# USE OF MACHINE LEARNING FOR THE PREDICTION OF DIABETES FROM PHOTOPLETHYSMOGRAPHY (PPG) MEASUREMENTS & PHYSIOLOGICAL CHARACTERISTICS

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**ABSTRACT**

**Prediction of Diabetes Using Non-Invasive Photoplethysmography (PPG) Measurements & Physiological Characteristics**

Type 2 Diabetes (T2D) is a chronic disease affecting millions of people worldwide. It is a result of impaired glucose regulation, leading to abnormally high levels of glucose causing microvascular and macrovascular problems. The failure to timely identify and treat, results in complications such as limb amputations, blindness and heart disease. Busy unhealthy lifestyles are a root cause and not much effort undertaken to obtain regular health checkups for early T2D detection.

Photoplethysmography (PPG) is a non-invasive, optic technique mostly used towards disease estimation in clinical environments. Recent technological advancements have integrated PPG sensors within smartphones and wearables. However, these signals suffer from various noise components, which is intensified in signals acquired in routine everyday environments. The research analysed the feasibility of short (~2.1s) PPG segments in order to address these limitations and identify biomarkers related to T2D. The identified biomarkers mainly relate to the vascular system of the body. Several classification algorithms were evaluated using cross validation to estimate T2D, focussing on a public PPG dataset. Linear Discriminant Analysis (LDA) achieved the highest area under the ROC curve of 79% for the estimation of T2D in a setting where healthy individuals, T2D only, T2D subjects with hypertension and prehypertension were present.

It is important to identify relationships between standard medical measures such as Fasting Blood Glucose (FBG) and PPG features, for better understanding T2D estimation. FBG measurements were collected, and several regression algorithms evaluated using leave-one-out cross validation to assess the suitability of predicting FBG using PPG features. The results were examined using the Clarke's Error Grid, where 75% & 22.5% of predictions were distributed in regions A & B respectively for both ElasticNet and Lasso Regression. The results were comparable with long PPG signal based approaches. The suitability of the method in practical environments was evaluated using simulated PPG signals with noise and motion artifacts. The ElasticNet Regression achieved 70% and 27.5% in regions A & B respectively. The analysis of short PPG segments shows promise towards the development of an early T2D estimation system in a routine everyday environment.

Keywords: Type 2 Diabetes, Photoplethysmography, Machine Learning, Classification, Regression

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| PPG | Photoplethysmography |
| APG | Accelerated Photoplethysmography |
| T2D | Type 2 Diabetes |
| FBG | Fasting Blood Glucose |
| ML | Machine Learning |
| CNN | Convolution Neural Networks |
| LSTM | Long Short-Term Memory |
| LDA | Linear Discriminant Analysis |
| AI | Augmentation Index |
| SVD | Singular Value Decomposition |
| BMI | Body Mass Index |

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**Chapter 1**

# INTRODUCTION

The current phase of human evolution is experiencing exponential growth in the fields of engineering and technology which has never been witnessed ever before. As responsible researchers it is our duty to identify important needs of the community and focus on providing solutions to overcome these challenges. Healthcare can be identified as a field of research which has great impact and urgency in the modern-day society. There are many diseases affecting millions of people worldwide resulting in death and suffering. Diabetes is one such chronic diseases which has affected 415 million people worldwide by 2015. Due to the current societal trends, it is expected that around 642 million people would be affected by the year 2045 [1]. It is important to highlight that this rapid onset of diabetes is more prominent in developing countries such as Sri Lanka due to the lifestyle changes, dietary changes and busy lifestyles of people.

There are mainly three types of diabetes namely, Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), and Gestational Diabetes. Nearly 90% of the diabetes population suffers through T2D which is the focus of this research. T2D is caused due the body's inability to regulate the increasing glucose levels in the blood due to inefficient use of insulin. The abnormally high levels of blood glucose for extensive periods of time would lead to complications such as premature heart disease, blindness, limb amputations and kidney failure. Hence it is important to identify T2D at the onset and ensure proper lifestyle modifications, medical treatment undertaken to avoid these adverse consequences. The early symptoms of T2D is less marked and usually detected several years after the onset, which results towards all the adversities of the disease. This highlights the importance of focusing on research to develop early disease estimation tools and methodologies.

It is advised by physicians that people undergo routine health checkups and tests such as HbA1c in order to identify T2D earlier. However, these best practices are rarely practiced due to the costs associated, negligence and the busy lifestyles hindering people to focus on their health. This is very unfortunate, where surveys estimate that out of the 30.3 million Americans (9.4% of the population) having diabetes, 1 in 4 does not know that they have diabetes. In Europe 66 Million people (9.2% of the adult population) are affected with diabetes and 38% do not know that they have diabetes (1 in 3 people) [2] [3]. The numbers are expected to be worse in developing countries where the focus and motivation towards healthcare is very less.

Such a disease background highlights the importance of developing a low cost, convenient system towards the early detection of T2D. Artificial Intelligence & Machine Learning (ML) can be identified as a novel paradigm shift in technology in many diverse fields. Artificial Intelligence in the field of healthcare presents many opportunities towards early disease prediction & diagnosis which would ensure massive value creation to humankind. In such light the interest towards early disease prediction has received immense attention and motivation. Wearable devices have gained immense popularity and massive advancements in the recent years. Many advanced sensors have been integrated in day to day devices such as wearables, smartphones and smart watches. A significant trend towards utilising these technologies to measure key health parameters and provide predictions can be identified.

Photoplethysmography (PPG) sensors have been integrated in many of the identified devices, which provides us with great intuition over the physiology of the human body. PPG sensors are low cost, non-invasive, optical sensors which can be used to measure the blood volume changes in blood vessels through which oxygen saturation, blood pressure, cardiac output can be measured [4,5]. Utilising PPG sensors along with machine learning has shown great promise in developing

intelligent systems capable of providing early insights towards cardiovascular diseases such as T2D and hypertension [6]. This research focuses on identifying relationships between the photoplethysmography signals, physiological characteristics and T2D. The investigation of biomarkers towards the detection of T2D utilising machine learning techniques is expected to pave the way towards the development of a convenient low-cost method for people to screen themselves for early indicators of T2D.

## 1.1 Problem

Diabetes is a chronic widespread disease mainly resulting due to the deficiency in glucose regulation. A significant amount of research is conducted in this area to address different aspects of the disease such as diabetes detection, management, artificial pancreas systems and glucose estimation techniques. However, the focus on systems for the early detection of diabetes is relatively recent. The limited T2D detection solutions mainly focus on T2D estimation at a clinical setting. It is important to explore and develop T2D estimation techniques which can be easily used in routine day to day life, which is the main motivator for this research.

The early detection of T2D is of utmost importance in order to safeguard people from the severe complexities of the disease. Complications such as blindness, limb amputations and cardiovascular diseases mainly arise due to prolonged periods of high blood sugar levels. The early detection of the disease eliminates the risks and would significantly reduce costs related to healthcare. Hence the main purpose of this research is to design a system to early detect diabetes using readily available data of people. Due to the costs and busy lifestyles, people are reluctant to undergo routine health checkups to evaluate their risk of T2D. This highlights us the importance of designing a system which would be of low cost and great convenience to the users to continuously screen themselves.

Disease classification is a complex task due to the overlapping disease conditions. Thus, it is important to identify unique biomarkers for T2D. The black box approach of machine learning algorithms can be identified as a major constraint towards the application of ML in the medical domain. Most such medical solutions are hard to interpret even though higher accuracies are being presented. It is important to focus on developing explainable models which would add great value to physicians and the medical community. For an example, in most disease prediction research, standard signal processing techniques are used for feature extraction. These extracted features do not necessarily convey a physical / biological meaning, or the meanings have not yet been identified by research. Thus, the final results lack proper understanding. Hence, it is important to focus on features which can be interpreted and work on an explanatory approach which would be more feasible towards the practical application of the solution.

## 1.2 Proposed Solution

This research focuses on utilising PPG signals and physiological characteristics to identify unique biomarkers towards T2D estimation. PPG sensors are currently widespread and easily accessible through smartphones and wearable devices enabling the development of a convenient solution to the users.

The photoplethysmography waveforms captures the blood volume changes within the blood vessels. Hence, useful physiological insights about the cardiovascular system could be obtained through the analysis of PPG signals. PPG signals have been mostly used towards disease identification in a controlled clinical environment. Hence, these approaches focus on long carefully recorded PPG signals. These PPG signals are affected by various kinds of noise and motion artefacts. This issue is intensified, when PPG signals are acquired during day to day activities from wearables devices. This motivates the focus on methods to analyse PPG signals under practical conditions, in order to develop a T2D estimation system in a routine

everyday environment. The research focuses on evaluating the feasibility of using short PPG signal segments (~2.1s) to address these limitations. This short PPG segments based analysis is expected to benefit the development of a convenient detection system robust to motion artefacts and noise in a routine everyday environment.

Morphological features of the signal would be extracted and analysed using machine learning to identify unique biomarkers for T2D prediction. In comparison to standard features extracted through different signal processing techniques, the focus is on identifying features which have a biological meaning. This is expected to provide better understanding and interpretation towards the final results. Classification algorithms will be evaluated to classify people with T2D from healthy controls, in a complex overlapping disease environment. The interpretability of the developed ML models would be a great benefit to knowledge discovery and understanding. It would also enable to bridge the uncertainties between the fields of ML and medicine. The obtained results can be mapped to concepts used by physicians towards the diagnosis of T2D, to enhance the explainability. FBG measurements can be identified as one of the main tests used by physicians to diagnose T2D. The identified PPG features would be analysed and regression algorithms would be evaluated towards predicting FBG levels. The accuracy in the classification of T2D patients and FBG level prediction, is expected to provide a better understanding on the suitability of the selected biomarkers towards T2D estimation. Finally PPG signals contaminated with noise and motion artifacts would be simulated to identify the accuracy of FBG predictions. This would provide valuable insights on the feasibility of utilising short PPG segments towards the development of a T2D estimation system for a routine everyday environment.

## 1.3 Contributions

The following contributions are presented in this thesis.

- Design a practical, convenient system to predict T2D in a routine everyday environment.

- Analysing physiological characteristics and short Photoplethysmography (PPG) waveforms segments toward the classification of T2D.

- Identification and extraction of unique morphological features from the PPG waveform.

- Identify unique biomarkers towards the detection of T2D in a complex disease environment.

- Identify suitable ML algorithms to develop a model for the classification of diabetes.

- Evaluate the relationship between PPG features and clinically accepted diagnosis criteria: Fasting Blood Glucose levels, through the analysis of machine learning algorithms.

- Evaluate the feasibility of using short PPG segment based features in a practical environment by simulating noise and motion artifact contaminated PPG signals, for FBG prediction.

## 1.4 Organisation

The rest of this document is organised as follows. Chapter 2 presents a literature review including related work, an overview of the PPG technology and its present applications along with a medical study related to T2D. Chapter 3 presents the main two research approaches focusing on T2D classification and FBG level prediction using PPG signals. The Chapter 4 comprises of the discussion and analysis of the obtained experiment results. The document concludes with Chapter 5, presenting the final conclusions and recommendations related to the research.

**Chapter 2**

# LITERATURE REVIEW

In this section different types of systems and tests developed to detect T2D would be analysed. These systems encompasses the standard tests in the medical domain and the most recent researches in the engineering domain. Next the photoplethysmography technology and its latest research applications would be discussed. Finally, a medical overview will be presented in order to understand the human body and the rationale of biomarker identification related to photoplethysmography signals.

## 2.1 Related Work

The first part of this research mainly focuses on developing a system to early detect T2D. At present there are different methods in place and researches conducted to develop such screening methods. The most prominent approach is the frameworks developed in the medical domain through the analysis of T2D populations. The Framingham study [7] is one such medical research which has identified guidelines to ascertain the risk of T2D based on factors such as Body Mass Index (BMI), weight, smoking behaviour, body fat etc. These frameworks would vary between different sample populations and could also be affected by other similar overlapping diseases (Ex: Hypertension).

The main T2D detection tests could be identified as HbA1c, Oral Glucose Tolerance Test (OGTT), Fasting Blood Glucose (FBG) [1]. Physicians prescribe these tests to diagnose T2D, and they can be considered as the gold standard towards diabetes estimation. Based on studies different blood glucose ranges have been identified which enable the diagnosis. The guidelines for diabetes diagnosing tests are presented in Table 2.1. The second part of this research would focus on the prediction of FBG utilising PPG waveforms.

|  | FBG (mg/dL) | HbA1c | OGTT (mg/dL) |
|---|---|---|---|
| **Healthy** | 70 - 100 | < 5.7% | < 140 |
| **Prediabetes** | 100 - 125 | 5.7% - 6.4% | 140 - 199 |
| **Diabetes** | ≥ 126 | > 6.5% | ≥ 200 |

**Table 2.1 American Diabetes Association Guidelines, Standards of Medical Care 2018.**

Previous research has also focused on methods to analyse Electronic Medical Records (EMR) to predict diabetes [8]. Such an approach is irrelevant to the focus research problem of developing a user centric, easily accessible T2D detection system. Noninvasive Peripheral Artery Tonometry (PAT) and Digital Thermal Monitoring (DTM) signals have been used to develop systems capable of predicting T2D [9]. However, the use of such sensors in a practical free-living scenario is infeasible. Heart Rate Variability (HRV) analysis can be identified to have significance importance in T2D prediction, where many research studies have focused on utilising ECG signals and PPG signals towards the extraction of HRV to predict T2D. HRV has been identified as a promising technique for T2D prediction and have been combined with morphological features of the PPG signal for predictions. Most recently HRV along with activity data of wearable sensory inputs have been effectively used in T2D prediction.

This research focuses on PPG signal-based approaches towards T2D prediction which can be identified as a straightforward physiological signal for T2D prediction. Ballinger et al (2018), developed the DeepHeart system which focused on utilising medical history, blood test results, previous diagnosis, HRV through PPG signals, step counts and other activity data captured by off the shelf wearables towards cardiovascular risk prediction. Semi supervised LSTM techniques were used to achieve an accuracy of 0.8451 (c-statistic) for diabetes prediction [6]. Swapna et al

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(2018) extracted HRV in a clinical setting using ECG recordings and reported an accuracy of 90.9% through CNN - LSTM techniques [10].

Reddy et al (2017) focused on analysing HRV and long recorded (5 min) PPG signal features towards the prediction of T2D. An accuracy of 89% and 90% was obtained utilising PPG signals extracted from a pulse oximeter and a Nexus 5 phone camera respectively using support vector machines [11, 12]. Moreno et al (2017) achieved an accuracy of 69.4% (area under the ROC curve) focusing on HRV, demographic features (weight, height, age, gender, BMI, body fat), long recorded PPG features and Cepstral Analysis [13]. Random Forest, Gradient Boosting, Linear Discriminant Analysis techniques were evaluated, and an activity detection algorithm developed to compensate for motion artefacts in long recorded PPG signals.

HRV can be identified as a key feature towards T2D prediction [14]. However, longer PPG signals need to be extracted to obtain a meaningful HRV signal. Main constraints towards the extraction of a quality PPG signal are the motion artefacts and ambient noise. To overcome such limitations activity detection algorithms have been utilised. Using Inertial Measurement Unit (IMU) sensors embedded in wearable devices to detect motion would also be a plausible approach to mitigate the effect from noise. This research focuses on identifying the best short segments (~2.1s) of the PPG signal and utilising the morphological features toward T2D prediction. This limits the analysis of the PPG signal based on its temporal characteristics. However, medical studies have identified that the amplitude characteristics of the PPG waveform possess more information regarding the vascular system, such as vascular ageing, arterial stiffness and endothelial dysfunction [15]. In the medical study presented in section 2.3 of this document we identify the importance of such measurements towards T2D. Hence, the focus on analysing short PPG segments in this research.

The second part of the research focuses on providing better understanding of the extracted features in order to enhance the interpretability of the system. The focus is to link the current medical domain diagnostic knowledge with the PPG signals. Current physicians mainly focus on HbA1c, FBG measurements towards the detection of T2D. Hence it is important to explore the possibility of utilising PPG measurements towards the estimation of such quantities. Moreno et al (2011) focused on glucose level estimation from long recorded (1 minute) PPG signals, where features such as HRV, autoregressive coefficients of the PPG, energy-based features were utilised [16]. This research obtained an accuracy of $R^2 = 0.90$ for glucose estimation and the distribution of the points on the Clarke error grid was 87.7% in Zone A, 10.3% in zone B and 1.9% in zone D. It is important to highlight that most of the features analysed in previous research are related to standard measures of a signal, and thus do not portray clear biological/clinical relationships towards T2D. This hinders the interpretability of the results.

The Clarke's error grid [34] analysis has been established to quantify the clinical accuracy of patient blood glucose estimates. The grid breaks down a scatter plot into five regions based on the actual and predicted glucose values, which quantifies the accuracy. The region A is related with predictions within 20% of the actual value, B is associated with points outside 20% but would not lead to improper treatment. Region C identifies the points which would lead to unnecessary treatment. Region D is related to points which would lead to dangerous failures to detect hypoglycemia or hyperglycemia and region E is related to the points which would cause confusion between the treatment of hypoglycemia and hyperglycemia.

The prediction of glucose is a complex task and there is significant variation even within the standard clinical tests such as HbA1c and FBG. This has been a main motivator towards the error analysis based on the Clark's error grid identified above compared to standard error metrics. The glucose measurements are mainly affected

by biological, pre-analytical and analytical variations. Due to biological variations the measured glucose level is expected to vary between 112-140 mg/dL for an individual with a FBG of 126 mg/dL. Pre-analytical variations are mainly due to medication, posture and sample handling. Analytical variations occur due to bias in laboratory equipment. Studies have established that this is less than the biological variation. However, a FBG reading of 100 mg/dL could have a bias between the range -6 to +7 mg/dL [35]. Hence, the estimation of blood glucose values is a challenging task.

After the consultation of an Endocrinologist the above findings were justified, and it was identified that the person's blood glucose range is of great importance for their current diagnosis, whereas the focus on the actual blood glucose value was minimal. It is important to highlight that the glucose value is only one factor towards the diagnosis, and many other factors such as age, heredity, weight are considered in the final diagnosis. These factors motivated towards the second part of the research where FBG values were predicted using PPG features. This helps improve the understanding between T2D and identified PPG based biomarkers, and is also expected to be valuable in T2D estimation.

## 2.2 Photoplethysmography Signal (PPG)

Photoplethysmography (PPG) can be identified as a non-invasive, inexpensive, optic technique which measures the blood volume changes in blood vessels through which oxygen saturation, blood pressure, cardiac output could be measured. In recent research it has been identified that PPG is a promising technique towards early screening of diseases as the PPG waveform possess significant information embedded within [4-5].

The sensor consists of a Red & IR LED and a photodetector which emits the light to the part of the body and captures the reflected waveform. The LED, photodetector

setup mainly can be either the transmittance type (the two sensors on opposite sides) or the reflective type (sensors on the same side). In both these setups the sensor function is based on the light absorption by the blood. The light is absorbed by the skin, tissues and the blood stream. The change in the light absorption is related to the change in the blood volume. It should be noted that the earlobes, fingertips and toes have been identified as the perfect regions for obtaining the PPG signal. Mobile phones use the fingertip to capture the signals and the smart wearables mainly focus on the wrist of the user. More advanced sensor setups can be seen in modern wearables where multiple PPG sensors are incorporated to improve the quality.

The PPG signals provide the capability of calculating the oxygen saturation of the blood by using the blood absorption differences in the IR & Red LED waveforms which can identify oxygenated hemoglobin and deoxyhemoglobin. Modern researches are being conducted to ascertain whether glucose measurements can be obtained through these sensors. The chemical and physical properties in sensor design falls outside the scope of this research. However, a machine learning approach is followed to analyse the FBG level measurements using the PPG waveform.

Massive interest towards this technology can be identified in the recent past, where researchers from Stanford University & Apple Inc have collaborated in the detection of Heart Arrhythmias using the PPG technology [17]. At present the PPG sensors are mainly used for Heart Rate estimation, whereas non-invasive BP, Blood Glucose estimation and disease prediction are comparatively novel fields of research. The latest studies have been able to detect Diabetes with an accuracy of 85% and Hypertension at an accuracy of 80% [6].

**2.3 Medical Study on T2D**

Diabetes is a chronic disease which occurs due to the body's ineffective use of insulin to regulate blood glucose levels. Insulin is a hormone produced by the pancreas of the body and is responsible for regulating blood sugar. It has been recorded that 415 million people have been affected by diabetes by the year 2015 and it is expected to worsen. Obesity and lifestyle is directly associated with T2D, and is widespread in developing countries mainly due to the lifestyle changes. The early symptoms of the disease are less marked and as a result it may lead to microvascular and macrovascular complications. Macrovascular complications include cardiovascular disease, heart attacks and strokes. Microvascular complications are due to the damage of small blood vessels. It includes damages to the eye (retinopathy) which can lead to blindness, the kidneys (nephropathy) leading to neural failure and nerves (neuropathy) leading to diabetes foot [18].

The PPG technology focuses on capturing the changes in the blood flow through the blood vessels. This technique is capable of capturing insights on the vascular system such as vascular ageing, endothelial dysfunction, arterial stiffness. Endothelial dysfunction is identified as a precursor of diseases such as diabetes, hypertension and renal failure [15]. The research focuses on utilising this relationship to explore relationships between T2D and features extracted from the PPG waveform.

An early prediction system requires the identification of potential biomarkers towards T2D prediction. Since the early symptoms of T2D are less marked and hardly distinguishable to the naked eye, we analyse the minute changes in the vascular system utilising the analysis of PPG signals. Diabetic retinopathy is a widely researched area which focuses on predicting T2D analysing the blood vessels in the human eye. This has been used as a diabetes screening technique.

Numerous medical studies have developed frameworks to predict the risk of T2D. However, there is a great disease complexity due to similar symptoms across a variety of diseases. Diabetes, hypertension, renal failure all can be identified as stemming from the metabolic syndrome. It is important to analyse the PPG waveforms focusing on different disease combinations and demographic characteristics in order to develop a unique disease profile. The relationship between HRV and T2D was identified in the previous section. Previous research has identified that the HRV decreases with age and the microvascular injuries to the blood vessels could reflect a change in the HR dynamics [13]. However due to the limitations in extracting quality continuous PPG waveforms in routine everyday environments, this research focuses on amplitude based (focussing on a single pulse) vascular characteristics arising from microvascular injuries in T2D.

**Chapter 3**

# METHODOLOGY

This section presents the methodologies proposed to address the identified research problem. The first research approach focuses on identifying suitable biomarkers for the classification of T2D. Next, FBG levels are analysed using PPG features to evaluate the possibility of FBG estimation.

The two methodologies presented, focus on analysing short segments of the PPG signal compared to other identified approaches in section 2. Single pulse PPG segments of the waveform will be identified based on a quality criteria, and features extracted towards the estimation of T2D and FBG level estimation. This pulse segment based focus is expected to be effective in the practical implementation with motion artifacts and noise in a routine everyday environment, compared to long signal analysis done in controlled clinical settings. The feasibility of using short PPG segments, is explored through the simulation of noise and motion artifacts contaminated PPG signals for FBG prediction.

## 3.1 Identifying Biomarkers for T2D and Classification

A classifier requires meaningful features in order to uncover the underlying relationships to perform a classification task. The development of a classification system to early estimation of T2D can be identified as the primary aim of this research. The physiological parameters of patients and features related to the PPG is extracted and analysed to identify the features related T2D.

Generally, standard features are extracted from signals towards analysis. Various energy metrics, auto regressive parameters, frequency parameters are some such features. Even though these features are capable of representing the signal, the

physical meaning of the features might not be clear, thus the meaning of classification models are harder to understand. This research identifies features which have biological / clinical meaning in order to provide more insights into the final results. T2D affects the vascular system of the body as identified in section 2.3. Through careful analysis of previous medical research in different disease domains, well established morphological features related to the vascular system of the body have been identified for this research.

The identified features are tested against multiple machine learning algorithms, and hyper parameters tuned to identify patterns and relationships for T2D estimation. The evaluation of the different models is conducted based on the area under the ROC curve which considers both the true positive rate and the false positive rate of the binary classification problem.

### 3.1.1 Dataset Description

The public datasets available in the domain of diabetes including PPG waveforms is very minimal. This research was conducted based on a recent open source clinical trial dataset by Liang, Yongbo, et al [19], which focused on blood pressure estimation using short photoplethysmography signals. The dataset mainly comprised of healthy, diabetes, hypertension subjects. Subjects with cerebral infarction and cerebrovascular disease were also present in the dataset and were excluded from this study. Healthy, diabetes & hypertension subject's data was selected, where signal processing and feature extraction algorithms were used to extract the target features. After the elimination of erroneous signals, a total of 150 subjects comprising of 51 healthy, 39 prehypertension, 28 hypertension and 32 diabetes patients were selected for analysis.

It is important to highlight that the dataset was imbalanced with comparatively fewer number of diabetes only subjects. However, diabetes subjects with hypertension and

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prehypertension were present which indicates the strong interconnection between the diseases. Diabetes is considered a risk factor for hypertension, and both the diseases derives from the metabolic syndrome. This signifies the importance of estimating T2D in a complex, practical disease setting. The analysis of other diseases related to the cardiovascular system would further enhance the proposed system. A summary of the analysed subjects is presented in Table 3.1.

| Subject Description | Number of Subjects |
|---|---|
| Healthy | 51 |
| Prehypertension Only | 39 |
| Hypertension Only | 28 |
| Diabetes Only | 9 |
| Diabetes & Prehypertension | 16 |
| Diabetes & Hypertension | 7 |
| Total | 150 |

**Table 3.1 Subject summary of the target dataset.**

## 3.1.2 Data Preprocessing & Feature Extraction

Identifying the biomarkers uniquely related to T2D is of utmost importance, in order to utilise classification algorithms in an environment where multiple similar diseases are present. Mainly two sets of features are identified in this research. The physiological features such as age, gender, height, weight, BMI were extracted from the selected dataset, and body fat percentage calculated utilising the formula given in [20] as an additional physiological feature.

The PPG signals of the identified subjects were utilised to extract the second set of features. The signals in the selected dataset was collected at a sample rate of 1KHz using a 12-bit ADC, and a hardware filter design of 0.5 - 12 Hz bandpass. The dataset comprised of three short signal segments (~2.1) for each subject. The best

signal was selected based on the Skewness Signal Quality Index (SSQI) as identified in a previous study [21]. Another previous study identified that the 8th Order Chebyshev II filter was appropriate for removing noise in a PPG signal [22]. Hence the same filter design was utilised for noise removal.

Focusing on the processed signal and its second derivative waveform (Accelerated Photoplethysmography - APG) an algorithm was developed using the MATLAB software to extract the identified features. A list of the extracted features is presented in Table 3.2, with a brief description on the characteristics of each feature. The extracted signal coordinates to calculate the features are presented in Figure 3.1.

It is important to highlight that developing a robust algorithm towards the extraction of targeted signal coordinate is tedious due to the noise and motion artifacts present in the signal. This is a practical challenge towards the utilisation of PPG signals towards T2D estimation. The approach targeting short signal segments simplifies the feature extraction process. Unsupervised Deep Learning based approaches can be focused towards automatic feature extraction which requires the collection of a large database of PPG waveforms, which is outside the scope of this research.
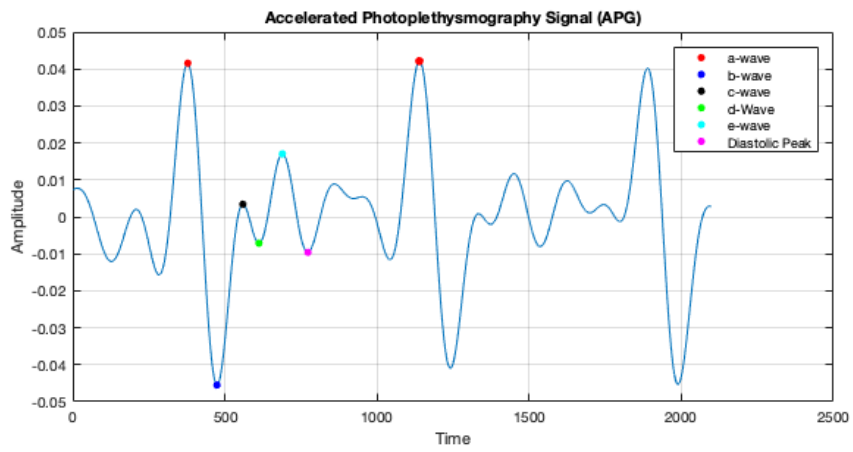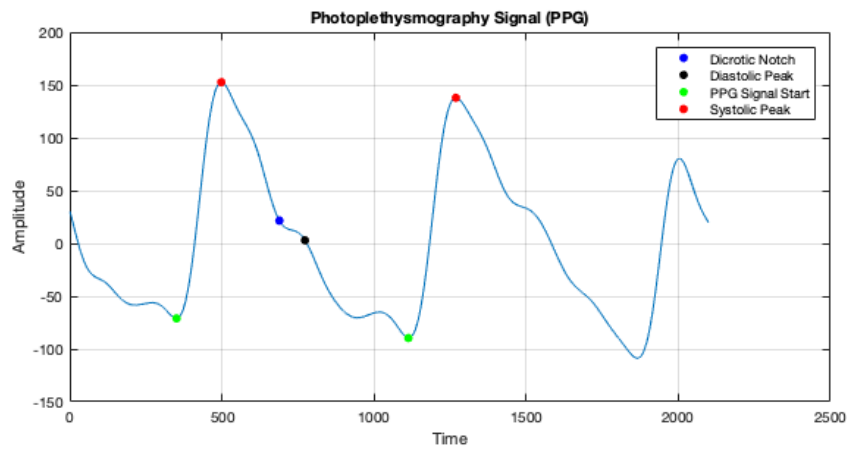
**Figure 3.1 Extracted data points from the PPG & APG waveform.**

| Feature | Description | ANOVA Test (Diabetes) | | ANOVA Test (Hypertension) | |
|---|---|---|---|---|---|
| **Physiological Features** | | F Value | P Value | F Value | P Value |
| Gender | | 1.313 | 0.256 | 1.929 | 0.15 |
| **Age** | | 11.170 | **0.001** | 20.158 | **3.13E-08** |
| Height | Centimeters(cm) | 0.267 | 0.607 | 0.078 | 0.925 |
| Weight | Kilograms(kg) | 1.125 | 0.293 | 3.040 | 0.0517 |
| BMI | Weight(kg) / Height$^2$ (m$^2$) | 0.569 | 0.454 | 3.989 | 0.0211 |
| Body Fat (%) | (1.2*BMI) + (0.23*Age) - (10.8*Gender) - 5.4 | 1.268 | 0.265 | 3.943 | 0.022 |
| **APG Signal Features** | | | | | |
| b/a Ratio; (for short: apg1) | Increase Arterial Stiffness | 0.845 | 0.362 | 4.414 | 0.0142 |
| c/a Ratio; (apg2) | Decreased Arterial Stiffness | 1.957 | 0.167 | 1.824 | 0.166 |
| d/a Ratio; (apg3) | Decreased Arterial Stiffness | 0.164 | 0.687 | 5.859 | 3.78E-03 |
| **e/a Ratio; (apg4)** | Decreased Arterial Stiffness | 5.642 | **0.021** | 0.571 | **0.566** |
| (b-c-d-e)/a Ratio; (apg5) | Vascular Aging | 0.053 | 0.818 | 6.429 | 2.26E-03 |
| (b-e)/a Ratio; (apg6) | Vascular Aging | 0.201 | 0.656 | 2.969 | 0.0553 |
| (b-c-d)/a Ratio; (apg7) | Sensation of Coldness Treatment | 0.827 | 0.367 | 6.602 | 1.93E-03 |
| (c + d - b)/a Ratio; (apg8) | Vascular Aging | 0.827 | 0.367 | 6.602 | 1.93E-03 |
| a-a Interval | Complete Heart Cycle | 0.205 | 0.652 | 0.498 | 0.609 |
| (-d/a) Ratio | Index Left Ventricular Overload | 0.164 | 0.687 | 5.859 | 3.78E-03 |
| **PPG Signal Features** | | | | | |
| Systolic Amplitude | Stroke Volume / Local Vascular Distensibility | 0.166 | 0.685 | 4.622 | 1.17E-02 |
| Pulse Area | Total Area Under the PPG Curve | 0.935 | 0.338 | 0.702 | 0.498 |
| Inflexion Point Area (IPA) Ratio | Total Peripheral Resistance | 0.309 | 0.580 | 0.186 | 0.831 |
| Pulse Interval (PI) | Complete Heart Cycle | 0.137 | 0.712 | 0.449 | 0.639 |
| **PI / Systolic Amplitude Ratio; (PI_Sys)** | Cardiovascular System Properties | 6.291 | **0.015** | 2.305 | **0.104** |
| **Augmentation Index (AI)** | Vascular Tone / Endothelial Dysfunction | 5.793 | **0.019** | 0.225 | **0.799** |
| **Adjusted AI; (adj AI)** | Vascular Tone / Endothelial Dysfunction | 5.793 | **0.019** | 0.225 | **0.799** |
| Large Artery Stiffness Index | Arterial Stiffness | 0.368 | 0.547 | 4.567 | 1.23E-02 |
| Rise Time (RT) | Cardiovascular Disease Classification | 0.016 | 0.899 | 5.102 | 7.53E-03 |

**Table 3.2 Feature selection results using ANOVA tests.**

### 3.1.3 Feature Selection

The above extracted features are clearly identified and described in Elgendi et all [4] and Allen, John et al [5]. These features have been previously analysed, mainly towards the understanding and interpretation of the cardiovascular system. As identified in an earlier section, the cardiovascular system is affected by a variety of diseases. Hence it is important to uniquely identify the biomarkers towards T2D estimation. Assuming a normal distribution of the data, an ANOVA test with a 95% confidence interval was undertaken, focusing on the 51 healthy and 9 T2D only subjects. It was identified that the Age, Augmentation Index (AI), Adjusted AI, e/a Ratio and the ratio between the Pulse Interval to the Systolic Amplitude are suitable features towards T2D estimation.

Previous studies [23-25], have also identified that the Augmentation Index (also known as the Reflection Index) can be used to detect endothelial dysfunction in diabetes patients. Endothelial dysfunction [26] occurs due to damages in the vascular endothelium affecting the operations of the vascular system. This may also lead to atherosclerosis, which is considered a major risk factor of cardiovascular disease. Hence, AI and Adjusted AI can be utilised towards T2D estimation, since hyperglycemia [27] is a major risk factor towards endothelial dysfunction. Through the ANOVA test it was identified that the ratio, Pulse Interval to its Systolic Amplitude is a unique feature for T2D estimation. This was previously identified by Poon et al [28] to understand the properties of the cardiovascular system. The e/a ratio can be used towards the estimation of T2D, which characterises the arterial stiffness as identified by Takazawa et al [29]. Takazawa et al demonstrated that the increase of the e/a ratio results in a decrease of arterial stiffness, and that e/a decreases with age. The Age was also identified as a key feature, which is mainly due to the higher probability of T2D among older subjects.

It should be highlighted that other features related to vascular ageing and arterial stiffness were not identified as predictors towards T2D, even though they represent the vascular system. To confirm that the selected features are unique towards T2D, a second ANOVA test with a 95% confidence interval was conducted focusing on 51 healthy, 39 prehypertension and 28 hypertension subjects. The earlier test results were justified as the e/a ratio, AI, Adjusted AI and the ratio of pulse interval to its systolic amplitude were not identified as prominent features towards the estimation of hypertension. Hence it can be concluded that the e/a ratio, AI, Adjusted AI and the ratio of pulse interval to its systolic amplitude are unique features towards the estimation of T2D. However, Age was identified as a predictor towards both T2D & hypertension. Box plot graphs of the selected features are presented in Figure 3.2.
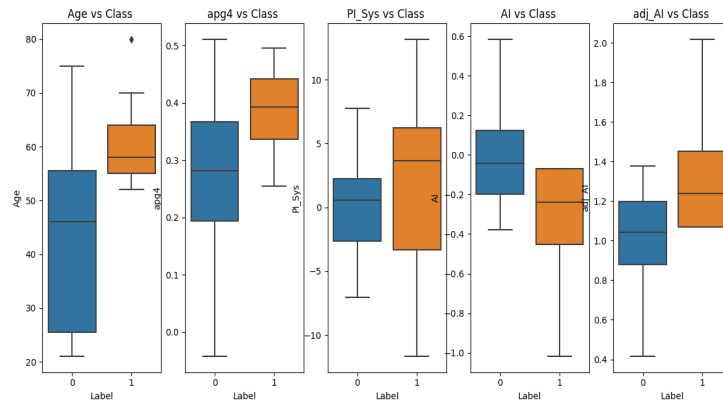


**Figure 3.2 Box plot graphs of selected features (Label 0: Healthy, Label 1: T2D).**

### 3.1.4 Machine Learning Models

Machine learning algorithms can be effectively utilised to identify relationships and develop classification models on the target dataset. This analysis focused on supervised learning techniques [30] to carry out a binary classification problem, where healthy and T2D subjects were estimated. The area under the receiver operating characteristic (ROC) curve was the target evaluation metric. A variety of algorithms were analysed, and the best performing algorithms were identified.

Statistical algorithms such as the Naive Bayes classifier, Linear Discriminant Analysis (LDA), logic-based algorithms like Decision Trees and its variants Random Forest & Adaboost focusing on ensemble and boosting methods, Logistic Regression and Support Vector Machine (SVM) were evaluated in this study.

The machine learning models were tuned with specific optimum hyper parameters using random search and stratified 10-fold cross validation used to optimise the target evaluation metric. Overfitting can be identified as a key phenomenon in machine learning which needs to be avoided, which is prominent in this case due to the relatively small number of data samples. Hence all the models were tuned ensuring the selection of suitable hyper parameters, and the best model selected. The scikit-sklearn python library was used to implement the machine learning models [31].

The binary classification was carried out by balancing the target classes through under sampling, in order to avoid the class imbalance problem. The analysis was carried out based on 4 classification settings. Healthy versus T2D only subjects, healthy versus T2D including those with prehypertension, healthy versus T2D including those with prehypertension and hypertension. The final classification focused on assessing the robustness of the PPG towards T2D estimation. Hence only the PPG based features were selected and subjects below the age of 30 were excluded in order to ensure an even distribution across the age groups, with healthy and T2D subjects. Figure 3.3 presents the age distributions of the subjects in the final classification setting.
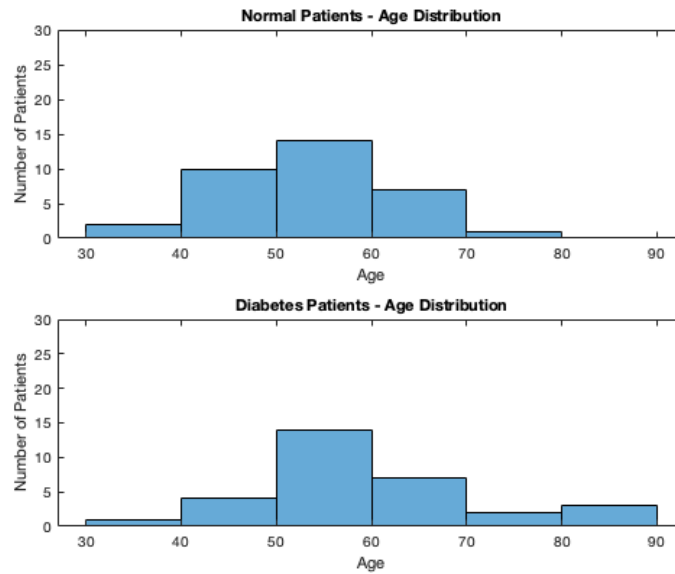
**Figure 3.3 Matched age distribution of healthy and T2D subjects in experiment 4.**

## 3.2 Fasting Blood Glucose Prediction using PPG Features

The interpretability of the biomarkers identified in the first section can be further enhanced. This can be carried out through establishing a relationship between the identified PPG features and a clinical measure towards T2D estimation. This approach focuses on identifying relationships between the extracted features and FBG levels. FBG can be identified as one of the main tests used by physicians toward the diagnosis of T2D. A dataset of PPG waveforms and FBG values were collected for the analysis. Previously identified features were extracted, and machine learning algorithms evaluated towards FBG prediction. Clinicians mainly focus on the FBG range of the patients towards diagnosis compared to the focus on the exact individual FBG measurement. This prompted the evaluation of the FBG prediction results based on the Clark's error grid analysis.

### 3.2.1 Experiment Setup

The experiment was conducted with the help of volunteer participants, who were informed about the experimentation process and consent obtained. Fasting Blood Glucose (FBG) measurements of the participants were obtained through a laboratory test performed by medical laboratory personnel. Next non-invasive PPG signals were recorded using a standard pulse oximeter (CMS50 Pulse Oximeter, sampling rate 60Hz), where a PPG clip was attached to the fingertip of the subject who was seated in a resting position.

Approximately signals of 2-3 minutes were recorded. Signal pulses in the middle of the recordings were utilised towards the analysis, to eliminate the motion artifacts during the attachment and removal of the PPG sensor. A total of 48 volunteers took part in the study, and the participants age, gender, prevalence of T2D, were also recorded. The use of Fasting Blood Glucose levels is expected to lower the impact from external effects resulting from food and medicine. However, it should be noted that the PPG and FBG measurements were not acquired simultaneously due to practical constraints, which resulted in a delay of a couple of minutes. The core focus of this research is to analyse parameters related to the vascular system of the body which does not change rapidly. Hence it is expected that the amplitude based features focussed in this research are not affected by such delays. However temporal features such as the heart rate would be affected by the delay. Data of 8 participants were removed due to the failure to adhere to the data collection protocol. The dataset description is presented in Table 3.3.

| Feature | Statistics |
|---|---|
| Age | 43.4 ± 16.8 |
| FBG | 101.65 ± 26.04 |
| FBG range | 68 - 195 |

**Table 3.3 FBG dataset summary.**

### 3.2.2 Data Preprocessing

The selected signals would be first filtered to remove noise as discussed in the previous section and similar features extracted. The signal segment towards the middle of the recording are focused for the analysis to remove motion artifacts in the beginning and the end of data collection. The focus of this approach is similar to the previous where short PPG segments would be extracted and analysed. In this analysis a 1 minute PPG segment was extracted and short (~2.1s) signal segments were obtained using a sliding window with 50% overlap. Skewness Signal Quality Index (SSQI) was identified, as explained in section 3.1.2 to be a valuable measure in establishing the quality of a PPG signal. This approach utilised the SSQI measure to filter erroneous short signal segments and identified PPG features were calculated.

The extraction of features from the PPG waveform is a tedious task due to the noise and motion artefacts as identified previously. Based on the multiple short signal segment features extracted, a subject and feature wise anomaly detection was carried through the calculation of a Z-score. It was assumed that the feature values would represent a gaussian distribution. The anomalous signal segments were removed and the remaining segments were averaged for the analysis.

### 3.2.3 Machine Learning Models

Different machine learning models were evaluated for the regression task to predict FBG values using the PPG features. Linear Regression, Ridge Regression, Lasso Regression, ElasticNet Regression, XGB Regression and Random Forest Regression models were selected for the analysis. All the previously identified PPG features except for the Large Artery Stiffness Index (LASI) was considered in the analysis. The LASI was omitted since it requires the subjects height for calculation which was not captured in the data collection. Age was the only physiological parameter included in the analysis. The rest were excluded due to data collection limitations.

The final analysis consisted of 40 subjects and incorporated 17 PPG based features and the Age. Singular Value Decomposition was used for dimensionality reduction. A leave-one-out cross validation was carried out due to the relatively small sample size, where at each fold 39 samples were used for training and 1 sample was used for testing. The mean absolute error and standard deviation was recorded for both training and testing phases for each fold. The Clarkes Error Grid was identified suitable for the final evaluation of the results based on the variability of FBG measurements previously identified in section 2.1. A Matlab library was used to calculate the Clarke's Error Grid [36].

### 3.2.4 Replication of Previous Research for FBG Prediction

It is important to benchmark and compare the results of the analysis. Hence, previously identified research by Moreno et al (2011) [16] was replicated. They focused on long PPG segments (1 minute) and identified features towards the prediction of glucose. An activity detection module was developed to select the best 1 minute signal segment, which was not replicated since it requires additional datasets and measurements. However, the same 1 minute signal segment used in this research was selected for the replication.

The weight and BMI was not collected in this dataset, hence these features were not incorporated. However, the rest of the features; Age, mean Spo2, autoregressive coefficients of the signal, Kaiser-Teager energy based features, entropy and log entropy based features along with HR features were incorporated. The mean Spo2 was calculated from the Spo2 measurement signal from the pulse oximeter. In total 31 features were implemented out of the total 33 features used in their research. The same regression algorithms were evaluated using a leave-out-cross validation using the calculated features. The results were compared based on the identified evaluation metrics.

**3.3 Simulating Noise Contaminated PPG Signals for FBG Prediction**

The importance of developing a continuous T2D screening system for a routine lifestyle, was identified previously. PPG signals from wearable devices can be utilised effectively in this regard. However, the PPG signals captured through these devices are susceptible to a variety of different noise and motion artifacts, in contrast to carefully recorded PPG signals in a clinical setting. In order to evaluate the feasibility of short PPG segments, the prediction of FBG was carried out with noise and motion artifacts contaminated PPG signals. A PPG dataset capturing various activities was used to simulate the noise and motion artifacts in the collected FBG dataset.

**3.3.1 Dataset Description**

The TROIKA dataset [37] which captures PPG signals from a wristband under resting and treadmill running at different speeds was used to extract motion artifacts. The dataset captured two PPG signals, ECG and accelerometer data of 12 subjects. It should be noted that this dataset comprises of a wide variety of motion artifacts ranging from simple hand movements and more complex motion artifacts during running. Generally PPG signal datasets with clinical measures such as FBG, Blood Pressure are captured in controlled clinical environments, with very limited motion

artifacts present. Hence the focus on using an additional PPG dataset to simulate noise and motion artifacts.

**3.3.2 Simulating Noise & Motion Artifacts in PPG Signals**

The PPG signals captured from standard pulse oximeters vary from signals captured through wearables such as wristbands. In general, a measured PPG signals is composed of the undistorted signal of interest with additive superimposed gaussian noise and motion artifacts [38]. Noise and motion artifacts were added to the FBG dataset in order to simulate signals captured under practical conditions. A 10 dB white gaussian noise was added to simulate the noise component [39].

A 1 minute signal segment each, from the 12 subjects in the TROIKA dataset was extracted to simulate the motion artifact component. The 1 minute signal comprised of a 30s rest period with hand movements and another 30s period of running. Both these activities were used in the simulation in order to better represent the practical conditions. Sebastian et al [40] used the TROIKA dataset to evaluate different approaches to model motion artifacts. They identified that the dynamic variance moving average model was suitable to represent motion artifacts. This model was replicated and the motion artifacts was extracted from the target 1 minute signal segment. The motion artifacts of the 12 subjects were randomly combined with the 40 subjects of the collected FBG dataset. The final simulated PPG signals comprised of the motion artifacts and the noise components. The original PPG signal and the simulated PPG signal of a subject is presented in Figure 3.4. The simulated signals were next used towards FBG prediction as explained in the previous section.
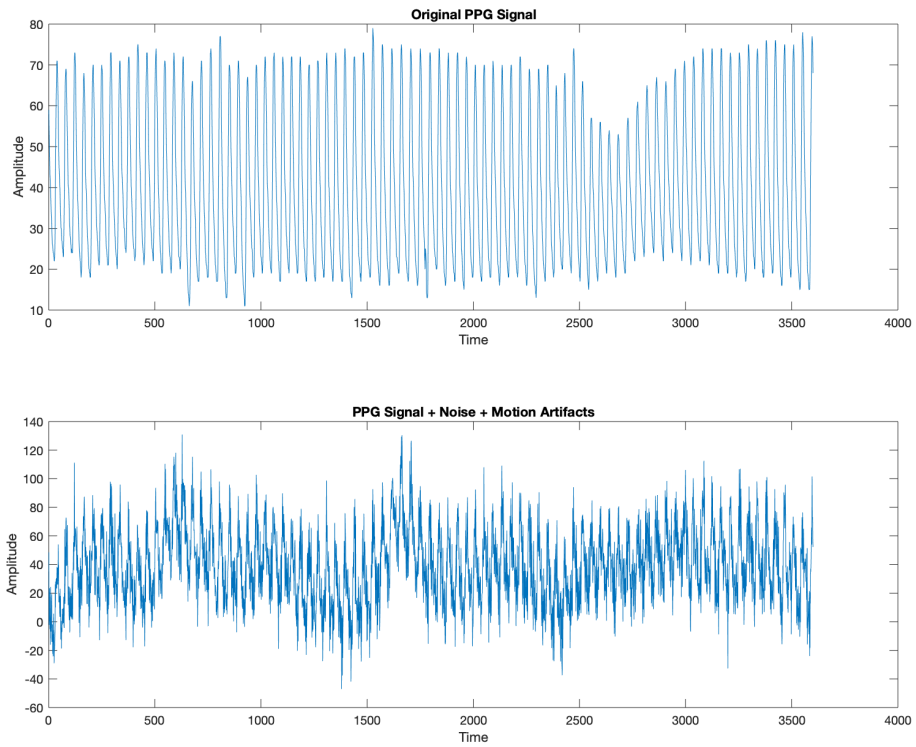
**Figure 3.4 Simulated PPG signal with noise & motion artifacts (Top: Original clean PPG signal, Bottom: PPG signal contaminated with noise and motion artifacts).**

**Chapter 4**

# RESULTS & DISCUSSION

This section aims to critically analyse the results obtained in the conducted sets of experiments, in order to estimate T2D, predict FBG based on the identified features and evaluate the feasibility of short PPG segments based analysis in a routine everyday setting. The limitations of the current study would also be analyzed for better understanding.

## 4.1 Biomarker Identification & T2D Classification

The conducted ANOVA tests were able to identify features unique towards T2D estimation. The e/a ratio, AI, Adjusted AI and the ratio of pulse interval to its systolic amplitude were the selected PPG features, along with the age of the subject, which were used for the classification of T2D. Some of these features were also identified in previous research relating to diabetes and endothelial dysfunction as explained in section 3. It is important to highlight that Age was identified as a unique feature due to the high prevalence of diabetes among elderly populations. However, it is important to focus on other robust features for classification.

Sensitivity and specificity can be identified as important metrics related to diagnosis tests frequently used in the medical domain. Sensitivity focuses on the ability of the classifier to detect a true positive (the diabetes class). It is important to have a high sensitivity in order to detect all diabetes subjects, as the failure in detection would lead to adverse consequences identified previously. However, generally higher sensitivities would lead to lower specificity values which mainly focus on the accuracy of predicting true negatives (the healthy class). It is important to balance these two metrics in order to design an effective diagnosis test. The ROC curve

provides valuable insights on how the decision thresholds of the classifiers can be adjusted in order to obtain target sensitivity and specificity values.

The T2D classification results are presented in Table 4.1. The Decision Trees and LDA classifiers achieved an accuracy of 83% and 82% respectively in classifying healthy subjects from T2D subjects. The LDA classifier achieved a higher sensitivity (89%) compared to the Decision Tree classifier (78%). However, the Decision Tree classifier achieved a better specificity value 89% vs 56%. It is important to carry out these tests with additional samples of people with T2D, in order to enhance the confidence of the results. The classification of healthy subjects from T2D only and T2D subjects with prehypertension & hypertension provided more confident results due to relative larger sample size.

The SVM technique estimated T2D with the presence of prehypertension with an accuracy of 71%, whereas LDA achieved an accuracy of 79% for estimating T2D in the presence of both prehypertension & hypertension. The third experiment captured the real-world scenario of overlapping disease combinations. LDA achieved 75% and 67% for sensitivity and specificity respectively in the third experiment. The SVM classifier achieved a slightly better sensitivity of 78% with an accuracy of 74% in the area under the ROC curve. It is important to focus on developing machine learning models capable of identifying T2D in practical environments.

The evaluation of the robustness of PPG signals for T2D estimation is focused in the final experiment. The feature Age was excluded from the analysis to solely focus on the selected physiological features. The Decision Tree classifier achieved an accuracy of 70% verifying the suitability of the focus on PPG signals for T2D estimation. Although, it is important to highlight that the sensitivity dropped to 67% when Age was removed as a feature.

| Experiment | Classification Algorithm | ROC | F1 | Precision | Recall (Sensitivity) | Specificity |
|---|---|---|---|---|---|---|
| **Normal (n = 9)** **vs** **Diabetes Only** **(n = 9)** **(3-fold stratified cross validation)** | NB | 0.54 ± 0.18 | 0.24 ± 0.17 | 0.28 ± 0.21 | 0.22 ± 0.16 | 0.67 ± 0.27 |
| | LR | 0.33 ± 0.16 | 0.5 ± 0.14 | 0.41 ± 0.07 | 0.67 ± 0.27 | 0.11 ± 0.16 |
| | AB | 0.78 ± 0.16 | 0.67 ± 0.24 | 1.0 ± 0.0 | 0.56 ± 0.31 | 1.00 ± 0.0 |
| | RF | 0.78 ± 0.18 | 0.67 ± 0.24 | 1.0 ± 0.0 | 0.56 ± 0.31 | 1.0 ± 0.0 |
| | **DT** | **0.83 ± 0.14** | **0.79 ± 0.21** | **0.92 ± 0.12** | **0.78 ± 0.31** | **0.89 ± 0.16** |
| | SVM | 0.63 ± 0.21 | 0.61 ± 0.2 | 0.51 ± 0.13 | 0.78 ± 0.31 | 0.33 ± 0.00 |
| | **LDA** | **0.82 ± 0.14** | **0.76 ± 0.13** | **0.67 ± 0.12** | **0.89 ± 0.16** | **0.56 ± 0.16** |
| **Normal (n = 25)** **vs** **Diabetes with Prehypertension (n = 25)** **(10-fold stratified cross validation)** | NB | 0.54 ± 0.23 | 0.03 ± 0.09 | 0.03 ± 0.08 | 0.03 ± 0.1 | 0.90 ± 0.30 |
| | LR | 0.66 ± 0.26 | 0.69 ± 0.04 | 0.53 ± 0.06 | 1.0 ± 0.0 | 0.08 ± 0.17 |
| | AB | 0.61 ± 0.25 | 0.52 ± 0.19 | 0.56 ± 0.27 | 0.57 ± 0.28 | 0.55 ± 0.33 |
| | RF | 0.60 ± 0.29 | 0.47 ± 0.35 | 0.50 ± 0.38 | 0.48 ± 0.37 | 0.75 ± 0.31 |
| | DT | 0.53 ± 0.28 | 0.38 ± 0.32 | 0.44 ± 0.39 | 0.37 ± 0.34 | 0.82 ± 0.24 |
| | **SVM** | **0.70 ± 0.22** | **0.52 ± 0.3** | **0.48 ± 0.28** | **0.62 ± 0.38** | **0.55 ± 0.37** |
| | LDA | 0.69 ± 0.21 | 0.68 ± 0.16 | 0.73 ± 0.23 | 0.72 ± 0.25 | 0.63 ± 0.34 |
| **Normal (n = 32)** **vs** **Diabetes with Prehypertension & Hypertension (n = 32)** **(10-fold stratified cross validation)** | NB | 0.69 ± 0.21 | 0.03 ± 0.09 | 0.03 ± 0.08 | 0.03 ± 0.1 | 0.90 ± 0.30 |
| | LR | 0.67 ± 0.23 | 0.67 ± 0.02 | 0.51 ± 0.02 | 1.0 ± 0.0 | 0.03 ± 0.08 |
| | AB | 0.69 ± 0.14 | 0.54 ± 0.16 | 0.58 ± 0.17 | 0.52 ± 0.19 | 0.62 ± 0.18 |
| | RF | 0.74 ± 0.16 | 0.59 ± 0.23 | 0.53 ± 0.20 | 0.69 ± 0.28 | 0.50 ± 0.24 |
| | DT | 0.68 ± 0.16 | 0.60 ± 0.25 | 0.58 ± 0.25 | 0.68 ± 0.32 | 0.58 ± 0.30 |
| | **SVM** | **0.74 ± 0.17** | **0.69 ± 0.10** | **0.65 ± 0.15** | **0.78 ± 0.18** | **0.53 ± 0.23** |
| | **LDA** | **0.79 ± 0.15** | **0.71 ± 0.15** | **0.74 ± 0.19** | **0.75 ± 0.23** | **0.67 ± 0.30** |
| **Only PPG Signal Features Target subjects with age >= 30. Normal (n = 31) vs Diabetes with Prehypertension & Hypertension (n = 31) (10-fold stratified cross validation)** | NB | 0.45 ± 0.20 | 0.05 ± 0.15 | 0.04 ± 0.12 | 0.07 ± 0.20 | 0.90 ± 0.30 |
| | LR | 0.43 ± 0.24 | 0.40 ± 0.25 | 0.35 ± 0.22 | 0.47 ± 0.31 | 0.40 ± 0.36 |
| | AB | 0.56 ± 0.21 | 0.47 ± 0.28 | 0.46 ± 0.29 | 0.53 ± 0.34 | 0.55 ± 0.37 |
| | RF | 0.51 ± 0.17 | 0.41 ± 0.28 | 0.47 ± 0.36 | 0.44 ± 0.34 | 0.65 ± 0.40 |
| | **DT** | **0.70 ± 0.22** | **0.66 ± 0.27** | **0.75 ± 0.29** | **0.67 ± 0.33** | **0.82 ± 0.19** |
| | SVM | 0.42 ± 0.25 | 0.51 ± 0.29 | 0.40 ± 0.23 | 0.73 ± 0.42 | 0.27 ± 0.42 |
| | LDA | 0.64 ± 0.15 | 0.56 ± 0.15 | 0.56 ± 0.18 | 0.58 ± 0.16 | 0.52 ± 0.22 |

**Table 4.1 T2D estimation results. (NB: Naive Bayes, LR: Logistic Regression, AB: Adaboost Classifier, RF: Random Forest, DT: Decision Tree, SVM: Support Vector Machine Linear Kernel )**

## 4.2 Analysis of Fasting Blood Glucose Prediction Using PPG Features

This research focuses on analysing features related to the vascular system in order to estimate T2D. The previous approach focused on identifying such biomarkers. However, the interpretability of the results can be further enhanced through establishing a relationship between clinically used measures for T2D diagnosis and PPG features. Hence, this analysis evaluates the possibility of predicting FBG measurements using PPG features.

Through the conducted leave-one-out cross validation, the test samples of each iteration was used to evaluate the accuracy of FBG prediction. A previous research focussing on long PPG segments was replicated to compare the results. The mean absolute error and standard deviations of the averaged train and test sets are presented in Table 4.2. However due to the inherent variation in blood glucose levels, the accuracy is analyzed using the Clarke's error grid. The percentage and number of points in each region of the grid is presented in Table 4.3.

| Experiment | Regression Algorithm | Train MAE | Test MAE |
|---|---|---|---|
| **FBG Prediction (SVD for Dimensionality Reduction)** | Linear Regression | 14.36 ± 0.79 | 19.85 ± 18.69 |
| | Ridge Regression | 14.43 ± 0.79 | 19.46 ± 18.32 |
| | Lasso Regression | 15.0 ± 0.69 | 18.42 ± 17.47 |
| | **ElasticNet Regression** | **15.27 ± 0.66** | **17.95 ± 17.22** |
| | XGB Regression | 0.41 ± 0.05 | 22.07 ± 21.75 |
| | Random Forest Regression | 8.3 ± 0.82 | 20.41 ± 20.27 |
| **Replication Task Moreno et al 2011 (Full Features)** | Linear Regression | 7.67 ± 0.68 | 42.93 ± 39.02 |
| | Ridge Regression | 12.32 ± 0.55 | 22.68 ± 25.38 |
| | Lasso Regression | 13.84 ± 0.64 | 19.02 ± 19.57 |
| | ElasticNet Regression | 13.86 ± 0.64 | 18.76 ± 19.38 |
| | **XGB Regression** | **0.29 ± 0.03** | **16.25 ± 17** |
| | Random Forest Regression | 6.39 ± 0.69 | 16.58 ± 15.13 |

**Table 4.2 FBG Prediction Using PPG Features.**

The experiment which replicated Moreno et al's research achieved the best results with XGB Regression where 75% of the points were classified in Region A and 25% points were classified in Region B. For the same experiment Random Forest achieved 72.5% in region A and 27.5% in region B. It is important to highlight that no points were present in regions C, D, E which leads to adverse consequences. However Moreno et al achieved 87.7% in region A and 10.3% in region B in their original research. The reduction in accuracy could be due to the fact that weight and BMI were not available in this experiment. Also in the original research a separate anomaly detection module was implemented in order to identify the best 1 minute signal segment.

| Experiment | Regression Algorithm | A | B | C | D | E |
|---|---|---|---|---|---|---|
| **FBG Prediction (SVD for Dimensionality Reduction)** | Linear Regression | 67.5% (27) | 30% (12) | 0% (0) | 2.5% (1) | 0% (0) |
| | Ridge Regression | 70% (28) | 27.5% (11) | 0% (0) | 2.5% (1) | 0% (0) |
| | **Lasso Regression** | **75% (30)** | **22.5% (9)** | **0% (0)** | **2.5% (1)** | **0% (0)** |
| | **ElasticNet Regression** | **75% (30)** | **22.5% (9)** | **0% (0)** | **2.5% (1)** | **0% (0)** |
| | XGB Regression | 57.5% (23) | 40% (16) | 0% (0) | 2.5% (1) | 0% (0) |
| | Random Forest Regression | 57.5% (23) | 40% (16) | 0% (0) | 2.5% (1) | 0% (0) |
| **Replication of Moreno et al 2011 (Full Features)** | Linear Regression | 30% (12) | 67.5% (27) | 2.5% (1) | 0% (0) | 0% (0) |
| | Ridge Regression | 65% (26) | 30% (12) | 2.5% (1) | 2.5% (1) | 0% (0) |
| | Lasso Regression | 70% (28) | 27.5% (11) | 0% (0) | 2.5% (1) | 0% (0) |
| | ElasticNet Regression | 67.5% (27) | 30% (12) | 0% (0) | 2.5% (1) | 0% (0) |
| | **XGB Regression** | **75% (30)** | **25% (10)** | **0% (0)** | **0% (0)** | **0% (0)** |
| | **Random Forest Regression** | **72.5% (29)** | **27.5% (11)** | **0% (0)** | **0% (0)** | **0% (0)** |

**Table 4.3 FBG Prediction Clarke's Error Grid Results**
**(Percentage & number of points in each region are presented).**

The short PPG segments base features in this research was able to achieve 75% in region A and 22.5% in region B for both Lasso Regression and ElasticNet Regression. However, both the models predicted 1 FBG sample (2.5%) in region D which is unfavourable.

When the results of the two approaches are compared it can be seen that Moreno 2011 performed slightly better compared to the proposed method. However the performance was very similar for 39 samples, only difference being the 1 sample which was classified in region D. The integration of additional features such as weight, BMI, Spo2 and larger training data could enhance the accuracies further. The Clarke's error grids to the above identified best scenarios are presented in Figure 4.1 & 4.2.



(a)                                              (b)
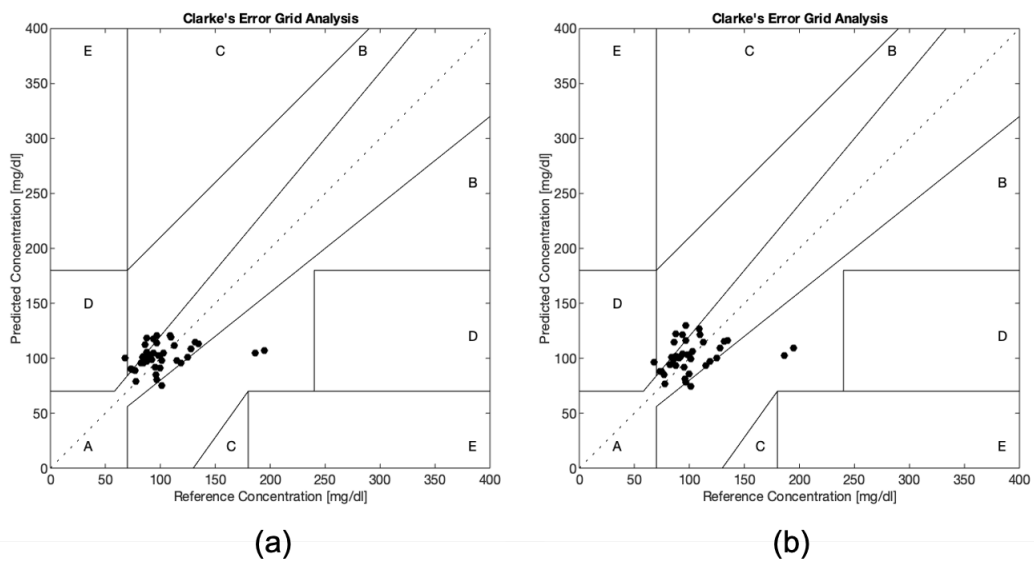
**Figure 4.1. Clarkes Error Grid results - short PPG segments analysis. (a) ElasticNet Regression Model, (b) Lasso Regression Model.**

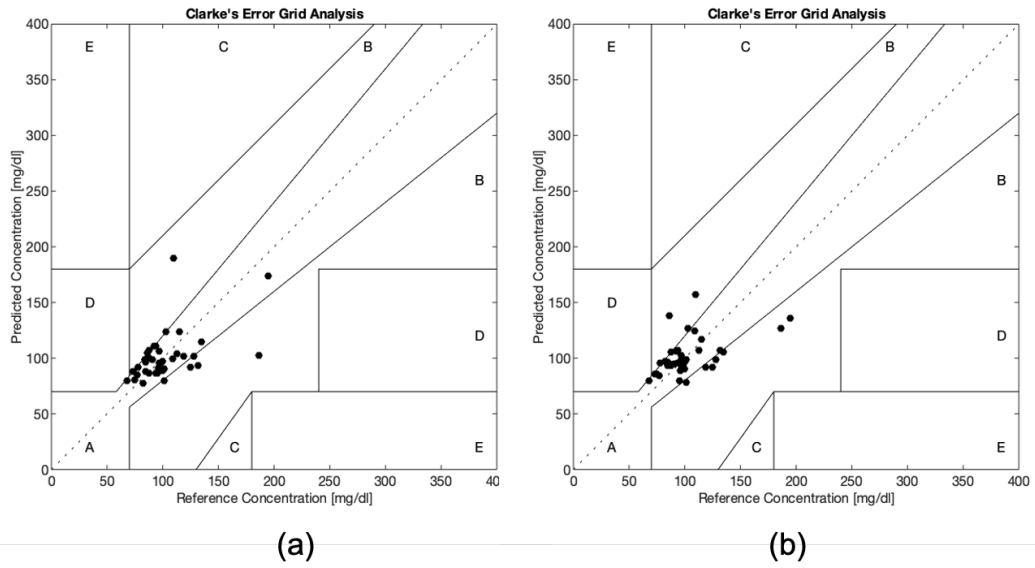**Figure 4.2. Clarke's Error Grid results - Moreno 2011. (a) XGB Regression Model, (b) Random Forest Regression Model.**

It should also be highlighted that blood glucose values greater than 150 mg/dL were less which limits the regression models to learn the prediction in that region. This could be observed in the above figures where such blood glucose values were predicted poorly.

**4.3 Analysis of Noise & Motion Artifact Simulated PPG for FBG Prediction**

Noise and motion artifacts were simulated in order to evaluate the feasibility of using short PPG segments for T2D estimation. The simulated signals were used to predict FBG values. The results based on short PPG segments and the replicated research of Moreno 2011 is presented in Table 4.4 & 4.5.

| Experiment | Regression Algorithm | Train MAE | Test MAE |
|---|---|---|---|
| **FBG Prediction on Simulated PPG Signals.** **(SVD for Dimensionality Reduction)** | Linear Regression | 13.1 ± 0.56 | 18.59 ± 20.52 |
| | Ridge Regression | 13.02 ± 0.55 | 18.28 ± 20.44 |
| | Lasso Regression | 13.03 ± 0.57 | 16.49 ± 19.37 |
| | **ElasticNet Regression** | **13.38 ± 0.58** | **16.26 ± 19.05** |
| | XGB Regression | 0.63 ± 0.06 | 23.67 ± 26.07 |
| | Random Forest Regression | 10.48 ± 0.64 | 20.35 ± 20.97 |
| **Replication Task based on Simulated PPG Signals.** **Moreno et al 2011** | Linear Regression | 9.48 ± 0.95 | 55.24 ± 34.55 |
| | Ridge Regression | 14.27 ± 0.75 | 21.98 ± 18.41 |
| | Lasso Regression | 13.82 ± 0.69 | 18.95 ± 18.83 |
| | **ElasticNet Regression** | **13.8 ± 0.69** | **17.8 ± 18.72** |
| | XGB Regression | 0.23 ± 0.03 | 19.06 ± 22.91 |
| | Random Forest Regression | 7.75 ± 0.9 | 18.87 ± 21.05 |

**Table 4.4 FBG prediction using noise & motion artifact simulated PPG.**

The results of the two approaches were similar where 70%, 27.5% and 2.5% of the predictions were in regions A, B and D respectively. The Clarke's Error Grids for the two approaches are presented in Figure 4.3 & 4.4. Upon analysing the grids and the mean absolute test errors it can be identified that the short PPG segments based analysis has a lower mean absolute error. However, the accuracy has dropped respective to the previous analysis where 75% of the samples were in region A for both the approaches.

| Experiment | Regression Algorithm | A | B | C | D | E |
|---|---|---|---|---|---|---|
| **FBG Prediction (SVD for Dimensionality Reduction)** | Linear Regression | 62.5% (25) | 37.5% (15) | 0% (0) | 0% (0) | 0% (0) |
| | Ridge Regression | 62.5% (25) | 37.5% (15) | 0% (0) | 0% (0) | 0% (0) |
| | Lasso Regression | 67.5% (27) | 32.5% (13) | 0% (0) | 0% (0) | 0% (0) |
| | **ElasticNet Regression** | **70% (28)** | **27.5% (11)** | **0% (0)** | **2.5% (1)** | **0% (0)** |
| | **XGB Regression** | **70% (28)** | **27.5% (11)** | **0% (0)** | **2.5% (1)** | **0% (0)** |
| | Random Forest Regression | 67.5% (27) | 30% (12) | 0% (0) | 2.5% (1) | 0% (0) |
| **Replication of Moreno et al 2011 (Full Features)** | Linear Regression | 15% (6) | 77.5% (31) | 7.5% (3) | 0% (0) | 0% (0) |
| | Ridge Regression | 60% (24) | 37.5% (15) | 0% (0) | 2.5% (1) | 0% (0) |
| | Lasso Regression | 65% (26) | 32.5% (13) | 0% (0) | 2.5% (1) | 0% (0) |
| | ElasticNet Regression | 65% (26) | 32.5% (13) | 0% (0) | 2.5% (1) | 0% (0) |
| | **XGB Regression** | **70% (28)** | **27.5% (11)** | **0% (0)** | **2.5% (1)** | **0% (0)** |
| | Random Forest Regression | 67.5% (27) | 30% (12) | 0% (0) | 2.5% (1) | 0% (0) |

**Table 4.5 FBG prediction Clarke's Error Grid results for noise & motion artifact simulated PPG (Percentage & number of points in each region are presented).**

It is important to highlight that the ElasticNet Regression model performed well in both the clean PPG and noise contaminated PPG experiment for the short PPG segments based approach. The model uses a combination of L1 and L2 regularisation which is suitable to ensure the prevention of overfitting.
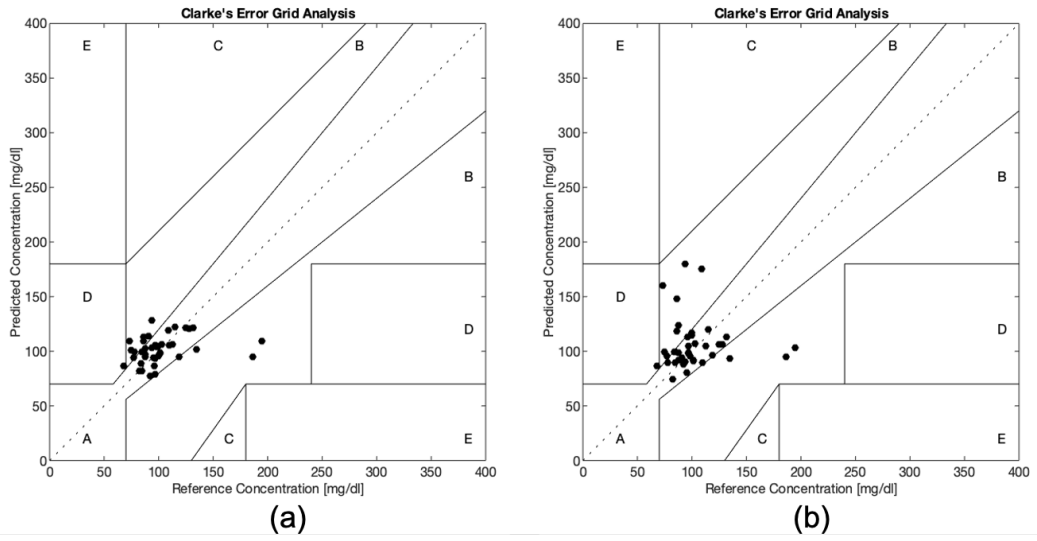
**Figure 4.3. Clarke's Error Grid results with noise simulated PPG - short PPG segments analysis. (a) ElasticNet Regression Model, (b) XGB Regression Model.**
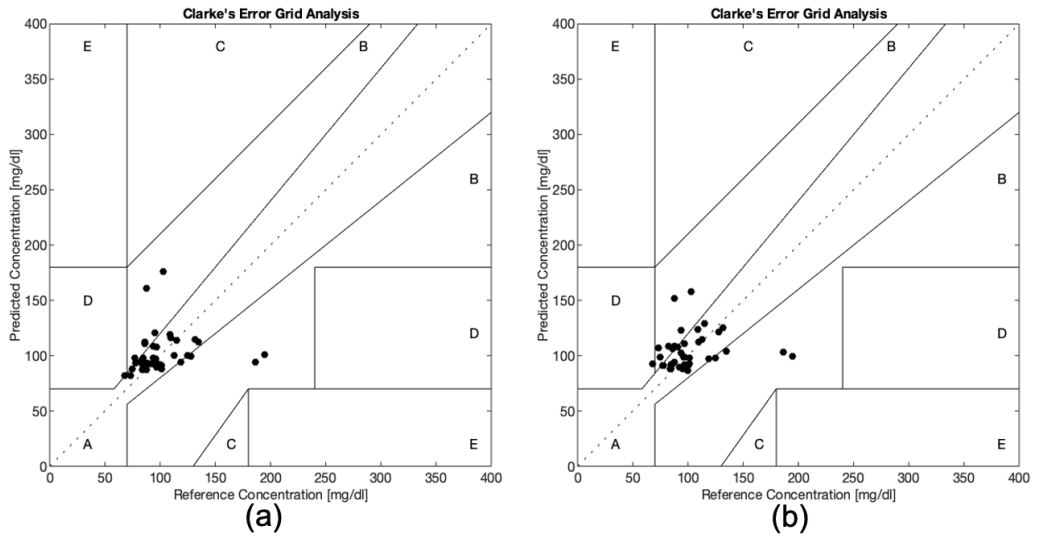


**Figure 4.4. Clarke's Error Grid results with noise simulated PPG - Moreno 2011. (a) XGB Regression Model, (b) Random Forest Regression Model.**

**4.4 Limitations of the Analysis**

The quality of data is of utmost importance to machine learning. This research focused mainly on an open source Chinese dataset which included PPG signals of healthy, diabetes and hypertension subjects. Since the core focus of the dataset wasn't diabetes, the number of diabetes subjects were relatively small. It should be noted that this was the only open source dataset available. The availability of large datasets is limited in medicine, which highlights the importance of well funded and equipped clinical trials. The limitations of the dataset size was countered through the use of different cross validation strategies. Data intensive models such as Neural Networks were omitted from the study and necessary precautions undertaken to avoid overfitting of models.

The second part of the research focused on predicting FBG using PPG features. The research protocol focused on collecting PPG signals after the standard medical tests were conducted by medical professionals to obtain FBG. Hence there is a time delay between the FBG and PPG recordings. However, this is expected to be negligible since extracted features are mainly related to vascular parameters which do not change rapidly. The collected FBG values were not evenly spread across the possible spectrum, which resulted in lower accuracy of the predictions in the range greater than 150mg/dL. Further data collection should be carried out to ensure that the sufficient data points are available to predict the entire FBG spectrum accurately.

There is inherent noise due to motion artifacts, skin colour and pressure on the PPG sensors. Necessary steps were carried out to minimise the noise. The feature extraction can also be subjective due to the noise present in the PPG signal. Even though necessary control mechanisms were deployed to extract the features, it would be interesting to explore automatic feature extraction techniques in machine learning in future research. However this might affect the explainability of the features.

The data collection protocol can be improved further incorporating variables such as the duration of diabetes, medication taken etc. A longitudinal study considering the effects of medications would provide valuable insights on the disease progression and be useful in T2D estimation. The datasets analyzed in this study does not possess the information regarding the medications and disease duration which is a limitation. Hypertension was the only other overlapping disease analyzed in this study. However, there are many other diseases with overlapping characteristics to diabetes which need to be analyzed further. The extracted features were assumed to be in a normal distribution for the application of statistical tests.

Noise and motion artifacts were simulated in order to analyse the effect in a routine everyday environment. However this doesn't capture any physiological changes which might affect the blood glucose values due to the routine activities. A dataset comprising of multiple glucose level readings captured in a non-clinical environment along with PPG signals would be ideal in this regard. It is also important to note that in this research FBG levels were analyzed using PPG features, only to evaluate the feasibility of the proposed approach. In a commercial application the identified features could be utilised to predict blood glucose levels as a step towards T2D estimation.

**Chapter 5**

# CONCLUSION & RECOMMENDATION

This research mainly focused on evaluating the feasibility of using short PPG signals towards T2D estimation. We evaluated morphological features of the signals and physiological characteristics in order to identify suitable biomarkers. These biomarkers are mainly related to the vascular system of the body. The selection of these features enhanced the explainability of the results compared to research which focus on standard signal characteristics as features.

The first part of the research conducted two ANOVA tests, and identified that the e/a ratio, Augmented Index, Adjusted Augmented Index and the ratio of pulse interval to its systolic amplitude are unique features for T2D classification. The e/a ratio provides insights regarding the arterial stiffness, the Augmented Index & Adjusted Augmented Index provides information regarding the endothelial dysfunction. The pulse interval to its systolic amplitude is a property of the cardiovascular system. These identified features provide an insight on the biological relationships between the vascular characteristics and T2D. The classification results identified in the previous section shows promise in utilising PPG signals towards T2D estimation. It is important to note that the accuracies presented are for the cross validation only. Hence, in order to improve the confidence of the results it is important to validate with additional subjects.

The system can be improved further by identifying additional PPG features towards T2D estimation. Although biomedical signal processing approaches [32, 33] are present to extract features from the PPG signal, it is difficult due to the motion artifacts, noise and practical constraints. These techniques require a great deal of parameter tuning and threshold setting which is hard to implement practically. Hence it would be beneficial to explore automatic feature extraction approaches utilising

latest machine learning techniques in future. This would ensure the development of a robust T2D estimation system.

The previous research related to PPG signals focused on analysing long signal segments. Moreno et al [13] achieved an accuracy of 69.4% focusing on HRV and cepstral analysis. Ballinger et al [6] achieved an accuracy of 84.51% (area under the ROC curve), where they combined medical health records, step counts and continuous heart rate measurements from the PPG signals. Our approach achieved an accuracy of 79% in estimating T2D at a practical environment setting (utilising short PPG signals) where T2D subjects with hypertension and prehypertension was also present. An 83% accuracy was obtained when healthy and T2D only subjects were present. These results suggest that a potential exists in utilising short segments of PPG signals towards the development of a system to estimate T2D.

The second part of the research focused on predicting FBG values using PPG features. It is important to identify clinical measures used for diabetes diagnosis and link with the target PPG features. This would provide further intuition on how PPG features possess information towards T2D estimation. The regression results identified that FBG values could be predicted, with an accuracy of 75% in region A and 22.5% in region B of the Clarke's Error Grid using Lasso Regression & ElasticNet Regression. These results were comparable with the replicated previous research by Moreno et al. However 1 FBG sample (2.5%) was classified into region D which was undesirable. The accuracy of the models can be further improved with more training data and better spread of data across the FBG spectrum. The additional readily available physiological variables such as BMI, height, weight can also be explored in future for better results.

The replicated research focussed on utilising features extracted from 1 minute PPG signals compared to the short (~2.1) PPG segment approach in this research. The

comparability of the results indicate the suitability of using short PPG segments based features for T2D estimation. A further analysis was carried out to simulate noise and motion artifacts which are present in routine everyday environments compared to controlled clinical environments. The accuracy was reduced to 70%, 27.5%, 2.5% in regions A, B, D respectively in the Clarke's Error Grid. However, the accuracy of short PPG segments based analysis and the replicated results were similar. Thus the proposed approach did not show improvement towards predictions focussing on noisy PPG signals. The focus on short PPG segments however, led to the analysis of a set of features with an established biological meaning, which enhanced the interpretability of the results. It is important to note that many previous research have focused on a variety of denoising techniques for different physiological signals which can be leveraged for PPG signals [41, 42].

Both the analyzed approaches can be combined in order to provide better estimates and understanding. The FBG estimates can be used as an additional feature towards the T2D classification carried out in the first approach. This analysis wasn't carried out in this research since the two approaches were based on two distinct datasets collected under different conditions. This would be interesting to analyse in future.

PPG signals in wearable devices can be utilised effectively for the development of a continuous T2D surveillance system. The T2D estimation in such a system can be enhanced by focussing on periodic readings and developing models for better predictions focussing on richer longitudinal PPG data. The development of a T2D estimation system is a hard task due to the uncertainty and large amounts of unknown variables affecting the state of diabetes and vascular characteristics. This research evaluated the feasibility of using short PPG segments for T2D estimation. The research shows promising results. However, it is important to analyse additional variables and overcome the limitations discussed in the previous section, in order to understand the biomarkers and their variability due to different factors. This would

enable the development of a low cost, convenient, non-invasive T2D estimation system suitable for a routine everyday environment.

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