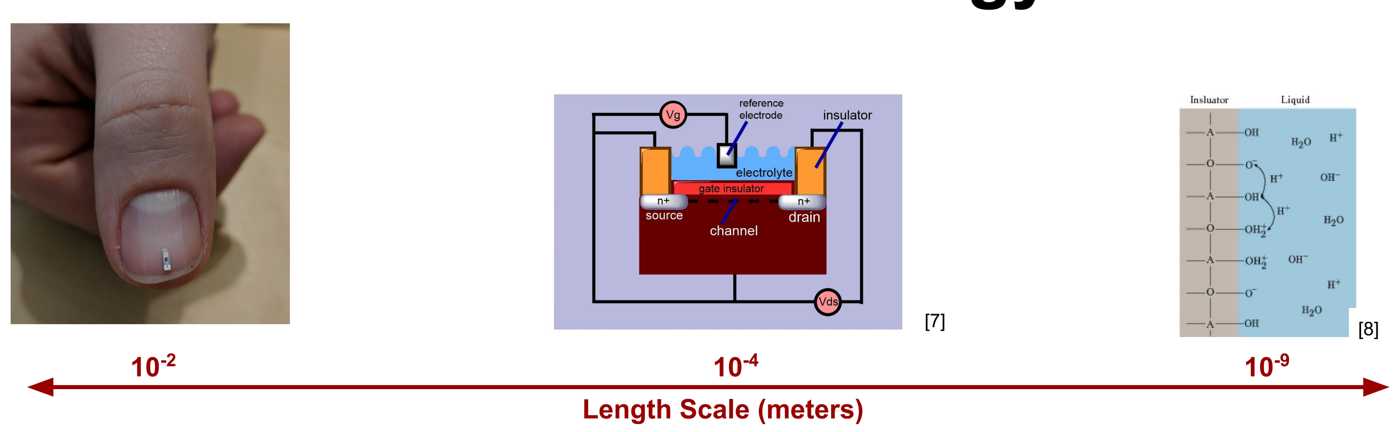


Figure 4: Left to right: Sentron ISFET sensor; Cross-sectional diagram of ISFET technology; Molecular interaction of pH on insulated surface

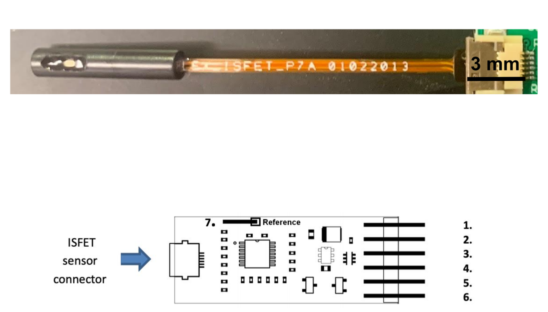
Field-Effect Transistor (FET):

- 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]

Experimental Sentron ISFET

- 3mm x 15 mm
- Sampling frequency: 3 Hz
- 52 mV/pH unit [10]

Analog Front-end pH Module



ISFET perturbed from resting voltage → Voltage output received by A/D convertor → Voltage equated to pH on serial monitor → pH value of sample recorded

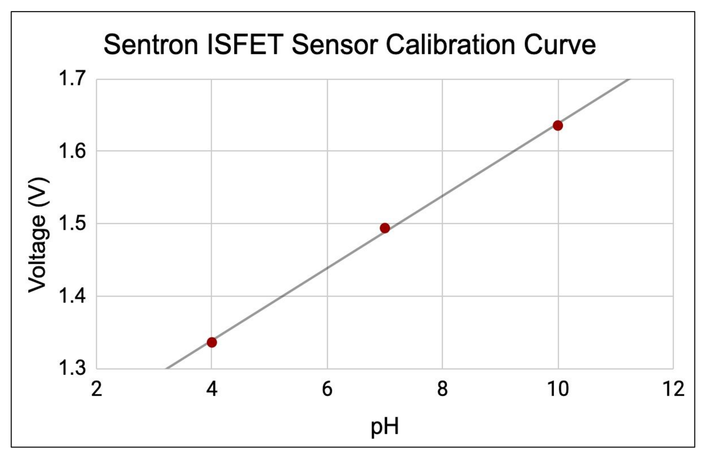


Figure 5: Left: Photograph of ISFET sensor FFC adaptor purchased from Sentron with provided schematic diagram pin assignments. Pin one: pH out, Pin two: 3.3V power supply, Pin 3: Digital Ground. Right: flow chart diagram of preassembled Sentron Sensor, after device has been calibrated.

Figure 6: Sentron ISFET pH kit calibration curve. Measurements at pH 4, 7, 10 were taken three times. Conversion equation:
(Voltage - 1.1393) / 0.0499 = pH R^2 = 0.999

Experimental ISFET Sensor pH Measurements

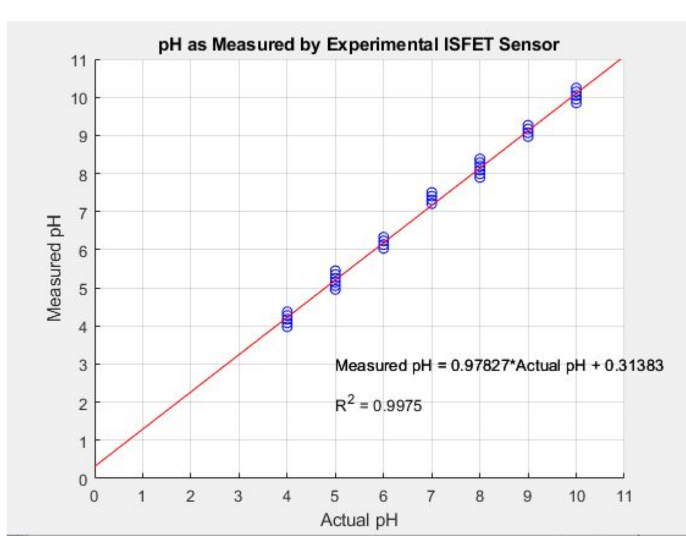


Figure 7: Agreement between pH measurements as reported by the standard glass bulb probe and experimental ISFET sensor.

<u>Key Points</u>

- The ISFET sensor is consistent across a wide range of pH values
- Mann-Whitney parametric test: Measurements from glass bulb probe, ISFET sensor are significantly different ($p < 0.05$)
- ISFET measurements are consistently ~0.1 pH units higher than glass bulb probe

Experimental ISFET *In Vitro* Drift Test

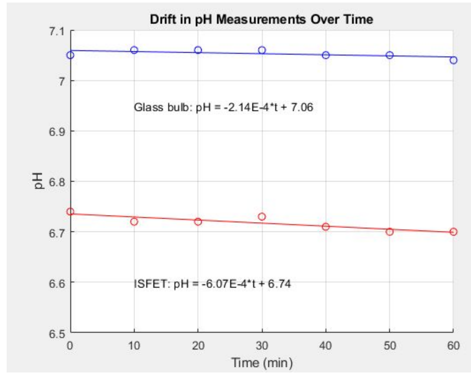


Figure 8: pH drift measurements for glass bulb and ISFET pH sensors over a one hour time period in a ph 7.0 buffer solution.

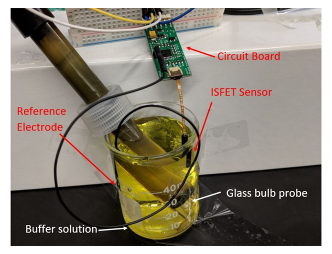


Figure 9: Experimental set-up for drift test. Glass bulb and ISFET sensors along with reference electrode all in solution.

<u>Key Points</u>

- Glass bulb pH probe showed negligible drift over one hour
- Experimental ISFET sensor drifted by ~ 0.5 pH units over one hour
- Expected diagnosis time (time sensor is in patient) is less than 15 minutes
- Experimental ISFET pH drift rate is suboptimal but still low enough for the sensor to be practical

ISFET Encapsulation

Encapsulation Prototype

<u>Key Points</u>

- PEEK casing and tubing protects ISFET chip and FCC cable
- PEEK encapsulant chosen due to its excellent biocompatibility, strength, and wear resistance [11]

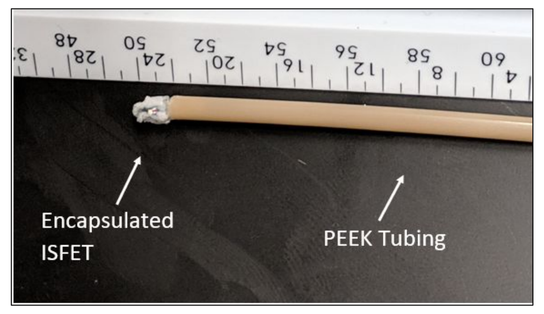


Figure 10: Solidworks model of encapsulated ISFET design made using PEEK encapsulant. Ion-sensitive membrane of the bare die is exposed to the surface to detect pH.

Final Encapsulation Design

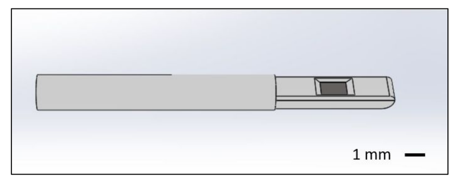


Figure 11: Solidworks model of encapsulated ISFET design made using PEEK encapsulant. Ion-sensitive membrane of the bare die is exposed to the surface to detect pH.

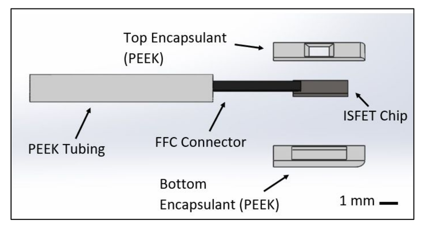


Figure 12: Solidworks model showing exploded view of encapsulated ISFET design. ISFET chip is held in place with epoxy and connected to a main circuit via an FFC cable.

Future Work

- Clean room fabrication
  - Micro-injection molding and PCB bonding - molding will require outsourcing
- Future Tests:
  - Sensitivity/Specificity - is measurement error caused by instrumentation?
  - Encapsulation: Does encasing the sensor alter its measurements?
  - *In vivo* study - does an ISFET accurately report pH in a canine model?

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