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

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***Abstract*—Monitoring the dosage of opioids such as fentanyl and morphine in clinical settings is critical to ensuring adequate pain relief for patients while preventing under/overdosage. Despite numerous hospital regulations and procedures to ensure the right dosage is being administered, medication errors still occur. These procedures rely on implicit trust that there were no mistakes in each verification step, but fail to ensure that the solutions were not tampered with before administration. This work addresses this problem by developing an electrochemical-based sensor and wireless potentiostat that measures opioid concentrations continuously while connected in line with an IV drip system. We present measurements of fentanyl and morphine concentrations and validate the clinical use case through real-time fluidic measurements connected to a flow cell.**

Keywords—fentanyl, morphine, potentiostat, wireless, opioid, electrochemistry

I. Introduction

Opioids, including morphine and fentanyl, are commonly used for pain management during and post-surgery due to their analgesic properties [1], [2]. However, their administration requires extreme caution as they pose risks of respiratory depression, and patients can develop dependency [1], [2]. Fentanyl, in particular, is 50 – 100× more potent than morphine [1]. Consequently, even minor dosage adjustments can have drastic effects on patients. Fentanyl is rapidly absorbed (within approximately 1 minute) and has a clearance time of 30 to 60 minutes [3], underscoring the need for precise dosing and prompt response to dosage errors.

Hospitals implement multiple procedures to ensure accurate opioid dosing before administration. Pharmacists and doctors are responsible for diluting the opioid to the prescribed dosage for each patient. Nurses meticulously verify that the concentration matches the prescribed dosage and that the correct volume is delivered to the patient [4]. During administration, patient vital signs (*e.g.*, oxygen saturation, heart rate, and respiration rate) are closely monitored to determine if dosage adjustments are necessary [1], [2]. While these monitoring methods are effective, they rely solely on the accuracy of the solution preparation without any form of analytical verification. Unfortunately, instances of tampering, where opioids were substituted with diluted substances or buffer solutions, have been reported, resulting in the patient receiving little or no pain medication during surgical procedures [5]–[9]. Implementing real-time measurements of the opioid being administered to patients would "close the loop" in this system, enabling doctors and nurses to respond rapidly to errors, mitigate potential harm, and ensure patients receive the prescribed medication.

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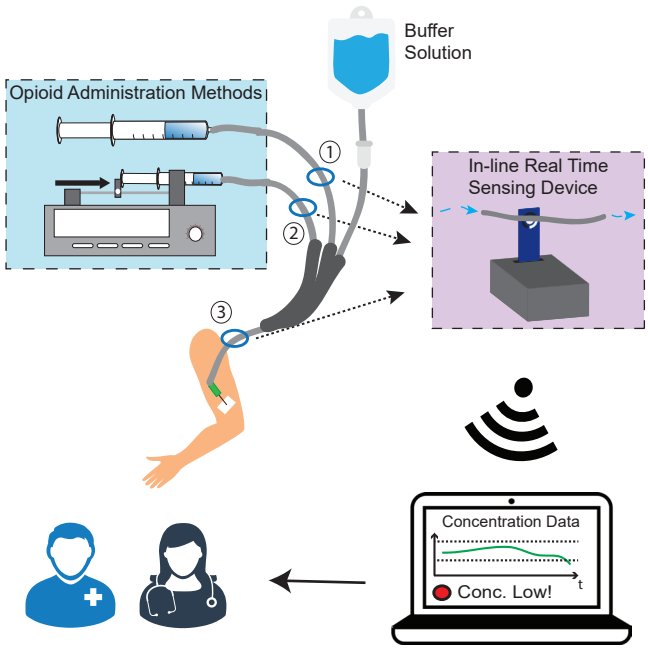

Fig. 1. Closing the loop of opioid administration by adding measurement (1) after bolus dosage, (2) after continuous IV dosage, or (3) after dilution with buffer solution.

With its high sensitivity and rapid response time, electrochemical analysis offers a promising avenue for real-time opioid monitoring in law enforcement and clinical settings [10]. During surgery, opioids are typically administered intravenously (IV) via bolus dosing (quick administration of the entire dose) or continuous infusion (slow administration over a prolonged time) [11]. A typical IV setup provides multiple points to monitor what is being administered to the patient, as shown in Fig. 1. A measurement device can be added directly in-line with the injection port, infusion pump, or downstream after mixing with saline. Such a device could also be added to patient-controlled analgesia pumps where patients self-administer controlled doses of pain medication (*e.g.,* morphine) to manage their pain levels.

This work reports an electrochemical measurement system that attaches to IV setups and provides real-time monitoring of opioids, specifically fentanyl and morphine. The measurement hardware was designed to be battery-operated and low-power (µW-level) with Bluetooth communication to a nearby data aggregator. A custom-designed flow cell was 3D-printed to package one-time-use electrochemical sensors.

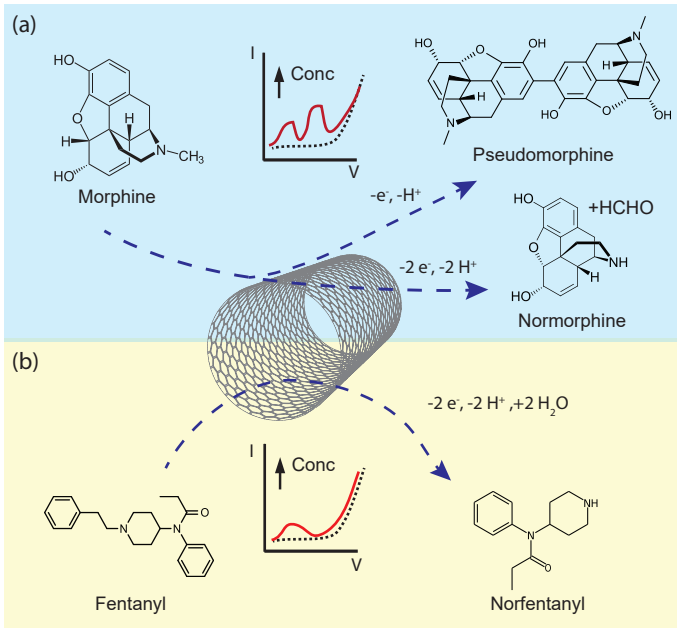

Fig. 2. Sensing principle showing direct electrooxidation of (a) morphine and (b) fentanyl.

II. Sensing Principle

The opioid is detected using an electrochemical sensing scheme based on direct electrooxidation, where oxidation of the compound results in direct electron transfer via a working electrode. Notably, this reaction occurs at the compound's redox potential, which depends on its chemical structure. Morphine's electroactivity stems from the phenolic and tertiary amine groups. Oxidizing the phenolic ring results in pseudomorphine and one electron, whereas oxidizing the tertiary group results in normorphine and two electrons (Fig. 2). As such, the voltammogram for morphine contains two anodic peaks, one at +340 mV and another between +830 – 940 mV, whose amplitudes depend on the morphine concentration [12]. Similarly, fentanyl is oxidized into norfentanyl through an N-dealkylation reaction [13], [14]. The resulting voltammogram has a distinct peak at +880 mV. Thus, the voltage where the reaction occurs can be used for compound identification. Direct electrooxidation is a simple, albeit non-specific, electrochemical technique to identify opioids without the need for a ligand (*e.g.*, aptamer) against an opioid [15], [16].

This oxidation reaction requires a carbon working electrode. We used a screen-printed electrode (SPE) from DropSens (SPE-150), which has a 4 mm carbon working electrode (WE), a platinum counter electrode (CE), and a silver reference electrode (RE). An SPE was chosen over a more conventional solid-metal electrode for cost reasons and because it can be discarded post-use to prevent cross-contamination. Measuring the reaction current is possible with several amperometric techniques, such as chronoamperometry (CA), cyclic voltammetry (CV), or pulsed voltammetry. We use differential pulse voltammetry (DPV) as it is highly sensitive and has better oxidation peak voltage resolution than more straightforward techniques like CV [17], despite requiring a more complex potentiostat to generate the waveform.

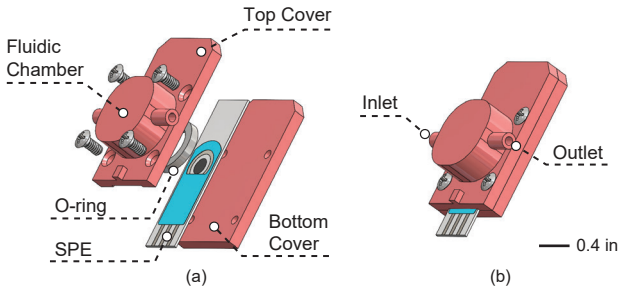

Fig. 3. (a) Exploded and (b) assembled view of the 3D-printed flow cell housing a screen-printed electrode.

III. Hardware

As this system is intended to sit in line with an IV bag and monitor opioid concentration levels continuously, the design should be fully wireless and battery-powered to support easy integration into existing IV setups while maximizing the battery lifetime. The reported system consists of a flow cell housing an SPE and a custom-designed potentiostat to perform the measurements, read out the data, and transmit it wirelessly to a smartphone or computer for visualization and analysis. All components (*i.e.*, the printed circuit board and battery) are enclosed within a 3D-printed enclosure to provide portability and eliminate the possibility of fluidic leakage onto the circuitry. The enclosure hangs from a standard IV setup.

A. Flow Cell

A flow cell is critical to ensure that the solution is measured with a constant flow rate and volume, and is seamlessly connected in line with an IV bag via tubing that mimics how fentanyl or morphine is administered clinically. The custom-designed flow cell (see Fig. 3) guides the solution through a cartridge that houses the SPE and serves as a fluidic chamber. The flow cell was designed using SOLIDWORKS and printed with a resin-based 3D printer (FormLabs 3B). It comprises two pieces (Top and Bottom) that sandwich the SPE using an O-ring for sealing. The flow cell has a total volume of 80 µL.

B. Potentiostat and Microcontroller

The measurement hardware (Fig. 4) consists of an Analog Devices AD5940 front-end connected to a Bluetooth-enabled microcontroller and power management circuitry. The AD5940's high-level integration, wide reconfigurability, and low-power consumption make it superior to once prevalent discrete potentiostat implementations [18], [19]. The front-end provides tunable amplification settings, filtering options, and a programmable wide-output-range digital-to-analog converter to generate any electrochemical technique waveform. These features maximize the chip's dynamic range while only requiring a handful of off-chip passive components and extend this device's utility beyond fentanyl and morphine.

A low-power Nordic nRF52840 Bluetooth Low Energy (BLE) System-on-Chip controls the AD5940 (*i.e.*, setting the measurement parameters and collecting the data) and supports wireless data telemetry. The device integrates an ARM Cortex-M4 microcontroller (MCU), a BLE radio, and all the necessary peripherals needed, including an internal analog-to-digital converter, serial peripheral interface (SPI) communication,

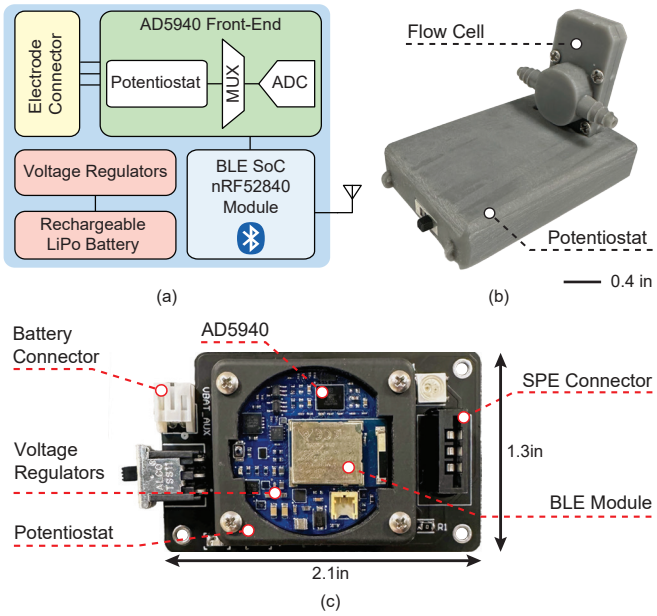

Fig. 4. Potentiostat hardware. a) Block diagram; b) Photograph of the fully assembled device in the case; c) Annotated image of the printed circuit board.

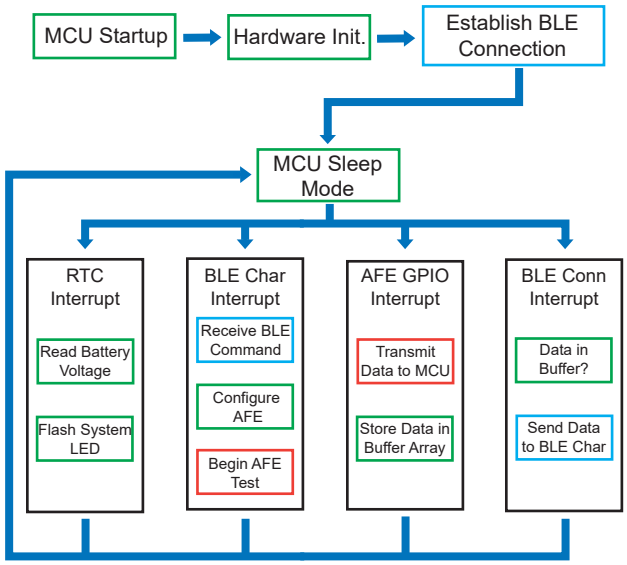

Fig. 5. Software flow diagram illustrating the event-driven operation.

timers, and general-purpose I/O pins (GPIOs). Furthermore, the radio consumes only ~6.4 mA during a BLE transmission, while the MCU can be placed into a low-power state (<10 µA). These are leveraged to significantly extend the battery lifetime.

C. Power Management

The opioid's high oxidation potential (~900 mV) requires a wide scan range (*i.e.*, >1 V). Furthermore, the CE has a significant overpotential (>300 mV) that the potentiostat must apply; thus, the AD5940 is operated at its maximum supply voltage (3.6 V) to increase the compliance voltage (*i.e.*, prevent CE clipping). The system is powered by a 3.7 V, 500 mAh Lithium-Ion Polymer battery (LP503035) [(Fig. 4(b)], located below the potentiostat. To utilize the battery's full range (3 – 4.2 V), an ultra-low quiescent power buck-boost converter (MAX17270) generates 3.6 V (for the MCU) and 4.1 V supply rails. The 4.1 V supply has a low-dropout regulator (TPS7A2036) to produce a ripple-free 3.6 V for the AD5940.

IV. Firmware

Following a brief hardware initialization period, the device begins advertising for external BLE central devices on power-up. After pairing to the device and establishing a BLE connection, the MCU enters a sleep state to reduce its idle power consumption. In this state, all subsequent functionality is handled via dedicated events, allowing the MCU and BLE radio to remain asleep and only wake up when needed. The potentiostat is also powered down in this state to reduce power consumption. As depicted in Fig. 5, four event routines are implemented. The first is a timer interrupt generated from the MCU's real-time clock (RTC) that periodically monitors the system battery voltage level and indicates the device status by blinking a light-emitting diode (LED). A second interrupt is triggered when the central device updates the BLE command characteristic, which stores commands from the central device about the potentiostat configuration, DPV parameters (*i.e.*, scan range, scan rate, current range, etc.), and start/stop commands to control the execution of a measurement. When the MCU finishes parsing the received commands, the potentiostat configuration is updated with any new settings.

The remaining two interrupts handle receiving and transmitting measured data from the AD5940 to the MCU and back to the central device. After the MCU initiates an electrochemical measurement, the potentiostat autonomously collects current and voltage data and stores the samples inside its internal buffer. The MCU remains asleep during this time to save power. When the buffer is full, the AD5940 triggers an MCU interrupt by pulling a pin low. At this point, the MCU wakes up and reads the data stored in the buffer over an SPI bus. Compared to Bluetooth classic, the advantage of using BLE in this application stems from the slow scan times and low data rates of DPV (each scan takes ~26 seconds and collects only 32 kB of data). This means the BLE radio does not need to run the entire time. Instead, the BLE radio is only active during dedicated connection intervals. These connection events occur at a fixed period, during which the MCU checks if data has been added to its internal buffer. If new data is available, it is transmitted to the central device during the connection interval; otherwise, the radio remains off. After executing any interrupt routine, the MCU returns to its idle sleep state.

The power-saving optimizations described and the careful selection of low-power integrated circuits allow the system to consume only 36 µA during sleep mode (including periodic BLE connection intervals and the RTC interrupt tasks) and 12.3 mA during electrochemical measurements. The device lifetime with a 500 mAh battery can be calculated with the sampling frequency. For example, with a 26-second measurement time, measuring once per minute results in an average current consumption of 5.35 mA and a 3.9-day battery lifetime, whereas sampling every 10 minutes reduces the average current to 567 µA, extending the lifetime to 36.75 days.

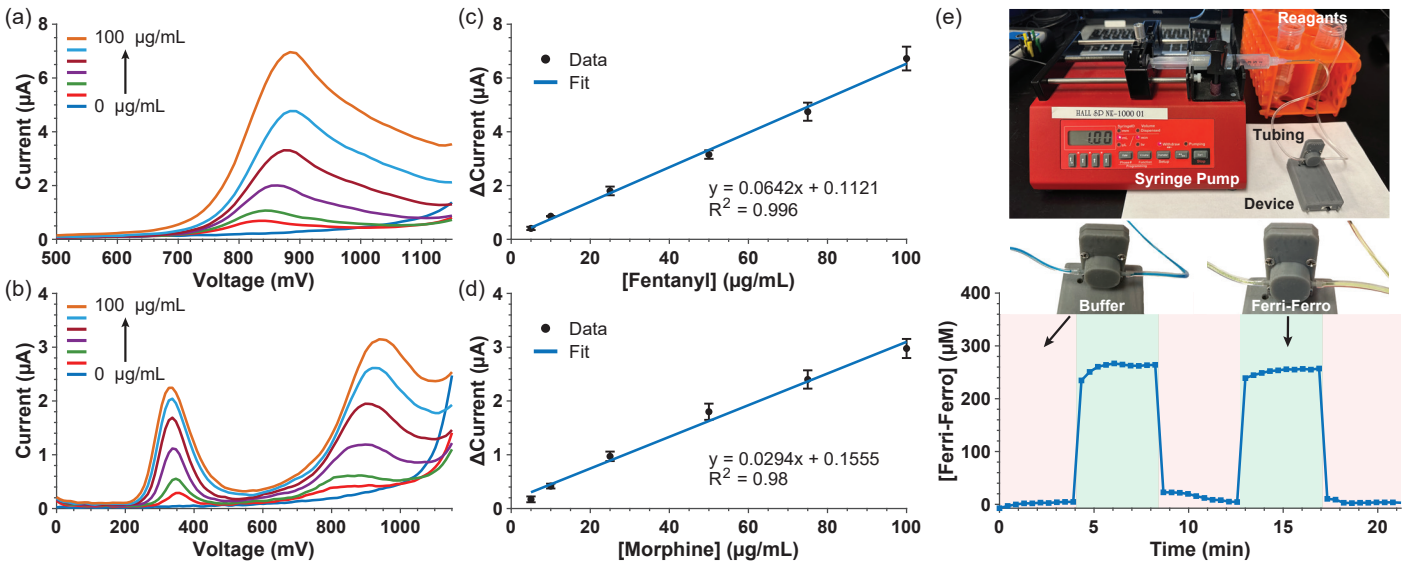

Fig. 6. Measured data for fentanyl and morphine. a,b) Voltammograms across the therapeutic range; c,d) Calibration curves (n = 3); e) Real-time measurements of ferri-/ferrocyanide using the reported flow cell and hardware. Insets show photographs of the measurement setup and flow cell at various time points.

V. Measurement Results

A. Reagents and Equipment

Fentanyl is sold to hospitals in 50 µg/mL doses and administered to patients at concentrations ranging from 5 to 50 µg/mL, depending on the required dosage calculated from the patient's weight [20]. Lower concentrations are preferred when volume administration cannot be finely controlled, and higher concentrations are preferred to prevent fluid overflow due to large volumes of liquid being administered to patients with lower weight (*e.g.*, children) [21]. Morphine, on the other hand, is sold at 1 mg/mL and can be diluted down to 0.1 mg/mL before administering to a patient [22]. Reference standards for fentanyl (F-013-1ML) and morphine (M-005-1ML) were purchased from Sigma Aldrich and tested across the clinical therapeutic range, which depends on how the drug is administered (Fig. 1). All concentrations were diluted in 1× phosphate buffer saline (PBS). Voltammograms were recorded using DPV scanned from 0 – 1.2 V with a 10.2 mV step voltage, 25 mV pulse voltage, 50 ms pulse, and a 51 mV/s scan rate.

B. Calibration Curves

The opioid was diluted in PBS from its stock concentration (in methanol) to final concentrations of 5, 10, 25, 50, 75, and 100 µg/mL for fentanyl and morphine (see Safety note below). The diluted opioid was then drop-cast on an SPE connected to the reported potentiostat and measured. The SPE was rinsed and dried after each solution. Each measurement was performed three times using different SPEs. Figure 6(a,b) shows overlaid voltammograms for fentanyl and morphine, respectively. For fentanyl, the voltammograms contain a single peak, whereas morphine has two peaks, as described earlier. The second peak was used to generate the morphine calibration curve due to its increased sensitivity and linearity compared to the first peak. The peak values were extracted using MATLAB, background subtracted, and plotted against the concentration to generate a calibration curve [Fig. 6(c,d)]. The limit of detection (LOD) is 1.26 µg/mL for fentanyl and 2.75 µg/mL for morphine [24].

Safety note: Fentanyl is potentially lethal, even as little as 0.25 mg [23]. All experiments involving fentanyl were conducted inside a fume hood, wearing personal protective equipment per a university-approved handling protocol.

C. *in vitro* Testing

After testing the sensor with a static solution, we installed the flow cell onto an SPE and connected it to a syringe pump. We alternated flowing 1× PBS (dyed blue for contrast) and an equal parts mixture of 250 µM potassium ferri-/ferro-cyanide ($K_3[Fe(CN)_6]$) / ($K_4[Fe(CN)_6]$) from Spectrum (P1286, P1296) (as a proxy for fentanyl to do testing outside a fume hood) at 1 mL/min with measurements every 26 seconds. Figure 6(e) shows the measured current vs. time and photographs at various time points. The clear increasing/decreasing pattern of the concentration data when the fluid was switched validates the ability of the reported system to conduct accurate and consistent fluid measurements at a flow rate comparable to those used in clinical opioid administration. The transient signal after switching fluids is due to mixing and flushing the flow cell.

VI. Concluding Remarks

This work reports a low-power, Bluetooth-enabled potentiostat integratable with several conventional IV opioid administration methods. The compact design consumes just 36 µA in the sleep mode, enabling more than a 30-day lifetime with a 10-minute sampling interval. Using differential pulse voltammetry, electrooxidation of fentanyl was detected at concentrations as low as 1.26 µg/mL and morphine as low as 2.75 µg/mL, including continuous real-time measurement. This work demonstrated fentanyl and morphine; however, many other drugs also have an electrochemical signature. While intended to verify the integrity of the opioid administered during and post-surgery, many other applications exist, such as monitoring opioid metabolites and controlling the upstream dosage to enable personalized medication.

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