Andrew Tran

Opidroid: A Fully Autonomous, Subcutaneous Drug Delivery Platform for Opioid Based Postoperative Pain Remediation

PROBLEM STATEMENT

The emerging opioid crisis has been a subject of interest across the scientific and medical community due to the increasing death toll. Research has shown that the underlying addiction mechanisms behind opioid misuse are rooted in postoperative pain management and persist thereafter. Currently, over 160,000 postoperative patients have reported opioid misuse. Without substantial change, the over 250 million annual postoperative patients who are prescribed opioids are at high risk of diversion or drug abuse.

In light of this, the scientific community has allocated its efforts on Abuse Deterrent Formulations (ADFs). ADFs utilize the reconfiguration of opiate compounds to prevent the chemical manipulation methods (crushing, snorting, etc.) for drug abuse. While initially promising, ADFs have three major flaws that make them unsuitable candidates for opioid abuse deterrence:

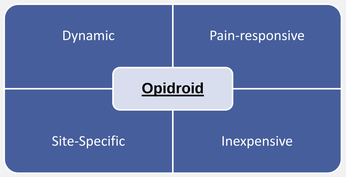
1) When ingested, ADFs may exhibit antagonistic roles within the gastrointestinal tract; for example, ADFs may inhibit gastric emptying, induce stationary motor patterns, and blockade the peristalsis ensue.
2) Patients are given fixed prescriptions that are not personalized to patients
3) **ADF prescription still relies on patients' subjective pain reports.** This method of prescription is a decades old technique that must be improved.

Other methods of opioid abuse deterrence require invasive processes, implanting a device that may or may not work. There must be a paradigm shift in the methods of opioid abuse deterrence in order to effectively solve this public health emergency. Rather than simply changing the chemistry of drugs, the solution must be targeted the towards the root of the crisis: pain management. Similar to the insulin pump, there must be a solution that is responsive to the body to administer the correct provision of medication.

The **Visual Analog Scale (VAS)** is displayed in the figure to the left. This is the current "state-of-the-art" method for pain assessment.

OBJECTIVE

Create an autonomous drug delivery platform that delivers opioids according to the patient's nociceptive expressions.



PRELIMINARY RESEARCH

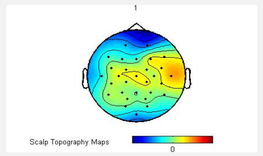
Pain is a function of phycological stress compounded by an inherent neurological emotional response

Physiological Stress Biometrics

- **Electromyogram (EMG):** Electrical activity from localized muscles (upper trapezius muscles).
- **Electrocardiogram (ECG):** Frequency of the bio-potential from electrical activity of the heart. Observed ventricular arrhythmias or other abnormal heartbeats are clear signals of stress that are reflected in the ECG.
- **Electrodermal Activity (EDA):** Observed changes in skin conductance from sweat gland permeability. Research has shown that the involuntary fluctuation of conductivity reflects emotional arousal. It is often referred to as Galvanic Skin Response (GSR).
- **Blood Volume Pulse:** A bio signal that measures arterial translucency from cardiovascular activity.
- **Respiration**: Respiratory patterns are subject to change during periods of stress. Often times faster breathing occurs when stressed.
- **Body Temperature:** The body's homeostasis is threatened or perceived to be so during periods of stress, leading to elevated body temperatures. Symptoms of a mild cold may be also shown due to the increase in temperature.
- **Three-axis acceleration:** Rapid fluctuations in an object's velocity, such as twitching, have been associated with higher levels of chronic stress.

Neurological Emotion Biometrics

- **Electroencephalogram (EEG):** An increase in theta (3 to 8 Hz) oscillations and beta oscillations in the frontal lobe constitute emotional responses to *chronic pain*. For *phasic pain*, neural activity is below 10 Hz 150 to 400 milliseconds after applied stimuli. Alpha and beta oscillations then increase 300 to 1000 milliseconds during *acute pain.* A neuroimaging technique called EEG brain topology is used to plot various EEG frequencies to a topological map.



A simplified **EEG topological map** is displayed in the figure to the left. Various colors are used to represent different frequencies in localized regions of the brain.

Opidroid Architecture

1 — Machine Learning (ML)

After data acquisition and exploratory analysis, two state-of-the-art machine learning models were built: a random forest classifier and feedforward neural network.

2 — Android Integration

Once integrated to the Opidroid app via TensorFlow Lite (FNN) and cloud computing (RFT), ML models analyze biometrics and transmit whether the patient is in pain (stress + negative emotion) to the Arduino apparatus.

3 — Hardware Deployment

The Arduino apparatus contains a HC-05 Bluetooth module that receives information on patient pain from the Opidroid app. Once received, the Bluetooth module transfers this information throughout the circuit and commands the motor to pump an opioid dose to the patient accordingly.

Data Acquisition

WESAD Dataset Synopsis: The FNN was performed on the Wearable Stress and Affection Dataset (WESAD) from UC Irvine's Machine Learning Repository. The data is split into training, validation, and testing datasets comprising over 30,000 data points in total. Chest and wrist modalities were used to assess stress. Both the RespiBAN chest worn device and a Empatica E4 wrist device was used to measure blood volume pulse, ECG signals, EDA signals, EMG signals, body temperature, and three-axis acceleration. These modalities encapsulate the *physiological biometrics of stress.*

(RespiBAN chest worn device) + (Empatica E4 wrist worn device) = (Stress)

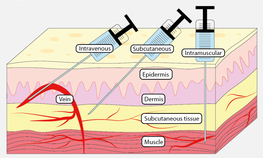
EEG Brainwave Dataset Synopsis: The EEG Brainwave dataset was collected from 1 male & female for 3 minutes per state - positive, neutral, negative. A Muse EEG headband was used and recorded the TP9, AF7, AF8 and TP10 EEG placements via dry electrodes. Six minutes of resting neutral data is also recorded, and the stimuli used to evoke the emotions are from brief film clips.

The figure above displays example EEG oscillations as a result of EEG topological neuroimaging in the dataset.

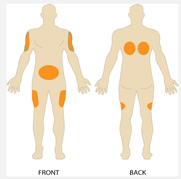
A visualization of the EEG dry electrode placements is shown above.

Subcutaneous (sub-Q) Drug Delivery

Subcutaneous (sub-Q) drug delivery involves injection at the site of the subcutaneous tissue (shown in the left diagram below). It is the least invasive of the methods of drug delivery (intrathecal, intravenous, intramuscular, etc.) and is subject to prolonged drug absorption. Prolonged drug absorption has been attributed to more controlled opioid administration because less of a dose is needed for the same type of pain alleviation, thus making it more efficient than traditional methods. For adolescents/adults over 12 years old, 0.375 and 0.625 inch long needles are typically used for injections that are 5-20 mg **of a morphine sulfate 10mg/mL solution**, the most common and effective narcotic solution used in sub-Q drug delivery.



The diagram displays various methods of drug delivery and their subsequent invasiveness



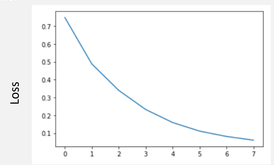
Various injection sites for sub-Q delivery are shown above

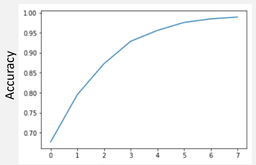
The injection sites of subcutaneous drug delivery are shown in the diagram above (right). The highlighted sites are as follows: lateral aspect of upper arm, abdomen surrounding umbilical region, thigh locale, lower loins, posterior region of upper arms, and upper posterior region. For more sustained drug absorption rates, the lower loins should be targeted.

RESULTS

Feedforward Neural Network (FNN)

FNN Computation: Opidroid's physiological stress classification scheme is a FNN. The FNN implements a deep neural network with an interconnected node architecture. TensorFlow's to_categorical API was applied to labels to transform them into numerical values for feasible computation. The FNN has three total dense layers with a 45 input dimension. Each layer is equipped with a training ReLU activation function, whereas the last layer has a Softmax activation function for classification. The is then compiled with a categorical cross entropy loss function and an "Adam" optimizer. Then, it is consequently fitted with seven epochs/iterations. Overall, it achieved a 96.80% accuracy on unseen test data and a 97.69% accuracy on training iterations.

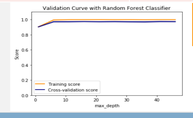




Random Forest Classifier (RFT)

RFT Computation: The Opidroid's neurological emotion classification scheme is a RFT. A RFT implements an ensemble of decision trees to make a classification of labels. Label encoding was used to parse labels into numerical values for feasible computation. Then, a Kullback-Leibler Divergence (InfoGain) feature selection algorithm with a 0.75 cut-off was performed using Weka Explorer to decipher important features. Finally, a pipeline RFT classifier was performed on the data with a 10-fold cross validation technique.

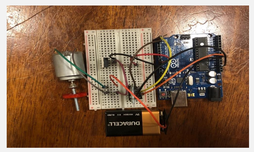
Evaluator	Ranker Cutoff	No. Attributes	RF Accuracy
One-Rule (OneR)	0.4	52	93.84%
Kullback-Leibler Divergence (InfoGain)	**0.75**	**61**	**97.61%**
Symmetrical Uncertainty	0.4	72	95.54%
BayesNet	0.4	67	95.16%



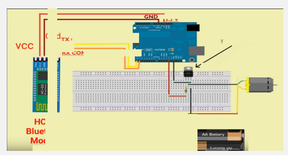
Kullback-Leibler Divergence

$$D_{\mathrm{KL}}(P \parallel Q) = -\sum_{x \in \mathcal{X}} P(x) \log\left(\frac{Q(x)}{P(x)}\right)$$

Opidroid Drug Delivery Platform



The Opidroid's "pump" is driven by the 6V DC motor that receives information on motor speed & time from the HC-05 Bluetooth Module.



The Opidroid's technical schematic is shown in the following diagram. Materials can be seen above.

The Opidroid's infusion set is composed of a cylindrical structure that is equipped with a tube that holds a thin cannula to deliver opioids.

CONCLUSION

This engineering pursuit presents the *Opidroid*, a novel fully autonomous drug delivery platform with dynamic opioid administration for patients suffering postoperative pain.

Upon completion, it was first concluded that the Opidroid was effective in assessing pain given various pain biometrics present in postoperative pain. The Random Forest Classifier (RFT) algorithm trained to analyze neurological biometrics performed at a 97.61% accuracy rate, which is a significant level of accuracy. Moreover, the Feedforward Neural Network (FNN) algorithm trained to analyze physiological biometrics performed at a 96.80% accuracy, which is also a significant level of accuracy.

Second, it was concluded that the Opidroid would enable the appropriate provision of morphine sulfate and reduce the risk of diversion in postoperative patients, making the Opidroid more reliable and efficient than traditional oral methods of opioid-based pain remediation. This is because the Opidroid takes a multi-faceted biotechnological approach that has not been done/tried before in the medical community. In doing so, researchers and others interested in both pain remediation and opioid-based pain treatment can utilize the comprehensive framework that the Opidroid has created for future in-silico applications.

Altogether, the Opidroid uses robust pattern detection and feature extraction techniques in tandem with deep learning to craft a novel paradigm that makes the much-needed shift in opioid-based postoperative pain treatment.

DISCUSSION

Further Research

A number of refinements are expected to be made: (1) Currently, Opidroid's machine learning models are not personalized towards individual users. This can present minor issues as different patients may exhibit different EEG oscillations in response to negative stimuli, for example. As an improvement, personalized data should be obtained prior to actual use. Nevertheless, the objective of this engineering pursuit is to design a robust framework for more sophisticated developments in opioid abuse deterrence. (2) In-vivo validation can be applied. Nevertheless, several efforts have been made to add layers of validation, such as computational analysis of machine learning accuracies, literature comparisons, and expert testimony. (3) A more robust framework of biomarkers for pain can be developed. However, there lacks a multimodal dataset that captures *all* of pain's biomarkers. For example, potential biomarkers that are left out include but are not limited to: neuroimages, protein-encoding genes within the blood (MFAP3, GNG7, GBP1, CCDC144B, LY9, etc.), epinephrine levels, cortisol levels, and sleep patterns. (4) Intravenous drug administration will be explored as another route, as research has shown this method is effective in postoperative pain remediation as well. (5) Further reconstruction can be done as a result of the relatively bulky size of the Opidroid compared to other drug delivery platforms. This can be done through obtaining smaller electrical components, or reduction in the sizes of algorithms. Alternatively, a peristaltic pump could replace the hardware architecture for size reduction.

Societal Implications

So far, the US has spent $78.5 billion on combating the opioid crisis and projections put costs at an excess of $2.5 trillion by 2025. Before, federal agencies would spend thousands of strenuous man hours of millions of dollars to make a change. With the Opidroid, however, patients can now enable the appropriate provision of pain without risk of diversion for an estimated $20. In doing so, patients can recover from intensive acute pain that typically follows surgery to prevent life-threatening chronic pain conditions. Additionally, because the Opidroid automates the analgesic process for patients, there is a greater availability for pain remediation to patients that aren't able to access postoperative patient controlled analgesia (PCA), such as babies, mentally-ill, or disabled.

Altogether, as the first-ever drug delivery platform that delivers medication in response to pain, the Opidroid also provides a robust computational and ideological framework for future novel biotechnological applications in opioid abuse deterrence. Future applications include, but are not limited to: novel addiction rehabilitation devices using computational analysis of addictive biomarkers, automated sedation for targeting intubated patients, rapid & automated pain diagnostics for analgesic prescription, and more.

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