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REAL-TIME DETECTION OF CRAVINGS IN INDIVIDUALS WITH SUBSTANCE ABUSE USING WEARABLE BIOSENSORS AND MACHINE LEARNING

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REAL-TIME DETECTION OF CRAVINGS IN INDIVIDUALS WITH SUBSTANCE ABUSE USING WEARABLE BIOSENSORS AND MACHINE LEARNING

by

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List of Abbreviations

AUC	Area Under the Curve
ANS	Automatic Nervous System
CBT	Cognitive Behavioral Therapy
CRF	Conditional Random Fields
ED	Emergency Department
ECG	Electrocardiography
EDA	Electrodermal Activity
ESM	Experience Sampling Method
FPR	False Positive Rate
FN	False Negative
FP	False Positive
FPR	False Positive Rate
HMPC	Hybrid Model Predictive Control
LDA	Linear Discriminant Analysis
ML	Machine Learning
NaN	Not a Number
PTSD	Post-Traumatic Stress Disorder
QDA	Quadratic Discriminant Analysis
ROC	Receiver Operating Characteristics

SVM	Support Vector Machine
SUD	Substance Use Disorder
TP	True Positive
TN	True Negative
TPR	True Positive Rate
VR	Virtual Reality
WHO	World Health Organization

ABSTRACT

Real-Time Detection of Cravings in Individuals with Substance Abuse using Wearable Biosensors and Machine Learning

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Deaths in the US have drastically increased over the past decade due to addictive behaviors and drugs. According to the World Health Organization (WHO), 1 in 20 adults between the age of 15 and 64 years are addicted to at least one illicit drug; globally, 29 million people are suffering from drug use disorder. The addiction of narcotics alters a person's primary function as well as critical areas of the brain due to multiple reasons like genetics, hereditary, stress or pressure, and mental health conditions. It not only affects an individual but also their families. Intensive research has been launched all over the world to spread awareness about how to prevent addiction. The current problem for efficiently managing and treating these addicted individuals is the lack of biomarker for detecting cravings. If clinicians could identify cravings in individuals, they might able to design appropriate intervention strategies, including mobile based mindfulness techniques, dialectical behavioral therapy (DBT) based exercises, or direct contact with support persons to mitigate risky situations (cravings) that could otherwise result in relapse. In our work, we explored the possibility

of employing wearable biosensors along with machine learning approaches to define a reliable biomarker of craving.

In this work, participants wore wrist-mounted biosensors on their non-dominant arm for all waking hours for a four-day period. An event marker was used to denote any time they perceived drug craving. For analysis, raw accelerometer data in three axes (*x*, *y*, and *z*) evaluated 20 minutes before and 20 minutes after each marked event. A sliding window technique with signal processing Hilbert transformation approach was applied to extract relevant features mean, variance, shape, scale, and Dk (a distance measure derived using six parameters in a hypothetical six-dimensional space). These features employed in machine learning approach with two different quadratic (non-linear) models to detect cravings. The collaborative work of two machine learning models provided us an accuracy of 72% in the detection of cravings.

CHAPTER ONE

INTRODUCTION

Addiction to drugs has become a global issue. Every country in the world is trying to create awareness about drug addiction by creating forums and, global meetings. According to US National Institute of Health, more than 64,000 Americans die yearly due to a drug overdose, a 3.5 percent increase in the death rate in two decades. Addiction should be treated at an initial stage to prevent the inevitable fatal consequences.

Addiction is a chronic, relapsing disorder which can include compulsive drug craving. It is also named as a brain disease as it changes the brain structure and its function. It disrupts the standard functionality of the underlying organs like brain, heart, lungs and kidneys. The changes can be long-lasting. As it progresses, it becomes ones' daily life. Its effect seen in all age groups and even the babies in their mother's womb.

1.1 Reasons for addiction

Addiction is a complex mental condition that can be due to multiple reasons such as environmental, biological and developmental factors. Some of these include:

- **Genetics**

  Addiction depends on genetic factors [1], however it can be overcome with personal choices (for example "will power"). Research shows that the susceptibility of a person to addiction is strongly influenced by genetics. According to National Institute on Drug Abuse estimates, 40-60 percent of developing addiction is based on genetics. Further, research is in process to understand contribution of genetics to addiction.

- **Environment**

  If there is anyone in the family has a history of drug or alcohol abuse, then it has an impact on their younger generation, consciously or subconsciously and they develop a drug or alcohol problem. Hereditary can also happen based on the environment they live in and the time, with whom they spend most outside the family, that may lead to a mental health disorder [1].

- **Stress or Pressure**

  The person gets accustomed to the alcohol or drugs, to get rid of pain due to stress like a deadline given by the company manager or something like a competitive exam. At the initial stage, the small amount of alcohol or drugs will make him feel like nurture from that pain and later gets used to amount or quantity the individual is taking, and the body begins responding less to that amount. As a result, they try to increase its amount little by little and reaches a point where it becomes an addiction [1].

1.2 Stages of addiction

Here we discuss different stages of addiction based on complicated mix of genetics and environmental factors determine if a person is at greater risk for addiction [2].

- **Stage One**

  During this stage, the addict will have the illusion of pleasurable mood and comfort. The addict develops sense of personal power. By this, the individual will avoid unpleasant situations. Once the effect of the drug is gone, the person starts to feel the pain or uncomfortable situation again and like to have drug again. This cycle continues, and the

person becomes an addict. This emotional craving results in the mental preoccupation with drug and ends in addictive behavior.

- **Stage Two**

  This is the intermediate stage; the addict surrenders to the power of addiction. The person becomes more preoccupied with drugs and makes drugs as a lifestyle. As a result, it becomes noticeable to the people around them. This behavior makes them isolated from others and strengthens the addictive process. This is the sign of the start of problems, people recognize addicts as strange, irresponsible and prone to be troublemakers. The addict becomes intolerant and impatient during this stage for which he craves drug more frequently and in dangerous ways. By the end of this stage, they drain more of their energy to maintain their balance with the internal emotions, thus limiting their ability to lead a healthy life.

- **Stage Three**

  The stage three is the final stage, where the addict is entirely under the control of addiction. During this stage, the intoxication begins to break down, and never-ending pain returns. The addict frequently displays anger, depression, guilt, loneliness, and hopelessness. Some of these individuals either die of suicide or accidental drug overdose. The remaining individuals continue to struggle to overcome addiction and some may eventually seek treatment for recovery.

1.3 Treatment and recovery

- **Cognitive Behavioral Therapy (CBT)**

  This therapy helps the addict to recognize, avoid and understand the situations, which may lead to drug abuse. CBT has shown positive results by addressing unhealthy thought patterns and replacing them with the new and healthy ones.

- **Contingency Management**

  The addict is encouraged to attend the counseling sessions or take medications as prescribed. In this method, rewards or privileges to make the addict feel good. This therapy consists of methadone programs and psychosocial counseling treatment programs.

- **Motivational Enhancement Therapy**

  In this session, therapists or counselors help the addict to get motivated to get rid of the drug by facilitating required treatment like giving examples of life threating experiences as well as providing the virtual environment to understand the pain.

- **Family Therapy**

  In this therapy, therapists or counselors approach the addicts drug problem with the help of family interactions and educate the addict about other risky behaviors. Family therapy helped both adults and adolescents. In this therapy, they engage families in applying the behavioral strategies during their sessions.

1.4 Cravings

Although understanding addiction and drug abuse are essential, one critical factor that might help clinicians to intervene effectively is to detect cravings. We focused our attention on understanding cravings and possibly a method for screening. We defined craving for the

participants as a strongest desire for something. Our participants were instructed to identify a craving event (and press the event marker) anytime they felt a strong urge to use their drug of choice and stress as a period of significant psychological distress. We left the threshold for pressing the button to indicate and event somewhat open- we told them to indicate events that were significant to them. The other factors which are related to craving are interlinked either directly or indirectly; for instance, smoking, reckless behavior to seek pleasure and drug abuse. The desire for food is entirely dependent on limbic systems and prefrontal cortex. Any needs may eventually lead to hopelessness and reduced quality of life. Hence it is essential to know the basic functioning of a craving to guide better clinical management of the underlying condition. A research study shows that limbic systems and prefrontal cortex regions are involved in alcohol addiction. Also, the neurobiology of addiction depends on personal preferences for low or high-risk life styles [3].

In this project we designed a machine learning algorithm which can be embedded into the wearable biosensors that can detect cravings by analyzing the activity data obtained from individual subjects.

To reliably identify the features from the data that can be used in machine learning algorithms, we studied the changes in the biosensor data when the individuals consumed an opioid drug. Then, we examined the changes in the biosensor profile data during opioid overdose and subsequent removal of the drug using an antidote (Naloxone). These studies conducted to understand the significant changes that might occur in the features derived from the biosensor data. Identifying reliable features that can respond to changes when an opioid is in the human body as well as subsequent changes when the drug is undergoing withdrawal from the system is very important for designing a machine learning model. After studying the changes in the features, we employed these features to build a machine learning algorithm for detecting cravings.

In chapter 2, we review previous background works which relate to our study. Chapter 3, provides details of different methods we used in our work, such as the Hilbert transform, non-linear Support Vector Machine (SVM), and discriminant. Chapter 4 provides details about algorithm implementation and results obtained during our work. Finally, Chapter 5 gives conclusion and future study.

CHAPTER TWO

BACKGROUND

In this chapter, we will briefly review previous research which was conducted to detect or reduce the number of deaths due to addiction, stress, cravings, smoking, and alcohol abuse. Also presented, is a detailed explanation of methods implemented in their papers and their results, and limitations.

Recent statistics from Center for Disease Control/National Institute on Occupational Safety and Health (NIOSH) showed that the workplace is the leading cause of life stress. Nearly 110 million people die every year as a direct result of stress. Among them, over thirty thousand people died due to the opioid epidemic [4]. To attenuate the count of deaths every year the research on this issue has seized the utmost priority.

To follow the biometric profile of an individual with an opioid in the system and opioid withdrawal from the system, we studied the biosensor profile, with drug administration and with naloxone as an antidote, for opioid overdose. Naloxone blocks the opiate receptors and reverses the toxic effects of opioids like respiratory depression after the drug overdose. It does not have an impact for a long time; the drug effect varies from 30-90 minutes [5]. When compared to the opioid, the antidote does not last much longer than the opioid that initially caused the overdose [6,7]. The patients who received the cure as overdose must be transported to the hospital for further observation to make sure that the opioid toxicity does not relapse, once the effect of the drug is done [8]. If patients are reluctant to return to the hospital, then opioid toxicity re-occurrence may have devastating consequences.

Since there were not many works done using wearable bio-sensors for the detection of cravings, we focused on other areas such as alcohol, drugs (opioid and naloxone), cigarette and its relapse, due to craving. In recent years, Fletcher et al. [9] used a wearable sensor platform and mobile application for use in Cognitive Behavioral Therapy for detection of drug addiction and post-traumatic stress disorder (PTSD). In their paper, they used the wearable sensor for studying autonomic nervous system (ANS) for mental health treatment and interventions. This study utilized two different sensors; a custom-designed electrocardiogram (ECG) monitor worn on the chest and the sensor band on the ankle which continuously monitors electrodermal activity (EDA). They were connected via Bluetooth to a mobile device to monitor the electrocardiogram (ECG). When a specific arousal event is detected, the mobile phone presented therapeutic and empathetic messages to the patient in the tradition of cognitive behavioral therapy (CBT). At the initial stage of work, their method was able to measure the person's mood or stress and helped the subjects to cope with episodes of cravings and understood the addiction or anxiety due to mental health disorder [9].

In another work, Bae et al. [10] implemented alcohol control utilizing mobile phones built-in sensors (e.g., accelerometer, location) and meta-data (e.g., communication logs) to detect and monitor behavioral patterns related to the initiation of drinking. A machine learning technique was created, by combining the collected data from these sensors and the use of Experience Sampling Method (ESM) to collect self-reports of alcohol use, the sample size was 30 young adults between 21-28 years for 28 consecutive days. Each day ESM report was found to be the most precise method to summarize the self-reports of drinking episodes instead of reporting at the end of the day or just after the events as the participants would usually ignore or forget to say. A daily survey would ask the participants the fundamental questions which would then be used to generate a

report. This machine learning-based technique they proposed provided a 96.6% accuracy for identifying drinking, non-drinking and drinking episodes. Disadvantages of using this method are the occasional device failure, a decrease in compliance of the subjects towards self-reporting decreased towards the end of the study due to voluntary shutoff of the mobile in case of battery drain or towards non-compliance to the test thus severely altering the official research results [10].

In another paper, Gupta et al. [11] used an interesting approach to reduce addiction to nicotine, marijuana and other addiction sources using Virtual Reality (VR) in the medical field. In their method, they used VR computer simulated environment where it creates experiences like the virtual taste, sight, smell, sound, and touch. In addition to that, they created gaming applications to understand the limitations of the person in different situations. The main idea of their project was to create fear in the person to reduce his/her addiction by giving them real-life pain or stress caused by addiction in the virtual world. This approach does not create any physical harm to the addict, but it gave him/her experiences of addiction [11].

Timms et al. [12] in their paper discussed control of smoking using a hybrid model predictive control (HMPC) strategy. In their analysis, 400 participants had given self-reports through a mobile technology during their smoking cessation clinical trial [12,13]. In their study, an intervention algorithm was developed, consisting of counseling and pharmacotherapies manipulated to reduce smoking and craving. By this method, they found suppressing of relapse and found time-varying stress. Although the success rate was not high, their model shows; decision framework adjusts counseling, bupropion (Zyban, GlaxoSmithKline) and lozenge (nicotine) doses over time by which craving levels were reduced [14]. In other research, basket et al. [15], they relied on questionnaires and interviews with examiners. This paper highly directed towards a smartphone-based wireless body area sensing system provides real-time interventions consisting

of several wearable sensors for measuring physiological data, a smartphone, and a web server together gave the accuracy of 90% [15].

Chatterjee et al. [16], explained that craving plays an essential role in the relapse phase of addiction. A craving estimation model known as mCrave, based on a linear-chain Conditional Random Fields (CRF) model, can continuously infer probability of strong craving for an entire day continuously every minute. CRF helps to make subsets of data on a minute by minute basis to determine desire and non-craving patterns. This model was created to eliminate recall-bias and noncompliance of participants in self-reporting experiments. The graphical model was used to determine the probability distributions involving inter-dependent random variables, by constructing the linear separating boundary between times of low and high craving. This model established a relationship of craving likelihood being inversely proportional to the probability of stress at that minute. The ROC curve was observed to find the performance of model being better for periods of high vulnerable hours than low vulnerable hours. The craving estimation for the likelihood of stress had an accuracy of 72.9% and kappa (κ) 0.429 [16].

All the previous research is related to the subjective detection of craving in patients with addiction (i.e. self-report by the addicts by pressing the button on the bio-sensor) and subsequent interventions. Our stay is novel in that it seeks to define an objective measure of drug craving, which can be detected automatically and serve as a trigger for key interventions.

2.1 Wearable sensors with accelerometer

In present days, we cannot imagine life without technology and wearable sensors; They are becoming more prevalent due to their application in the medical field. Sensors help the addicts and clinicians by providing continuous feedback like calories burned and hours of sleep activity.

Sensors also monitors physiological signals, temperature, heart rate, blood pressure volume and skin temperature. Complexity in the selection of the smartwatch and its application has increased, as there are more than ten smartwatches available in the market today. The discussion below will give the idea about different kind of smartwatches and how easy it is to select them based on individual interest [17]. We did a preliminary investigation on the specification of the existing wearable sensors before choosing the sensor that we employed in our work.

2.1.1 Different kind of watches

Here is the list of watches used in medical field:

- Empatica E4 and Empatica Embrace
- Philips Family (Actiwatch 2, Actiwatch Pro and Actiwatch Spectrum Pro)
- Fitbit Family (Ionic, Blaze and Charge 2)
- Act Trust and Motion Watch 8
- Actigraph Link and Night Shift
- Micro Motionlogger and SOMNO watch

The Empatica E4 is reasonably well-suited watch for research when compared to other watches. Empatica E4 acquires six different parameters and has a software dock, as well as event marking button. It also includes, flash memory on the device and all the raw data can be easily downloaded. However, there are many kinds of watches/devices available in the market which can be used based on the required physiological data for research (for example, data from accelerometer). After a preliminary investigation of available commercial watches, we found smartwatches that are quickly adaptable for our work. Figure 1 provides a comparison of watches.

Table 1 Comparison table for different watches

Options	Empatica E4	Empatica Embrace	VU-AMS	Philips Actiwatch 2	Philips Actiwatch Spectrum	Fitbit Ionic	Act Trust	Motion Watch 8	Actigraph Link	Night Shift	Micro Motionlogger Watch	SOMNOwatch
EDA	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Activity	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
BVP	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Temperature	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
IBI	YES	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
HR	YES	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES
Gyroscope	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Heart Rate Variability			YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Respiratory Sinus Arrhythmia(RSA)			YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Pre-Ejection Period(PEP)			YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Left Ventricular Ejection Time (LVET)			YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Respiration Rate (RR)			YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Stroke Volume (SV) and Cardiac Output (CO)			YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
Skin Conductance Level (SCL) and Skin Conductance Responses (SCRs)			YES	NO	NO	NO	NO	NO	NO	NO	NO	NO
APP	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO	NO

2.2 Machine learning approaches

In today's world of complex and diverse data ranges, classification becomes quite a tedious job on a group of sample space. Machine Learning models, ease classification of highly variant data. There are two broad methodologies for categorizing the data into defined groups: supervised and unsupervised learning models.

2.2.1 Supervised learning

Supervised machine learnings consist of predefined algorithms, data and its results already initialized into the training module of the model. Later when the model is input with a new variable, it compares with the data in the training set and accordingly the data is classified [18]. The supervised learning model describes the input variable as predictor while the classified category acts as the response variable. A general example of supervised learning is the model with an equation of $y = 3x + 5$, so an input x will be mapped to the corresponding value y, where y is dependent, and x is a predictor.

2.2.2 Unsupervised learning

Unsupervised learning builds its training model by learning through different inputs without labeled responses. Unlike supervised model, the unsupervised model doesn’t have any predefined algorithms or training set; they are left alone to devise and discover the respective classifications from the input data. In general terms, unsupervised learning works by providing sets of data as input and analyzing the data output; the new information is classified accordingly [19].

CHAPTER THREE

METHODOLOGY

In this chapter, methods used in this work are explained. We first discuss data collection using Empatica E4. This is followed by preprocessing of data. After the completion of preprocessing, we extracted the relevant features which will be used to develop a machine learning algorithm. Prior to the development of machine learning model, we studied whether the relevant features are significantly different with the drug in the system compared to no drug in the system. The features during the no drug condition were used as a standard threshold in the machine learning process.

An overview of machine learning approaches was presented in Chapter 2. In this chapter, machine learning algorithms of Quadratic Support Vector Machine (SVM) and Quadratic Discriminant are used for detecting cravings as a function of stress.

3.1 Data collection

In this work, we considered three data sets where all the participants provided the informed consent and the study protocol was approved by the Institutional Review Board of the University of Massachusetts Medical School:

Set 1: Opioid administration protocol (The subjects had taken opioid and it is in the system)

Patients presenting to our Emergency Department (in Worcester, MA) who are admitted to the hospital for acute or chronic pancreatitis and have a pain management plan that includes opioid analgesics. We had in total of 11 subjects (6 male and 5 female) with mean age of 56.5 (min: 36; max: 77).

Set 2: Naloxone administration protocol (Drug withdrawal from the system)

The patients were people presenting to the Emergency Department (ED) after opioid overdose treated with naloxone. A wearable biosensor (Empatica E4) was placed on their non-dominant wrist of each participant from the time of arrival to the ED until one of three clinical endpoints were reached: A) discharge from the ED, B) admission to the hospital, C) one-hour post administration of a repeat dose of naloxone. Nearly 19 participants (16 male, 3 female) were enrolled with mean age of 36.4 (min:21; max: 62).

Set 3: During treatment and recovery (cravings vs stress)

An observational trial of individuals enrolled in an intensive outpatient treatment program for substance use disorder (SUD). Participants wore a wrist-mounted biosensor (Empatica Embrace) on their non-dominant arms during waking hours for a four-day period. Thirty participants were enrolled in this data collection. These subjects comprised 17 males and 13 females and had a mean age of 32.3 (min:18; max: 67).

The experiment protocol to collect physiological data in all the sets was the same. The subjects were asked to wear the device on their wrist. Physiologic parameters were measured continuously including heart rate, skin conductance, and skin temperature. Accelerometer data from three axes (x, y and z). In set 3, an event marker was used to denote any time they perceived drug craving or stress by a press of a button on the watch. The patients were given specific information as to identify their perceived cravings as strong desire for something and stress as a period of significant psychological distress.

3.2 Preprocessing of data

Data obtained included some unusable values, such as out of range, empty spaces, and NAN values. Using a simple MATLAB code, we removed these unwanted values and used the data to extract features for machine learning.

3.3 Implementation

Preprocessed accelerometer data were analyzed, two moments of data 20 minutes before and 20 minutes after each event marker was analyzed. In set 1, the event marker represented the administration of opioid; in set 2, the event marker was naloxone administration, and in set 3, the event marker represented self-reported craving or stress. The subjects in set 3, kept a separate diary to note whether the event marker is craving or stress.

To understand how the physiologic and accelerometer features will change before and after an event marker, a sliding window technique was used to assess the features in a five-minute window with a four-minute overlap (four minutes of old data followed by one minute of new data). Within each window, mean, variance, and features (shape, scale) obtained using a Hilbert transformation [20] were estimated. The Hilbert transform is widely used signal processing tool to estimate the predominant amplitude from a nonstationary signal. The data we obtained from the wearable device are nonstationary and we used the Hilbert transform to estimate amplitude, which reflects the fluctuations in data, we used Hilbert transform.

After applying the Hilbert transform, the amplitude of accelerometer data showed skew distribution rather than a normal distribution [21], suggesting that the amplitude fluctuations were not random. Gamma functions generally used to find the shape and scale of such a skew distribution [21]. The scale represents the overall height of the distribution whereas the shape

represents the degree of skewness. This signal processing feature extraction technique included (i) an estimation of μ (average) of the original data; (ii) variance of the original data; (iii) shape of accelerometer data (iv) scale of the amplitude distribution obtained using Hilbert transform of the original data and (v) the distance vector derived using shape and scale. The device has three axes (*x*, *y* and *z*) and therefore we obtained five features for each axis resulting in a total of 15 features. Gamma distribution formula is below $\Gamma(a)$ is given below

$$\boldsymbol{\Gamma(a) = \int_0^{\infty} t^{a-1} e^{-t} dt} \tag{3.1}$$

Gamma function and gamma (x, a, B) shown below is the probability density function where a is Shape and B is Scale.

$$\boldsymbol{gamma(x, a, B)} = \begin{cases} \boldsymbol{\frac{1}{B^a \, \Gamma(a)}}, & \boldsymbol{x \geq 0} \\ \boldsymbol{0}, & \boldsymbol{otherwise} \end{cases} \tag{3.2}$$

The mathematical expression for D_k is given below where α and β represent the shape and scale parameters respectively.

$$\boldsymbol{D_k = \sqrt{\alpha_x^2 + \beta_x^2 + \alpha_y^2 + \beta_y^2 + \alpha_z^2 + \beta_z^2}} \tag{3.3}$$

3.4 Support vector machine (SVM)

In machine learning, an SVM is also called a support vector network. It is chiefly used in supervised learning models where data can be analyzed using classification and regression. SVMs

can separate data into two classes by both linearly and nonlinear separation functions. If the analyzed data may be linearly separated, linear SVM is best for accuracy. In opposite, non-linear SVM maps the input vectors to a high-dimension feature space [22].

3.4.1 Linear support vector machine

Figure 2 represents Linear SVM, where the linear equation separates two groups $wx + b = 0$ called the optimal plane. If a new value is given to the function f then, based on the values of $wx + b$, appropriate classification for that value is determined. If the value of $wx + b > 0$ then it falls into group A and if the value of $wx + b < 0$ then it falls in to group B.

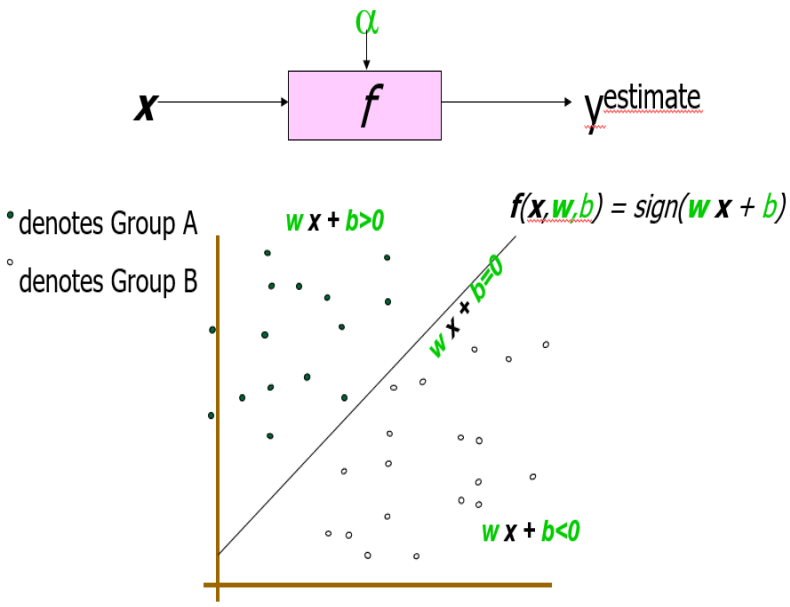
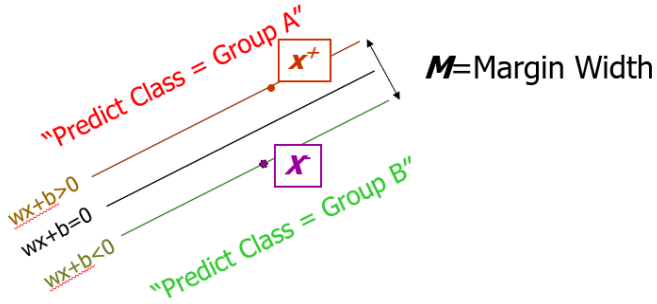


Figure 1. Linear SVM [23]

In figure 3, the line passing through the boundary points x^- and x^+ are called support vectors. To get accurate results then the Margin width should be maximum, and it is calculated by the formula M shown in the figure 3.



$$M = \frac{(x^{+} - x^{-}) \cdot w}{|w|} = \frac{2}{|w|}$$

Figure 2. Margin width for linear SVM [23]

3.4.2 Non-linear SVM

As our data sets are not linearly separable, then we had to map data to higher-dimensional plane considering Non-Linear SVM.

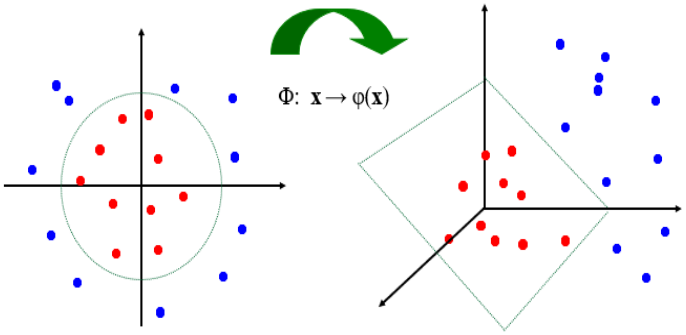


Figure 3. Non-linear SVM [24]

In figure 4, ϕ(x) is feature space representation; this optimal plane mapped to higher dimensional space with which we can classify between two groups. The method implemented by kernel trick [25]. It plays the role of dot produced in the feature space. The kernel basis function of Gaussian SVM is given by $K(x, y) = exp\left(\frac{-|x-y|^2}{2\sigma^2}\right)$; here x and y are the feature vectors and

σ is a, free parameter. In this process SVM, defines hyperplane in the feature space and classifies points in that space [26].

3.5 Quadratic discriminant

Quadratic discriminant analysis (QDA) is one of the best standard tools for supervised classification of data. The only difference between linear discriminant analysis (LDA) and QDA is it estimates separate variance/covariance for each class. It is one of the simplest and most-flexible approaches since the number of its parameters scales quadratically with the number of its variables.

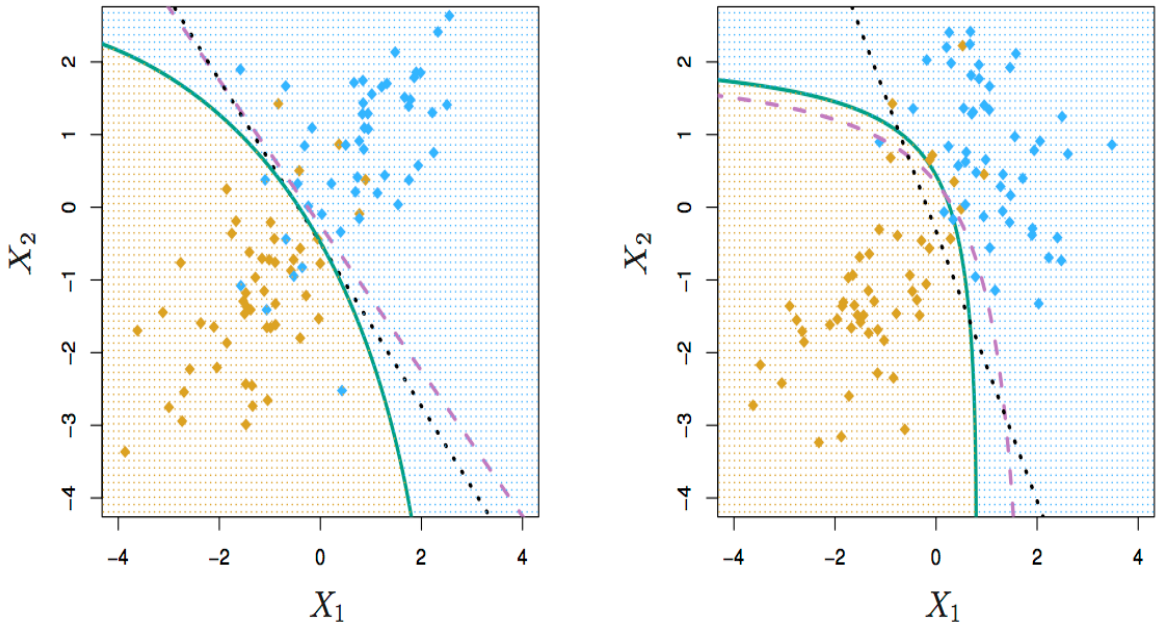


Figure 4. Comparison of LDA and QDA [27]

It models the likelihood of each class is a Gaussian distribution and then uses posterior distributions, explains many different approaches for quadratic discriminant analysis. One of the criteria is to reduce the data dimensionality before estimating the Gaussian distribution, and its formula given below; has also explained how Bayesian can yield one result if standard deviation and variance is solved differently with the equation below [28].

$$\begin{aligned}\delta_k(x) &= -\frac{1}{2}(x-\mu_k)^T\boldsymbol{\Sigma}_k^{-1}(x-\mu_k) - \frac{1}{2}\log|\boldsymbol{\Sigma}_k| + \log\pi_k \\ &= -\frac{1}{2}x^T\boldsymbol{\Sigma}_k^{-1}x + x^T\boldsymbol{\Sigma}_k^{-1}\mu_k - \frac{1}{2}\mu_k^T\boldsymbol{\Sigma}_k^{-1}\mu_k - \frac{1}{2}\log|\boldsymbol{\Sigma}_k| + \log\pi_k\end{aligned}$$

Figure 5 is the comparison of LDA and QDA, where the Black dotted line is LDA boundary, Purple dashed line is Bayes's boundary, Green solid line is QDA boundary. QDA fits better, in comparison, Left X1 is best fit for LDA as it has the same variances for both of the classes, but it is different for Right X2 as their variance for both types is not identical.

In machine learning model, we used both the models mentioned above are working collectively to detect the difference between the cravings and stress.

3.6 Performance metrics for classifiers

After building a model in Machine Learning using extracted features, we need to check how effective the model detects on test subjects. To monitor the performance of it, we need to determine classification performance by metric such as classification accuracy, Log-Loss, Receiver Operating Curve (ROC) or Area Under the Curve (AUC), and Confusion Matrix. In this work, we assessed the effectiveness of our classifier by ROC and Confusion Matrix [29].

3.6.1 Confusion matrix

The confusion matrix is form of a matrix and gives the complete performance of the model by providing the correctness and accuracy of the model. The classification matrix can be more than two classes (i.e., some predictors and right classes can be more than two). To understand the confusion matrix, we need to look at True Positive(TP), True Negative(TN), False Positive(FP) and False Negative (FN). Figure 6, below illustrates the concept of a confusion matrix.

		Actual Class	
		Positive	Negative
Predicted Class	Positive	True Positive	False Negative
	Negative	False Positive	True Negative

Figure 5. Confusion matrix

- **True Positive:**
    - It is a True Positive if the actual class of the model is True and predicted class is also True. The model has predicted correctly.
- **True Negative:**
    - If the actual class of the model is False and predicted class of the model is False, we call this result a True Negative. The model has predicted correctly.
- **False Positive:**
    - If the actual class of the model is False and predicted of the model is True, we call it a False Positive. The model has mispredicted.
- **False Negative:**
    - if the actual class of the model is True and predicted of the model say False, then we call it a False Negative. The model has mispredicted.

3.6.2 Classification accuracy

Accuracy can be given by the correct predictions (True Positive and True Negative) to the total number of samples (TP, TN, FN, FP). It is the values of leading diagonal amounts to the total

number of samples. The figure 7 and formula below gives the mathematical expression for accuracy.

$$Accuracy=(TP+TN)/ (TP+FP+TN+FN)$$

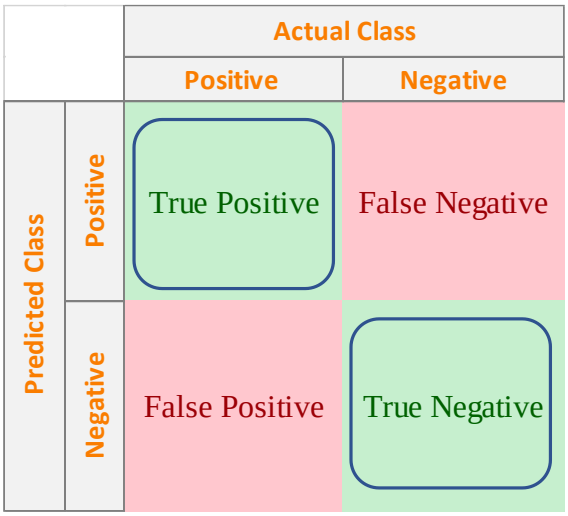


Figure 6. Explanation of accuracy calculation

3.6.3 Receiver operating curve (ROC)

Area Under the Curve (AUC) is one of the most widely used metrics for evaluating binary classification models. To know more about AUC, we need to understand two terms:

- True Positive Rate (Sensitivity): defined as TP/ (FN+TP). True Positive Rate corresponds to the proportion of positive data observations correctly considered as positive, concerning all positive data observations.
- False Positive Rate (Specificity): False Positive Rate is FP / (FP+TN). False Positive Rate corresponds to the proportion of negative data samples that are considered mistakenly as positive, concerning all negative data samples.

Both, the False Positive Rate (FPR) and the True Positive Rate (TPR) have values in the range [0, 1]. An AUC curve is drawn by varying the discrimination threshold and finding its corresponding FPR and TPR. Figure 8 below, shows the example of AUC threshold values such as (0.00, 0.02, 0.04, …., 1.00). AUC is the area under the curve of plot False Positive Rate vs. True Positive Rate at different points in [0, 1] and the measured area is 0.79.

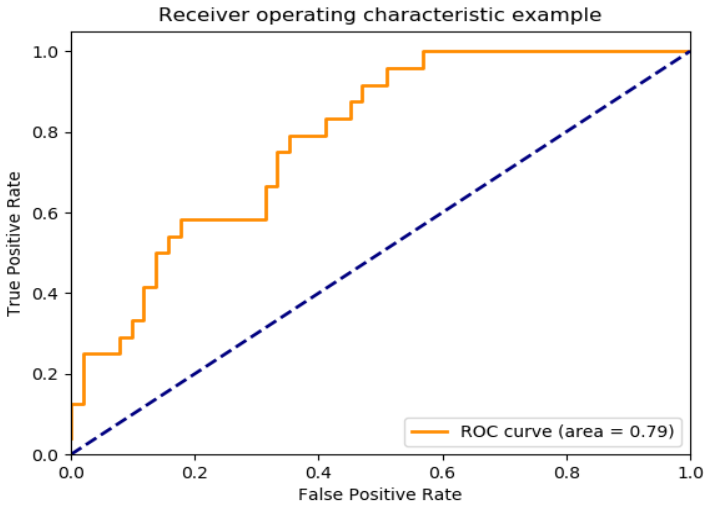


Figure 7. Plot of ROC with different thresholds [30]

CHAPTER FOUR

IMPLEMENTATION AND RESULTS

In this chapter, we will explain three different approaches to understand the biosensor profile in an individual with an opioid in the system and during opioid withdrawal with naloxone as antidote from the system. Therefore, we studied the features of the opioid in the system and removal from the system. This analysis provided us an idea of how characteristics will change, and we used that knowledge to differentiate cravings from stress. As defined in Chapter 3, in section 3.3: Implementation, we followed the same procedure for the analysis and to extract the relevant features like mean, variance, shape, scale and D_k, the vector distance measure using shape and scale.

4.1 Analysis of opioid drug administration

Based on the previous work done by S. Carreiro et al. [21], we applied sliding window approach on the data received from nine participants (target accrual: N=40) reported chronic opioid use when admitted to the hospital for acute exacerbation of pain. The opioid administration was documented in the Medication Administration Record and by participants pressing the event-marking button.

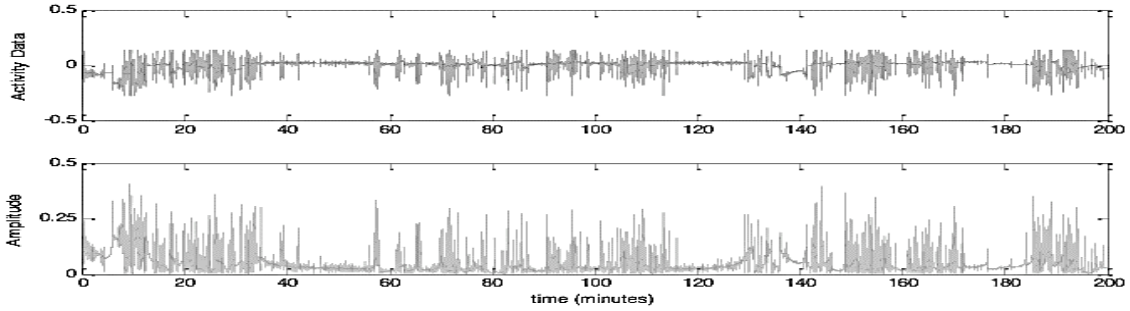


Figure 8. X-axis data for single participant

After applying the Hilbert transform method to biometric data to identify the characteristics of the biosensor recorded data patterns pre- and post- opioid administrations. Figure 8 shows *x*-axis data for single participant, the opioid administration at *t*=100 minutes. The top picture is the actual raw data and below subplot is the rapid fluctuations (amplitudes) after applying Hilbert transform. Figure 9 shows the average of the shape parameter after applying the gamma distribution to the amplitude distribution. As presented in the figure, there is a significant change in the shape parameter after opioid administration *t*=100 minutes indicating that the opioid influences the accelerometer amplitude distribution.

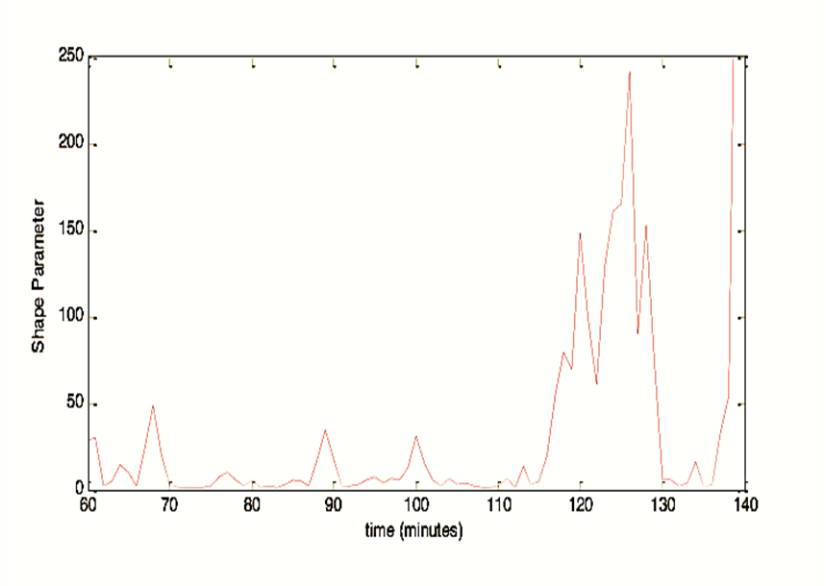


Figure 9. Distribution of average shape parameter for *x*-axis accelerometry data

After understanding the biosensor profile of the effects of opioid administration, we analyzed 131 opioid administration events on nine participants to differentiate between heavy and non- heavy users using the standard statistical analysis (*t*-test). Opioid administration consistently produced a striking decrease in the shape parameter in the *x*-axis in the 30min following administration. This pattern persisted across repeat dosing, and chronic opioid users demonstrate a specific reduction in short amplitude movements not present in opioid-naive individuals.

Among the nine participants, the results of the statistical analysis to differentiate between heavy and non-heavy user based on change in shape parameter shown in Table 2. Based on the features we could detect all the three heavy users; however, we could detect only five non-heavy users out of six.

Table 2 Comparison of clinical data vs. biometric data between heavy and non-heavy user

Participant	Predicted use pattern-based on accelerometry	Use pattern based on clinical data
1	Non-heavy	Non-Heavy
2	Non-heavy	Non-Heavy
3	Heavy	Non-Heavy
4	Non-heavy	Non-Heavy
5	Heavy	Heavy
6	Non-heavy	Non-Heavy
7	Heavy	Heavy
8	Heavy	Heavy
9	Non-heavy	Non-Heavy

4.2 Analysis of naloxone (antidote to opioid)

As opioid abuse is rapidly escalating in the United States, and opioid reversal naloxone is efficiently used. The administration and the effect of the drug (Naloxone) does not last long as its actions last up to 90 minutes. To understand the biometric impacts of this antidote, we calculated the characteristic parameters of the distribution 30 minutes before and after the N90 (drug wears off after 90 minutes, it is like an event marking). In this analysis, we analyzed accelerometer along with other parameters at N90 like Heart Rate (HR), Electrodermal Activity (EDA) and Temperature. During this analysis, there were in a total of 11 active participants with the mean average age of 36 years (min:23; max:50). A similar approach applied at the N90 mark, but to understand and evaluate at the 90-minute post-naloxone time point. We have introduced a new

feature D_k, a six-dimensional hypothetical space with two measures, shape and scale for each of the three axes.

We determined time N90 (marked as time = 0 and a green vertical line) based on documented time of naloxone administration and applied Hilbert transform to obtain the amplitude for each of the axes separately. Prior to applying Hilbert transform, we subtracted the mean from the raw data. Figure 11 represents the amplitude calculated for each of the axes from a 5-minute segment ***before*** (yellow shading on Figure 10) and ***after*** (green shading on Figure 10).

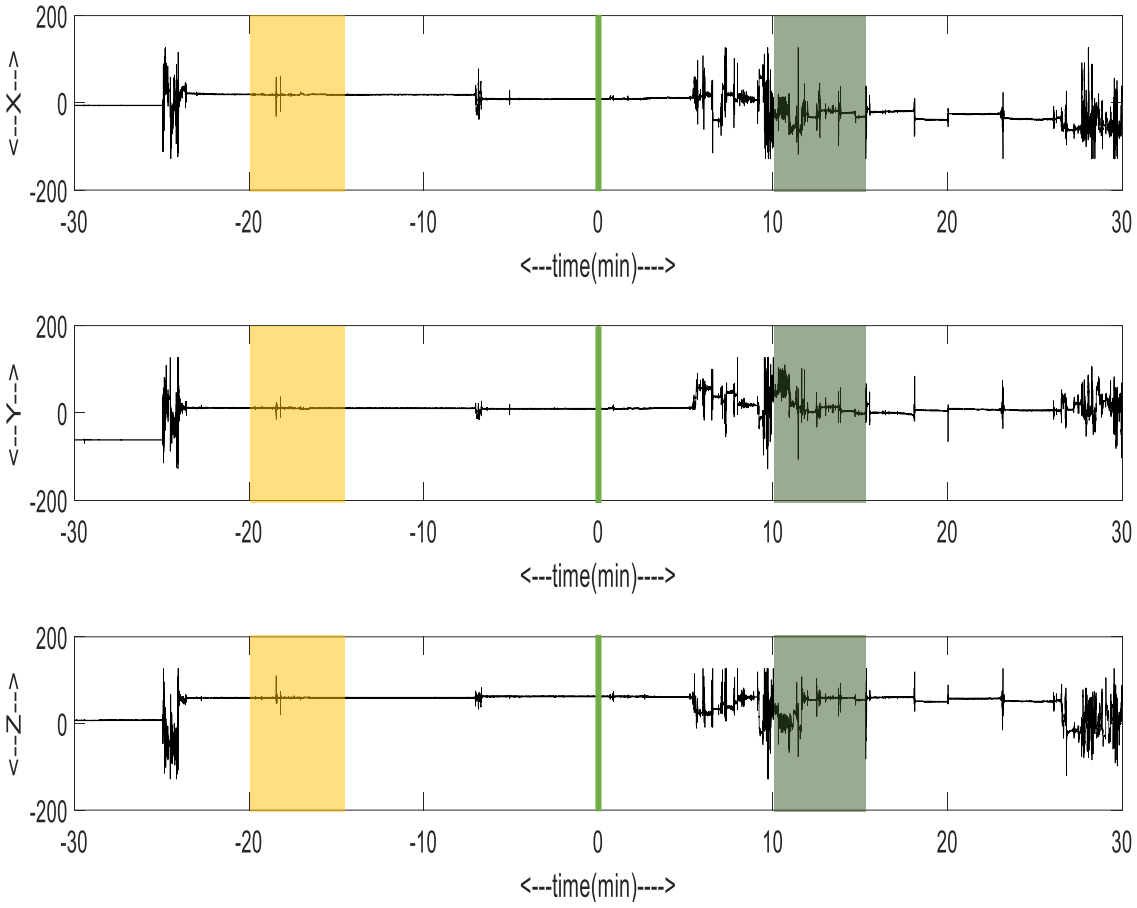


Figure 10. Accelerometer data from three axes XYZ from one of the subjects. The green line marked at time =0 represents N90. The yellow and green shading represents a representative 5 minutes window before and after N90 respectively.

After applying the Hilbert Transform at N90, we found that the amplitude follows the widespread tail distribution and by using Gamma probability density function (pdf) we discovered that there is a change in their shape. Figure 12 the amplitude estimation using the Hilbert transfrom for one of the 5-minute windows is depicted.

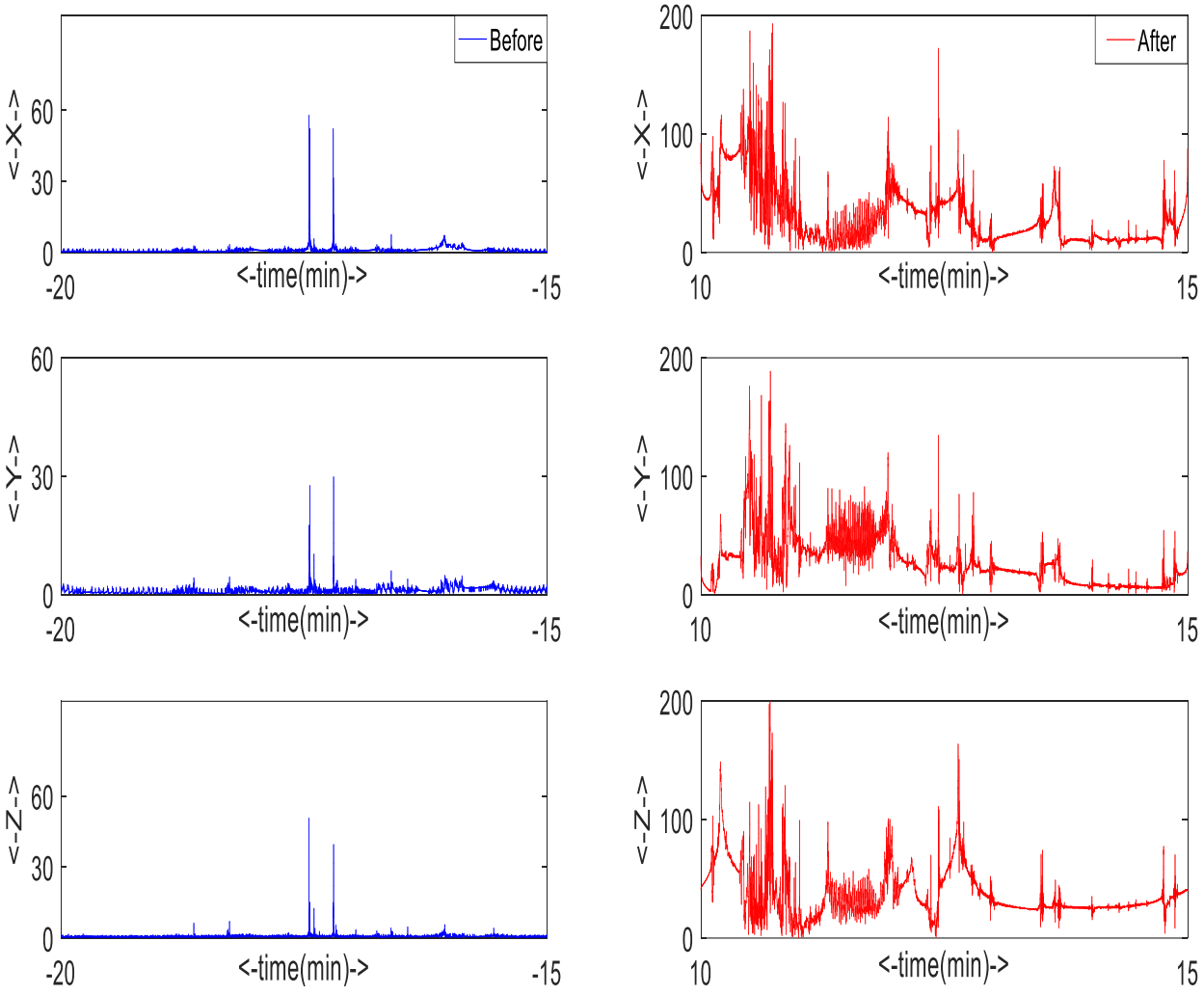


Figure 11. Amplitude estimated using Hilbert transform for the 5 minutes window. Left panels with blue lines represents before and right panel with red lines represents after

We did investigate whether the fluctuations observed in these measures are significantly different between before and after in each of the 11 participants. Table 3 shows such analysis. In seven of the participants, we found that some of the measures are significantly different between before (blue) and after (red). The red asterisk in Table 3 means the subject is significantly different between before and after.

Table 3 Mean and standard deviation (SD) for D_k, HR, EDA, and skin temperature for all participants

Subjects		**Dk**			**Heart Rate**			
	mean	SD	mean	SD	mean	SD	mean	SD
1	19.36	3.26	13.51*	5.37	86.20	2.38	85.48	3.13
2	13.92	7.67	11.95	2.99	116.82	4.12	108.10*	4.85
3	10.08	5.05	7.48 *	4.41	81.09	3.47	78.66*	1.40
4	12.75	2.17	14.42	6.94	80.30	2.77	79.91	8.81
5	13.71	4.64	6.04 *	3.95	92.42	19.93	77.39 *	1.49
6	12.19	4.83	8.95 *	3.09	118.51	20.61	115.05	15.31
7	16.26	5.56	10.85*	2.58	90.60	11.31	80.60 *	9.91
8	15.04	6.80	8.18 *	3.55	93.21	6.85	94.19	3.34
9	19.59	3.94	19.82	3.12	94.15	12.37	76.95 *	5.61
10	11.86	9.33	14.91	7.46	106.63	7.03	93.80 *	10.60
11	16.50	6.90	20.91 *	3.90	98.61	3.27	95.89 *	4.38
Subjects		**EDA**			**Temperature**			
	mean	SD	mean	SD	mean	SD	mean	SD
1	0.17	0.03	0.23 *	0.03	36.31	0.63	36.92 *	0.33
2	0.23	0.26	0.23	0.09	35.53	0.23	35.64 *	0.20
3	0.01	0.00	0.01	0.00	32.15	0.33	33.41 *	0.62
4	0.45	0.03	0.49 *	0.02	38.93	0.14	38.98	0.46
5	0.17	0.04	0.48 *	0.15	31.32	0.44	33.20 *	0.53
6	1.05	0.45	0.18 *	0.19	33.52	0.70	32.97	0.45
7	1.73	1.67	0.19*	0.05	37.35	3.13	38.88 *	0.66
8	0.28	0.18	0.32	0.08	32.09	5.47	35.47 *	0.74
9	1.17	0.57	0.67 *	0.29	32.26	0.70	32.37	0.55
10	0.26	0.10	0.30	0.07	27.02	1.93	29.11 *	0.14
11	0.08	0.01	0.14 *	0.04	28.12	0.15	29.81 *	0.81

However, significant differences in all the measures only found in three of the participants. Figure 12 represents the overall mean of D_k, heart rate, EDA and temperature along with their respective standard error. We found that in group comparison, D_k is not significant p=0.11), heart rate is significant (p =0.007), EDA is not significant (p =0.22) and, the temperature is significant (p =0.01). This mixed result is not surprising due to inter participant variability that is often observed in their response to naloxone.

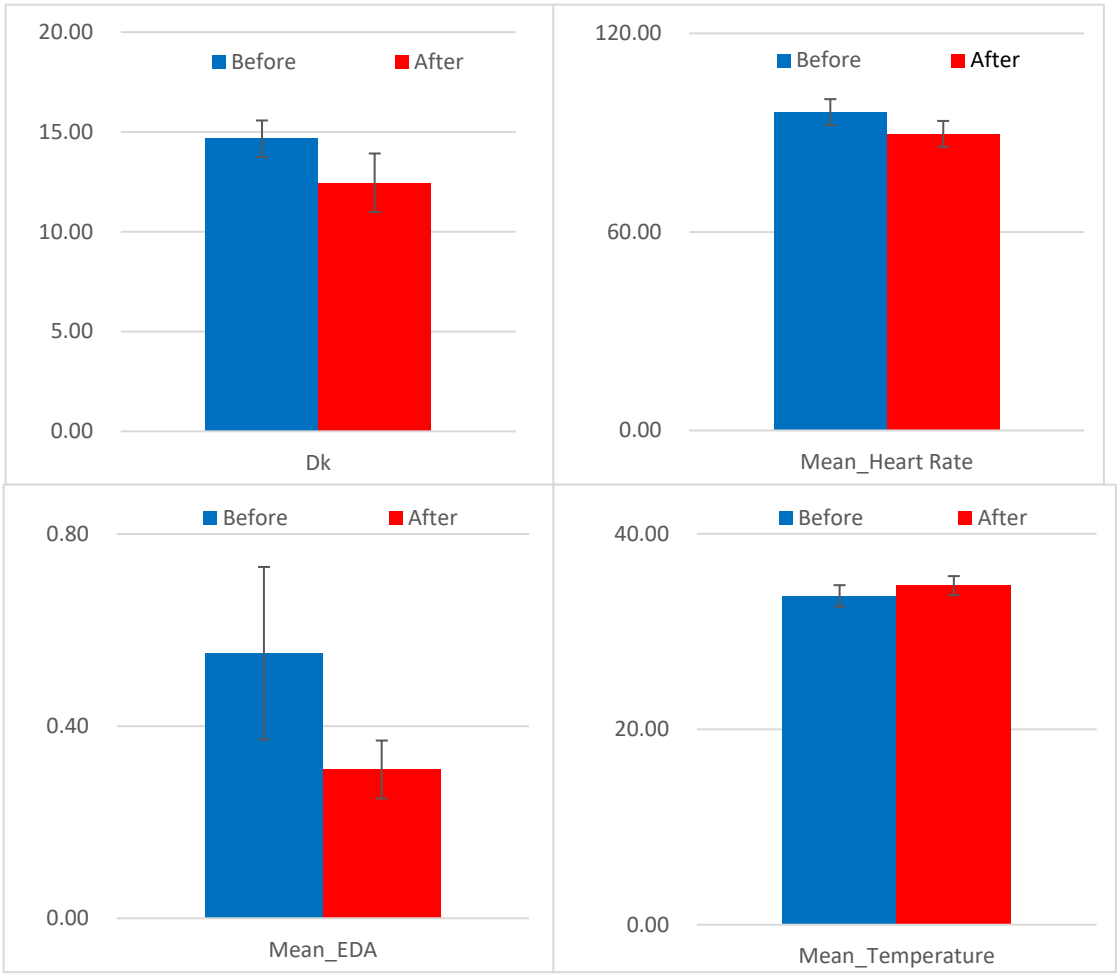


Figure 12. Mean and standard error of D_k, HR, EDA and Temperature values obtained from all subjects (N=11) before and after N90

4.3 Detection of cravings using machine learning approach

In this analysis, we are trying to detect the cravings and distinguish it from an experience of stress. These detections help the patients who are suffering from a high rate of relapse. It is an observational trial of individuals enrolled in an intensive outpatient treatment program for Substance use disorder (SUD). For this analysis, raw biosensor data evaluated 20 minutes before and after each marked event. A similar kind of approach is used even in this analysis too; a slide window technique was used to evaluate 5-minute windows with a 4- minute overlap. Within each window mean and variance, were calculated, and shape and scale parameters were extracted using the Hilbert transform. The six-dimensional open space was used to characterize pre- and post-event data. First, we tested whether the features (Mean, Variance, Shape, Scale and D_k from each axis) are significantly different during stress vs baseline and cravings vs baseline. There were in total of 145 self-reported observations (104 stress events and 41 craving events). Craving episodes showed significantly different parameters than baseline on the y axis (p=0.00), and significantly different parameters than stress episodes on the x (p =0.009) and y (p =0.00). In comparison with stress and cravings episodes, all the episodes were significantly different x (p =0.00), y (p =0.003) and z (p =0.03).

After observing the significant difference in the statistical results of stress vs. cravings, we considered these features in machine learning for real time detection. The main idea of our research is to support the clinicians for accurate treatment as well as patients to detect the cravings for drugs and what causes it, allowing them to know the consequences of it in ahead of time.

With the help of 145 observations from 30 participants, we built two different models to detect cravings along with stress. In building the model, we used 60% of the data were reserved for constructing the models and 40% for validation.

Using Quadratic SVM classifier as shown in the confusion matrix given in Table 4, we were able to detect 32 stress episodes out of 42 whereas we could catch ten craving episodes out of 16. The TPR (Sensitivity) is 0.84 and FPR is 0.5. We achieved an accuracy of 72.4 and AUC of 0.70.

Table 4 Confusion matrix for Quadratic SVM for stress vs. cravings

		Actual Class	
		Stress	Craving
Predicted Class	Stress	32	10
	Craving	6	10

Using Quadratic Discriminant classifier as shown in the confusion matrix given in Table 5, we were able to detect 30 stress episodes out of 42 whereas we could identify ten craving episodes out of 16. The TPR (Sensitivity) is 0.83 and FPR is 0.54. We got an accuracy of 68.9% and AUC of 0.72.

Table 5 Confusion matrix for Quadratic Discriminant for stress vs. cravings

		Actual Class	
		Stress	Craving
Predicted Class	Stress	30	12
	Craving	6	10

CHAPTER 5

DISCUSSION AND CONCLUSION

During our research, we collected data from three different areas which are interlinked. Firstly, the analysis on opioid drug overdose helped us to understand the effect of drugs on the human body and how it affects the addicts. Secondly, Naloxone, an antidote, explained how the impact of the drug control and how long a remedy lasts inside the body. Finally, the analysis on the observational trial of individuals provided a clear picture of the cause (Cravings and its effect) for individuals with substance abuse. In total, raw accelerometer data extracted from more than 50 participants; ranging from one day to three days. Most of the work was done on accelerometer data and extracted relevant features from it. By which, it gave us significant statistical results to differentiate between heavy user and non-heavy user; pre- and post- administration of naloxone; stress and cravings. In the end, we were able to build two different models Quadratic discriminant and SVM to detect craving along with stress.

5.1 Discussion

With shape and scale parameters with six-dimensional space (D_k) we were able to detect cravings in addicted persons. The non-linear SVM is a better model for detecting stress and non-Linear Discriminant is better model for detecting cravings. The six-dimensional space (D_k) has played a key role in the detection of cravings as the accuracy has increased from 56% to 72% and AUC curve increased from 0.53 to 0.72. The Table 6 and Table 7 provides the summary of our findings

Table 6 Summary table for heavy and non-heavy user

Classifier	Accuracy (%)	AUC
Quadratic SVM	57.7	0.6
Quadratic Discriminant	61.5	0.68

Table 7 Summary table for stress and cravings

Classifier	Accuracy (%)	AUC
Quadratic SVM	72.4	0.70
Quadratic Discriminant	69	0.72

In this research, fifteen features which were extracted from the accelerometer data using Empatica E4 for the train and build different types of ML models to detect stress and cravings in real time application given below.

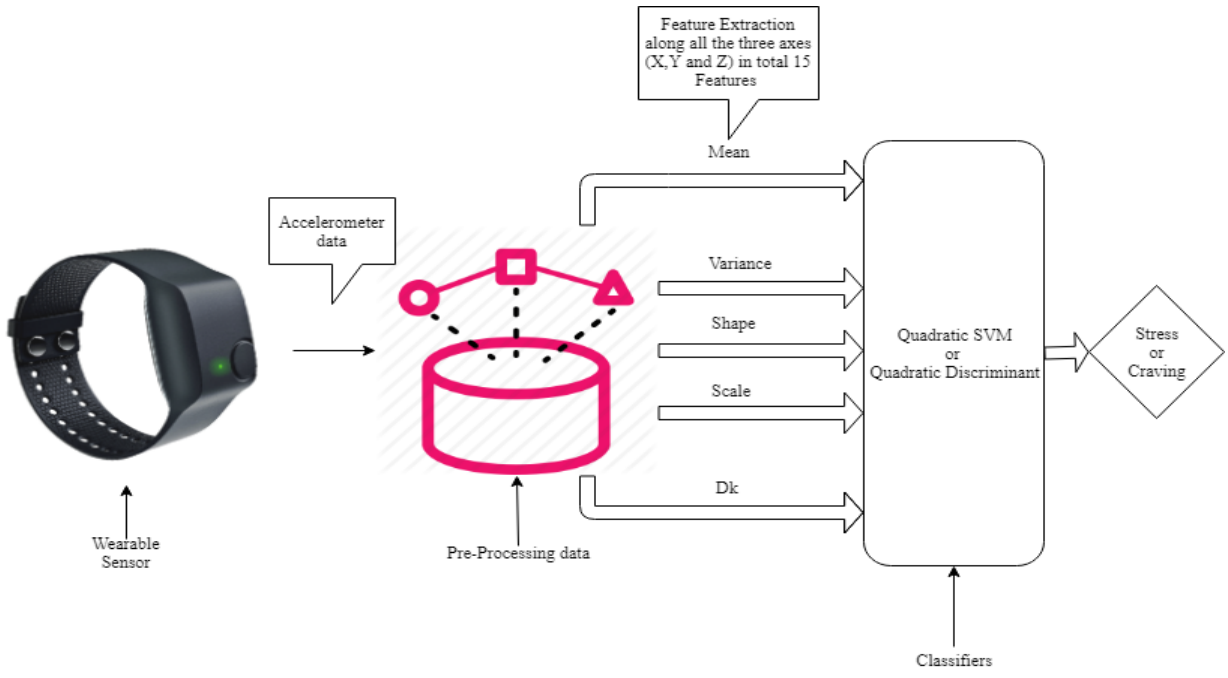


Figure 13. Framework for identifying Cravings or Stress

5.2 Limitations and future work

There were few control subjects and less objective markings of craving in controls. The death due to addiction is increased drastically not only in young adults but, also in other adults irrespective of age. Improvising ML approaches to detect cravings might help clinicians to identify the root cause of substance abuse and might help them to save lives of thousands.

The designed machine learning model should be embedded into the smart wearable devices at low cost to deploy the device to as many individuals as possible who are suffering from addiction in the world. Apparently, the tools which we are currently being used in present medical field are costly. Another limitation we found is that many wearable devices are not capable of proving real-time monitoring with a docking system as well as the number of parameters it can detect. The Empatica E4 can provide additional physiological parameters such as heart rate, temperature and electrodermal response (EDA). The further analysis should be done on different parameters like heart rate, EDA and temperature to increase the accuracy of the detection.

5.3 Conclusion

This study demonstrates that wearable biosensors can detect physiologic parameters consistent with opioid effect wear off naloxone administration and drug craving in individuals during treatment for substance abuse disorder. A signal processing method, the Hilbert transform can be applied to wearable biosensors to detect significant changes in physiology because of the drug. The advancement in technology, machine learning approaches and development in smartwatches can help the patients as well as the clinicians to treat them in an efficient manner.

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