Ensuring pain medication dosage: A real-time intravenous opioid monitoring system

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Opioid Tampering Puts Patients at Risk!

United States Attorney's Office

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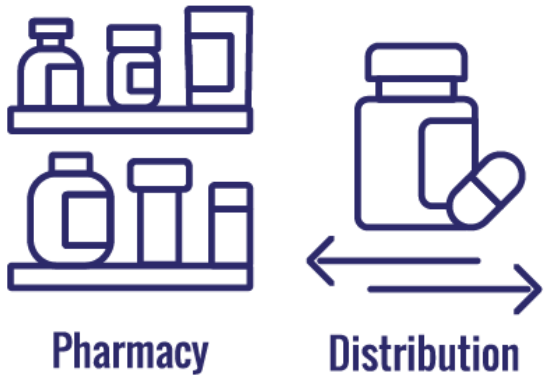
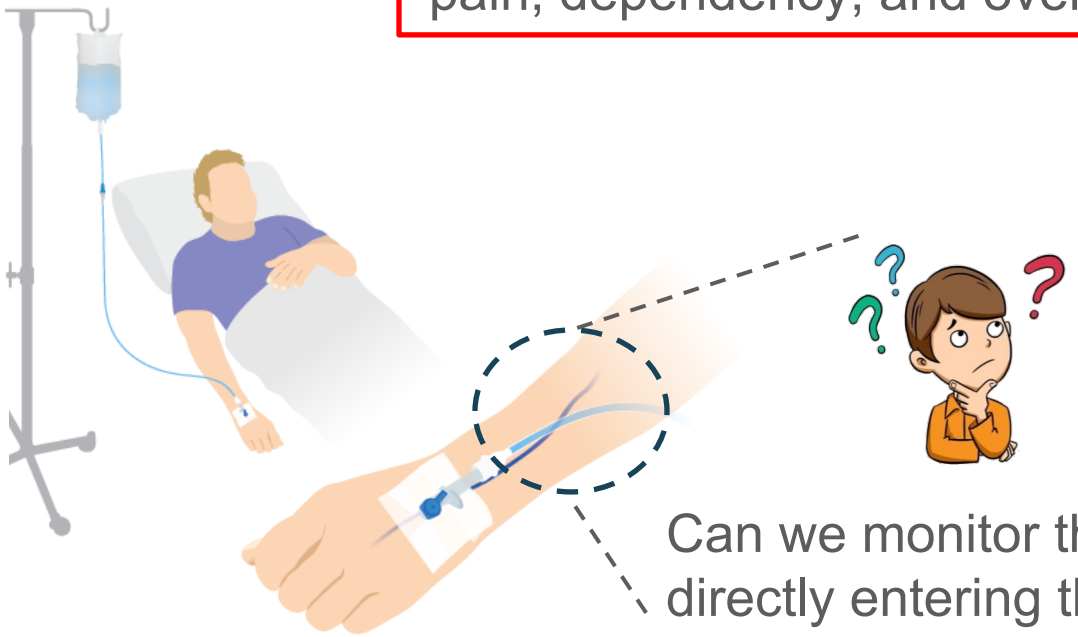
How can this Tampering Happen?

Current hospital procedures for opioid administration:

- Pharmacists dilute drug samples
- Doctors calculate the required concentration
- Monitoring vital signs

Medication errors put patients at risk of respiratory depression, increased pain, dependency, and overdosing!





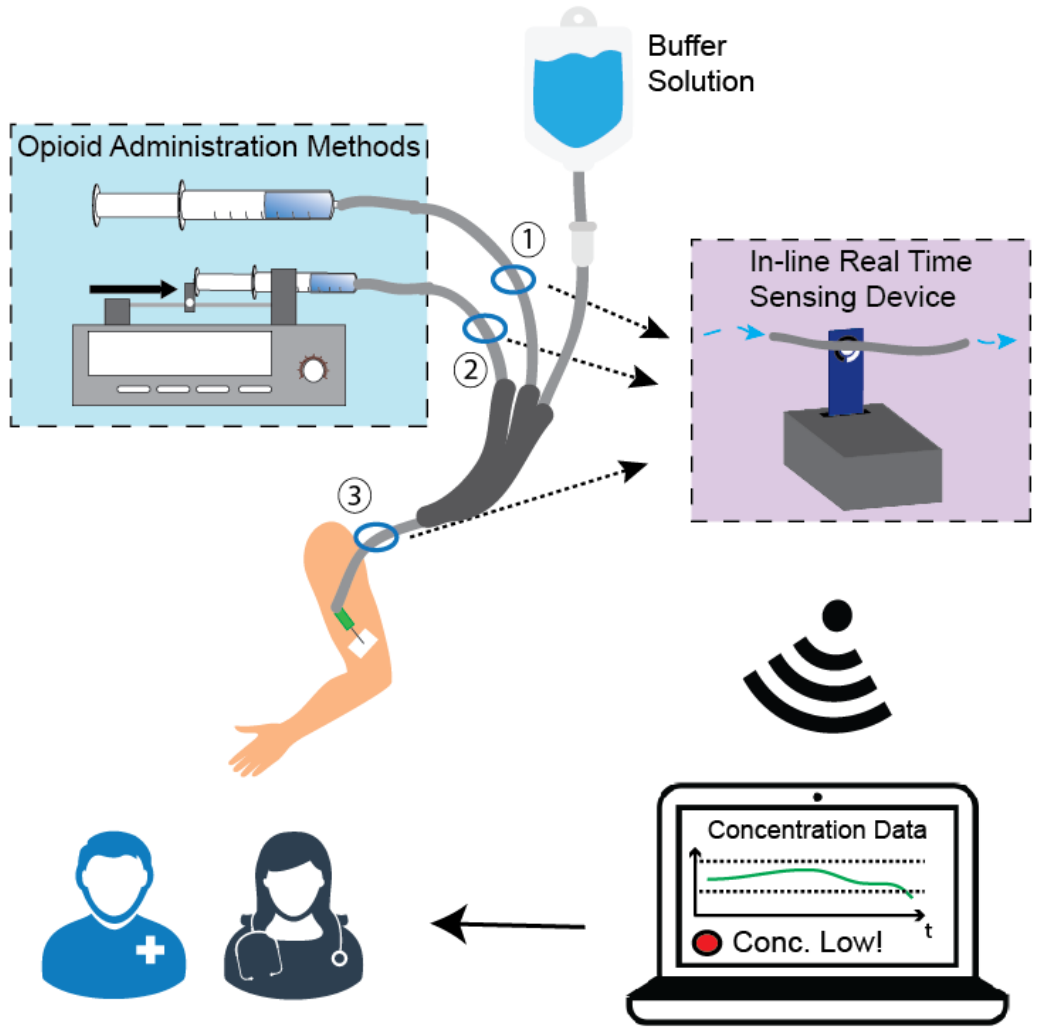
Can we monitor the opioid directly entering the patient?

Current opioid administration procedures rely on trust and lack quantification!

“Closing the Loop” in Opioid Administration

Possible Sensing Locations:

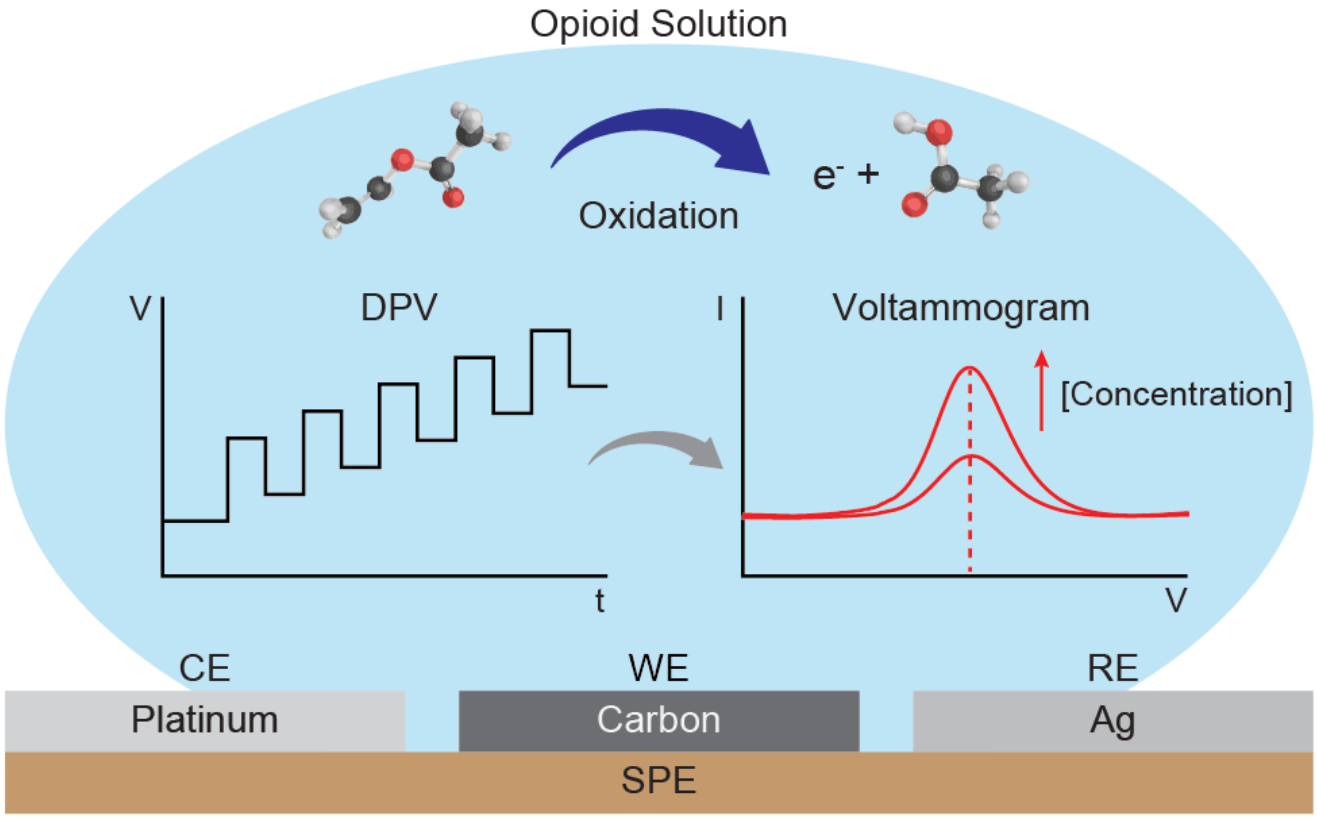
1. After bolus dosage
2. After continuous IV dosage
3. After dilution with buffer solution

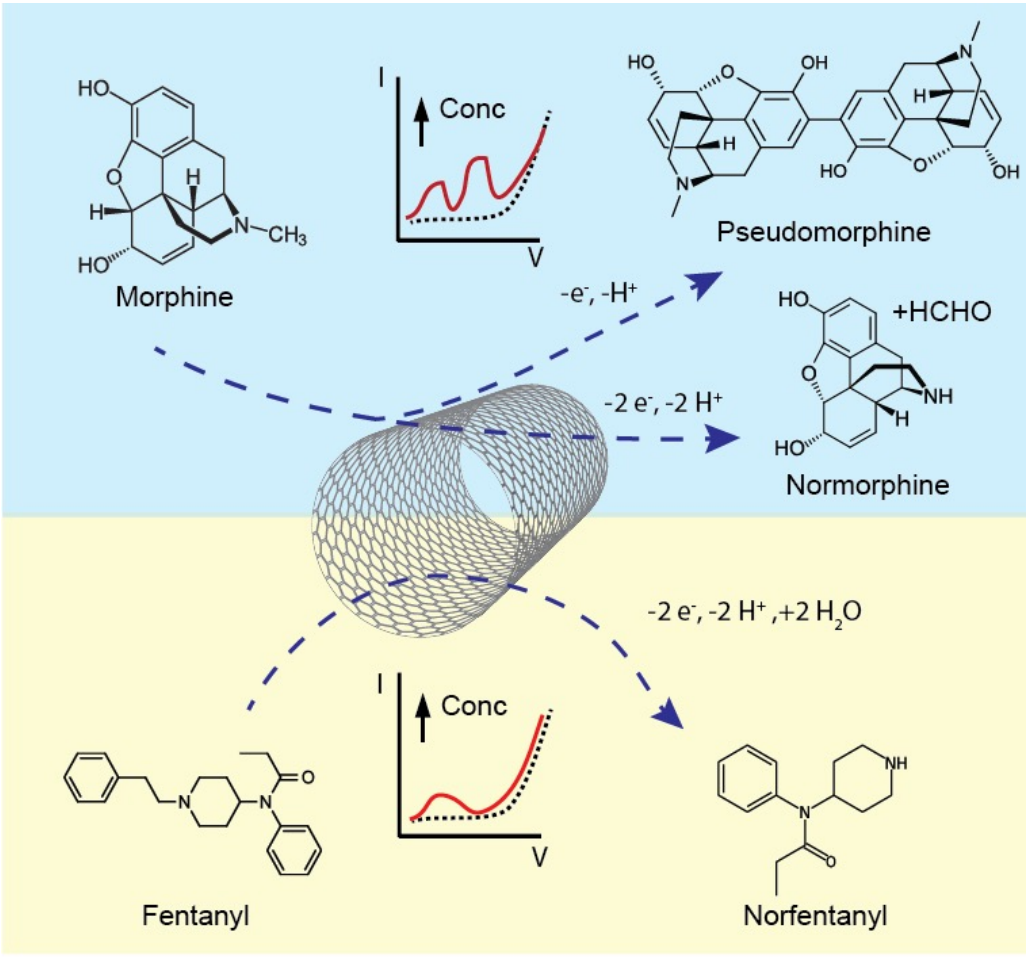


Goal: Enable real-time analytical verification of intravenous opioid concentrations

Electrochemical Detection of Opioids

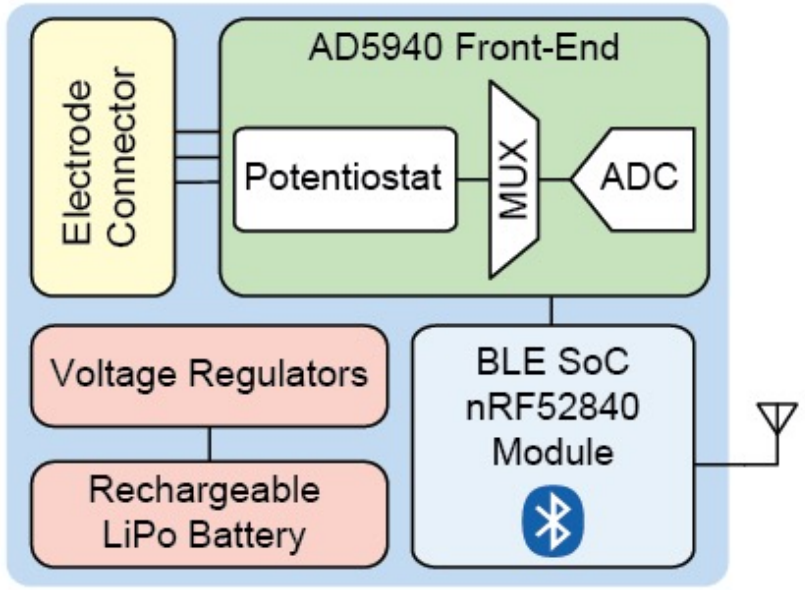
Direct Electrooxidation

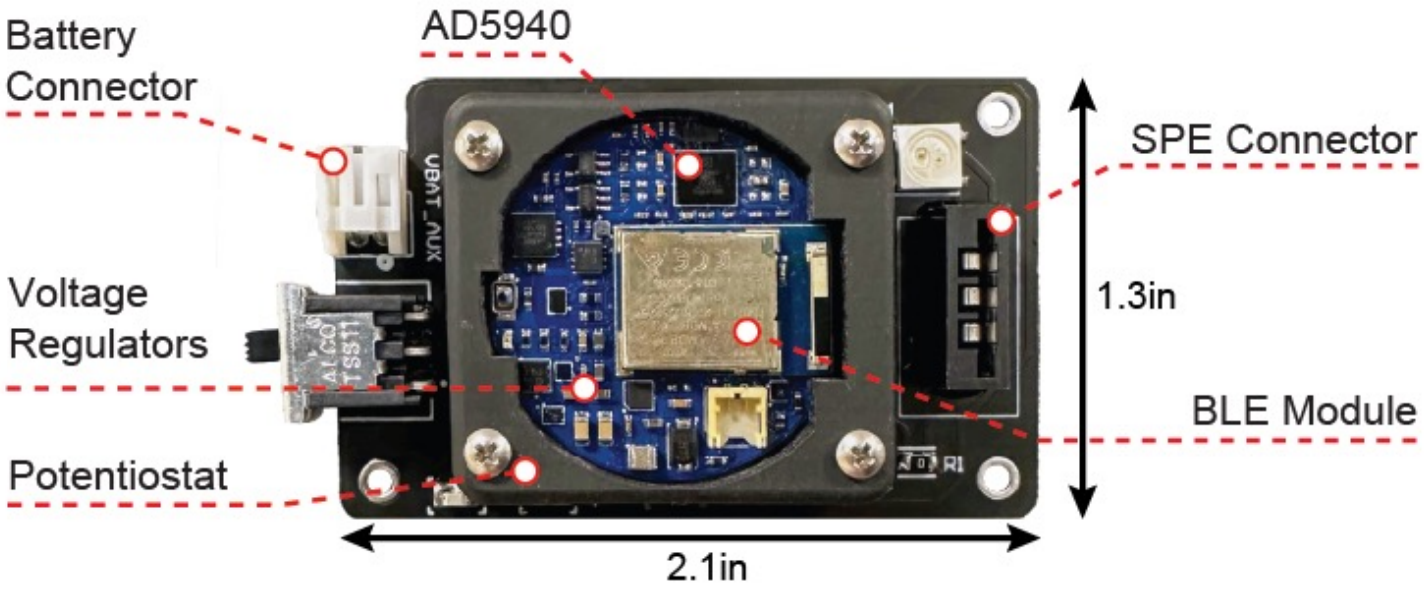




- Direct electrooxidation allows opioids to be detected through their voltage peak positioning
- Differential Pulse Voltammetry (DPV) chosen for enhanced sensitivity

Implemented System

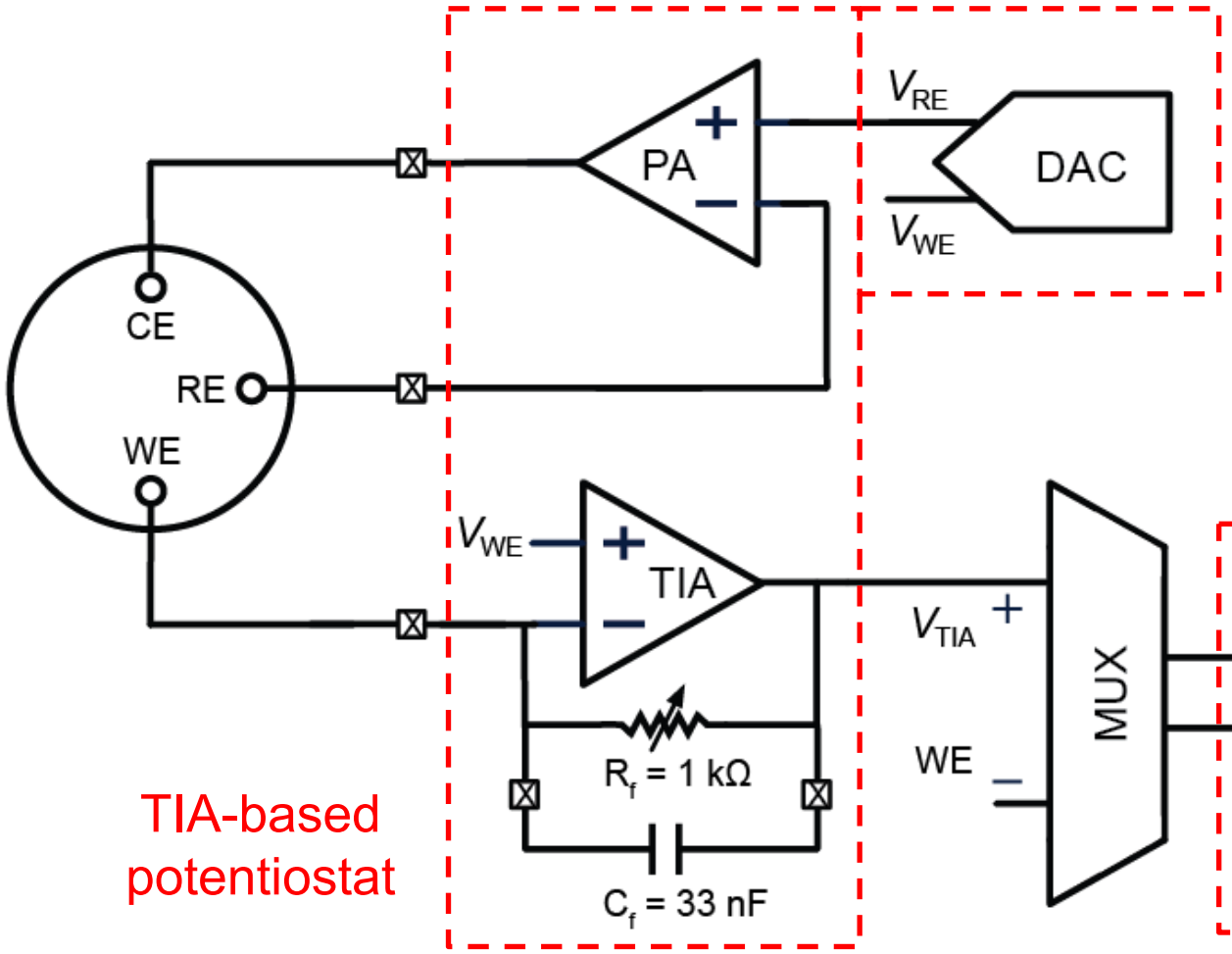




- Miniaturized electrochemical sensing system
- Battery-powered and wireless electronics
- Built around the fully integrated AD5940 potentiostat chip

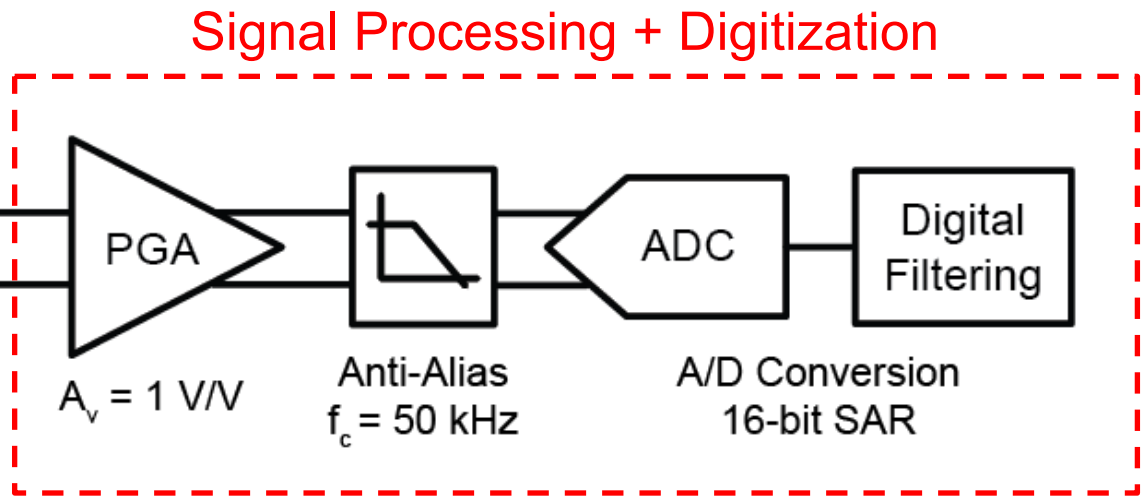
Signal Path for DPV Scans

All blocks shown are integrated inside the AD5940:



Dual output DAC controls the cell voltages:

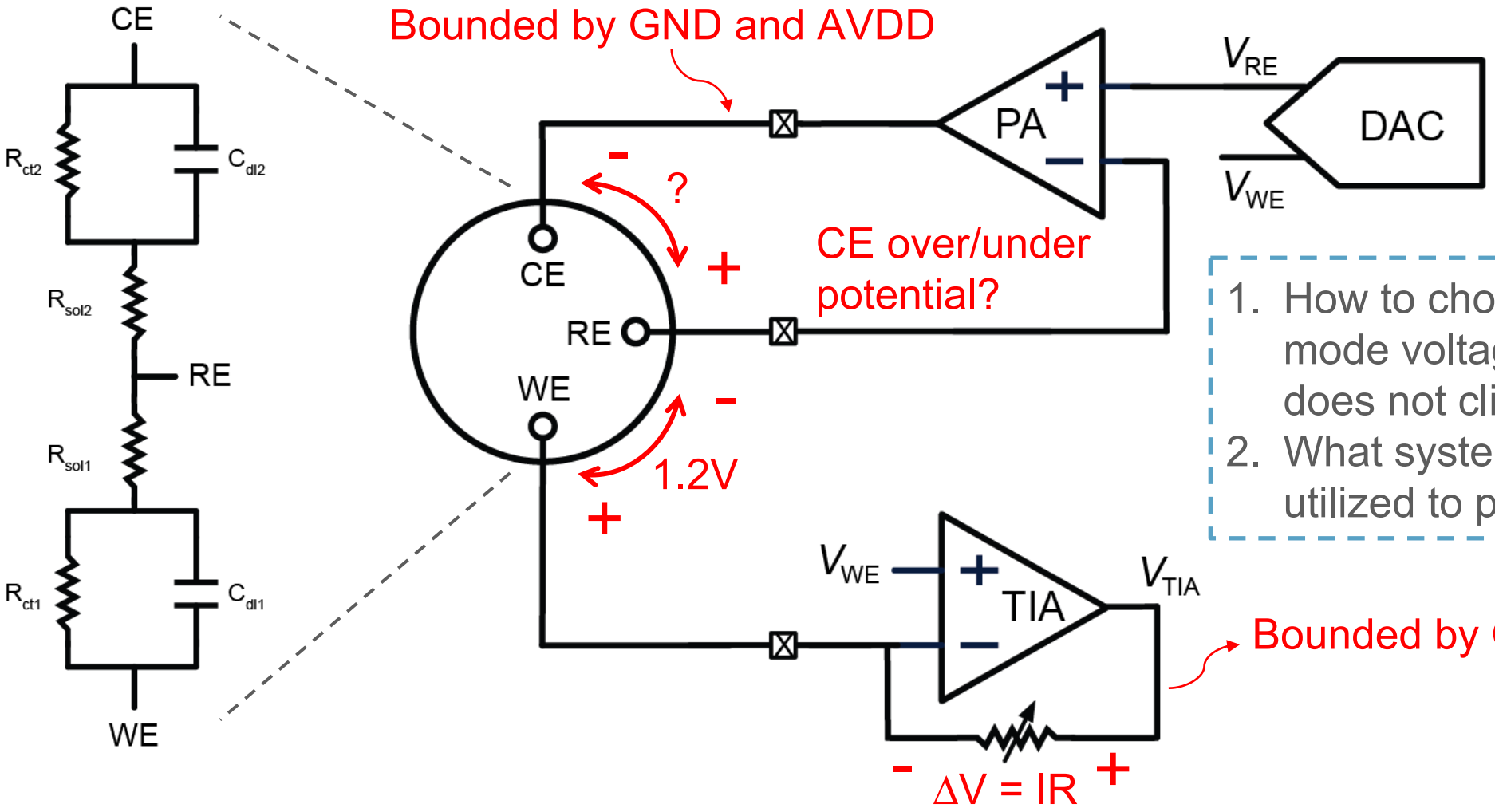
- 12-bit output controls the RE
- 6-bit output controls the WE
- The RE is swept during a DPV scan, while the WE is held constant



Reconfigurability of the front-end enables detection of other opioids beyond fentanyl/morphine

The Challenge of CE and TIA Clipping

Electro-oxidative detection of fentanyl and morphine requires **DPV scans up to ~1.2V**

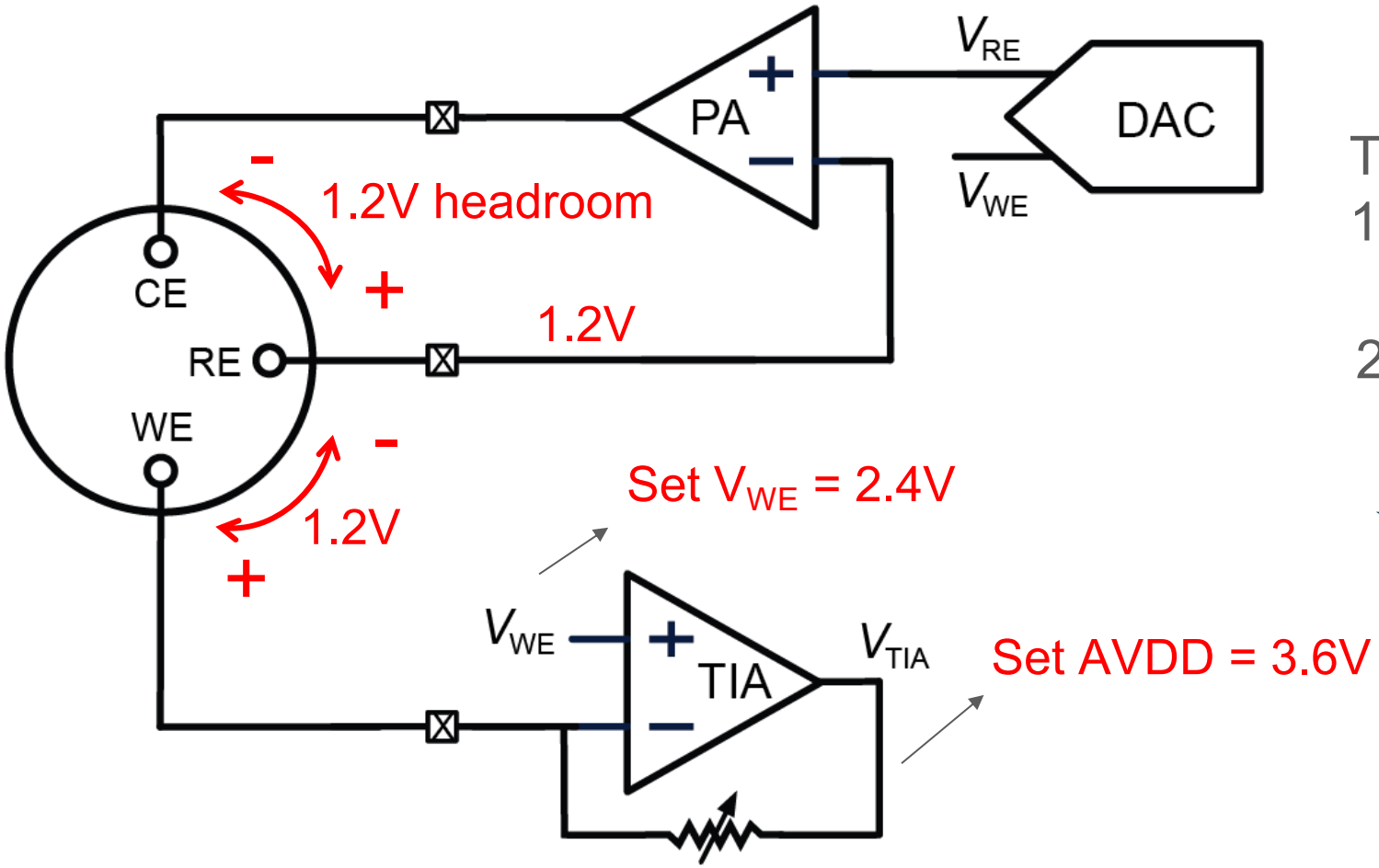


1. How to choose the WE common mode voltage to ensure the CE does not clip at GND?
2. What system AVDD should be utilized to prevent TIA clipping?

Clipping at the amplifier outputs causes incomplete settling and measurement distortion

Mitigating Clipping Inside the Potentiostat

CE clipping can be mitigated by maximizing V_{WE}, however…



The AFE supports:

- $0.2V \leq \boldsymbol{V_{WE}} \leq 2.4V$
- $2.8V \leq \textbf{AVDD} \leq 3.6V$

Two ways to avoid TIA clipping:

1. Reduce TIA gain
   - Loss in sensitivity *(unacceptable)*
2. Maximize supply voltage AVDD
   - Increased power consumption

Additionally, utilizing a lower resistance CE material (ie: Pt instead of Carbon) can greatly reduce the CE overpotential

Scanning up to a large potential requires maximizing the potentiostat compliance voltage

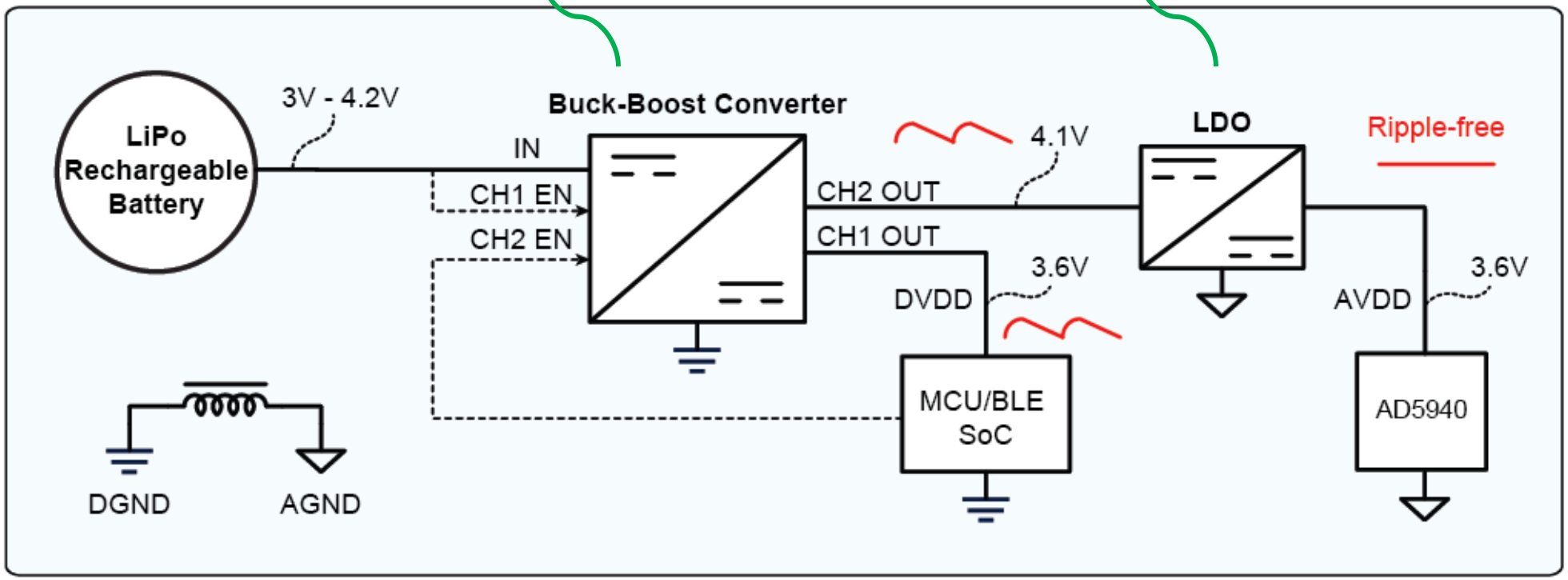
System Power Management

MAX17270:

- Triple output, single inductor, Buck-Boost
- I_Q = 1.05µA (two channels)
- Allows for power gating the AFE in sleep mode

TPS7A2036:

- Low noise, high PSRR, LDO
- I_Q = 6.5µA
- Provides ripple-free supply at 3.6V for the AFE



Architecture leverages the entire battery range while consuming ultra-low quiescent power

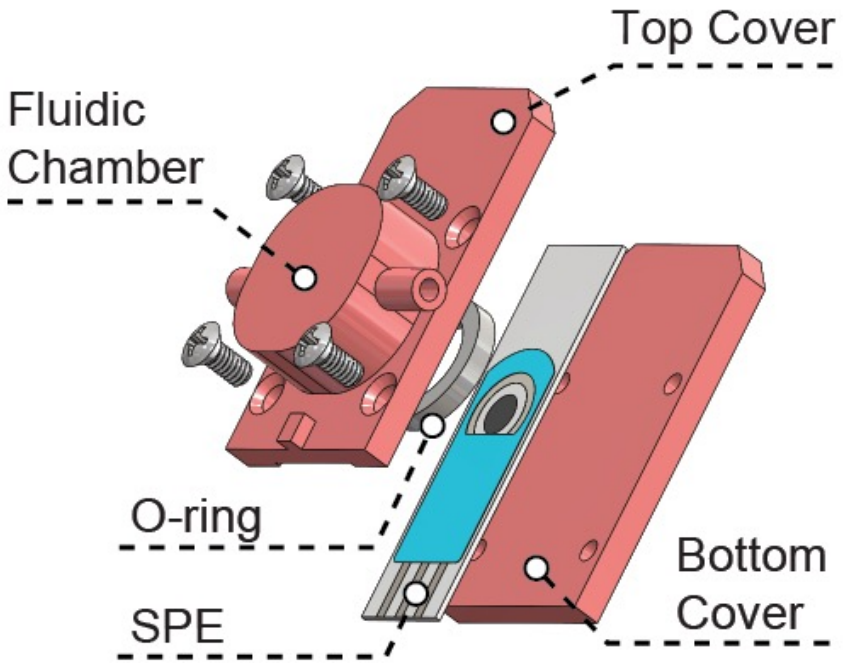
3D Printed Flow Cell and Mechanical Assembly

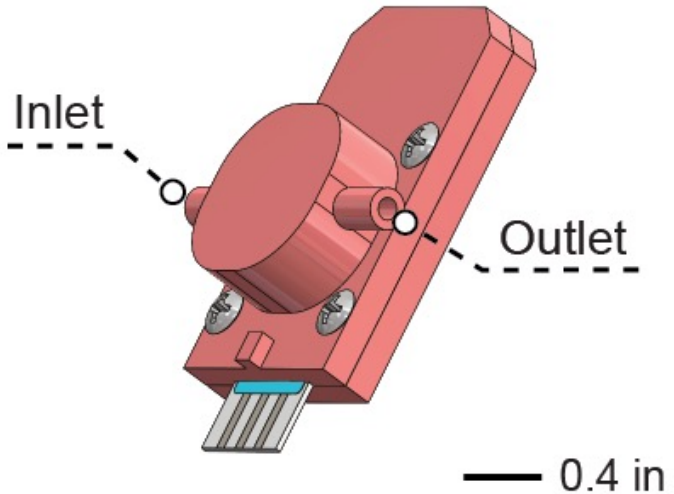
Flow Cell houses the electrochemical sensor:

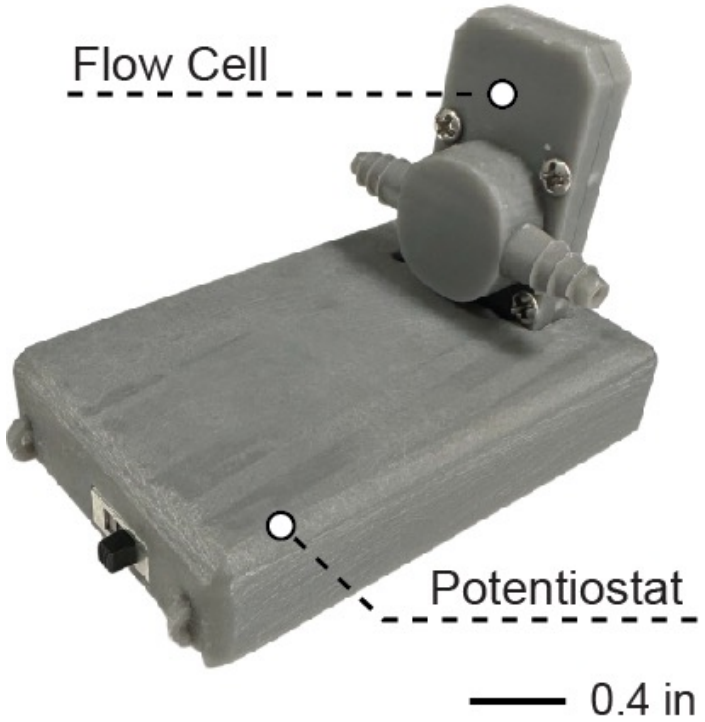
- Serves as a fluidic chamber with O-ring sealing
- In/outlet allow for connection to IV bag tubing
- Volume of ~80µL

Potentiostat casing:

- Easy dis/assembly for one-time-use SPEs
- Battery placed inside casing





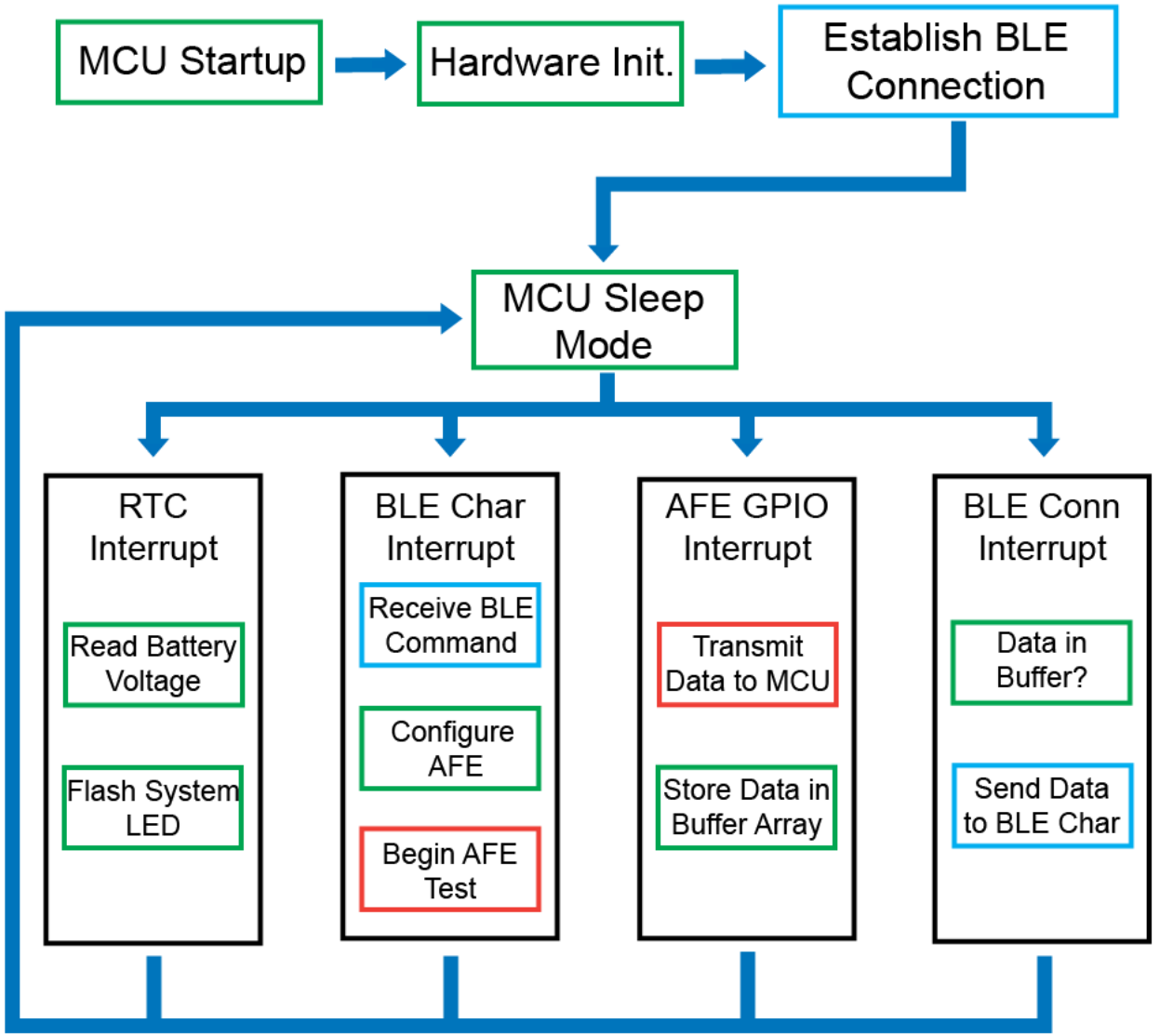


Device Firmware Operation

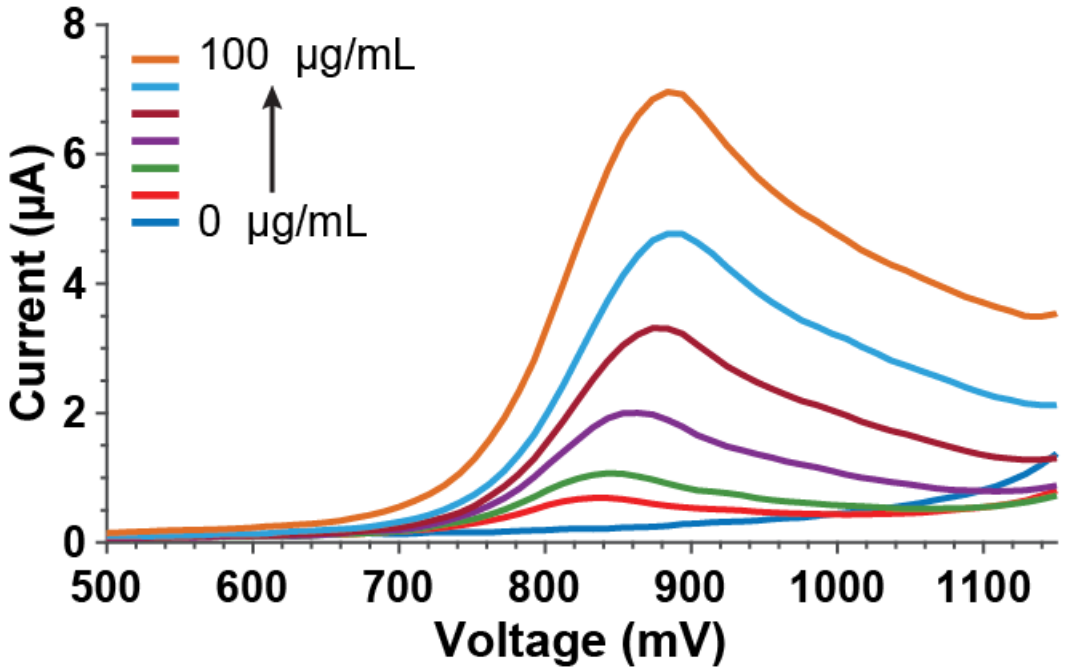
MCU enables interrupt-based tasks:
- Majority of time spent in sleep mode

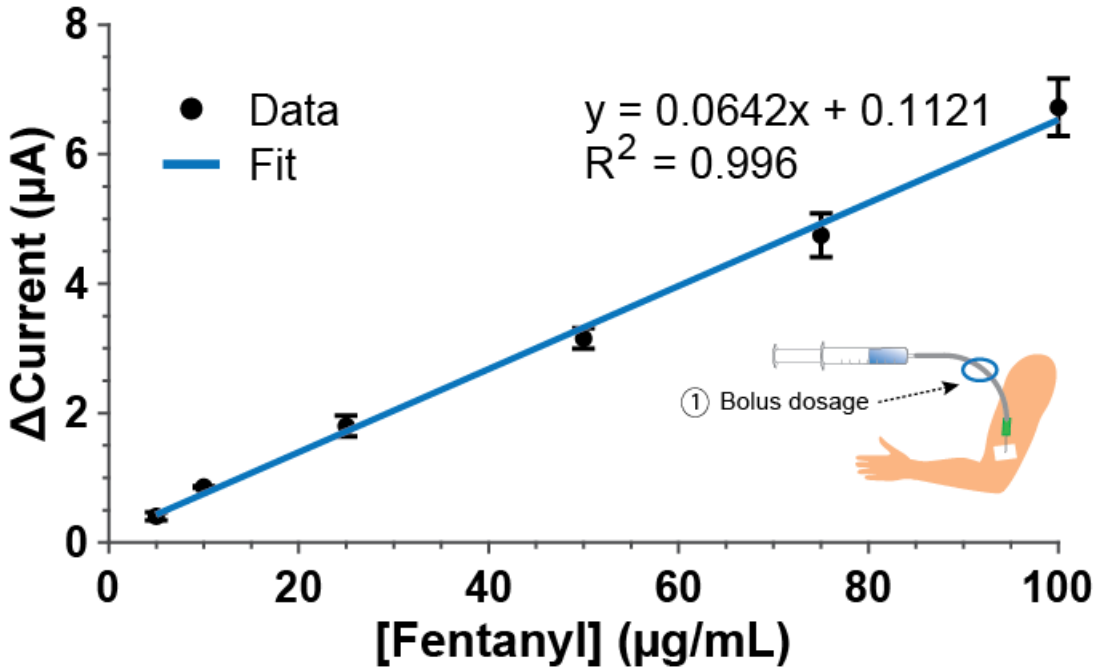
System Power Consumption:
- Sleep Mode: **36µA** (including BLE)
- Active Mode: **12.3mA** (running DPV)

Battery Lifetime (500mAh LiPo):
- 3.9 days (sampling every minute)
- 36.75 days (sampling every 10 minutes)



Fentanyl Measurements

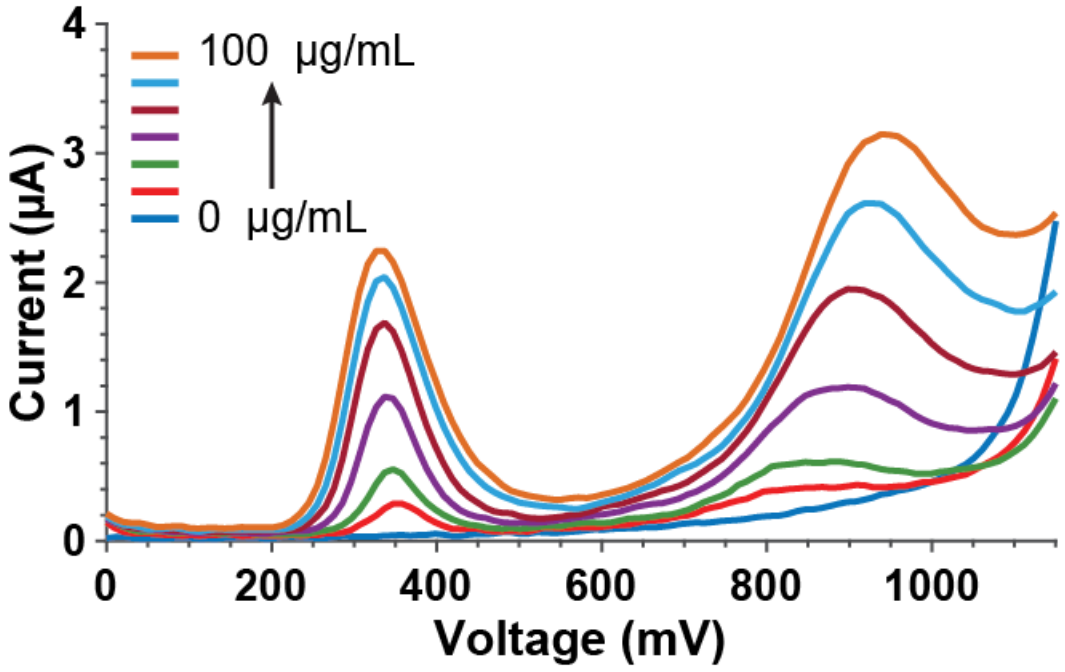


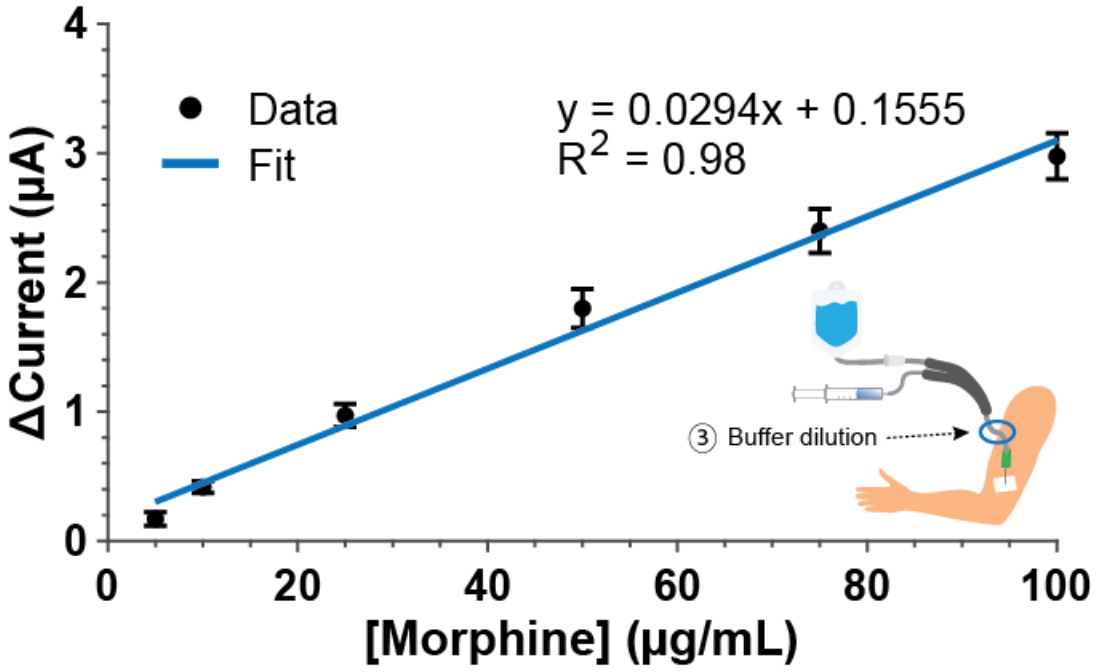


- Fentanyl solution measured at 0, 5, 10, 25, 50, 75, and 100 µg/mL
- Measured using SPE-150: platinum CE, carbon WE, silver RE
- DPV parameters: Estep = 10.2mV, Epulse = 25mV, tpulse = 50ms, Scan rate = 51mV/s
- Sensitivity = 64.2nA / (µg/mL)

Sensor achieves a linear response with an LoD = 1.26µg/mL

Morphine Measurements

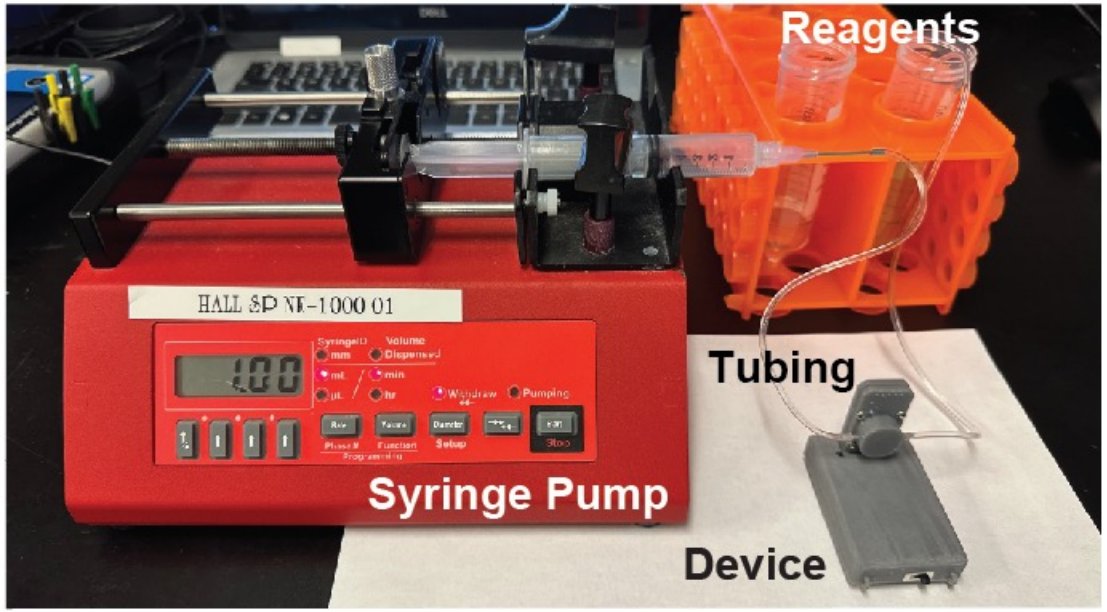


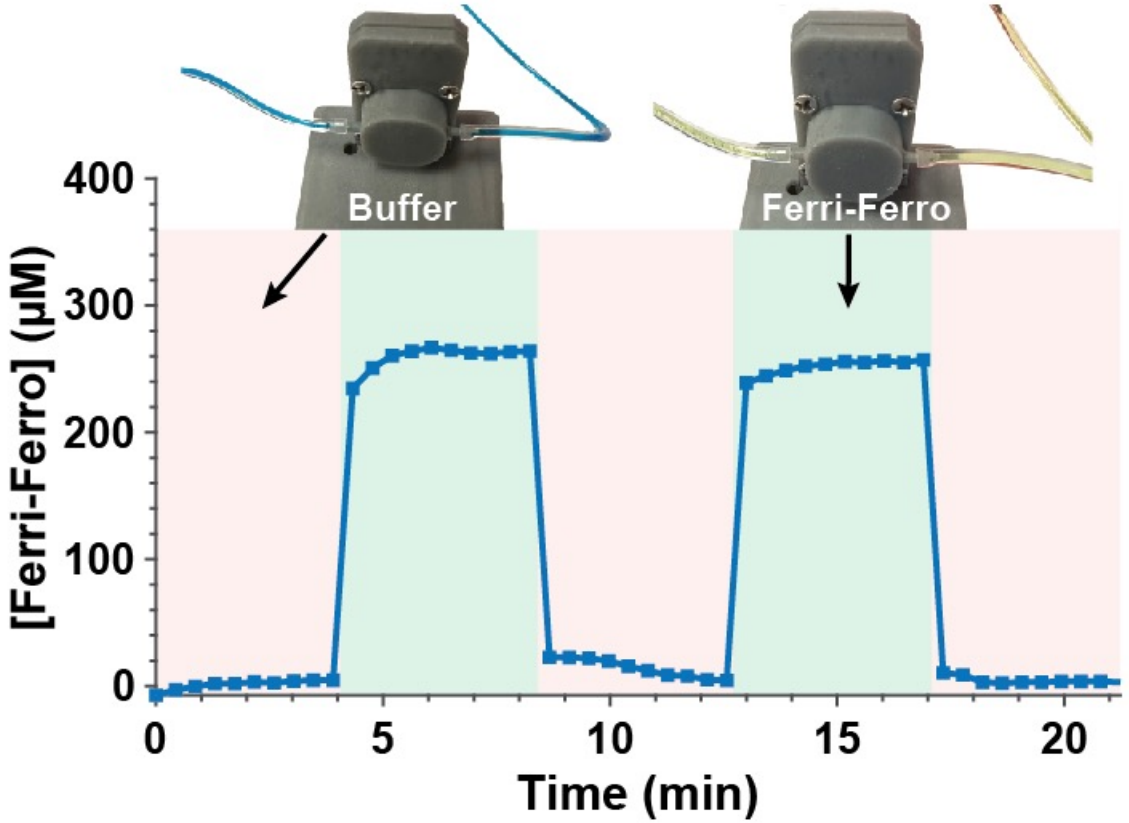


- Morphine solution measured at 0, 5, 10, 25, 50, 75, and 100 µg/mL
- Measured using SPE-150: platinum CE, carbon WE, silver RE
- DPV parameters: Estep = 10.2mV, Epulse = 25mV, tpulse = 50ms, Scan rate = 51mV/s
- Sensitivity = 29.4nA / (µg/mL)

Sensor achieves a linear response with an LoD = 2.75µg/mL

Real-time Flow Measurements





- The flow cell, SPE, and wireless device were installed onto a syringe pump
- Alternated 1x PBS and 250µM potassium ferri-/ferro-cyanide ($K_3[Fe(CN)_6]$) / ($K_4[Fe(CN)_6]$)
- Flow rate set to 1mL/min to mimic clinical opioid administration rates

Square wave data validates the reported system for accurate real-time fluidic measurements

Conclusions and Outlook

- A system for **real-time** intravenous opioid monitoring was presented to **prevent solution tampering** and **ensure accurate pain medication dosage** to patients
- Custom hardware and firmware was designed to enable battery-powered and wireless measurements:
  - System consumes **36µA** in sleep mode and **12.3mA** in active mode
  - Long lasting battery lifetime was achieved (**> 1 month** sampling every 10 minutes)
- Fentanyl and Morphine concentration curve data were measured via direct electrooxidation and DPV using SPEs
  - LoDs of **1.26µg/mL** and **2.75µg/mL** were achieved for fentanyl and morphine, respectively
- Continuous flow rate measurements were taken to validate the system's utility in a clinical IV drip bag scenario
- But…many other drugs have an electrochemical signature! This platform could be extended to applications like personalized medicine and metabolite monitoring

Thanks and Questions