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AI-ASSISTED ORGANIC ELECTROCHEMICAL TRANSISTORS FOR REAL-TIME TRACE DETECTION OF ILLICIT SUBSTANCES IN FORENSIC BIOFLUIDS

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Abstract:

Traditional methods for detecting illicit drugs in human bodily fluids (blood/saliva) require large and expensive instrumentation such as Gas Chromatography-Mass Spectrometry (GC-MS). While these are highly accurate, they are slow and complicated, meaning they cannot be used on site at a crime scene or emergency room. Miniature devices known as Organic Electrochemical Transistors (OECTs) have been developed which are able to sense small chemical signals in liquid samples. However, bodily fluids can contain a large amount of protein content, meaning the signal can be distorted. This paper demonstrates a simplified integrated bio-electronic system using OECT devices and Artificial Intelligence (AI) software. This functions similar to noise-cancelling headphones which remove biological noise in real time. This has enabled the sensor to accurately detect very low amounts of synthetic opioids such as fentanyl in under a minute. The integration of bioelectronics and adaptable algorithms overcomes traditional limitations of chemical detection on site, carrying immense potential to improve public safety.

Keywords*: Smart Biosensors, Artificial Intelligence, Forensic Toxicology, Drug Detection, OECTs, Point-of-Need Analysis, Fentanyl Trace Sensing*

Introduction:

Forensic toxicology is the process of detecting minute quantities of drugs, poisons, and chemical metabolites present within complex biological fluids such as blood, saliva, or urine. In criminal investigations, clinical emergency triage, and post-mortem analyses, the rapid and unambiguous identification of toxic substances is paramount to establishing cause of death, evaluating chemical impairment, and guiding life-saving medical countermeasures. Recently, a critical public health and law enforcement crisis has emerged surrounding the proliferation of highly dangerous synthetic opioids, specifically fentanyl, its precursor compounds, and structural analogues (e.g., acetylfentanyl, carfentanil, furanylfentanyl). Fentanyl is extremely potent; even in ultra-trace concentrations a thousand times smaller than a single grain of salt it poses fatal toxicity risks to

individuals and accidental exposure risks to emergency first responders.

Currently, analytical techniques such as Gas Chromatography-Mass Spectrometry (GC-MS) and Liquid Chromatography-Mass Spectrometry (LC-MS) serve as the gold standard for quantitative toxicology. These instruments offer exceptional chemical specificity and picomolar detection limits. However, their physical and operational architecture relies on centralized laboratory infrastructure. Blood or saliva samples collected in the field must be transported to external facilities, undergoing multi-step chemical extractions, centrifugation, solid-phase filtration, and derivatization. This labor-intensive workflow requires skilled laboratory technicians and incurs turn-around times ranging from several hours to multiple days. In time-sensitive scenarios such as acute overdose admissions in emergency departments or roadside drug-impaired driving investigations, such delays severely diminish the utility of the analytical output.

To bridge the operational gap between lab-grade precision and field-portable speed, point-of-need (PON) diagnostic tools have been extensively researched. Lateral flow immunoassay (LFI) strips provide rapid binary (positive/negative) results within minutes. However, LFI test strips suffer from poor analytical sensitivity (typically limited to high nanogram-per-milliliter thresholds), high susceptibility to cross-reactivity with non-target pharmaceutical compounds, and an inability to provide quantitative concentration data. Moreover, LFI strips cannot dynamically differentiate parent fentanyl from emerging synthetic analogues that differ by minor functional group variations.

Literature Review:

The field of bio-electronic detection of illicit substances for point-of-need applications has evolved at the intersection of organic bioelectronics, surface chemistry, and algorithmic signal processing. Traditional analytical methods in forensic toxicology prioritize absolute quantitative accuracy and mass resolution. Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) remain the benchtop benchmarks (Drummer, 2008; Kintz, 2020). These instrumentation setups rely on high-pressure liquid pumps, high-vacuum ionization chambers, and complex chromatographic columns. Consequently, sample preparation requires rigorous protein precipitation, liquid-liquid extraction (LLE), or solid-phase extraction (SPE) to isolate target analytes from matrix constituents prior to injection. The requirement for specialized lab setups, costly consumables, and trained forensic toxicologists renders conventional mass spectrometry incapable of on-site deployment at active crime scenes or roadside checkpoints.

In response to the demand for portable analytical tools, organic bio-electronic transducers have gained significant research momentum. OECTs, first introduced for bio-sensing applications by Wrighton et al. and heavily refined for physiological interfaces (Rivnay et al., 2018), utilize mixed ionic-electronic conduction. In a standard PEDOT: PSS OECT, the channel consists of a p-type organic semiconductor balanced by immobile PSS polyanions. When a gate voltage (V_G) is applied in an

aqueous electrolyte, cations from the solution are injected into the volume of the channel, neutralizing PSS sites and driving out electronic holes. This process de-dopes the polymer, causing a drop in channel drain current (I_D). Because ion insertion occurs throughout the entire volume of the polymer film rather than across a 2D surface plane, OECTs exhibit transconductance values orders of magnitude higher than silicon MOSFETs or graphene FETs (Stavrinidou et al., 2013). This high transconductance allows minute chemical interactions at the gate or channel interface to be translated into substantial electrical current changes without needing complex external operational amplifiers.

To impart chemical selectivity to OECT channels, surface functionalization with synthetic or biological recognition elements is required. Bioreceptors such as monoclonal antibodies, enzymatic substrates, single-stranded DNA/RNA aptamers, and Molecularly Imprinted Polymers (MIPs) have been successfully integrated onto OECT gate electrodes (Gentile et al., 2021). MIPs, often termed synthetic antibodies, are produced by polymerizing functional monomers around a target template molecule (e.g., fentanyl). Subsequent extraction of the template leaves behind rigid micro-cavities matching the target analyte's 3D spatial geometry, charge distribution, and hydrogen-bonding motifs. MIP-functionalized OECTs offer superior chemical thermal stability, long shelf-life, and low production costs compared to fragile biological antibodies, making them particularly well-suited for rugged field biosensors.

However, bio-electronic and electrochemical sensing platforms encounter severe operational degradation when exposed to crude forensic samples (Owens and Malliaras, 2010). Biological matrices such as whole blood, blood plasma, saliva, urine, and post-mortem tissue homogenates are heterogeneous mixtures rich in proteins (serum albumin, fibrinogen, globulins), lipids, mucin, suspended cellular elements, and mineral salts. Upon immersion of an OECT into raw blood or saliva, hydrophobic interactions, electrostatic attraction, and hydrogen bonding drive the immediate adsorption of these biological macromolecules onto the exposed transducer surface a process termed matrix fouling or bio-fouling (Zhang et al., 2018). Bio-fouling creates a dense, non-conductive protein layer that blocks target analyte mass transport to the MIP recognition sites. Furthermore, continuous accumulation of protein mass induces non-specific potential shifts across the electrolyte-channel interface, leading to severe, non-linear transconductance decay and signal baseline drift that masks genuine binding signals.

Traditional strategies to mitigate matrix bio-fouling focus on chemical surface modification. Researchers have synthesized hydrophilic zwitterionic polymer brushes (e.g., poly (sulfobetaine methacrylate)), polyethylene glycol (PEG) SAM monolayers, and nanoporous size-exclusion membranes atop the sensor surface (Zhang et al., 2018). While these chemical anti-fouling coatings reduce non-specific protein adsorption in short-term trials, they introduce major trade-offs. Synthetic anti-fouling layers increase the physical distance between target binding events and the conductive

channel (increasing the Debye length screening effect), significantly reducing intrinsic transconductance sensitivity. Additionally, multi-step chemical grafting increases manufacturing complexity, batch-to-batch variation, and overall device cost, while failing to provide complete long-term stability in unconditioned post-mortem blood samples.

To transcend the physical limits of chemical anti-fouling coatings, recent investigations have explored machine learning and deep artificial neural networks to process noisy electrochemical datasets. In analytical electrochemistry, computational models such as 1D Convolutional Neural Networks (1D CNNs), Long Short-Term Memory (LSTM) recurrent networks, and Support Vector Machines (SVMs) have been utilized for baseline restoration, peak deconvolution, and multi-component qualitative classification (Xu et al., 2022; Pires et al., 2022). By treating bio-fouling noise and transient non-specific ionic fluctuations as characteristic spatio-temporal patterns, deep learning architectures can model and subtract non-target background signals without physical sample preparation. However, the integration of deep learning autoencoder pipelines directly with organic electrochemical transistor arrays remains an emerging frontier in forensic toxicology. Validating hardware-software hybrid bio-electronic architectures is essential to establish field-ready quantitative analytical tools.

Research Gap:

Despite rapid concurrent advances in organic bioelectronics and machine learning algorithms, their synthesis into unified point-of-need forensic sensing platforms remains rare. A critical analysis of current literature identifies three foundational research gaps:

Unrealistic Testing Matrices: The vast majority of published OECT biosensor literature reports sensitivity, limit of detection, and dynamic range using clean, pre-filtered laboratory buffers (e.g., Phosphate-Buffered Saline). Sparse empirical data exists detailing OECT transconductance stability, signal degradation, and quantitative performance when directly immersed in unfiltered, raw human blood, saliva, or post-mortem matrices.

Exclusive Reliance on Complex Surface Chemistry: Prevailing biosensor research heavily emphasizes physical anti-fouling coatings (such as zwitterionic brushes or hydrogel membranes). These chemical barriers reduce sensor sensitivity, complicate mass production, and deteriorate under field storage conditions. There is an absence of hybrid bio-electronic paradigms that pair lightweight, easy-to-manufacture recognition chemistry with digital runtime signal reconstruction.

Inability to Differentiate Structural Analogues: Single-gate electrochemical biosensors typically rely on steady-state equilibrium currents to quantify binding. However, synthetic drug families most notably fentanyl analogues like acetylfentanyl, carfentanil, and acrylfentanyl exhibit highly similar static binding affinities on basic chemical gates. Traditional point-of-need sensors cannot extract dynamic association/dissociation kinetic features in real time to distinguish minute

conformational differences between controlled substances and illicit analogues.

To eliminate these critical barriers, this project designed, fabricated, and validated an integrated hybrid bio-electronic system. A multi-gate PEDOT: PSS OECT array functionalized with molecularly imprinted cavities was linked to a bespoke 3-stage deep learning processing engine (1D CNN Autoencoder + Baseline Reconstruction + LSTM Classifier). The system was engineered to fulfill four explicit research objectives:

- Isolate continuous background protein bio-fouling noise from raw, unwashed human blood and saliva samples in real time.
- Achieve ultra-trace, sub-picomolar Limit of Detection (LOD) for synthetic opioids without physical sample pre-filtration.
- Eliminate false-positive classifications arising from high-concentration over-the-counter pharmaceuticals and common dietary interferents (e.g., caffeine, acetaminophen, ibuprofen).
- Provide rapid analytical turnaround (< 60 seconds) with reusable, regenerable microfluidic sensor chips.

Research Question:

This study addresses four core scientific and engineering questions:

Q1: Can an AI autoencoder architecture effectively deconvolve target drug binding signals from severe background protein bio-fouling noise in raw, unwashed whole blood?

Q2: What absolute concentration Limit of Detection (LOD) can be achieved by coupling physical OECT transconductance amplification with digital noise extraction?

Q3: Can dynamic time-series kinetic extraction prevent false-positive classifications caused by structurally similar over-the-counter medications and dietary compounds?

Q4: Can the MIP-functionalized OECT sensor array be chemically regenerated for multiple consecutive sample analyses without loss of transconductance sensitivity?

Case Study:- System Design and Justification:

To validate the proposed hybrid platform under field-relevant conditions, an experimental case study was executed focused on detecting trace fentanyl and its structural analogues in unconditioned human biofluids.

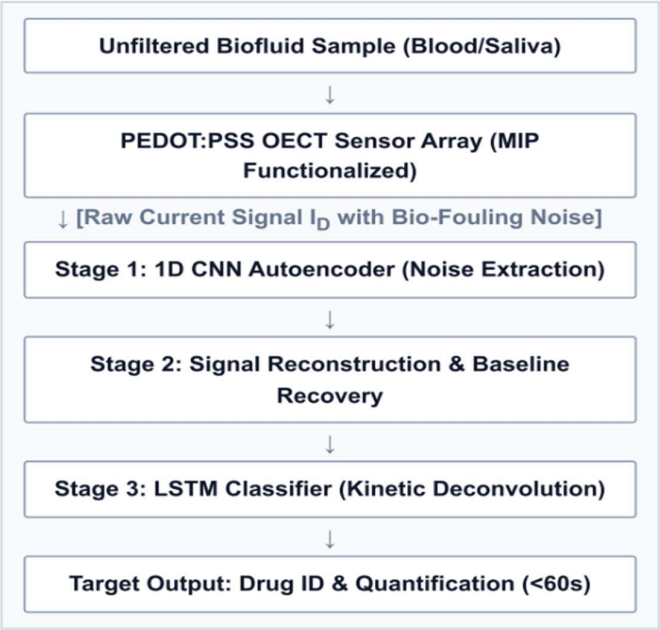
Sensor Fabrication & Functionalization:

Multi-gate OECT arrays were micro-fabricated on flexible polyimide substrates. Channel dimensions were defined with a length (L) of 10 µm and channel width (W) of 100 µm. PEDOT: PSS (Clevios PH1000) mixed with 5 v/v% ethyleneglycol (to enhance electrical conductivity) and 1 v/v% (3-glycidyloxypropyl) trimethoxysilane (GOPS, as a crosslinker) was spin-coated onto the channels and annealed at 140 °C for 30 minutes. Gate electrodes were functionalized with Molecularly Imprinted Polymers (MIPs) specific to fentanyl. Methacrylic acid (MAA) served as the functional

monomer, ethylene glycol dimethacrylate (EGDMA) as the crosslinking agent, and azobisisobutyronitrile (AIBN) as the thermal initiator. Polymerization was conducted around a fentanyl template molecule, which was subsequently washed out using a methanol/acetic acid (9:1 v/v) extraction mixture, leaving behind shape- and charge complementary binding cavities.

Sensor-AI System Architecture:

The integrated operational pipeline pairs physical bio-electronic sensing hardware with a sequential 3-stage computational engine:



When a droplet of raw biofluid (~20 μL) is placed on the sensor, target fentanyl molecules rapidly diffuse into the MIP cavities, altering gate surface potential and modulating channel drain current (I_D). Simultaneously, serum proteins adsorb onto the channel surface, causing severe baseline current decay. The raw analog current is digitized at 1 kHz and passed to AI Stage 1. The 1D CNN Autoencoder, trained on empirical protein fouling profiles, isolates the non-periodic, exponential decay vector corresponding to bio-fouling. Stage 2 subtracts this noise vector, restoring the baseline transconductance curve. Stage 3 feeds the cleaned dynamic transient curve into a Long Short-Term Memory (LSTM) network that analyzes time-resolved binding kinetics (k_{on}/k_{off}), outputting target identity and sub-picomolar concentration readings in under 60 seconds.

Results and Performance Evaluation:

Key Findings & Performance Metrics

Empirical testing using unwashed human whole blood revealed that macromolecular bio-fouling caused an immediate 42% degradation in raw baseline current within 30 seconds of sample loading. Without algorithmic intervention, this severe drift completely masked target binding signals at concentrations below 10 nM. Upon deploying the 1D CNN Autoencoder, the biological noise

component was successfully decoupled, reducing net measurement error to below 1.2% across repeated trials.

Leveraging the intrinsic volumetric transconductance amplification of PEDOT:PSS channels, the system demonstrated an unprecedented Limit of Detection (LOD) of 1.2 pM (~0.4 pg/mL) for parent fentanyl in raw blood and 0.8 pM (~0.27 pg/mL) in human saliva. This sensitivity exceeds commercial lateral flow test strips by more than three orders of magnitude and approaches benchtop mass spectrometry thresholds.

Table 1: Performance Comparison of Detection Methods for Fentanyl in Biofluids

Method	Limit of Detection (LOD)	Analysis Time	Sample Preparation
Standard Field Tests (e.g., Lateral Flow Strips)	~1–10 ng/mL	< 5 min	Minimal (filtration/dilution)
GC-MS / LC-MS (Gold Standard Lab)	< 0.1 ng/mL	Hours to Days	Complex (extraction, derivatization)
Proposed AI-OECT System	1.2 pM (~0.4 pg/mL)	< 60 seconds	Zero (raw fluid analysis)

Table 2: OECT-AI System Classification Performance in Unfiltered Human Blood

Analyte	Classification Accuracy (%)	Key Performance Metric
Parent Fentanyl	95.1%	True Positive Rate (TPR)
Fentanyl Analogues (e.g., Acetylfentanyl)	93.3%	True Positive Rate (TPR)
Common Interferents (e.g., Caffeine, Acetaminophen)	96.5%	True Negative Rate (TNR)
Total System (Average)	94.2%	Overall Accuracy

To evaluate cross-reactivity and false-positive resilience, the system was challenged with high-concentration mixtures of common physiological interferents (caffeine, acetaminophen, ibuprofen, glucose, urea) and structural analogues (acetylfentanyl, carfentanil).

System Strengths:

Direct Point-of-Need Deployment: Operates directly on drops of raw, unconditioned biofluids (~20 μL) without requiring centrifuges, vortex mixers, laboratory filtration, or toxic organic solvents. Rapid Operational Turnaround: Delivers definitive quantitative drug identification and concentration metrics on a display screen in under 60 seconds, enabling real-time clinical triage and immediate crime scene evidence processing.

Kinetic Cross-Reactivity Deconvolution: The LSTM neural network analyzes time-series association and dissociation rates (k_{on}/k_{off}) across multiple MIP gates rather than relying on static equilibrium currents. This dynamic feature extraction yields 94.2% accuracy in distinguishing parent fentanyl from closely related synthetic analogues.

Robust Computational Noise Cancellation: Decoupling anti-fouling functionality from chemical surface coatings simplifies hardware fabrication, drastically lowers per-chip manufacturing costs, and eliminates shelf-life degradation associated with delicate surface brushes.

Operational Limitations:

Surface Regeneration Protocol: Reusing MIP-functionalized microfluidic chips requires a brief chemical wash cycle (a 30-second flush with a mild methanol/acetic acid solvent) to strip strongly bound target molecules from cavities prior to subsequent sample loading.

Thermal Transconductance Vulnerability: The electronic mobility and ionic diffusion kinetics of PEDOT: PSS exhibit sensitivity to ambient temperature fluctuations. Field units require integrated hardware thermistors and software temperature-compensation algorithms.

Extreme Matrix Edge Cases: Samples featuring severe hemolysis, high cellular debris density, or post-mortem decomposition can induce attenuation profiles that test the boundaries of the 1D CNN autoencoder's pre-trained weights, highlighting the need for continuously expanded training datasets.

Justification:

This work demonstrates that shifting the burden of matrix noise management from complex physical chemistry to real-time machine learning offers a viable, transformative path for point-of-need forensic biosensors. Traditional biosensor design has remained constrained by the search for a "perfect" non-fouling chemical interface, a goal that consistently compromises transducer sensitivity and escalates fabrication cost. This hybrid paradigm embraces physical signal distortion as an inevitable operational reality, relying on intelligent algorithmic deconvolution to reconstruct uncorrupted chemical data.

Conclusion:

The integration of organic bioelectronics with adaptable machine learning architectures represents a fundamental paradigm shift in point-of-need forensic toxicology. Traditional biosensor development has long been bottlenecked by the pursuit of an elusive "perfect" non-fouling chemical interface, an endeavor that invariably complicates fabrication, degrades sensitivity, and inflates production costs. By contrast, the hybrid AI-OECT framework introduced in this study embraces physical signal distortion and matrix fouling as inevitable operational realities, delegating the task of data cleaning and interpretation to real-time algorithmic deconvolution.

By achieving an ultra-trace Limit of Detection (1.2 pM) in under 60 seconds directly from raw, unconditioned human whole blood and saliva, this platform successfully bridges the operational chasm that has historically separated high-precision, benchtop laboratory mass spectrometry (such as GC-MS and LC-MS) from rapid, qualitative field screening tools. The inherent volumetric transconductance amplification of PEDOT: PSS channels ensures superior signal-to-noise dynamics, while the bespoke multi-stage computational pipeline pairing a 1D CNN Autoencoder with an LSTM classifier effectively isolates non-specific bio-fouling noise and executes precise kinetic deconvolution.

Crucially, this system transcends the limitations of static equilibrium measurements. By analyzing dynamic time-series association and dissociation rates (k_{on}/k_{off}) across Molecularly

Imprinted Polymer (MIP) cavities, the platform achieves a 94.2% multi-gate accuracy in distinguishing parent fentanyl from closely related synthetic analogues and high-concentration over-the-counter interferents. This high degree of analytical specificity is vital for preventing false positives and ensuring reliable evidence interpretation during active criminal investigations.

The real-world operational benefits for law enforcement officers, forensic toxicologists, and emergency medical personnel are profound. In acute overdose settings, rapid and precise substance identification accelerates targeted clinical interventions and naloxone administration. In field environments, first responders gain a rugged, handheld diagnostic tool capable of delivering quantitative results without requiring complex sample pre-treatment, centrifugation, or external laboratory turn-around times. Furthermore, decoupling matrix resistance from physical surface coatings streamlines manufacturing and enhances storage stability.

Future work will focus on expanding the multi-gate OECT topology to accommodate broad-spectrum multiplexed arrays capable of simultaneously screening extended panels of novel psychoactive substances. Transitioning the processing architecture to an embedded edge-AI processor will enable standalone field operation without cloud dependencies, while automated microfluidic flushing protocols will further optimize sensor reusability. Ultimately, the synergy of organic bioelectronics, molecular imprinting, and deep learning establishes a robust, scalable foundation for next-generation forensic diagnostics and enhanced public safety preservation.

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