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« L'internet des objets intelligents (IdO) pour les applications biomédicales.

Cas Pratique : Pancréas intelligent) »

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Dedicates

This thesis is dedicated to:

My parents, *have provided me with their encouragement, love, and understanding during my whole life. sacrifices have made it possible for me to achieve academic success, and I am forever grateful for their unconditional love.*

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اللّهُمَّ إِنّا نَسْأَلُكَ عِلْمًا نَافِعًا، وَعَمَلًا

Abstract

The Internet of Things (IoT) has revolutionized the healthcare industry and has the potential to connect physical and virtual objects through communication capabilities, providing data collection, management, and other services. Particularly, research has been conducted on the use of IoT in mHealth applications, with a focus on diabetes self-management. This thesis proposes a novel architecture for an IoMT health system for diabetes self-management, particularly an artificial pancreas. The system is composed of three different parts: a novel approach for continuous glucose monitoring based on ECG signal, an intelligent algorithm (model predictive controller) to predict the insulin rate required for maintaining the blood glucose in the normal range, and an IoMT-platform architecture based on a smartphone application to connect the different devices and permit remote monitoring. The proposed system is designed to ensure that the blood glucose level is always within the normal range, providing real-time BG monitoring using a non-invasive, affordable device, an insulin rate calculator coupled with an autonomous injection system, and alert and advisory services to prevent potentially life-threatening scenarios. The system is remotely monitored by healthcare administrators, making it an indispensable aspect of diabetes management. The proposed system is reliable, scalable, and user-friendly, and the intelligent algorithms used for ECG data analysis and insulin rate calculation are suitable for the specific requirements and characteristics of the IoT project. Remote health monitoring technologies are revolutionizing the healthcare business and enhancing people's lives, and this thesis contributes to that revolution by proposing a novel architecture for an IoMT health system for diabetes self-management.

Résumé

L'industrie de la santé a été transformée par l'Internet des objets (IoT) en permettant la connectivité de divers objets physiques et virtuels grâce à des capacités de communication avancées, offrant des services de collecte, de gestion et de traitement de données utilisant l'apprentissage automatique. Les applications mobiles de santé (mHealth) ont été étudiées avec une attention particulière à l'autogestion du diabète. Une nouvelle architecture pour un système de santé IoMT dédié à l'autogestion du diabète, plus précisément un pancréas artificiel, est proposée dans cette thèse. Trois parties distinctes composent le système : une nouvelle méthode de surveillance continue de la glycémie basée sur le signal électrocardiographique (ECG), un algorithme intelligent (contrôleur prédictif de modèle) pour prédire le taux d'insuline nécessaire pour maintenir la glycémie, et une architecture de plateforme IoMT basée sur une application smartphone qui permet la connectivité de divers dispositifs et la surveillance à distance. En fournissant une surveillance en temps réel, un calculateur de taux d'insuline associé à un système d'injection autonome et des services d'alerte et de conseil pour prévenir les situations potentiellement mortelles, Le but du système proposé est de s'assurer que la glycémie reste dans une plage normale. La surveillance du système par les administrateurs de santé à distance est essentielle à la gestion du diabète. Les algorithmes d'apprentissage automatique utilisés pour l'analyse des données ECG et le calcul du taux d'insuline sont adaptés aux exigences et aux caractéristiques spécifiques du projet IoT, et le système proposé est fiable, évolutif et facile à utiliser. Cette thèse propose une nouvelle architecture pour un système de santé IoMT pour l'autogestion du diabète, contribuant ainsi à la révolution du secteur de la santé et de la qualité de vie des patients.

Abstract

ملخص

لدينا الآن القدرة على ربط الأشياء الفعلية والافتراضية من خلال قدرات الاتصال، مما يوفر جمع البيانات والإدارة والخدمات الأخرى. تم إجراء البحوث حاليًا حول استخدام الإنترنت للأشياء (IoT) في تطبيقات الصحة المحمولة (mHealth) ، مع التركيز بشكل خاص على إدارة السكري الذاتية. تقترح هذه الأطروحة بنية معمارية جديدة لنظام صحة IoMT لإدارة السكري الذاتية، ولا سيما البنكرياس الصناعي. يتكون النظام من ثلاثة أجزاء مختلفة: نهج جديد لمراقبة الجلوكوز المستمر بناءً على إشارةECG ، وخوارزمية ذكية (متحكم تنبؤي في النموذج) لتوقع معدل الأنسولين اللازم للحفاظ على مستوى الجلوكوز في النطاق الطبيعي، وهندسة معمارية IoMT على أساس تطبيق الهاتف الذكي لربط الأجهزة المختلفة مع بعضها البعض والسماح بالمراقبة عن بعد. يتم تصميم النظام المقترح لضمان أن مستوى الجلوكوز في الدم دائمًا في النطاق الطبيعي، وتوفير مراقبة في الوقت الحقيقي للجلوكوز في الدم، وآلة حاسبة لمعدل الأنسولين مقترنة بنظام حقن ذاتي. وبالإضافة إلى ذلك، يجب أن يوفر النظام خدمات التنبيه والاستشارة لمنع السيناريوهات التي يمكن أن تهدد الحياة. وعلاوة على ذلك، يتم مراقبة هذه الخدمات عن بعد من قبل المسؤولين الصحيين، مما يجعلها جانبًا لا يمكن الاستغناء عنه في إدارة السكري. يتم تصميم النظام المقترح ليكون موثوقًا به وقابلاً للتوسع وسهل الاستخدام، ويتم تكييف خوارزميات التعلم الآلي المستخدمة لتحليل بيانات ECG وحساب معدل الأنسولين لتلبية المتطلبات والخصائص الخاصة لمشروع IoT المحدد. تقوم تقنيات المراقبة الصحية عن بُعد بثورة في صناعة الرعاية الصحية وتحسين حياة الناس، وتساهم هذه الأطروحة في هذه الثورة من خلال اقتراح بنية معمارية جديدة لنظام صحة IoMT لإدارة السكري الذاتية.

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Abbreviations list

DM: Diabetes Mellitus

IDF: International Diabetes Federation

IoT: Internet of Things

I^2oT: Intelligent IoT

IoMT: Internet of Medical Things

RFID: Radio Frequency Identification

NFC: Near Field Communication

AI: Artificial Intelligent

ML: Machine Learning

AP: Artificial Pancreas

ATP: Adenosine Triphosphate

BG: Blood Glucose

ANS: Autonomic Nervous System

SNS: Sympathetic Nervous System

PNS: Parasympathetic Nervous System

ECG: Electrocardiogram

SA Node: Sino-Auricular Node

AV Node: Atrioventricular Node

T1DM: Type 01 Diabetes Mellitus

T2DM: Type 02 Diabetes Mellitus

HHS: Hyperosmolar Hyperglycemia Syndrome

DAN: Diabetic Autonomic Neuropathy

OGTT: Oral Glucose Tolerance Test

WHO: World Health Organization

CT: Conventional Therapy

IT: Intensive Therapy

DCCT: Diabetes Control and Complications Trial

MDII: Multiple Daily Insulin Injections

CSII: Continuous Subcutaneous Insulin Infusion

CGM: Continuous Glucose Monitoring

ISF: Interstitial Fluid

BGC: Blood Glucose Concentration

SAP: Sensor-Augmented Insulin Pump

HR: Heart Rate

ECG: Electrocardiogram

EEG: Electroencephalogram

AUC-ROC: Area Under the ROC Curve

HRV: Heart Rate Variability

PPG: Photoplethysmography

GSR: Galvanic Skin Resistance

BR: Breathing Rate

RAM: Random Access Memory,

GPU: Graphics Processing Unit

CPU: Central Processing Unit,

AMD: Advanced Micro Devices

FFT: Fast Fourier Transform

LSTM: Long Short-Term Memory

ConvLSTM: Convolutional Long Short-Term Memory

DR-CNN: Deep Recurrent Convolutional Neural Networks

RNN: Recurrent Neural Network

HMM: Hidden Markov Models

TP: True Positive

TN: True Negative

FP: False Positive

FN: False Negative

iECG: Intracardiac Electrocardiogram

MAE: Mean Absolute Error

MSE: Mean Squared Error

RBG: Real Blood Glucose

CBG: Calculated Blood Glucose

ADA: American Diabetes Association

EASD: European Association for The Study of Diabetes

GPR: Gaussian Process Regression

RMSE: Root Mean Squared Error

R2: R-Squared

TSS: Total Sum of Squares

RSS: Residual Sum of Squares

PID: Proportional-Integral-Derivative

MPC: Model Predictive Control

MD/Fuzzy: Metaphone Double/Fuzzy

IIR: Insulin Infusion Rate

HCL: Hybrid Closed-Loop

LMPC: Linear Model Predictive Controller

FHOCP: Finite Horizon Optimal Control Problem

SIP: Syringe Infusion Pump

DC: Direct Current

USB: Universal Serial Bus

Vdc: Volts Direct Current

SRAM: Static Random Access Memory

EEPROM: Electrically Erasable Programmable Read-Only Memory

SPI: Serial Peripheral Interface

PWM: Pulse-Width Modulation,

SPP: PWM: Serial Port Protocol

ICR: Insulin-To-Carbohydrate Ratio

API: Application Programming Interface

MEMS: Micro-Electro-Mechanical Systems

PDMS: Polydimethylsiloxane,

BLE: Bluetooth Low-Energy

DIY: Do-It-Yourself

CT: Communication Technologies

RFID: Radio Frequency Identification

SMS: Short Message Service

DMH: Disease Management Hub

Wi-Fi: Wireless Fidelity

5G: Fifth Generation

6LowPAN: IPv6 over Low-Power Wireless Personal Area Networks

LAN: Local Area Network

NFC: Near Field Communication

AAL: Ambient Assisted Living

GPRS: General Packet Radio Service

ABLD: Abnormal Blood Glucose Detection

XML: Extensible Markup Language

FDA: Food and Drug Administration

WBAN: Wireless Body Area Network

LTE: Long-Term Evolution

AWS: Amazon Web Services

GCP: Google Cloud Platform

MySQL: My Structured Query Language

MongoDB: Humongous Database

General Introduction

Recent advancements in smart sensor technology, including wearable sensors, smartwatches, and smartphones, have made it simpler and more practical to monitor a variety of physiological indicators and gather large amounts of data. By harnessing big data, researchers can obtain a more profound comprehension of the body's physiology and innovative healthcare solutions. Furthermore, the advent of IoT technologies like cloud and fog computing has enabled the instantaneous analysis of this data permitting advanced real-time monitoring. The widespread use of body sensor networks by diabetic care devices to provide clinical data and therapeutic strategies is a great example of this clinical significance.

Diabetes mellitus is a long-term medical disorder characterized by elevated blood glucose (BG) concentration (hyperglycemia) due to the body's incapacity to manufacture or appropriately utilize insulin, a hormone that regulates glucose metabolism. There exist two major types of diabetes mellitus. Type 1 diabetes (T1DM) is an autoimmune disease in which the immune system attacks and destroys insulin-producing cells in the pancreas. Individuals with T1DM rely on external insulin administration to regulate their BG levels. Conversely, type 2 diabetes (T2DM) happens when the body manifests insulin resistance or fails to manufacture sufficient insulin. Obesity, sedentary activity, and inadequate eating habits are usually associated with this kind of diabetes [1].

As stated in the International Diabetes Federation's (IDF-2019) report, Diabetes Mellitus (DM) has grown into a pandemic pathologic that poses a serious threat to world health. Accordingly, the pervasiveness of this chronic disease has surged to 10.5% of the populace, with an estimated 537 million diabetics in 2021. Projection models predict that by 2045, this number will have risen to around 783 million diabetes cases. Among these cases, 73.8 million adults (aged 20 to 79 years) are localized in the MENA Region, where Algeria has the second-highest prevalence [2].

The ongoing pandemic has emphasized the need for medicinal solutions that enable remote care, remote monitoring, and support for diabetic self-management technologies while embracing an environmentally sustainable approach. Successful self-management of diabetes is aimed at maintaining BG levels to normal to mitigate the progression of complications such as diabetic retinopathy, nephropathy, and neuropathy[3, 4]. For DM patients insulin therapy, generally, includes frequent blood glucose monitoring and the delivery of Multiple Daily Insulin Injections (MDII) or

Continuous Subcutaneous Insulin Infusion (CSII). Recently, The use of CGMs sensors with CSII pump devices in an open-loop combination has been proven to provide clinical advantages over the conventional MDII treatment [5].

If these last have been combined in a closed-loop system, it can be called it Artificial Pancreas (AP). With the advent of cutting-edge wireless technologies and smart sensors, the revolutionary concept of the Artificial Pancreas (AP) has emerged. This medical device is designed to automate the administration of insulin. It comprises a CGM system that measures the BG level, which is used then by an intelligent algorithm to control an insulin pump that administrates insulin into the body based on the immediate requirements. The device's primary objective is to imitate the physiological role of a healthy pancreas, which controls blood sugar levels by releasing insulin in response to fluctuations in BG levels.

The employment of artificial pancreas systems (the closed-loop system), has shown immense potential in enhancing diabetes management and mitigating the risk of associated complications [6]. In recent years, the emergence of the Internet of Things (IoT) technology has presented a robust tool for augmenting the efficiency and efficacy of healthcare systems [7, 8]. Considering this, the present thesis proposes an innovative approach for diabetes self-management, practically, an AP system, forged through the utilization of Internet of Things (IoT) technologies.

IoT devices have the potential to gather and exchange data with various devices and systems via the internet. In the context of the artificial pancreas, IoT technology can be used to improve the device's functionality and usability. For instance, IoT sensors can be utilized to monitor a patient's physical activity levels, which can impact glucose levels and insulin requirements. This information can be employed to make real-time adjustments to insulin delivery, thereby enhancing the accuracy and efficacy of the device. Additionally, IoT technology can be leveraged to remotely monitor the artificial pancreas, enabling healthcare providers to track a patient's glucose levels and insulin administration in real-time. This can facilitate early detection and intervention in urgent cases. In summary, the integration of IoT technology into the artificial pancreas system has the potential to revolutionize diabetes self-management, elevating the quality of life for diabetic patients[9–11].

One of the key trends in the development of IoT platforms for AP systems is the integration of CGM, physiological signals, electrophysiological signals, and insulin delivery systems. IoT platforms for AP systems are engineered to incorporate these devices, enabling seamless data exchange and

communication between them. Another trend in the development of IoT platforms for AP systems is the use of machine learning and predictive algorithms. These algorithms can be used to analyze data from CGMs, physiological and electrophysiological signals, and data from other connected devices, to make real-time predictions about future glucose states. This information can be utilized to optimize insulin administration, enhance glucose control, and prevent hypoglycemia and hyperglycemia episodes.

All the AP system components, including the insulin pump, CGM sensor, and control algorithm, should be accessible to establish and improve an IoT platform for AP systems. The fact that we are unable to locate the market for such devices in Algeria is a significant difficulty for our investigation. As a consequence, we decided to develop the three components to propose a novel IoT architecture for an AP system based on a non-invasive CGM [9–11].

To ensure optimal diabetes self-management, continuous glucose monitoring is an essential component. Traditional methods of BG monitoring involve invasive finger prick tests at least four to five times a day, which is not only burdensome but also does not allow for continuous monitoring [12]. Fortunately, CGMs nowadays can determine BG concentration in real-time, every five minutes. This has significantly improved BG control for diabetic patients. Nonetheless, CGMs still have limitations such as the 7-14 day working time limit and the invasive nature of the device, which requires cannula insertion into the subcutaneous tissue. Additionally, they are cost-effective and require finger prick calibration every day [13–17].

Considering the limitations of CGMs, non-invasive approaches to BG monitoring, such as optical-polarimetry [18], fluorescence technology [19], and Raman spectroscopy [20], have recently been proposed. The Internet of Medical Things (IoMT) and smart technologies such as wearable sensors, smartwatches, and smartphones have made medical solutions and services more accessible and affordable. These technologies can provide wireless, and smart monitoring in real-time, making continuous monitoring of individuals more prevalent in their daily lives [21]. In recent years, researchers have attempted to integrate biosignals [22] into the artificial pancreas to predict hyperglycemic and hypoglycemic events [23–25], As a result, Machine Learning has been used to construct early warning systems, specifically, the electrocardiogram signal (ECG). Various studies investigate the relationship between the changes in ECG signal and BG fluctuation, and it has been demonstrated that hypoglycemia and hyperglycemia episodes affect the electrophysiology of the

heart. However, they have not established a direct relationship between BGC and electrocardiogram (ECG) parameters to estimate directly the BG value [24–26]. Hence, in this work, we have confirmed the linear relationship between BGC and ECG features. Furthermore, we propose a novel approach using recurrent convolutional neural networks and machine learning for BG estimation based on ECG features.

The second component of our AP system comprises an intelligent control algorithm that determines the optimum insulin dose to inject depending on the patient's current BG level. The objective of this control algorithm is to maintain the patient's BG level within a predetermined range, minimizing by that the risk of both hypoglycemia and hyperglycemia. Various types of control algorithms have been developed for AP systems, including proportional-integral-derivative (PID) control [27] and model predictive control (MPC) [28]. The choice of the algorithm is determined by the AP system's specific needs as well as the patient's specific features we attend to integrate into the AP system. Considering the preceding, we have developed a linear model predictive controller, which is a version of MPC that employs a simplified linear model of the patient's glucose-insulin dynamics. This approach is distinguished by its multivariable nature, computational efficiency, and suitability for real-time implementation.

The primary objective of this thesis is to examine the potential of Internet of Things (IoT) technologies in augmenting the performance and usability of the artificial pancreas (AP) system. To this end, we have developed an intelligent, wearable infusion system that is based on a smartphone application, intending to showcase the transformative impact of mobile health on diabetes self-management [29]. In addition, we provide a comprehensive review of cutting-edge IoT technologies that can be harnessed to construct an IoT platform for an AP system and evaluate their efficacy in enhancing diabetes self-management. Lastly, we propose a novel IoT architecture for an AP system that utilizes an electrocardiogram (ECG) signal for BG monitoring and incorporates the components that were previously developed

This thesis is divided into five chapters, which are listed below.

Chapter 1 Provides an insight into the Internet of Medical Things (IoMT) and her role in diabetes self-management at first. Then, a comprehensive and detailed exploration of diabetes mellitus disease is presented. Before this, the chapter expounds upon the impact of the physiology of glucose, Autonomic Regulation of Glucose Homeostasis, and their interrelation with the activity of the heart.

Additionally, the chapter delves into a thorough account of the latest technologies that aid in the support of diabetes self-management promoting the use of the biometric variables in the artificial pancreas AP. Finally, we will conclude our theoretical research with the main problematic of our thesis.

Chapter 2 of this study comprises an extensive review of the existing research on non-invasive continuous glucose monitoring technologies. In addition to this, we advance innovative approaches for determining BG levels through ECG signals, leveraging advances in machine learning. Before that, the chapter provides a detailed description of the data used, also, the process chosen for data analysis (Filtering-segmentation-characterization), using recurrent convolutional neural. Finally, we discuses the implications of the findings for diabetes self-management by highlighting, the potential use of this approach in IoT platforms for more effective and efficient blood glucose monitoring technologies.

In Chapter 3 of this work, we undertake a comprehensive comparative analysis of the control algorithms presently employed in closed-loop artificial pancreas (AP) systems. Particularly, we demonstrate the several advantages of employing a linear model predictive control (LMPC) technique in an IoT platform of AP system. The simulation setup and validation methods were then discussed in detail. Lastly, we offer the approach's findings along with a discussion emphasizing the need to use the control algorithm to assure the safety and efficacy of an AP system.

In Chapter 4, at first, we provide a brief section of the advanced Syringe infusion pumps (SIPs) available, then we highlight the need for lightweight, microliter-precision, and wirelessly controlled syringe pumps. we detail the development of such a smart, wearable insulin infusion system, that operates based on a smartphone application (hardware-software). In addition, we present the results obtained and their discussion. Finally, the chapter emphasizes the use of mobile health technologies in an AP system to improve diabetic self-management.

Chapter 5 provides a detailed and analytical overview of the most recent and sophisticated IoT technologies that can be seamlessly incorporated into artificial pancreas (AP) systems. Furthermore, in this chapter, we propose a highly innovative internet of things (IoT) architecture platform for an AP system, which is based on the electrocardiogram (ECG) signal. The chapter describes the architecture design and discusses its impact on the field of self-management technologies for diabetic patients. Furthermore, we present its limitations and future perspectives.

The concluding section of this thesis provides a summary of the key findings and contributions of the thesis, discusses the implications for diabetes management and healthcare, and suggests directions for future research. Overall, this thesis contributes to the emerging field of IoT-enabled healthcare by proposing novel approaches to an AP system that uses a wearable ECG device as a continuous glucose monitor. The findings of this thesis have important implications for improving the efficiency and effectiveness of diabetes management and reducing the risk of complications in a cost-effective manner. Finally, this thesis is a ground-breaking innovation with the potential to transform the whole field of diabetes management and healthcare.

Chapter

I. State of art

1. Introduction:

The prevalence of Diabetes Mellitus (DM) has surged to 10.5% of the world's population, with approximately 537 million individuals diagnosed with diabetes in 2021. Predictive models indicate that this figure is expected to climb by approximately 783 million cases by 2045, making it a significant threat to global health [2]. Thus, the International Diabetes Federation (IDF) has recognized DM as a pandemic pathology problem, further highlighting the necessity for medical solutions that enable remote care, remote monitoring, and promoting diabetes self-management technologies, all the while embracing an eco-friendly ethos. The prevalence of DM, accompanied by its specific complications and the involvement of other chronic conditions that frequently coexist with diabetes, highlights the fact that it is one of the most important social and public health issues of our day [30].

Providing an insight into the Internet of Medical Things (IoMT) and her role in diabetes management at first, the current chapter endeavors to provide a comprehensive and detailed exploration of the disease of diabetes, including its associated complications. Before this, the chapter expounds upon the impact of the physiology of glucose, Autonomic Regulation of Glucose Homeostasis, and their interrelation with the activity of the heart. Additionally, the chapter delves into a thorough account of the latest technologies that aid in the support of diabetes self-management promoting the use of the biometric variables in the artificial pancreas AP. Finally, we will conclude our theoretical research with the main problematic of our thesis.

2. IoT in diabetes management:

The Internet of Things (IoT) has been hailed as a technological revolution, representing a network of physical objects - popularly referred to as "things" - that are equipped with electronics, software, sensors, and connectivity, enabling them to intercommunicate and exchange data. The IoT is a new and rapidly expanding concept that is founded on a diverse range of objects - such as Radio Frequency Identification (RFID), Near Field Communication (NFC), sensors, and smartphones, among others - that can interact with each other through the employment of unique addresses. Moreover, AI is often integrated within IoT to enable efficient decision-making, action initiation, and problem management. These objects undergo a transformation from a "dumb" state to a "smart" one through the utilization of underlying

technologies such as pervasive computing, embedded devices, communication technologies, sensor networks, protocols, and applications [31, 32].

As shown in **Figure I-1,** the Internet of Medical Things (IoMT) is a network of linked medical sensors and specific medical devices and services. In response to the emergence of several healthcare challenges, including COVID-19, diabetes mellitus, cardiovascular issues, obesity, and an aging population, along with the rising expenses of healthcare, has spurred individuals to embrace the concept of self-management through intelligent IoMT [33, 34]. IoMT facilitates a personalized, cost-effective, and proactive approach to healthcare management [9]. Besides, it enables healthcare providers to extend their reach beyond the conventional clinical setting, and it furnishes researchers with an extensive corpus of data, thereby promoting continuous innovation [9].

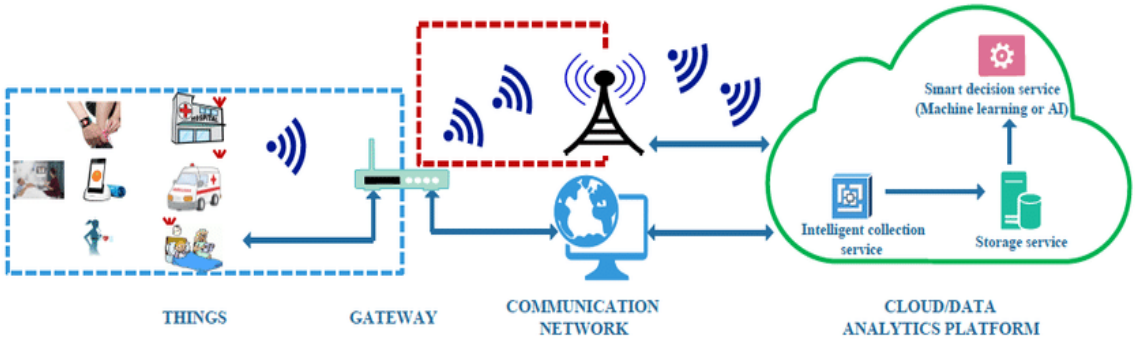


Figure I- 1: An overview of a typical IoT-based healthcare system

In another meaning, Recent advancements in smart sensor technology, including wearable sensors, smartwatches, and smartphones, have made it simpler and more practical to monitor a variety of physiological indicators and gather large amounts of data. By harnessing big data, researchers can obtain a more profound comprehension of the body's physiology and devise novel healthcare solutions [35]. Furthermore, the advent of IoT technologies like cloud and fog computing has enabled the instantaneous analysis of this data permitting real-time monitoring. The widespread use of body sensor networks by diabetic care devices to provide clinical data and therapeutic strategies is a great example of this clinical significance [36].

In this context, the emergence of the internet of things (IoT) has had a profound impact on several domains, most notably the artificial pancreas. The artificial pancreas, being an IoT system in itself, has revolutionized diabetes self-management and has gained immense

popularity [37]. The components of the Internet of Medical Things (IoMT) platform for an AP system may comprise but are not restricted to, wearable sensors that detect blood glucose concentration (BGC), wireless communication devices that transmit sensor data to the control algorithm, the control algorithm that processes the data and computes the appropriate insulin dose, the insulin pump that dispenses the insulin dose, and cloud-based data storage and analysis for large physiological information datasets. Furthermore, the platform may encompass mobile applications that offer real-time data to users and enable remote monitoring of patients by healthcare professionals [38]. The development of the IoMT platform for an AP system is an active research and innovation domain, and various companies and organizations are contributing to its progress. In chapter 5, the existing AP systems and IoMT healthcare platforms for diabetes self-management are detailed.

3. Physiology of Glucose Insulin System:

Glucose serves as the main source of energy in the human body. The intracellular glucose molecules are catabolized to produce triphosphate (ATP) molecules, which are high-energy molecules that fuel numerous cellular processes, making glucose the primary metabolite necessary for proper bodily function. The transportation of glucose molecules to cells takes place through the bloodstream, where they can be utilized to generate ATP or stored as energy, contingent on the target tissue [1, 39]. The physiology of the glucose-insulin system is shown in **Figure I-2**.

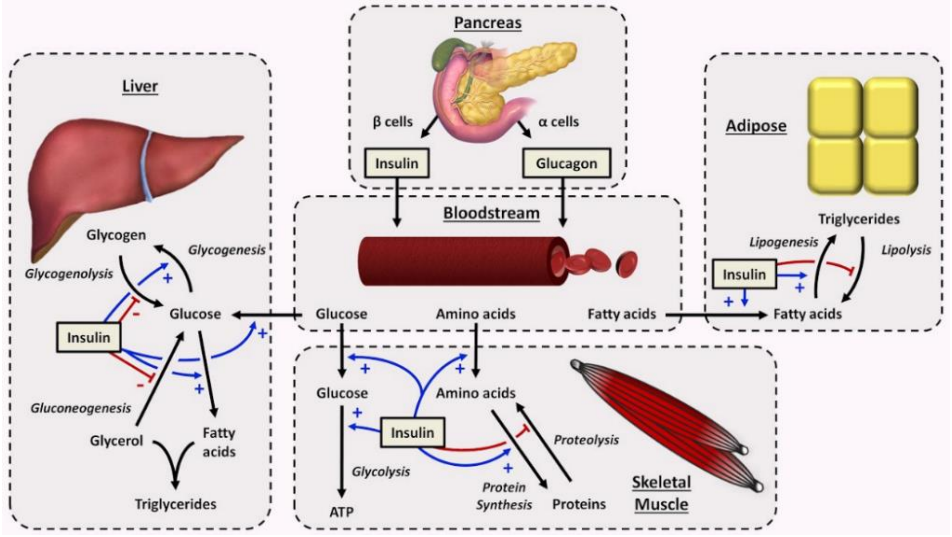


Figure I- 2: physiology of glucose

As a result, it is essential to maintain a relatively constant glucose level in the circulation to guarantee an unchanging supply of glucose to the cells. In a healthy individual, BG is habitually sustained within a restrained range (70-110 mg/dl or 3.9-6.1 mmol/l). Complex negative feedback control mechanisms monitor changes in the body and initiate procedures to counteract such variations to re-establish a normal physiological state and maintain BG in the normal range. The negative feedback mechanisms play a pivotal role in glucose regulation, ensuring a balance between blood glucose and glucose being utilized by the body. The two primary hormones involved in glucose homeostasis are insulin and glucagon, produced by the endocrine cells (islets of Langerhans) [1, 39].

3.1. Pancreas:

It is located in the upper left abdomen, behind. The pancreas is a mixed gland that performs both exocrine and endocrine functions. The exocrine pancreas discharges enzymes that participate in the degradation of lipids, carbohydrates, and proteins into the duodenum. The endocrine portion of the pancreas contains islet cells that manufacture and release vital hormones into the bloodstream. Insulin and glucagon, regarded as pivotal in glucose homeostasis, represent the primary hormones secreted by the endocrine cells located in the pancreatic exocrine tissue. Insulin and glucagon are secreted by Beta cells and alpha cells respectively, both of which are released in response to blood glucose levels, but in opposing directions.

3.2. Insulin:

Following a rise in blood sugar levels, typically post-meal, Beta cells initiate insulin secretion. The metabolic effects of insulin include:

- Stimulation of bodily cells to heighten their glucose absorption rate from the circulation.
- Promotion of cellular glucose consumption as a source of energy.
- Increasing glycogenesis (transformation of glucose molecules into glycogen, which takes place primarily in the hepatic and skeletal muscular cells).

- Fat production from glucose catalyzed in liver cells and adipose tissue. The cumulative effects of insulin, ultimately, culminate in the restoration of blood sugar levels to normal levels.
- Insulin secretion encompasses two stages: the first stage, known as the basal insulin level, is independent of blood glucose levels, while the second stage is triggered by an increase in blood sugar

3.3. Glucagon:

In instances where blood glucose levels dip below the standard range, such as on an empty stomach, as a result of exercise or starvation, insulin secretion is curtailed, and pancreatic cells initiate glucagon secretion. Glucagon elicits several effects, primarily on liver cells, including:

- Stimulation of glycogen breakdown (glycogenolysis) into glucose, which is subsequently delivered into the circulation to prevent low blood glucose levels.
- Increases fat breakdown to fatty acids and glycerol in adipose tissue, resulting in their liberation into the circulation.
- Promoting glucose synthesis in the liver, utilizing absorbed glycerol from the bloodstream, and releasing it into the blood. The cumulative effect of these mechanisms is the restoration of blood glucose levels to their range.

Insulin and glucagon feedback processes ensure that blood sugar levels remain within precise ranges, ensuring a steady supply of glucose to body tissues.

4. Autonomic Regulation of Glucose Homeostasis:

The Autonomic Nervous System (ANS) serves as an integrative mechanism for coordinating the involuntary functions of organs such as the heart, pancreas, and intestines. It functions as a regulatory system that ensures homeostasis in response to diverse physiological demands aimed at maintaining internal stability and equilibrium. The ANS is bifurcated into two subsystems, namely the Sympathetic Nervous System (SNS) and the Parasympathetic Nervous System (PNS). The SNS is primarily in charge of the “fight or flight” response, whereas the PNS is critical to the body's "rest and digest" state [40, 41]. The maintenance of glucose absorption, consumption, and storage is governed by a complex system of neural regulatory and hormonal components collectively referred to as the glucose homeostasis system. Among these

components, ANS has been identified as a key determinant of glucose homeostasis. The ANS exerts its influence on the pancreatic islet through its sympathetic and parasympathetic branches, as well as the sympathoadrenal system, which innervates pancreatic α and β-cells, controlling their hormone production and cell number. Notably, these autonomic inputs exhibit different thresholds of activation in response to BG levels. With BG levels between 85 and 75 mg/dl (normoglycemia), the parasympathetic nervous system is engaged, while the sympathoadrenal system is activated when the BG decreases between 75 and 65 mg/dl. Furthermore, measurements of pancreatic norepinephrine spillover have demonstrated that the pancreatic sympathetic nerves become activated at around 35 mg/dl in the case of hypoglycemia. Consequently, by the time BG levels reach 50 mg/dl, when clinical hypoglycemia symptoms become apparent, a duo of the tripartite autonomic inputs has formerly been triggered. Insulin-induced hypoglycemia triggers the activation of the ANS, which promotes glucagon release from the alpha-cell. Similarly, in hyperglycemia, glucose uptake increases the activity of the sympathetic nervous system [42].

Figure I-3 illustrates the complex mechanisms engaged in blood glucose regulation. In healthy individuals, the ingestion of food leads to a rise in BG levels. This increase in blood glucose is interpreted by the body as a stress stimulus, thereby culminating in the elicitation of a sympathetic nervous system (SNS) response.

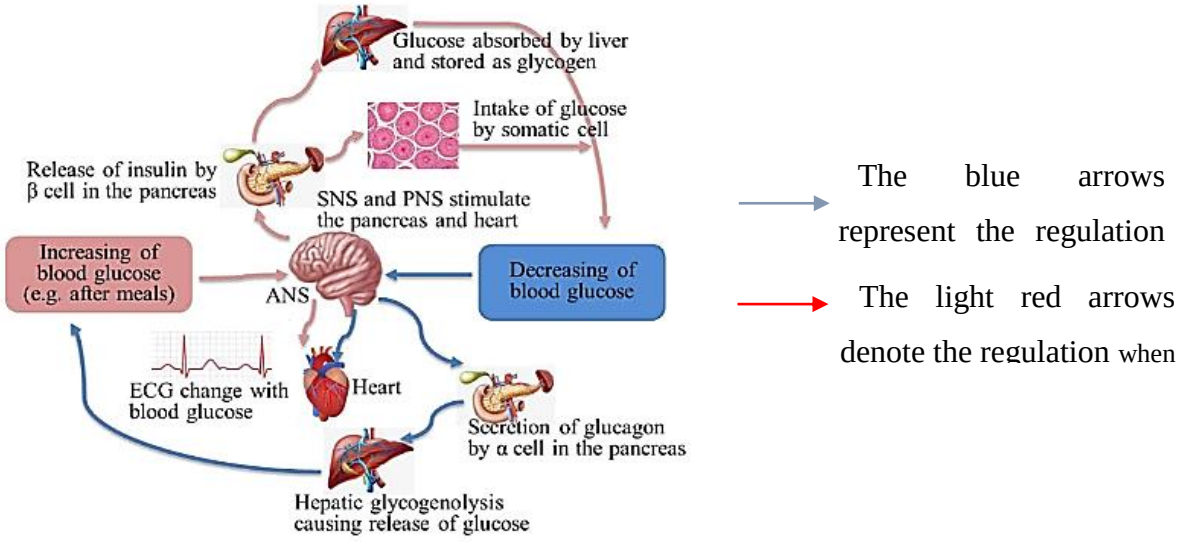


Figure I- 3: A depiction of how vital organs interact in glucose homeostasis

The SNS triggers the release of adrenaline from the adrenal medulla, which, in turn, stimulates insulin release from the pancreatic Beta-islets. Insulin promotes glucose absorption into liver

cells, muscle cells, adipocytes, and other tissues, thereby promoting the synthesis of fat and protein and decreasing blood glucose levels. Adrenaline also increases heart rate and breathing frequency. Once blood glucose levels return to normal, the parasympathetic nervous system (PNS) releases the hormone acetylcholine, which slows down the heart rate. In the event of hypoglycemia, as blood glucose levels continue to decrease, the ANS stimulates epinephrine secretion, leading to the release of glucagon from the islet alpha-cell. Glucagon release triggers a chain reaction of kinase activity, leading to the release of glucose from liver glycogen stores through glycogen lysis [42, 43].

An increase in sympathetic nervous system (SNS) activity is responsible for various physiological changes in the body, including an increase in heart rate, contractility of the cardiac muscle, blood pressure, epinephrine secretion, sweat production, and breathing frequency, all aimed at preparing the body for action. These changes in SNS activity can lead to alterations in the Electrocardiogram (ECG) morphology signal, as evidenced by previous research [44]. In contrast, the parasympathetic nervous system (PNS) produces opposite effects to the SNS, resulting in a slowing of heart rate, breathing frequency, and relaxation. It follows that changes in BG levels can stimulate the ANS, leading to alterations in ECG signals that reflect critical information about the structure and function of the cardiovascular system, as well as ANS changes. Nonetheless, the relationship between hypoglycemia and ANS is intricate and warrants further investigation.

5. Heart:

The heart, as the primary circulatory organ, plays a pivotal role in maintaining the vitality of the body. Composed, predominantly, of myocardial tissue, the only muscle that can contract regularly and persistently without tiring. The heart is composed of four chambers, namely two atria and two ventricles, separated by valves that ensure unidirectional blood flow. The rhythmic alternation of atrial and ventricular systolic and diastolic cycles facilitates efficient blood circulation throughout the body [45].

The heart rhythm, or pulse, is generated through an intricate interplay between the autonomous cardiac pacemaker system and various regulatory mechanisms. The autonomous cardiac pacemaker system functions as an intrinsic control mechanism, generating rhythmic contractions of the myocardium. However, the pulse rate is also modulated by the nervous

system and endocrine signaling pathways. Specifically, two hormones, adrenaline, and noradrenaline, released by the adrenal glands in response to emotional stimuli, augment the contractile rhythm of the heart. Additionally, noradrenaline is also released by sympathetic nerve fibers that innervate the myocardium. In contrast, acetylcholine, a neurotransmitter released by parasympathetic nerves, exerts an inhibitory effect on the heart, decelerating the pulse rate. Consequently, the pulse rate can vary widely, ranging from 70 beats per minute during rest to 180 or even 210 beats per minute during intense exertion [45].

5.1. Electrical heart activity (Electrocardiogram):

The sinus node, also known as the Sino-Auricular (SA) node, is a specialized cluster of myocardial cells located at the superior aspect of the right atrium that constitutes the primary pacemaker of the heart. The SA node generates a periodic excitation wave, characterized by a few millivolts of electrical potential, at a frequency of approximately 0.8 seconds. This wave propagates rapidly, within 0.1 seconds, through the muscular tissue of the atria, causing their contraction in a coordinated manner that facilitates the expulsion of blood into the ventricles. The corresponding electrical activity of the atria is reflected in the P wave of the ECG. Subsequently, the excitation wave reaches the Atrioventricular (AV) node, situated at a lower level between the atria, which functions as a relay station for the wave, transmitting it to the walls of the ventricles via the atrioventricular bundle (or His bundle) and the Purkinje fibers. This results in the depolarization and contraction of the ventricular myocardium and is reflected as the QRS complex in the ECG signal. During this phase, the atria remain inactive while the ventricles contract rapidly, generating a heartbeat sound, caused by the sudden closure of the valves [46]. **Figure I-4** demonstrates the mechanism of the electrical impulsion generation and propagation.

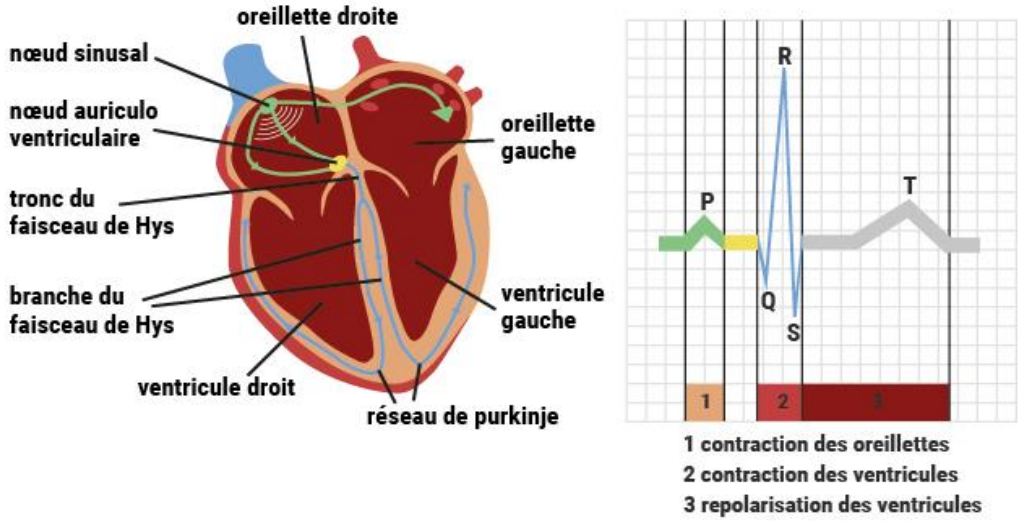


Figure I- 4: The mechanism of the electrical impulsion generation and propagation.

The Electrocardiogram (ECG) is a diagnostic tool that provides a visual representation of the electrical activity of the heart. This is achieved via the use of an electrocardiograph, which measures the potential difference between various points on the surface of the body. By utilizing this non-invasive technique, clinicians can obtain valuable information on the functional status of the heart. The ECG signal illustrated in **Figure I-4** pertains to the initial ECG lead of a healthy heart. This waveform is comprised of distinct deflections. The various components of ECG waveform correspond to specific electrical phenomena that occur within the heart during the cardiac cycle. Specifically [46],

- P-wave represents the electrical depolarization of the atria,
- QRS complex signifies the depolarization of the ventricles.
- QT segment of the ECG is indicative of the plateau phase of the ventricular action potentials.
- T-wave, on the other hand, represents the electrical repolarization of the ventricles.
- U-wave, which is not always present, can be attributed to a delayed repolarization of the M cells or a mechanical factor that corresponds to the relaxation of the myocardium.

6. Diabetes Mellitus:

The term diabetes has its origins in the Greek language, where it signifies “to run through.” This nomenclature was inspired by the observation that after consuming liquids, diabetic individuals would quickly expel the liquids, much as water would flow through a conduit. Furthermore, the term mellitus, also of Greek origin, means honey. Thus, diabetes mellitus refers to a chronic metabolic illness characterized by the inability to control blood glucose levels adequately, which leads to the development of persistent hyperglycemia, marked by deviations in carbohydrate, lipid, and protein metabolism. The etiological basis of diabetes mellitus is primarily attributed to either the inadequate secretion of insulin, which is due to the destruction of beta cells, or diminished cellular responsiveness to insulin action [47].

As a consequence of the inadequate control of blood glucose levels, the majority of cells in the body become incapable of utilizing or storing glucose as an energy source. These cells adopt an enhanced reliance on the catabolism of lipids and proteins for energy production, culminating in the liberation of free fatty acids, cholesterol, and phospholipids into the circulatory system. The cumulation of these compounds in the bloodstream can result in the impairment, dysfunction, and failure of many organs in the body. Chronic hyperglycemia is linked to the development of acute ketoacidosis, as well as micro- and macrovascular diseases. The former arises due to the accumulation of ketones, which are by-products of the breakdown of fats and proteins, in the bloodstream. If left untreated, ketoacidosis can be fatal. Diabetes mellitus can be classified into two primary types [47, 48]:

6.1. **Type 01 Diabetes Mellitus (T1DM):** “insulin-dependent diabetes mellitus” or “juvenile diabetes”

Type 1 diabetes mellitus (T1DM) is a chronic condition defined by the body’s inability to process glucose due to the deficiency of insulin, which results from the immune system’s destruction of pancreatic β-cells. Hyperglycemia occurs when only a small fraction of beta cells, approximately 10% to 20%, remain functional.

Blood sugar levels in T1DM patients may range from 300 to 1200 mg/dl, which is 8 to 10 times higher than those in healthy people. The factors that trigger the autoimmune reaction against the pancreas remain elusive. Yet, it is widely thought to be the result of a complex

interaction between various predisposing genes and other environmental factors, such as viruses, toxic substances, food, and physical inactivity, among others [2].

The symptoms of T1DM include polydipsia (intense thirst), polyphagia (abnormally increased appetite), polyuria (excessive urination), and massive weight loss [49]. Around 10% of patients with diabetes are affected by T1DM, and its prevalence is steadily increasing worldwide. T1DM can manifest at any age, but it is more commonly diagnosed during childhood, adolescence, or early adulthood [2].

6.2. Type 02 Diabetes Mellitus (T2DM): "non-insulin-dependent diabetes mellitus"

Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, characterized by the pancreas producing insulin, but the body's cells not responding to it effectively due to unknown reasons, resulting in high blood sugar levels or hyperglycemia. Insulin secretion accumulates in the bloodstream over time, resulting in decreased insulin production in the body and, in some cases, long-term T1DM. Unlike T1DM, T2DM is, generally, asymptomatic. The underlying reasons for cells' inability to respond to insulin properly remain unidentified. T2DM is thought to be primarily influenced by a combination of genetic predisposition and several factors such as obesity, sedentary lifestyle, fetal malnutrition, and diet [2, 49].

6.3. Diabetes-related complications:

If diabetes remains untreated or poorly controlled, it can lead to a variety of complications that affect many different sections of the body. Some common diabetes-related complications include:

6.3.1. Short-term complications:

- Hyperglycemia, a hallmark of diabetes, is typically characterized by symptoms such as polyuria, polydipsia, nausea, vomiting, and abdominal pain. In cases where there is a severe deficiency of insulin, the body may resort to increased fat metabolism to provide the cells with energy, culminating in a state of ketoacidosis that may lead to a coma. Another acute complication associated with hyperglycemia is Hyperosmolar Hyperglycemia Syndrome (HHS). HHS occurs when the body is unable to compensate for polyuria caused by high blood glucose levels with an equivalent intake of fluids, resulting in increased serum osmolarity. This

condition can cause damage to various organs, including the brain, and potentially result in a state of coma. Interestingly, HHS is more commonly observed in cases of type 2 diabetes compared to type 1 [47, 50].

- Hypoglycemia not only disrupts the body's metabolic and autonomic functions, but it also impairs neuronal function, which can manifest as symptoms such as fatigue, weakness, dizziness, and cognitive or behavioral changes. In severe cases, hypoglycemia can lead to seizures, coma, and even death [48, 51].

6.3.2. Long-term complications:

- DM is known to exacerbate the pathogenesis of atherosclerosis, leading to arterial stiffening, and consequently increasing the incidence of occlusive vascular diseases including cerebral stroke, and peripheral gangrene, myocardial infarction. Notably, patients with type 2 diabetes have a higher risk of developing these complications [48].
- Diabetic Autonomic Neuropathy (DAN) is a neuropathic disorder that typically manifests within the first decade of T1DM and T2DM. The pathogenesis of DAN is primarily attributed to the compromised blood supply to the nerves, resulting in structural changes. DAN can significantly impact the mortality and morbidity of diabetic patients, as it can affect several body systems, including the cardiovascular, gastrointestinal, genitourinary, pupillary, sudomotor, and neuroendocrine systems[48, 51].
- Nephropathy can occur resulting from vascular disorders. The kidney blood vessels can be affected which disturbs the kidneys and causes kidney failure and irreversible kidney disease[48, 51].
- Diabetic patients are susceptible to retinopathy. It refers to eye vision problems involving the retina, which can lead to progressive loss of vision[48, 51].
- In diabetics, infections of the skin, respiratory tract, gums, bladder, and vagina are difficult to treat. Moreover, poor blood circulation slows the healing process after an injury[48, 51].

6.4. Diagnostic:

Diabetes mellitus (DM) is diagnosed clinically based on established criteria that include several parameters [6, 52]. These include:

- A fasting blood sugar level exceeding 126 mg/dL,

- A random blood sugar level greater than 200 mg/dL in the presence of symptoms such as thirst, polyuria, unexplained weight loss, and others.
- An Oral Glucose Tolerance Test (OGTT) results in greater than 200 mg/dL, as measured two hours following an oral load of 75 g of glucose,

A definitive diagnosis of DM requires confirmation of the results by repeating the diagnostic tests on at least two occasions.

- Another diagnostic test, The HbA1c test determines how much glucose is attached to hemoglobin12. It is a good predictor of diabetes complications because it evaluates average BG level over the past 2-3 months.

6.5. Treatment:

Correcting hyperglycemia and preventing hypoglycemia are the primary goals of managing diabetes. The following points apply to both T1DM and T2DM.

- hypoglycemia can be remedied with sugar donation (sugar cubes or sugary drinks) if the patient is conscious, or intravenous glucose injection if the patient is unconscious [52].
- A healthy lifestyle is critical for preventing diabetes and its complications. Diabetic patients are advised to follow a balanced and varied diet that includes a source of carbohydrates at each meal and to avoid excessive fat intake and alcohol consumption [52].
- Physical activity is essential in diabetic patients not only for blood sugar control, but also for lowering cardiovascular risk factors, controlling weight, and improving well-being and mental health. It must be tailored to the patient's age and disability. In general, the World Health Organization (WHO) recommends 150 minutes of moderate-intensity physical activity per week or 75 minutes of vigorous physical activity per week [53].

People with T1DM and those with T2DM have different medical treatment options to correct hyperglycemia.

6.5.1. Type 1 diabetes Mellitus:

In reality, transplantation of a pancreas or islets of Langerhans remains the only effective treatment for T1DM. However, this procedure is often hampered by immunological factors and carries a significant risk profile. The transplanted Langerhans islet cells are frequently targeted by the body's immune system, much like the original islet cells, rendering transplantation a viable option only for individuals with highly resistant diabetes [54]. The primary treatment method for T1DM is insulin-therapy, which is tailored to each patient's characteristics, including the type of insulin used, its onset, peak, and duration of effect, as well as the number, amount, and timing of insulin doses. Generally, T1DM therapy may be divided into two categories depending on insulin regimen and glucose monitoring: Intensive Therapy (IT) or Conventional Therapy (CT):

- CT involves one or two self-monitoring of blood glucose levels, one or two daily insulin injections with no dose adjustment outside of medical visits, and no specific glucose goals beyond preventing hyperglycemia and hypoglycemia symptoms [55].
- In contrast, intensive therapy (IT) utilizes the administration of multiple insulin injections, typically thrice a day, or an external insulin pump. The dosages are adjusted based on a minimum of four self-monitored glucose measurements per day, food consumption, and pre-planned physical activity. IT also encompasses a set of daily glucose targets, including blood glucose levels ranging between 70-120 mg/dL before meals and a postprandial glucose level that is below 180 mg/dL. [6, 55].

The Diabetes Control and Complications Trial (DCCT) investigated the efficacy of two therapeutic modalities in treating T1DM, ultimately establishing the benefits of intensive glycemic control [5]. This study found that intensive blood glucose control lowers the occurrence of microvascular problems associated with T1DM, such as neuropathy, nephropathy, and retinopathy. Nevertheless, the risks associated with intensive glucose control, such as severe hypoglycemia, weight gain, and increased therapy costs, limit its clinical use. Considering these limitations, researchers are currently focusing on developing optimal treatment protocols and autonomous system architectures that ensure the appropriate feedback between changes in BG levels and continuous insulin administration. This research led to the appearance of an Artificial pancreas system or the closed-loop system that will be discussed in depth in the coming section.

6.5.2. Type 2 diabetes Mellitus:

The treatment for T2DM primarily involves changes to the patient's diet and lifestyle. In cases where glycemic targets are not achieved, pharmacological intervention is necessary. This typically involves the administration of oral medications, such as metformin or a combination of metformin and sulfonylureas, if the targeted glucose levels are not achieved. If glucose levels continue to rise, a third type of drug, either an oral hypoglycemic or an injectable medication (such as insulin), is given with metformin and sulfonylureas [6].

7. Advanced technologies for intensive therapy diabetes:

This section delves into the present state of diabetes technologies intending to offer a historical context and current insights for researchers working on the development of a closed-loop system (Artificial pancreas).

7.1. Insulin Administration:

The conventional therapy for insulin administration entails the delivery of one to two daily injections of insulin, without any adjustments to the dosages. This therapeutic approach can be executed through the utilization of either syringes or injection pens for the subcutaneous administration of insulin. Conversely, Insulin-o-therapy in intensive mode necessitates Multiple Daily Insulin Injections (MDII), which can be accomplished by employing syringes, refillable injection pens, or pre-filled injection pens. In this scenario, rapid-acting or short-acting insulin is administered before each meal following carbohydrate/insulin ratios, with fixed doses referred to as boluses, while long-acting insulin is administered once or twice per day, typically in the evening and morning [55].

Another effective instrument employed in intensive mode therapy is the insulin pump, which shown to significantly improve glycemic control. The Continuous Subcutaneous Insulin Infusion (CSII) system, which is formulated to emulate the physiological secretion of insulin, can be either implantable or external. This system delivers regular rapid-acting insulin, as needed, via a Teflon catheter to the subcutaneous tissue of the abdomen, thighs, or arms. Various insulin delivery scenarios can be programmed using the insulin pump over 24 hours. The basal rate is programmed in units per hour, while boluses are triggered by the patient via the pump or a remote-control during meals. This system offers several advantages, including the ability for patients to manage metabolic changes related to daily conditions, such as the

dawn phenomenon (a glycemic rise in the early morning due to the elevation of hyperglycemic hormones), unstable diabetes, or diabetic gastroparesis (which is responsible for early post-prandial hypoglycemia). Patients can also set a temporary basal rate at any time (e.g., lower it during physical activity to avoid hypoglycemia) and administer boluses gradually (over 1 or even 2 hours in the case of gastroparesis) [56].

An insulin pump typically consists of two disposable components: an insulin reservoir and an infusion set connected to the reservoir via a thin, flexible tube. The infusion set is composed of a cannula, which is a small plastic tube inserted into the subcutaneous fat beneath the skin. A needle is contained within the cannula and is used to puncture the skin during set insertion. After insertion, the needle is removed, and the cannula remains in place [56].

7.2. Blood glucose monitoring:

Measuring blood glucose levels can be done through several methods, including the enzymatic-amper-o-metric and hexokinase techniques, which are widely employed for this purpose. Nevertheless, these invasive procedures involve the application of a droplet of blood onto an electrochemical probe or a colored enzyme-treated strip, typically obtained through a finger prick. Such techniques are often uncomfortable, necessitating frequent and intrusive monitoring, particularly at night, and may pose a risk of infection, thereby placing diabetic individuals in a vulnerable position [13].

An alternative methodology has been implemented to ensure continuous monitoring of blood glucose levels - the Continuous Glucose Monitoring (CGM) approach. It can determine the Blood Glucose Concentration (BGC) value in real-time and continuous intervals every 5 minutes. CGM devices consist of a sensor, a transmitter, and a receiver. The sensor is inserted under the patient's skin, usually in the abdomen, and measures glucose levels in the interstitial fluid. The transmitter sends the data from the sensor to a receiver, which displays the glucose levels in real-time. Some CGM devices can also send the data directly to a smartphone or other mobile device. The utilization of minimally invasive Continuous Glucose Monitoring (CGM) systems is prevalent, considering the global spread of diabetes, resulting in substantial expenses, not only for the device's acquisition but also for the disposable sensor needles. The augmented employment of lancets, microneedles, and lancing pens is responsible for a substantial buildup of household waste, which poses various public health and environmental

concerns. This condition has prompted domain specialists to proactively introduce innovative systems to alleviate these limitations [16, 17].

This technology has significantly improved the control of BG levels for diabetes patients. However, they have many limitations such as the maximum duration of use is two weeks. As the measurement of blood glucose levels is conducted at the Interstitial Fluid (ISF) level instead of the blood level, a time lag issue cannot be avoided. Additionally, the defined CGMs require calibration more than twice a day using the conventional technique [14, 15, 57].

7.3. Closed loop system (Artificial pancreas):

During the 1960s, researchers initiated an ambitious project to create a device that could automatically calculate and administer the requisite dosage of insulin to the human body. This pursuit ultimately gave rise to closed-loop control systems [58]. One such experiment yielded the Biostator, which became the first artificial pancreas device. The initial version of this device was confined to hospital settings due to its cumbersome size and reliance on intravenous glucose sensing [59]. Nevertheless, it demonstrated the plausibility of external glucose regulation and encouraged further technological progress. The subsequent developments in continuous glucose monitoring [60] facilitated the expansion of the device applications beyond intensive care units [61]. Their deployment as an open-loop system has exhibited superior clinical outcomes compared to MDII treatment [62]. The artificial pancreas consists of 03 main components [56] as shown in **Figure I-5**:

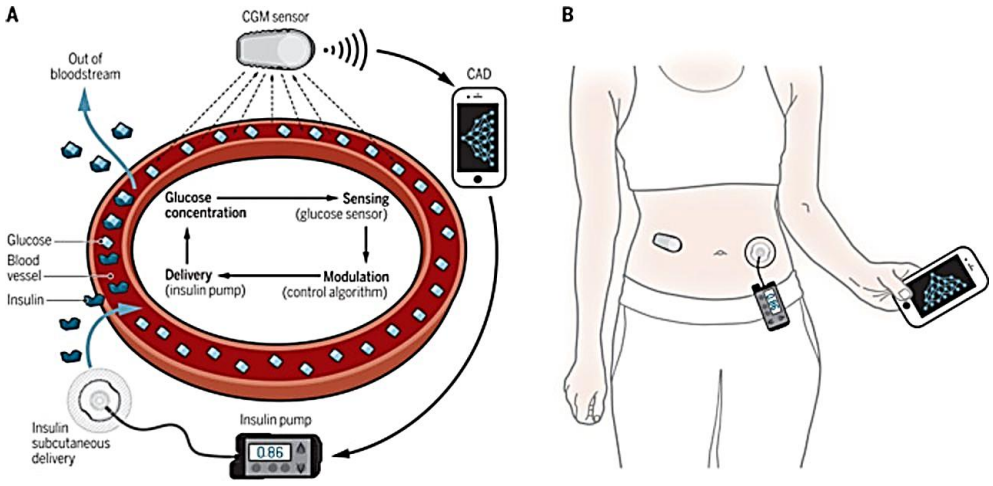


Figure I- 5: Artificial Pancreas (closed loop system)

- CGM sensors, report Blood Glucose Concentration (BGC) almost every 5 minutes allowing real-time continuous monitoring.

- A control algorithm that computes the appropriate insulin delivery rate using the sensor's data.
- An Insulin pump that administers the calculated amount of insulin.

Researchers have directed their efforts towards integrating CGM with self-controlled insulin pumps utilizing intelligent control algorithms, which are more intricate than those implemented in open-loop systems. As of now, the intelligent control algorithms developed for closed-loop systems can forecast the blood glucose level half an hour ahead, according to the present BG reading, the amount of insulin administered, and other crucial variables. For instance, Sensor-Augmented Insulin Pumps (SAPs) enable continuous communication feedback between the CGM and insulin pump, facilitating basal rate adjustments based on real-time glucose measurements. The insulin pump can automatically decrease the basal rate to prevent a sugar level drop, thereby decreasing the probability of severe hypoglycemic episodes. Nevertheless, SAPs still require manual adjustments and inputs from the user, such as the quantity of carbohydrates to be consumed [63]. Given that this technology is still in its early developmental phase, further research is required to fully comprehend its advantages and disadvantages [64].

Integration of closed-loop systems also referred to as artificial pancreas, has exhibited significant potential in comparison to conventional insulin therapy approaches currently employed [48, 49].

- The artificial pancreas technology holds promise in alleviating the discomfort associated with the frequent finger pricks required for glucose level measurement and insulin administration.
- Enhancing the efficacy, security, and overall management of blood glucose control during overnight, postprandial, and other settings represents a vital objective.
- Improve the quality of life: BG level fluctuations have a negative effect on physical and mental health in patients, caregivers, and their families. These mental health problems can be caused by either high or low BG levels. The artificial pancreas allows DM patients to be more flexible in their daily lives without having to constantly think about their diabetes and reduces stress.
- Reduced cost of treating complications relating to type 1 diabetes and reduced hospitalizations for diabetic ketoacidosis.

- The primary objective is to mitigate and avert the occurrence of immediate and enduring complications stemming from diabetes, while simultaneously alleviating the daily challenges associated with diabetes management.

8. Biometric variables in the AP system:

The utilization of an AP system has been demonstrated to be both a secure and efficacious practice in extensive clinical investigations as well as commercial settings. However, researchers are currently endeavoring to further augment AP systems by integrating additional sensing modalities. As previously expounded in Section II, in healthy individuals, glucose level control in the bloodstream is accomplished through a complex negative feedback control system. This system continuously monitors physiological shifts and triggers mechanisms that counteract those variations, returning physiological conditions to normal. While AP has exhibited improvements in postprandial glucose control and overnight management, achieving target blood glucose levels in everyday situations remains a significant challenge. This is mainly because blood glucose levels impact the autonomic nervous system (ANS), which governs bodily functions, and the underlying physiology that variations in blood glucose levels with other bodily functions have yet to be fully elucidated. Consequently, researchers have concentrated their efforts on developing an external closed-loop system (i.e., AP system) that can mimic the natural regulatory system. To achieve this, it is essential to furnish the intelligent control algorithm with all the pertinent data that may influence glucose or insulin metabolism in the body.

In the case of stress or physical activity, a multitude of physiological or electrophysiological parameters should be identified and integrated into the control algorithm to achieve optimal outcomes of the glucose profile [65, 66]. Likewise, in the case of meal consumption, the smart AP system should be capable of automatically detecting the amount of ingested carbohydrates utilizing wearable devices [67]. Given this feedback, the system should be able to adapt to the variations that emanate from medical conditions, physical activity patterns, and nutritional practices. So far, the primary focus of studies has been centered on controlling blood glucose levels during and after exercise, as well as predicting episodes of hypoglycemia and hyperglycemia.

8.1. Physiological signals:

Maintaining regular physical activity is imperative for individuals with diabetes mellitus to ensure optimal BG levels and minimize the risk of complications, thereby improving insulin sensitivity. Consequently, managing patients with T1D during and after exercise is a challenging task for both patients and caregivers, regarding insulin management and hypoglycemia prevention and rescue. In light of the current breakthroughs in the Internet of Things, wearable sensors, and artificial intelligence, researchers have been directing their efforts toward assessing physical activity and leveraging it to improve closed-loop glucose control.

Several biometric variables, including accelerometer signal/Heart Rate (HR) [68, 69], skin temperature, skin impedance [66, 70, 71] galvanic skin response, and energy expenditure [66, 70–72], have been analyzed to most appropriate biometric indicators for predicting hypoglycemia during and after physical activity. They aimed to comprehend the impact of these biometric variables on the metabolic response to exercise. The findings suggest that all these biometric characteristics influence blood glucose control. Nevertheless, it is recommended that an exercise sensor should only be integrated into an artificial pancreas (AP) system if it minimizes the possibility of hypoglycemia [66].

8.2. Electrophysiological signals:

A. Electroencephalogram signal:

EEG measures the electrical activity of brain cells, which is categorized into four bandwidths: beta (16-31 Hz), alpha (8-15 Hz), theta (4-7 Hz), and delta (4 Hz). Because the brain is highly susceptible to hypoglycemia, Since 1990, changes in EEG signals have been studied to explain the symptoms associated with this event. Regan and Browne Mayers reported that there was a decrement in alpha frequencies and an increment in delta frequencies after insulin injection. These changes were observed to steadily amplify with the progression of hypoglycemia, which was attributed to the insufficiency of metabolic fuel [58]. In response to hypoglycemia, total EEG power increase and frequency slowing have been observed[73, 74], as shown in **Figure I-6**, leading to cognitive impairment, reduced response times, slurred speech, loss of consciousness, seizures, and even death. The threshold for hypoglycemia-induced EEG alterations varies between individuals, and the mechanism for this difference is not yet established, although cerebral glycogen levels, glucose transfer into brain cells, and cerebral

blood flow are potential factors. EEG changes have been found to occur 120 minutes before coma, at a time when patients are typically aware. Therefore, researchers are developing hypoglycemia warning systems (alarms) to predict episodes before they occur [23].

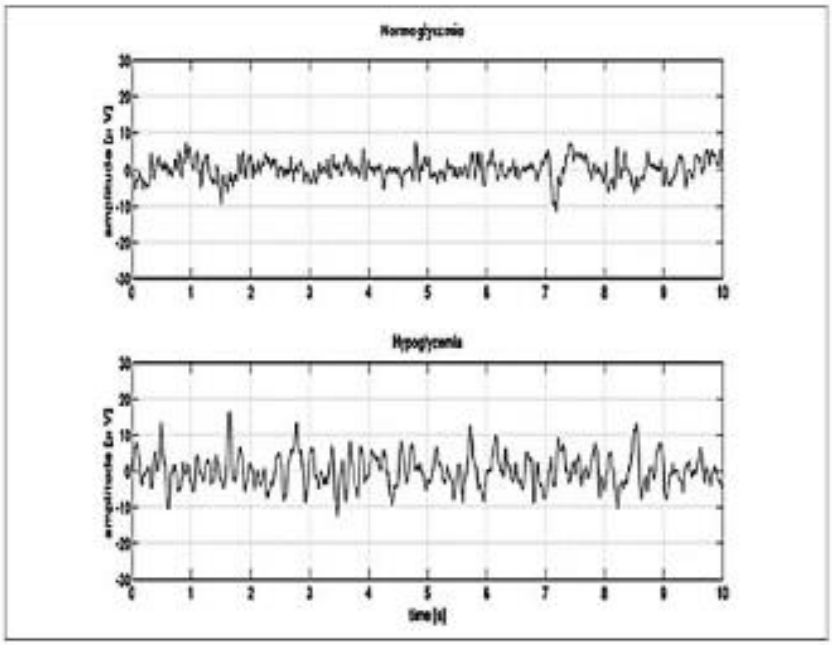


Figure I- 6: Examples of single-channel EEG recordings during normoglycemia and hypoglycemia in the same person (daytime)

Clewett et al. conducted a study [75] to assess the practicality of EEG-based hypoglycemia warning in a single case. In a separate investigation, Blaabjerg et al. devised a subcutaneous EEG alarm device dubbed hyposafeTM SubQ [76] that leverages brain activity to forestall hypoglycemic episodes. Their inquiry elucidates on a diminutive EEG implant installed beneath the skin posterior to the ear, which records EEG signals. Several machine learning-based techniques have been proposed to detect reduced glucose levels by utilizing diverse amalgamations of EEG parameters [76–78].

The most prominent and early indicators of hypoglycemia were found to be changes in EEG frequencies. However, the limitations imposed by the power consumption and miniaturization requirements of electroencephalogram technologies prevent the development of embedded wearable circuits that measure and analyze EEG data. These obstacles could make it more difficult to integrate electroencephalogram data into an Internet of Things platform for an autonomous artificial pancreas system [22].

B. Electrocardiogram signal:

Various changes in ECG signal are associated with the ANS response and variations in blood sugar levels. Studies have examined combinations of ECG features and BG in both healthy subjects and diabetic patients [79, 80]. Lipponen et al. [81] explicate the underlying mechanisms responsible for these transformations, which embrace hypokalemia and the debilitation of the neural regulatory system. Hypokalemia enhances the potassium conductivity in myocardial tissue, culminating in shorter action potentials, which may exert an impact on heart activity. A change in the ECG occurs simultaneously with the onset of lower blood glucose levels since both neuronal regulation and hypokalemia are rapid processes. Furthermore, it is well-established that blood glucose levels affect hormonal secretion, such as adrenalin and noradrenaline, which may lead to a postponement in the ECG in correlation to the onset of hypoglycemia [42].

Recent studies have corroborated that hypoglycemia can lead to QT interval prolongation in patients with T1DM, which can culminate in sudden death [81, 82]. Additionally, an increase in corrected QT (QTc) is strongly linked with an increase in adrenaline [26]. T-wave flattening is another characteristic feature of hypoglycemia that is employed in the identification of hypoglycemic and euglycemic episodes [26, 79]. However, Porumb et al. [24] assert that changes in T-wave amplitude can be subjective. Nguyen et al. [73] examined the impact of hypoglycemia on several other heart rate activity metrics, such as increased HR, PR interval, corrected TpTec interval (TpTec) (T-peak to T end) and corrected RT interval (RTc). Their findings suggest that reduced blood glucose levels are linked with prolonged RTc, QTc, and TpTec [83]. These metrics furnish valuable information that can be harnessed to detect hypoglycemia in individuals with diabetes. The primary goal of all the aforementioned studies was to develop an alarm system that can prognosticate episodes of hypoglycemia and hyperglycemia.

- A preliminary investigation was conducted on utilizing deep learning for the identification of hypoglycemic episodes based on electrocardiography (ECG) data, as outlined in [24]. The researchers investigated four healthy participants, utilizing a non-invasive wearable device to record raw ECG signals. In addition, they introduced a visualization method, allowing clinicians to discern which specific part of the ECG signal (such as the T-wave or ST-interval) exhibits a significant correlation with the

hypoglycemic occurrence in each subject. The outcomes indicate that the deep learning models achieve notable sensitivity, specificity, and accuracy of approximately 84% in detecting hypoglycemic events among the study subjects.

- The objective of the study conducted by Cordeiro et al. [25] was to develop a Deep-learning model that could detect hyperglycemia using ECG parameters characterized through the fiducial feature technique. A large dataset comprising 51,518 samples from 1,119 subjects was utilized to achieve this goal. The fiducial feature technique, a widely used method in ECG analysis, was employed to identify characteristic points on the ECG waveform such as the QRS complex, to retrieve relevant features. The Deep Learning model was designed to predict hyperglycemia in real time. The study determined that the proposed model displayed high accuracy in detecting hyperglycemia, with an area under the receiver operating characteristic curve (AUC-ROC) of 0.93.
- In 2019, a proof-of-concept study [84] was conducted to investigate the effectiveness of the wearable device known as the "VitalPatch" (VitalConnect) in monitoring heart rate and detecting hypoglycemic events in 23 outpatients with T1DM. The device was positioned on the chest for five days. Results from the study indicated that Heart Rate Variability (HRV) alone could detect 55% of both daytime and nocturnal hypoglycemic events, with 27% of these events presenting an atypical pattern.
- In recent years, Nguyen et al. [85, 86] have proposed alternative approaches for detecting hypoglycemic episodes, which utilize extreme learning machines or neural networks. These methods incorporate corrected QT interval (QTc) and HRV as inputs and employ a learning strategy that does not account for inter-individual differences. The team achieved a promising result using a dataset of 15 children, demonstrating a sensitivity of 80% and specificity of 50% for identifying nocturnal hypoglycemia.

9. Conclusion:

Diabetic mellitus has a profound impact on both the individual and societal levels, with significant human and economic consequences. However, present treatment modalities remain less than optimal, as they fail to fully understand glucose hemostasis and its full impact on the different bodily functions to maintain the blood glucose in the normal target range. In this chapter, we were able to highlight the impact of blood glucose level fluctuation on the ANS system and the heart rate activity. Furthermore, the recent technologies that support diabetes

self-management have been revealed. The current standard of care for DM self-monitoring is based on the use of CGMs and involves multiple daily injections or continuous subcutaneous insulin infusion (CSII) through an insulin pump. While these methods have proven effective in controlling blood glucose levels, they are not without their limitations. Through a thorough examination of the possible benefits of IoMT technology in enhancing the efficacy and practicality of AP systems, the integration of this technology into the realm of diabetes self-management represents a promising avenue for mitigating these challenges. Wearable and smart sensors, IoT technologies, and AI enable the integration of electrophysiological signals specifically ECG signals in the AP system as a non-invasive, wearable, smart, and affordable continuous blood glucose monitor.

The motivation for this thesis stems from the pressing need for improved diabetes management solutions. The integration of IoMT technology and machine learning approaches in diabetes self-management presents an opportunity to integrate electrophysiological signals specifically ECG signals in the AP system as a non-invasive, wearable, smart, and affordable continuous blood glucose monitor. this thesis aims to contribute to the development of more effective and patient-centered diabetes management solutions

Chapter

II. Blood glucose determination based on ECG signal

1. Introduction:

The need for continuous and painless blood glucose monitoring that is reliable, non-invasive, and affordable is crucial for an AP system. In this context, numerous approaches have been suggested as non-invasive techniques for BG monitoring (without the need for skin puncturing). Including optical polarimetry[18], fluorescence technology[19], and Raman spectroscopy[20]. These methods are based on the changes in tissue properties induced by fluctuations in glucose levels. Nevertheless, these approaches have challenges such as sensitivity to external interference caused by biometric variables such as sweat, body temperature, skin moisture, variations in skin thickness, and body motion. Thus, the accuracy of non-invasive methods is not always guaranteed. Another significant disadvantage is the durability of the aforementioned technologies, as well as the high cost of the system components.

Another Approach has been investigated these last years, consisting of the use of wearable devices of physiological signals as non-invasive blood glucose monitors. Among these methods, is an apparatus that utilizes multiple body signals. The estimation of the BG measurement is based on the change in glucose absorption according to BG level. Other physiological signals (ECG, PPG, SpO2, GSR, etc.) were then employed as an auxiliary input to adjust and improve the estimated blood glucose levels. This method necessitates a high number of physiological inputs, increasing the measurement error rate and making the gadget weighty and unpleasant for portable usage and continuous self-monitoring.

Other researchers have focused on the use of photoplethysmography (PPG) as a low-cost, non-invasive option for estimating blood glucose levels. PPG analyzes changes in blood volume within the arteries and determines glucose levels in the circulation using a smartphone-based technique. The approach comprises converting video of the fingertip acquired with a commercially available smartphone camera to a PPG signal and extracting features using signal processing and regression models. Following that, machine learning techniques are used to forecast blood glucose levels. Empirical data have shown that this pioneering approach has potential, while improvements are still needed.

It is widely acknowledged that electrocardiography (ECG) has primarily been employed in the cardiology domain for diagnosis aiding and monitoring of heart disease. However, it is noteworthy that blood glucose levels can have an impact on cardiac electrical activity. This finding has motivated further investigation into this relationship to obtain a deeper understanding of this relationship. Based on the state-of-the-art presented in Chapter 1, studies have been conducted to predict hyper-hypoglycemic episodes, However, they do not enable the direct measurement of real-time glycemia values from the ECG signal. To the best of our knowledge, we are the first whom propose a direct method for estimating BGC utilizing ECG features. Furthermore, wearable ECG devices are widely accessible in the market nowadays as smartwatches, belts, and bracelets. These non-invasive, affordable [87] devices are easy to integrate into an artificial pancreas using advanced technologies on the Internet of Things.

In this chapter, we propose two novel approaches for BG determination based on ECG signals. The first involves mathematical equations to calculate blood glucose concentration value, whereas the second applies to machine learning to estimate the BG value utilizing ECG features as input. Before that, the chapter describes the process of data collection and analysis (filtering- segmentation) using a convolutional neural network. Finally, we discuss the implications of the findings for diabetes management and healthcare.

2. Materials:

In our work, we utilized two databases described as follows:

2.1. D1namo dataset:

It is a multi-modal dataset designed to facilitate studies on non-invasive T1DM management. This dataset comprises recordings from a diverse sample of twenty healthy individuals and nine patients diagnosed with T1DM. Alongside ECG data and blood glucose measurements, the dataset also includes respiration, accelerometer data, and annotated meal photos. This dataset was collected in real-world settings, thereby incorporating significant amounts of noise and missing data [88]. These devices, as well as the protocols used to collect the data:

a. Zephyr-BioHarness 3 wearable device:

The Zephyr BioHarness 3 is a wearable device designed to monitor a range of physiological signals, including electrocardiogram, respiration, and skin temperature. Its versatile design enables it to be used in various settings, including healthcare, sports performance, and research[88, 89]. The device is compact and lightweight, rendering it easy to wear, maneuverable, and can be worn for extended periods without causing irritation or discomfort. It is equipped with a wireless connection to a mobile device or computer, allowing real-time monitoring and data analysis [88, 89].

As depicted in **Figure II-1**, this device resembles a sports chest belt and is composed of three electronic detectors for the measurement of physiological signals. The first detector captures ECG signals using two electrodes, while the second detector measures respiration via chest expansion. The third detector is used for capturing three-dimensional accelerations. Additionally, Furthermore, the device can calculate supplemental measurements such as Heart Rate (HR), Breathing Rate (BR), and activity level.

The Zephyr BioHarness 3 ECG is recorded using an I-lead sensor, which comprises a pair of silver-coated nylon electrodes that operate while in contact with the skin. The electrocardiogram was produced at a frequency of 250 Hz and up to 54.89 mV. As part of the prescribed protocol, individuals (diabetic patients and healthy subjects) are instructed to put on the BioHarness at least one hour per day. This routine must be followed for four days consecutively [88, 89].

Figure II- 1: The Zephyr BioHarness 3

b. Bayer Contour XT glucose meter:

The glucose levels of healthy people were monitored using the cutting-edge Bayer Contour XT glucose meter in conjunction with Bayer Next strips. individuals used the Microlet 2 Lancing Device and its matching Microlet Colourful Lancets to retrieve a blood sample [90]. The full protocol

followed included six glucose readings per day, one before each meal, namely breakfast, lunch, and supper, and an extra reading two hours after consumption [88].

c. iPro2 Professional CGM sensor:

To measure the glucose levels of diabetes patients continuously throughout the day and night, the iPro2 Professional CGM sensor was employed, allowing for a 5-minute interval between two successive readings. The iPro2 Professional CGM sensor measures the BG level from the interstitial fluid. The device utilizes a petite and pliable sensor that is comfortably inserted just below the skin as shown in **Figure II-2**, along with a separate transmitter that seamlessly transmits data wirelessly to a display device, including a receiver, smartphone, or insulin pump [91].

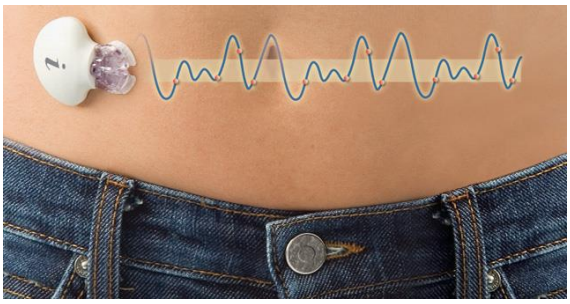


Figure II- 2: iPro2 Professional CGM sensor

In our study, a comprehensive examination of the entire dataset was conducted, tokenizing just ECG signals and BG readings from diabetes patients. Nonetheless, our target audience encompasses individuals beyond people suffering from type 1 diabetes. The reason behind utilizing this specific group is that it assists a greater range of blood glucose levels, notably hypoglycemia, hyperglycemia, and euglycemia. Healthy individuals' data, on the other hand, only includes 6 BG measures each day, and in some cases, even fewer, i.e., 4/5 [91].

2.2. QT- Dataset:

The QT-Database from Physionet comprises electrocardiograms that were rigorously chosen to highlight a broad range of QRS and ST-T morphologies. The recordings were typically obtained from pre-existing electrogram datasets. The database includes information gathered from Holter recordings of patients who died unexpectedly during the recordings, as well as age and gender [92, 93]. The data consists of extensive recorded collections of varied and meticulously characterized data,

supplemented by reference annotations that precisely provide ECG waveform boundary positions. In each recording, between 30 and 100 typical beats were carefully annotated by expert cardiologists. meticulously identifying critical points including the beginning and the end of the P-wave, the QRS-complex, and the T-wave [92, 93].

The QT-Dataset contains 15 minutes of ECG signal records obtained from 105 people using 2-lead ECGs, which have been carefully chosen to reduce the influence of baseline wander or other artifacts. All records were made at a sampling rate of 250 hertz. [92, 93]. Notably, this database served as the pivotal training dataset for the segmentation model employed in the present study.

2.3. Properties of a computing station:

In the present work, we employed MATLAB R2019b software for the simulation. This last was executed on an advanced computing system that featured an AMD Ryzen Threadripper 1950X 16-Core Processor, 16 GB RAM, and NVIDIA GeForce GTX 1080 GPU. It is a member of AMD's Threadripper series of processors, which are designed to deliver unparalleled processing power and performance. The CPU has 16 cores and 32 threads, enabling it to multitask and run resource-intensive tasks at the same time. Additionally, it has a base clock frequency of 3.4 GHz and a turbo frequency of 4.0 GHz.

3. Methodology:

Figure II-3 depicts the methodology followed to estimate the blood glucose monitoring using ECG data. It shows that ECG data will travel through several phases such as the preprocessing step, segmentation step, and characterization step. These serve to provide us with the required ECG features to estimate the BGC using the two approaches.

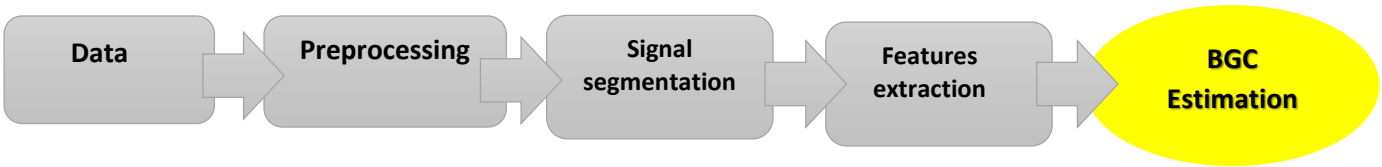


Figure II- 3: ECG processing

3.1. ECG signal preprocessing:

The preprocessing stage is critical in ensuring the precision and suitability of the signals for subsequent analyses, thereby improving the accuracy of the outcomes. The electrocardiogram signal is acquired as a series of amplitudes referenced to a baseline signal. Each wave of the ECG is specified by its frequency spectrum, whereas the QRS spectrum is typified by a central frequency range of 10-25 Hz. Furthermore, the P-wave and T-wave have frequencies below 20 Hz.

The waveform segmentation algorithm was trained using the highly precise filtered ECG signals available in Physionet's QT dataset. Conversely, the D1namo database was gathered under real-world. Given the existence of diverse sources of noise, including electrode displacement and motion artifacts induced by the participant, the ECG signals obtained encompass supplementary noise that can impair the precision of the segmentation phase, the retrieved ECG parameters, and the estimated BG values. As a result, extensive signal cleansing and conditioning are imperative to achieve accurate segmentation. The preprocessing stage adopted in our work consists of the following steps:

- After applying the FFT (Fast Fourier Transform) to the ECG signal, a band-pass filter with a pass-band frequency range of [0.5 Hz, 40 Hz] was constructed. The primary aim of this filer was to effectively eliminate wandering lines and high frequencies. As illustrated in **Figure II-4**.
- During our research, we intentionally chose only the signal segments that were considered clean and free of any distortions or interferences, with the ultimate aim of achieving exceptional levels of precision and accuracy during the segmentation process. Sections of the ECG signal that are distorted by noise caused by electrode movement and other motion-related activities are systematically removed and disregarded.

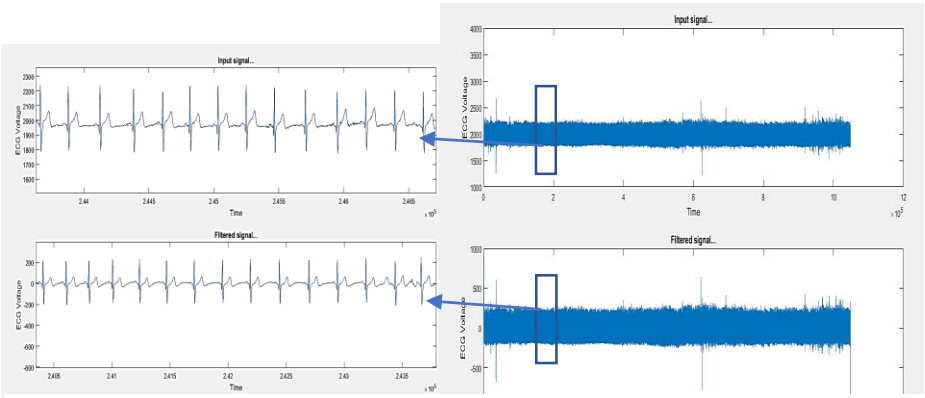


Figure II- 4: Filtered portion of ECG signal

3.2. ECG segmentation:

Following the preliminary phase, the next stage comprises automated waveform segmentation, which is done to guarantee an accurate characterization of the ECG's temporal parameters. ECG segmentation is a crucial phase of signal processing that involves identifying and isolating different segments of the ECG waveforms, such as T-wave, P-wave, and QRS complex.

The main difficulty associated with ECG segmentation is that ECG waves vary significantly. They can differ in terms of morphology, amplitude, duration, and frequency. These discrepancies result from differences in patients, surveillance devices, ECG lead location, etc. Therefore, an automated technique that can handle these changes is highly required to achieve high accuracy. In previous years, numerous studies have been conducted to develop accurate and reliable ECG segmentation algorithms. One of the most commonly used algorithms is the Pan-Tompkins algorithm [94], which is designed to detect the QRS complex. Unfortunately, it has difficulties in identifying the beginning and offset of the P-wave and T-wave. To overcome these limitations, researchers have proposed various methods

Among the recent advances in segmentation algorithms, one particular algorithm utilizing the discrete wavelet transform [95] exhibited an impeccable sensitivity of 99.84% with a 99.92% positive prediction value in detecting the QRS complex’s onset and offset. A unique approach based on the Phasor transform [96] was revealed for T-wave segmentation. Peaks, onset, and offset of the T-wave have been detected with a sensitivity of 97.78%, 97.81%, and 95.43%. Furthermore, another technique based on Multi-scale Morphological Derivate [97] showed remarkable sensitivities of 99.81%, 98.17%, and 99.56% during the detection of the P-wave's peak, start, and offset. Moreover, probabilistic approaches, such as Hidden Markov Models [98], have shown remarkable results since they are capable of assimilating factual data and adapting to particular conditions. Nevertheless, these approaches are frequently more sophisticated and need training [99].

The previously mentioned studies have been able to segment the beginning and the end of at least two ECG waves and characterized with extensive computational time. Other approaches based on deep learning have been lately employed to identify the onset and offset of the different ECG waves and segments at the same time. For a specific application, the Long Short Term Memory (LSTM) based framework with filtering kernels has been employed to segment ECG waves [100]. The results of these algorithms were significantly above conventional rule-based and HMM-based techniques,

proving deep learning's efficacy. The suggested technique expands on [100, 101], which proposes a ConvLSTM neural network architecture for segmenting ECG waveforms.

The Deep Recurrent Convolutional Neural Networks (DRCNN) adopted in this work enable the automated annotation of various electrocardiogram waveforms. A Long/Short Term Memory (LSTM) network employed in the training of DRCNN can preserve lengthy temporal dependencies [102] and overcome the issue of vanishing or inflating gradients that a vanilla RNN has. This occurs when, over a relatively short period, the derivative component of the error concerning weights tends to be null or infinite [103]. The used DRCNN architecture is as follows:

- set parameter sequence input layer of 40 input features to the number of frequencies.
- define an L&STM layer with the "Sequence" output mode to provide a classification for each sample of the signal. Use 200 hidden nodes for optimal performance.
- define the parameters of the connected layer with an output size of 4 corresponding to four-wave classes (P wave, QRS wave, T wave, and indefinite wave (transition between waves)).
- Add SoftMax layer and classification layer parameters to generate estimated labels.

Our technique has been enhanced with a temporal frequency analysis, which is implemented using the Fourier Synchro-Squeezed Transform (FSST), to properly reflect the non-stationary aspect of ECG signals. This sophisticated function computes frequency spectra for each signal sample and then classifies the relevant data of the converting result. To enable full and precise analysis, the FSST's real and imaginary aspects are processed independently before being incorporated into neural.

The accuracy metric has been assigned as the main performance indicator in our research for evaluating the efficacy of the CNN Algorithm. It is determined as follows:

$$\boldsymbol{Accuracy = TP + \frac{TN}{TP} + TN + FP + FN} \ \boldsymbol{\ldots\ldots\ldots\ldots} \ \textbf{(1)}$$

where TP is True Positive, TN is True Negative, FP is False Positive, and FN is False Negative.

Combining CNN and LSTM (convLSTM) allows us to use the FSST approach, which effectively reduces noise while also creating additional characteristics given a superior outcome as shown in **Figure II-5**. This approach improved the algorithm’s accuracy rate to 94 %, as illustrated in **Figure**

II-6, outperforming the previous version of the method available in MATLAB Toolbox, which had an accuracy of 91%.

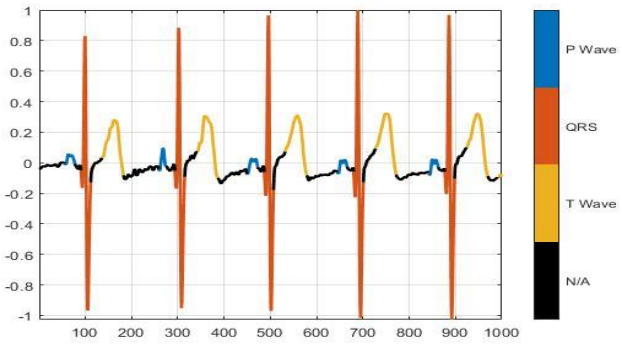
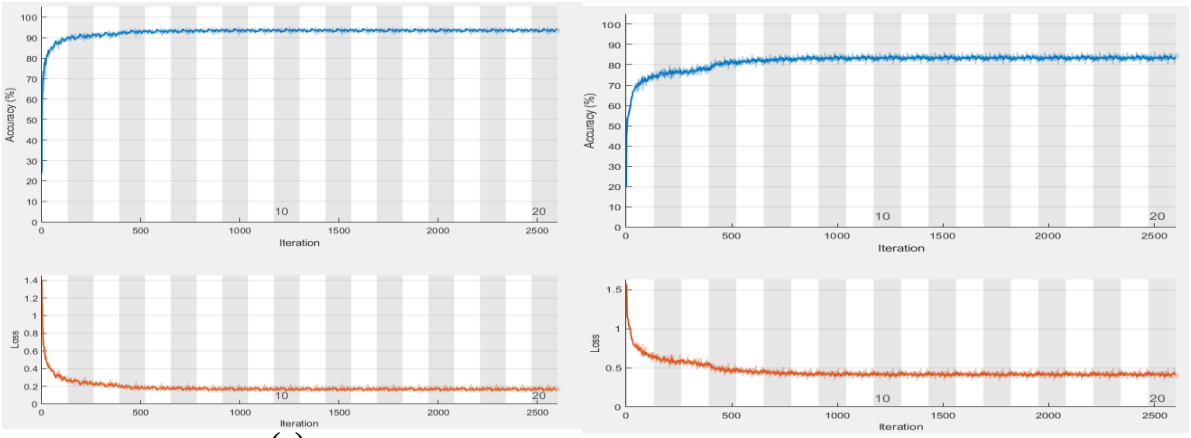


Figure II- 5: results segmentation for 1000 samples with standardization



(a) (b)

Figure II- 6: training accuracy and loss. (a) using FSST. (b) without using FSST

3.3. Characterization:

According to chapter (1), an ECG signal is a diagnostic tool that monitors the electrical impulses of the heart. The ECG waveform is comprised of a diverse array of waves, each with its own shape and time interval. These nuances are critical in determining the complexities of heart function [46]. The fundamental ECG waves used in our approach are:

- **The P-wave:** symbolizes the depolarization process of the atria, which is synonymous with the top heart chambers' contraction. This wave manifests as a little upward deviation and serves as a warning indicator of atrial depolarization.
- **The QRS complex:** is symbolic of the depolarization of the ventricles, which corresponds to the contraction of the lower heart chambers. This intricate event is characterized by three waves, namely Q, R, and S. The ventricular depolarization occurs around 160 ms after the onset of the P wave.
- **The T-wave:** the T wave represents the repolarization of the ventricles, indicating the crucial recovery phase of the heart after contraction.

In addition to the aforementioned waves, a plethora of other intervals can be discerned in an ECG signal. Such as the PR interval, which signifies the segment between the onset of the P-wave and the onset of the R-wave. Similarly, the ST segment denotes the temporal interval between the end of the QRS complex and the start of the T-wave. Another important integral component of an ECG signal is the QT interval, which indicates the time interval between the beginning and the end of the complex QRS [46].

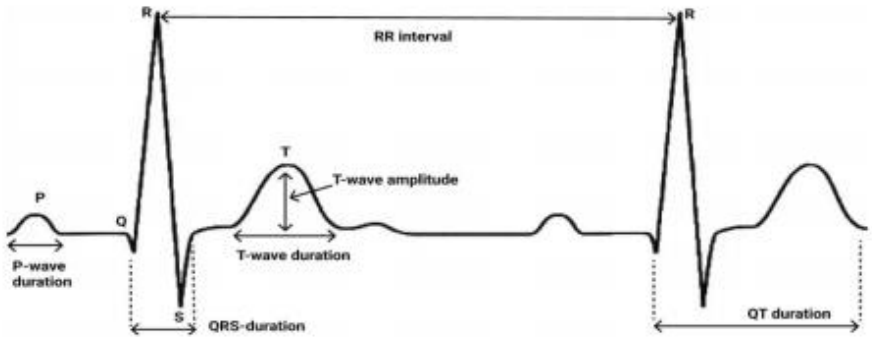


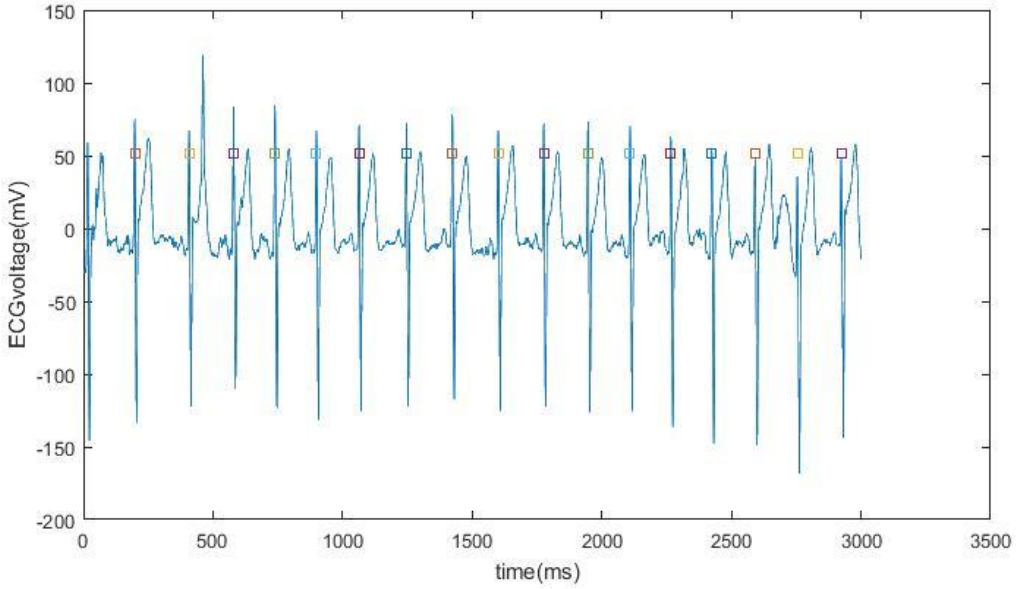
Figure II- 7: Typical ECG graph containing the different features used in this work

.

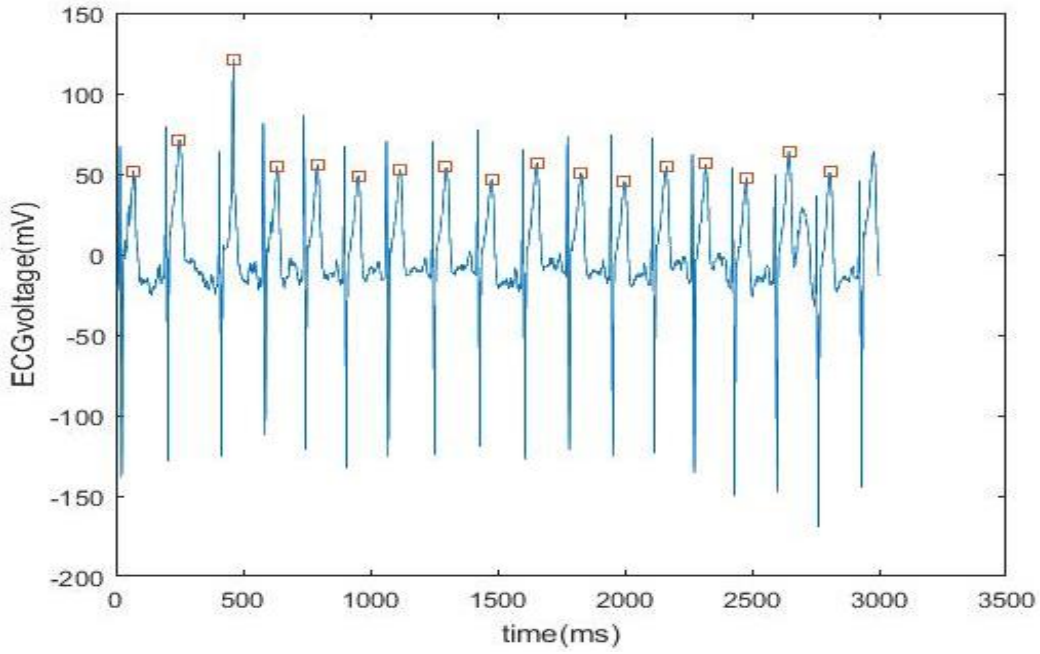
To calculate the BGC, the models were fed a set of ECG characteristics, including the P wave, T wave, QRS durations, T amplitudes, Heart Rate (HR), and corrected QT interval. **Figure II-7** depicts a comprehensive description of these characteristics.

The process of characterizing and determining these features was conducted in an automated manner, and executed as follows:

Following the segmentation and classification of the ECG signal, the P-wave, T-wave, QT, QRS intervals, and QTc were retrieved in a fully automated manner. Further, the QTc was derived by utilizing the Bazett formula[104], as illustrated below:



(a)



(b)

Figure II- 8: Recognizing: (a) RR peaks, (b) the amplitude of T-wave.

$$QTc = \frac{QT}{\sqrt{HR}} \text{ ..... (2)}$$

The identification of R peaks was accomplished through the utilization of the MATLAB® function known as *find-peaks*, the graphical output of which is illustrated in **Figure II-8(a)**. After this step, the RR intervals were computed by determining the precise spatial distance between each R peak. The HR then, was determined by reversing the RR interval value as shown below:

$$HR(bpm) = \frac{60}{RR(interval)} \text{ ..... (3)}$$

Similar to heart rate assessment methods, we used MATLAB's *find-peaks* function to determine T-wave amplitude. With a rigorous and well-defined approach focused on precision and accuracy, we were able to retrieve the T-wave amplitude data for each cardiac cycle, as illustrated in **Figure II-8(b).**

To reduce the error's probability, a meticulous visual confirmation process was carried out, whereby the peaks of both the T-waves and R-waves were checked and validated for each window.

3.4. Blood glucose estimation:

As far as our comprehension extends, a technique for computing the BG value through electrocardiogram characteristics remains non-existent. To address this lacuna, two different methodologies were employed in our work.

3.4.1. *First approach:*

Within the context of patents published in 2006 and 2010, authored by Mark W. Kroll,[105, 106] original technique was introduced that leverages the use of intracardiac signal (iECG) remotely relayed from a pacemaker placed in a T1DM patient to monitor blood glucose levels. Diverse characteristics of the intracardiac signal (T-wave amplitude, corrected QT ($QTc_{(delta)}$)) were collected and then integrated into a mathematical formula, Eq 4, to determine the BGC.

$$Blood\ Glucose\ Concentration = A - B * QT_{c(delta)} - C * T_{wave\ amplitude\ fraction} \text{ ..... (4)}$$

Where:

- $T_{wave\ amplitude\ fraction}$ is calculated by subtracting the baseline value from the $T_{wave\ amplitude}$.
- A, B, and C are predefined constants or coefficients of calibration for a specific individual.

Mark W. Kroll's formula was originally validated utilizing a limited dataset consisting of five intracardiac signal samples collected from a single patient [106]. Based on this, our work advances the research by demonstrating the efficacy of utilizing surface ECG signal features to validate the previously established equation. Moreover, through the application of this equation, we further proposed an additional formulation, Eq 5, which serves to better understand the dynamic interplay between HR and BGC fluctuations, specifically in the context of hyper- and hypoglycemic episodes.

$$Blood\ Glucose\ Concentration = A - B * QT_{c(delta)} - C * \frac{T_{wave\ amplitude\ fraction}}{HR} \quad \textbf{.....(5)}$$

We will test the feasibility of the aforementioned equations using a thorough equation-solving procedure to compute the values of A, B, and C. After calculating these coefficients, we will use them to calculate the BGC of the remaining dataset samples.

From the D1namo collection, we were able to treat the electrocardiogram signals of four diabetic patients (details present in **Table II-1)**, over numerous days. The signals of the other individuals were removed since some of them acquired their ECGs at a separate time than they recorded their BGCs. Some did not correctly wear their electrocardiography belt. The two equations were validated by four patients, each of whom underwent many days of readings, for a total of 1600 samples.

Table II- 1: The description of the dataset used in the first approach

	AGE	**GENDER**	**HEIGHT(CM)**	**WEIGHT (KG)**	**BG RANGE**
PATIENT2	20-29	Man(male)	170-179	60-69	7-11.5
PATIENT7	30-39	Women	160-169	70-79	5-15
PATIENT8	60-69	women	150-159	50-59	2-5
PATIENT6	30-39	Man	190-199	70-79	11-15

The performance metrics employed to evaluate our findings and our system are:

- Mean Absolute Error (MAE) for calculating the disparity between the Real BG (RBG) and Calculated BG (CBG),
- Mean Squared Error (MSE) for depicting the system's behavior employed in estimating Blood Glucose Concentration.

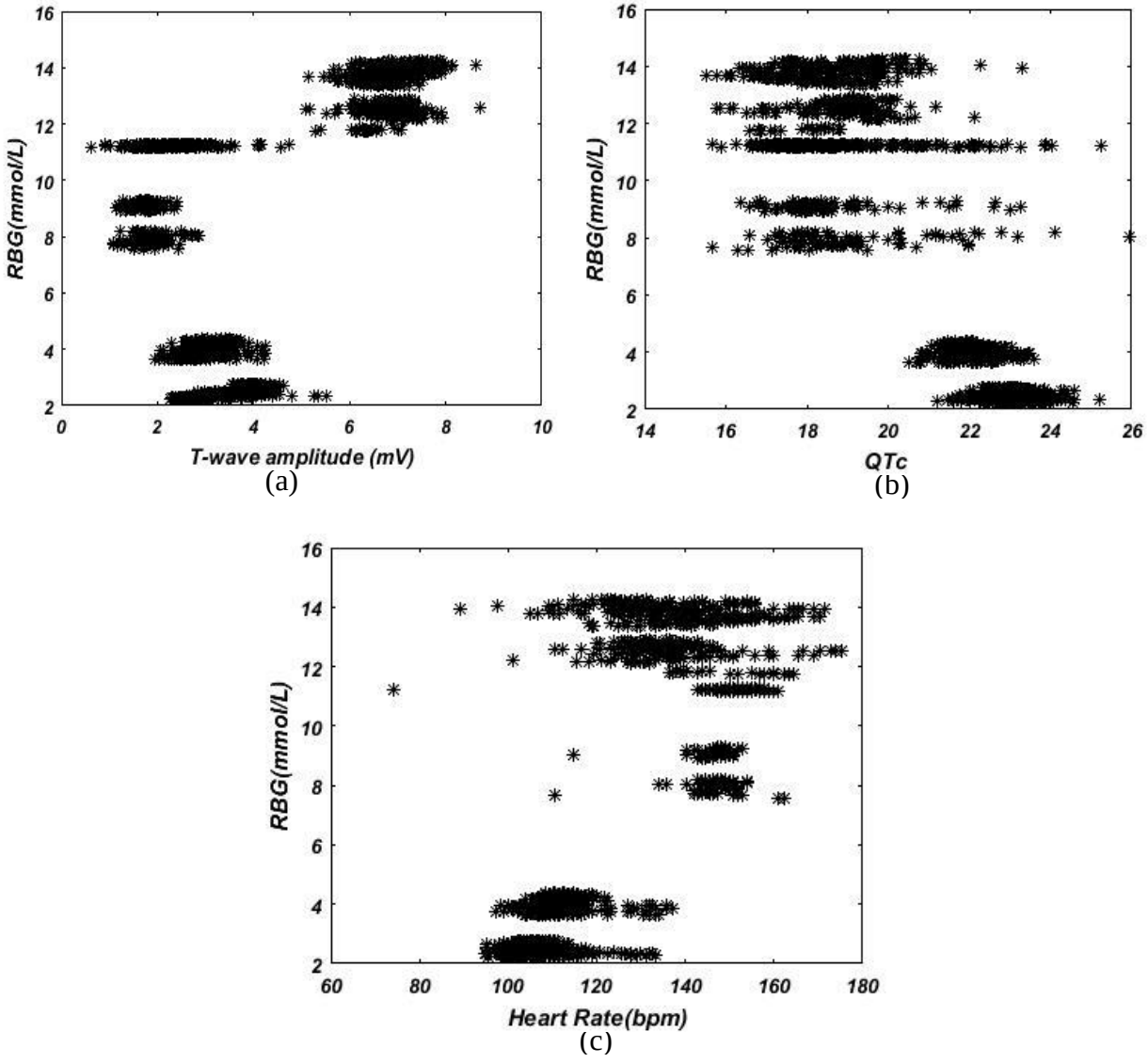


Figure II- 9: Distribution of BGC according to (a) T-wave amplitude, (b) QTc, and (c) Heart Rate.

The method utilized in computing these metrics is delineated as follows:

$$MAE = \frac{1}{N} \sum_{t=1}^{N} |y_i - \hat{y}_i| \text{ ..... } \mathbf{(6)}$$

$$MSE = \frac{1}{N}\sum_{t=1}^{N}(y_i - \hat{y}_i) \text{ ..... (7)}$$

The real BGC of a specific sample *i* is represented by y_i, while the computed BGC is denoted as $\hat{y}$i, with N, indicates the total number of BGC samples employed in the analysis.

Throughout our investigation, we calibrate the predefined coefficients A, B, and C for each patient. These parameters were updated whenever a significant change in blood glucose levels occurred. **Figure II-9** depicts the distribution of blood glucose concentration concerning QTc, HR, and $T_{wave\ amplitude}$.

According to the findings, there is a relationship between changes in blood glucose concentration and variations in QTc, T-wave amplitude, and HR. **Figure II-9 (b)** demonstrates the existence of an inverse relationship between blood glucose concentration and QTc. These results have been supported by numerous other studies [26, 107].

Figure II-9 (a) depicts the dispersion of RBG levels with T-wave amplitude. As mentioned earlier [24, 79, 85, 108], our findings demonstrate a proportional correlation between changes in blood glucose levels and T-wave amplitude during normoglycemia and hyperglycemia events. Nevertheless, during hypoglycemia (3.9 mmol/L), we observed an inverse correlation between blood glucose and T-wave amplitude (data from patient three). This suggests that patient 04 has a significantly higher average T-wave amplitude for heartbeats with low BG levels compared to those with normal BG levels. These results are consistent with those reported by Michal Porumb [24]. Our hypothesis implies that a variation in T-wave shape can be influenced by a variety of interpersonal factors. Firstly, it is important to note that the data was gathered from real-life settings in which hypoglycemia episodes occurred throughout diurnal hours. In contrast to nocturnal hypoglycemia, the diurnal variant may be subject to a plethora of hormonal counter-regulation components [109]. Additionally, various factors, including meals [110, 111], physical activity [110, 112], or drugs [111], have the potential to influence T-wave amplitude shape. Recent research has shown that a drop in T-wave amplitude is typically detected within thirty minutes after eating [110, 111]. Similarly, consistent T-wave amplitude alterations were observed during exercise [112]. Additionally, low potassium levels have been linked to T-wave flattening. As a result, more research may be needed to determine any simultaneous drops in potassium levels with natural glucose declines [79], while considering meal consumption, physical activity, medications, and cardiovascular disease.

Moreover, in **Figure II-9 (c)**, a substantial rise in heart rate was seen in parallel with an increase in BGC within the hyperglycemia range. Yet, the rate of increase was slower under the hypoglycemia clamp compared to the euglycemia clamp, which is consistent with previous research [81].

The results obtained for each patient utilizing the 02 formulas are displayed in **Table II-2**. Furthermore, **Figure II-10** depicts a visual representation of each patient's various blood glucose profiles, which include both the RBG and the CBG using the two mathematical formulas. Notably, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended a specific threshold to differentiate between the various blood glucose ranges, including hypoglycemia, hyperglycemia, and euglycemia [113].

- Hypoglycemia: glycemic below 3.9 mmol/l (below 70 mg/dl)
- Hyperglycemia: glycemic above 10 mmol/l (above 180 mg/dl)
- Euglycemia: glycemic ranging between 3.9-10 mmol/l (70-180 mg/dl).

Table II- 2: MAE and MSE according to the different glycemic

	Patient 1		**Patient 2**		**Patent 3**		**Patient 4**	
	Eq. (1)	**Eq. (2)**	**Eq. (1)**	**Eq. (2)**	**Eq. (1)**	**Eq. (2)**	**Eq. (1)**	**Eq. (2)**
MAE	0.2522	0.2784	0.3502	0.2608	0.1486	0.1423	0.0788	0.0797
MSE	0.1066	0.1358	0.2409	0.1085	0.0447	0.0397	0.0110	0.0112

The obtained mean absolute error (MAE) varies between patients. We observe that equation 1 yielded the greatest MAE of 0.3502. Utilizing the same formula, the lowest MAE (0.0788) was also obtained. These variations might be due to inaccurate retrieval of ECG components or inherent patient factors.

The introduction of heart rate to the calculation has some influence on the findings. It lowers the MAE to a desired 0.0063 in hypoglycemia. Conversely, it has a negative influence on hyperglycemia, lowering the MAE value by 0.0262. Among the fourth group of patients, patient 04, whose glucose profile comprises normoglycemia and hyperglycemia, has the best results with MAE values of 0.0788 and 0.0797 and MSE values of 0.0110 and 0.0112, respectively using Eq (1) and Eq (2).

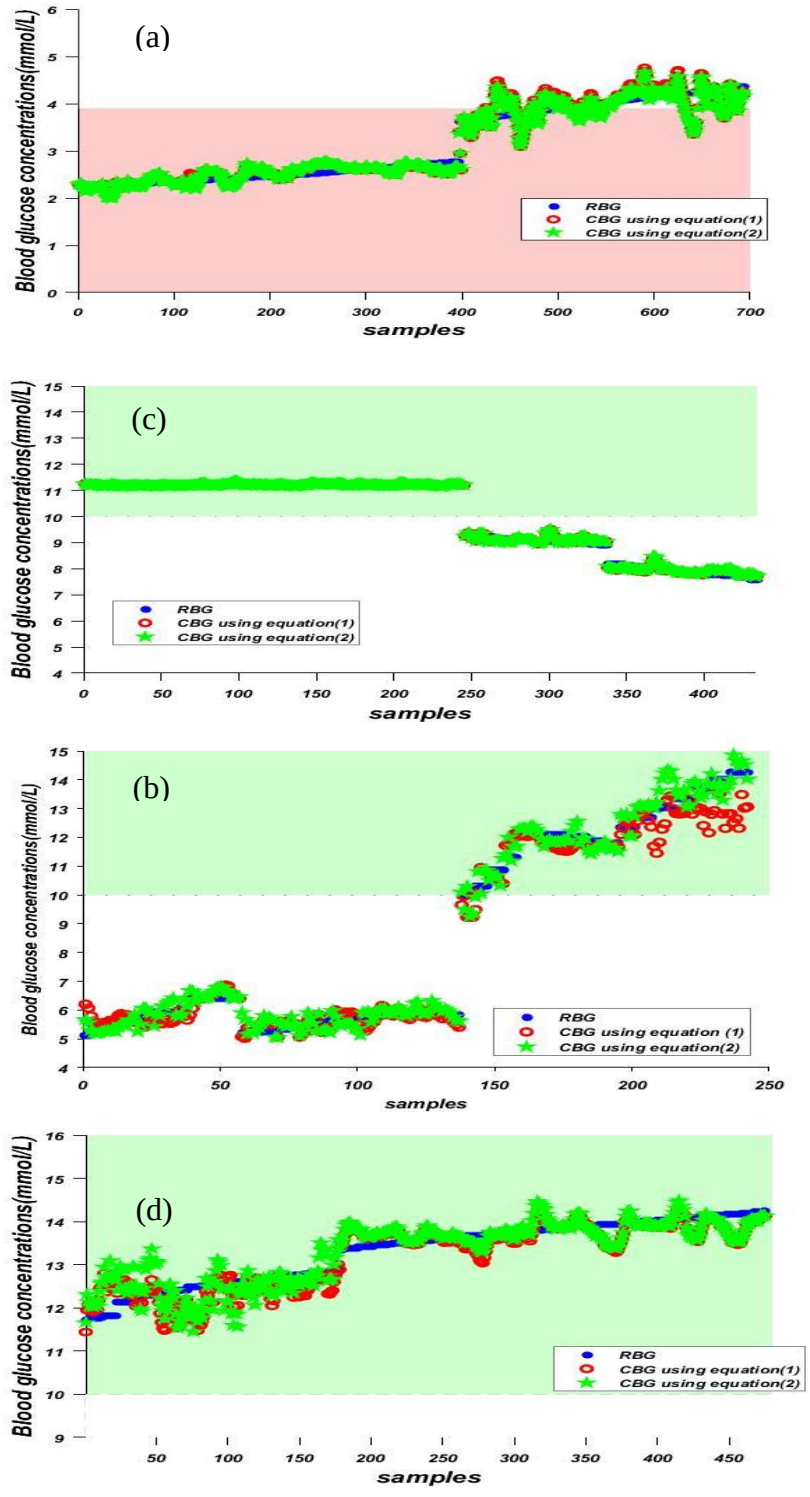


Figure II- 10: The evolution of real blood glucose and calculated blood glucose utilizing three equations for: a) patient (1), b) patient (2), c) patient (3), and d) patient (4).

To present the results more clearly, **Figure II-11** depicts the BG profiles of all patients in comparison to the estimated BG values using the two mathematical equations. Equation 1 provides an MAE of 0.0539 and an MSE of 0.1604 when all data is used. The MAE for Equation 2 was 0.0602, while the MSE was 0.1657.

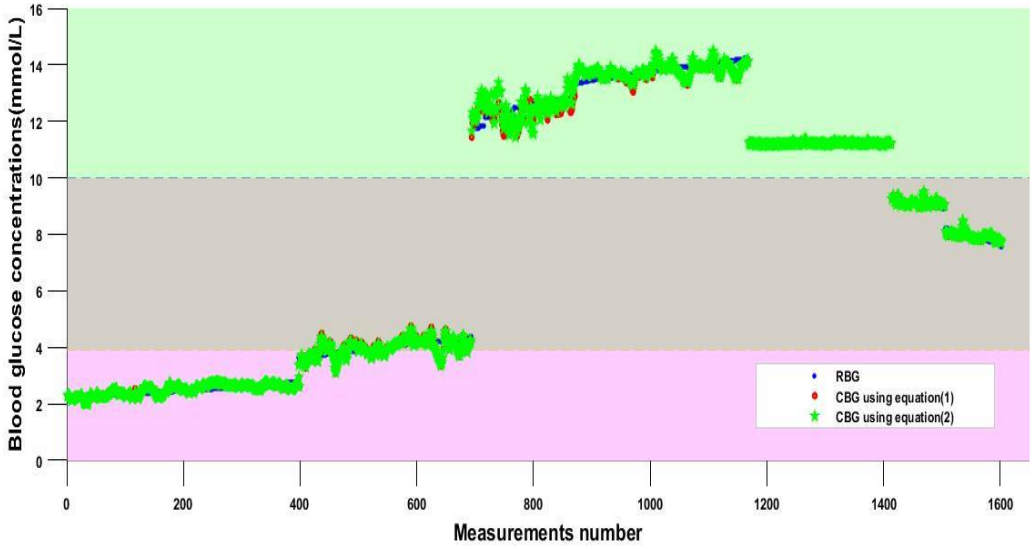


Figure II- 11: The evolution of RBG and CBG using Eq.1 and Eq.2 of all patients' BG profiles.

The Equations 1 and 2 results are used to demonstrate the linear correlation between BGC and ECG parameters. To demonstrate this, we show the distribution of real blood glucose versus calculated blood glucose using the aforementioned formulae. **Figure II-12** illustrates the curve fitting, which demonstrates a strong linearity between RBG and CBG. Equations 1 and 2 were used to fit the CBG to the RBG, yielding RMSEs of 0.23 and 0.24, respectively.

We demonstrated and confirmed the feasibility of Eq.1, which is based on ECG characteristics rather than iECG, for calculating BGC. Equation 2 was designed to help us better understand the relationship between changes in BGC and heart rate (HR). To sum up, our work proposes the prospective utilization of ECG features to determine blood glucose concentration. Furthermore, we validated the linear correlation between blood glucose concentration and ECG parameters which may introduce novel avenues for physiological modeling. Additionally, the findings indicate the possibility of deploying electrocardiography as a non-invasive wearable device for continuous blood glucose monitoring.

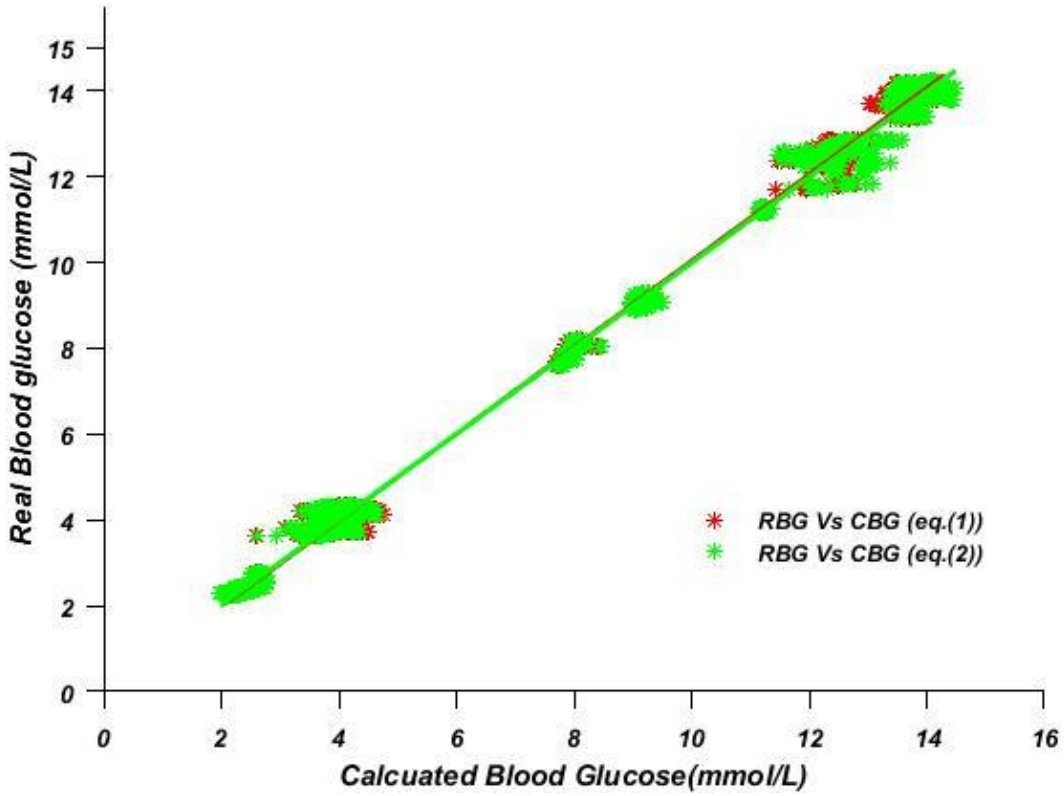


Figure II- 12: RBG Vs CBG.

3.4.2. ***Second approach:***

Through the first method, we successfully obtained the BG value for 04 patients over numerous days of measurements, utilizing ECG parameters with minimal error. Nevertheless, it should be noted that this method necessitates calibration each time there is a remarkable change in the BGC range. Despite this limitation, the results achieved are quite satisfactory, making the method very promising. In the second method, we aim to leverage the advancements in ML to estimate Blood Glucose Concentration values based on ECG parameters utilizing, specifically an artificial neural network. By doing so, we hope to overcome the calibration issues noted with the use of mathematical equations in the first approach.

A variety of regression and classifier techniques have been used by several researchers to forecast hypoglycemia and hyperglycemia episodes. In this work, however, regression models are applied to directly estimate the BGC value. The regression models used as input for the regression models the

sixth features collected from the characterization stage, which are T-wave amplitude, corrected QT, heart rate, and T-wave, QRS, and P-wave durations. The present study explored a variety of regression models, including Nonlinear Regression, Linear Regression, Ensemble, tree, and Gaussian Process Regression (Exponential GPR),

We trained and tested data regression models utilizing data of 03 T1DM patients from the D1namo dataset, for an overall duration of eight days: one patient across two days, and the other two patients over three days. There were 3394 samples in all. The allocation of the data for training and testing is presented in **Table II-3.** A split of two-thirds of the data was designated for training purposes, while the remaining one-third was aside for testing

Table II- 3: training and testing data.

	PATIENT 1	**PATIENT 2**	**PATIENT 3**
TRAINING/TEST	1006/503	309/154	948/474

performance metrics were applied to evaluate the regression models, which were included in the first experiment:

- Root Mean Squared Error (RMSE): This metric measures the square root of the variance of residuals and reflects the proximity of the estimated BG values to the real values.
- R-Squared (R2): This statistical metric, also known as the coefficient of determination, evaluates how close the EBG values are to the fitted regression line.

The difference between estimated and real BGC values was indicated using Mean Absolute Error (MAE) in the second experiment. The formulations for these widely used performance metrics are:

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(y_i - \hat{y}_i)} \quad \textbf{..... (8)}$$

$$R^2 = 1 - \frac{RSS}{TSS} \quad \textbf{..... (9)}$$

With:

$$RSS = \sum_{i=1}^{n}(y_i - \hat{y}_i)^2 \quad \textbf{..... (10)}$$

$$TSS = \sum_{i=1}^{n}(y_i - \bar{y}_i)^2 \text{ ……..… (11)}$$

$$MAE = \frac{1}{N}\sum_{i=1}^{N}|y_i - \hat{y}_i| \text{ …… (12)}$$

The RBG value of sample *i* is denoted by y_i , while the corresponding EBG value is represented by $\hat{y}_i$. The total number of test samples used in the regression models is denoted by N.

We trained and tested the data collected from each patient separately across all days. **Table II-4** summarizes the results of the first experiment.

Table II- 4: Model performances (Experiment 1)

Model	Patient 1		Patient 2		Patient 3	
	RMSE	R^2(%)	RMSE	R^2(%)	RMSE	R^2(%)
Linear regression	0.96	88.57	0.56	63.85	0.68	69.9
Exponential GPR	**0.32**	**98.14**	**0.41**	**80.01**	**0.67**	**70.22**
Ensemble (Bagged trees)	0.78	92.53	0.55	62.52	0.75	63.39
Tree (Medium tree)/	0.79	92.29	0.63	54.33	0.71	67.01
Nonlinear regression	0.85	5.78	0.77	32	1.14	13.86

Upon comparison of the results obtained from the various regression models, it was found that the nonlinear regression model exhibited the worst performance. On the other hand, the Exponential GPR model outperformed all other simulated models, with RMSE values of 0.32, 0.41, and 0.67, and R-squared values of 98%, 80%, and 70% for patients 01, 02, and 03, respectively.

In the second experiment, a mixed dataset was used as input to our regression models. It comprises samples from all patients and was utilized to gain a better comprehension of the nature of the relationship between the blood glucose concentration changes and ECG signal. The same data division method was employed, to validate the suggested methodology, with 2263/1131 samples used for training/testing. The difference between estimated and real BGC values was evaluated via Mean Absolute Error (MAE). **Table II-5** summarizes the acquired results

Table II- 5: Model performances (Experiment 2)

Models	**Linear regression**	**Exponential GPR**	**Ensemble (Bagged trees)**	**Tree (Medium tree)/**	**Non-linear regression**
RMSE	0.65	0.62	0.78	0.68	4
R^2(%)	97.44	97.73	96.38	97.23	4.88
MAE	0.52	0.46	0.61	0.55	3.61

According to the findings of the second experiment, we can conclude that increasing the amount of data utilized for training leads to improved performance. **Table II-5** shows that all models yield high R-squared values, except for the nonlinear regression model which has a near-zero R-squared value. Particularly, with an RMSE of 0.62, an R-squared value of 98%, and an MAE of 0.46, Exponential GPR yields the best results. This implies that nearly 98% of the variance in blood glucose concentration can be explicated by the electrocardiogram features employed as inputs in the used model. We may also see that the linear regression closely approximates the outcomes of the exponential GPR.

Consequently, we can deduce that intra-individual variations do not impact the relationship between the BG level and ECG features. Furthermore, in both studies, the nature of this relation can be described as linear, where the non-linear regression model consistently produces suboptimal results.

To facilitate the visualization of the findings, we provide a comparison between the real and the estimated BGC obtained using linear regression and Exponential GPR. **Figure II-13** illustrates that The BG value has been estimated with minimal error in the euglycemia clamp. Conversely, some errors are noticeable in the hypoglycemia and hyperglycemia clamps. These errors could potentially contribute to the high sensitivity observed between changes in blood glucose values and alterations in the morphology of ECG signals.

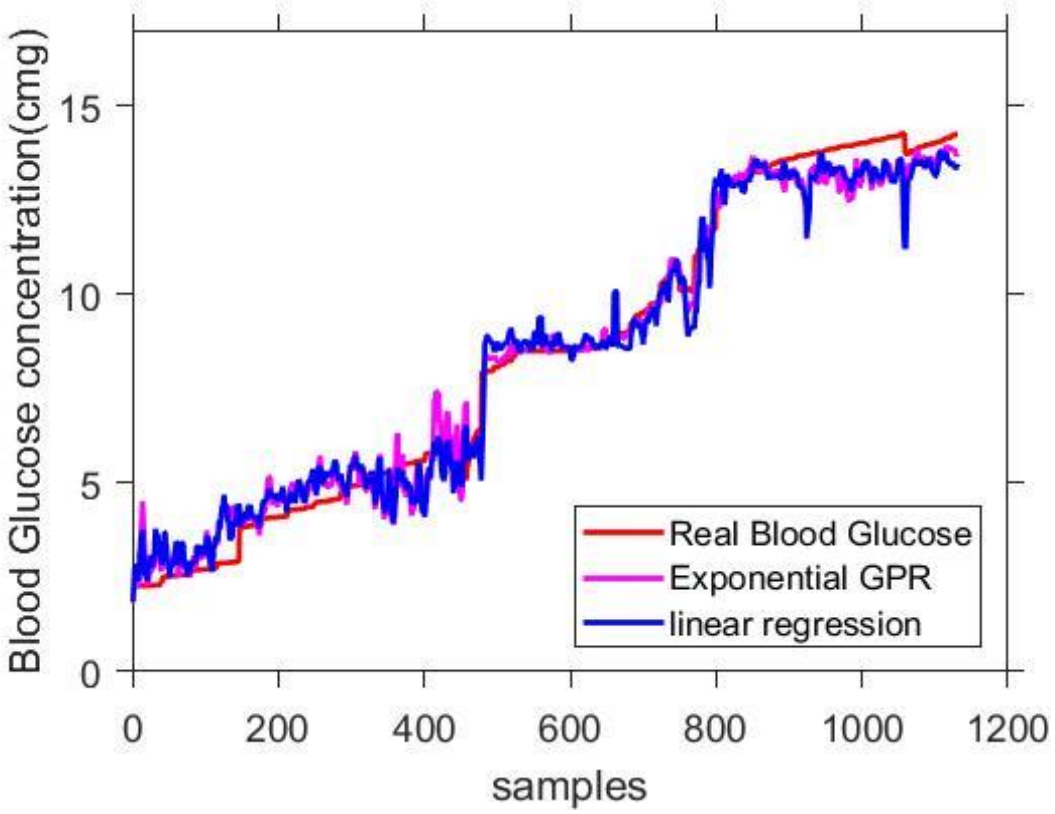


Figure II- 13: The evolution of RBG and EBG using linear regression and Exponential GPR

Numerous studies have attempted and succeeded in the prediction of hypoglycemia and hyperglycemia occurrences using ECG features. Despite this, they were unable to determine blood glucose values directly using ECG features. In the second experiment, we presented an innovative approach that leverages the power of AI to make this estimation, thereby paving the way for the invention of a novel non-invasive method for blood glucose monitoring. While there exist alternative methods, they are fraught with limitations. For instance, electrochemical non-invasive (NI) sensors such as saliva analysis[114], ocular fluid (tear) analysis[115], and exhaled breath analysis[116], all of which are readily accessible, contain numerous proteins (in the case of saliva and tears) or breath biomarkers (in the case of exhaled breath), making accurate monitoring a challenge[117]. Similarly, continuous glucose monitoring (CGM) techniques exhibit a time lag from the actual blood glucose levels. Additionally, these techniques necessitate the use of biomaterials, which can provoke allergies. Furthermore, electromagnetic non-invasive monitoring techniques are typically applied over the skin, necessitating the use of a minimally invasive device [117].

Lastly, our pilot study must be viewed considering its limitations, which also constitute crucial recommendations for new research areas.

- The success of our approach to ECG-based blood glucose level estimation depends highly on the accuracy of the data preprocessing and feature extraction steps. This is because even minor errors in the ECG feature values can significantly affect the accuracy of BG value estimation. The D1namo dataset, which we have utilized in our approach, was recorded under real-life conditions that are subject to various factors that may affect the ECG signal recording. For instance, the electrode contact may become loose due to sweat or sensor displacement, while body movements can introduce extra noise into the ECG recording. Given the impact of these factors on the accuracy of ECG parameter extraction, it is crucial to implement an advanced preprocessing algorithm that can effectively filter out the noise and artifacts from the ECG signals. This is particularly important when utilizing convolutional neural networks (CNNs) for ECG segmentation, as the accuracy of the network's predictions is highly sensitive to the input data quality. Therefore, precise and careful preprocessing and feature extraction steps are necessary to ensure the high accuracy of ECG-based BGC estimation.
- ECG features' identification is extremely sensitive to ECG anomalies like significant changes in T-wave morphology. Since there is a link between the severity of electrolyte imbalance and changes in the ECG wave shape. Because of this, it is essential to undertake additional investigation must be conducted to determine whether other clinical problems that cause electrolyte imbalance should be considered in the proposed approach. Further tests should be completed on a wider population, comprising healthy subsets, and diabetic patients who may have additional clinical problems.
- To enhance the accuracy of ECG-based blood glucose level estimation, a multivariable trial could be conducted to explore the correlation between BG value and other electrocardiogram parameters, such as Tp-Te interval, PR interval, and ST segment. By increasing the input number of the regression systems, the impact of other clinical conditions on individual ECG features could be minimized, thereby providing a more comprehensive and robust set of data. As a result, the accuracy and reliability of the BGL estimation would be improved, and the possibility of misdiagnosis due to the influence of other clinical conditions would be minimized.

4. Conclusion:

The widespread availability of user wearable devices equipped with electrocardiogram (ECG) acquisition capabilities has made them increasingly accessible to the general public. These devices are cost-effective, non-intrusive, user-friendly, and durable, thereby rendering them ideal for integration into the artificial pancreas as wearable sensors for continual glucose monitoring. Considering this, numerous machine learning-based approaches and ECG feature extraction techniques have been employed to predict hypoglycemia and hyperglycemia events using diverse classifiers. However, none of these studies have attempted to estimate blood glucose concentration utilizing ECG features. In this work, we suggested a new approach for estimating blood glucose levels based on ECG features. Our regression models have yielded highly accurate blood glucose concentration estimations, with a precision of 98%. Our primary objective is to demonstrate the potential use of ECG wearable devices as a non-invasive device for continuous blood glucose monitoring.

The implementation of this method heralds a new epoch in the realm of real-time, wireless, and non-invasive blood glucose monitors. With the continuous advancements in the Internet of Medical Things (IoMT) technologies and intelligent processes, it is feasible to develop an affordable trend for an artificial pancreas using ECG devices.

Chapter

III. Model Predictive Controller

(Closed loop system)

1. Introduction:

The achievement of closed-loop glycemic control, and hence the automation of insulin administration, is highly required in the implementation of an AP system. The algorithm control is a set of decision rules depending mainly on the controlled blood glucose levels. Various control theory approaches have been employed in numerous attempts to design an appropriate control algorithm. This research began in the 1960s [118]. One such study resulted in the development of the Biostator [58, 119]. The first commercial artificial pancreas device, was initially designed for hospital usage and relied on intravenous glucose sensing [59]. These bulky devices proved the feasibility of external glucose controllers, laying the foundation for future technological advancements that ultimately expanded beyond the confines of intensive care units [8, 61, 120, 121]. This expansion was only made possible through the development of continuous glucose monitoring [60, 122].

After the aforementioned advances, a plethora of control algorithms have been suggested, ranging from traditional techniques such as Proportional-Integral-Derivative (PID) [27, 123, 124] to more sophisticated algorithms such as Model Predictive Control (MPC) [28, 125, 126] and adaptive control. Other control algorithms have also been applied, including the MD/Fuzzy logic algorithm [127, 128] and neural network algorithms [129]. Among them, the Model Predictive Controller has proven to be a very effective technique for improving postprandial glucose management. Yet, appropriate management algorithms are still required to maintain BGC within the prescribed range in a variety of scenarios.

This chapter aims to provide a comprehensive analysis of the control algorithms employed in the AP system, specifically the PID and MPC models. The study begins with a detailed descriptive comparison between these algorithms, highlighting their respective strengths and limitations. Subsequently, the implementation of the proposed approach control algorithm (Linear MPC) is described. Finally, the different results are presented, along with a discussion of the observed limitations. The chapter concludes with a concise summary of the findings.

2. Comparative study (MPC vs PID):

2.1. Proportional–integral–derivative control (PID):

The PID approach has been used to imitate B-cell insulin production (physiologic insulin delivery) [130]. It's a closed-loop algorithm control that reacts to fluctuations in glucose concentration after they happen. The controller continually regulates the Insulin Infusion Rate (IIR) based on three distinct components: the proportional component, which directly corresponds to the error term, the integral component, which aggregates the error, and the derivative component, which regulates the error's rate of change [130].

$$\boldsymbol{IIR = Kp\,(G - Gr) + Ki\,\int (G - Gr) + Kd\frac{dG}{dt}} \text{ ..... (13)}$$

In other term: $$\boldsymbol{PID(n) = P(n) + D(n) + I(n)} \text{..... (14)}$$

With:

$$\boldsymbol{D(n) = Kp.T_0.\frac{dSC(n)}{dt(n)}} \text{ ..... (15)}$$

$$\boldsymbol{I(n) = I_{(n-1)} + \frac{Kp}{T}[SC(n) - Target]} \text{ ..... (16)}$$

$$\boldsymbol{P(n) = Kp[SC(n) - Target]} \text{ ..... (17)}$$

- Component P plays a crucial role in enhancing insulin delivery when blood sugar levels exceed the target threshold while reducing insulin delivery when glycemic levels fall below the target threshold. However, when glucose levels are at the desired target range, this component remains ineffective and does not contribute to the basal threshold required to keep fasting BG levels at the target level.
- In contrast, Component I serves to regulate blood sugar levels when they are above or below the target range while maintaining a steady level of insulin delivery when BG levels are within the range. It is the only component that performs a similar function to basal insulin production.

- Lastly, Component D functions to promote insulin administration when BG levels increase and decrease insulin infusion when glucose levels decline, thereby stabilizing the system and mitigating glycemic fluctuations via an appropriate variation in insulin administration [123, 124, 130].

The utilization of the PID controller in subcutaneous systems poses a significant challenge due to the delays in insulin uptake, action, and BG sensing. These limitations make the postprandial BG control more challenging [8, 124, 131]. Despite these limitations, there have been numerous clinical and randomized investigations that have demonstrated the efficacy of the PID controller for the nocturnal management of hypoglycemic episodes [132]. Furthermore, considerable efforts have been made to enhance the robustness and effectiveness of the PID controller through various studies. The Minimized Hybrid Closed Loop (HCL) system has adopted this controller commercially, demonstrating its potential for widespread use in the future [133].

2.2. Model Predictive Controller:

Insulin delivery is often characterized by delayed insulin action peaks resulting from subcutaneous absorption. This has posed a significant challenge. To address this limitation, a novel approach known as the Model Predictive Controller has been developed. The MPC utilizes a sophisticated mathematical model, which utilizes the fundamental gluco-regulatory processes, to predict glucose dynamics [134, 135]. This enables it to effectively mitigate the time lags that are commonly associated with subcutaneous glucose sensing and insulin delivery. Thus, the MPC is an advanced technique to control plasma glucose concentrations, particularly postprandial glucose levels [27, 136]. It can easily incorporate meal information and insulin delivery constraints that reflect physical limitations and required performance. Additionally, its utilization allows for patient-specific parameters to be integrated, which is particularly effective for managing BG under different situations such as stress or physical activity [27, 134–136].

Generally, MPC does real-time dynamic optimization on a finite horizon. At each time step, a model is invoked to forecast the impact of both present and future input adjustments (insulin rate) on a desired output (BG level) [27]. To achieve this, the optimization process must minimize a cost function, using a plant evolution model (mathematical model). This

optimization process guarantees the tracking of a target glucose level, either as a setpoint or within a given zone [137]. Furthermore, the system's various parameters, including prediction horizon, control horizon, and weights, must be introduced and accurately calibrated [138, 139].

Several randomization studies have demonstrated that personalized MPC outperforms the PID control technique, achieving nearly 75% of the time within the target range, even in the case of an unannounced meal [140]. Furthermore, the personalized MPC algorithm integrated into Omnipod has shown remarkable performance enhancements [141]. Moreover, the multivariable structure of MPC allows for the incorporation of additional relevant signals[142].

3. Materials and methods:

3.1. Linear Model Predictive Controller (an overview):

Multiple MPC algorithm implementations exist, according to the objective function and model selected [125, 126, 137, 143, 144]. We utilized a linear model predictive controller (LMPC) law in our project. As described by Soru et al [145], LMPC employs a discrete linear model (plant) of insulin-glucose dynamics around equilibrium points (basal values). Consider the discrete-time linear model given below.

$$\begin{cases} X(k+1) = Ax(k) + Bu(k) + Ed(k) \\ y(k) = Cx(k) \end{cases} \quad \text{..... 18}$$

Where $x(k) \in R^n$ represents the state vector, $u(k) \in R^m$ represents the difference between administered insulin and its basal value, $d(k) \in R^l$ represents the meal vector, $y(k) \in R$ is the difference between the subcutaneous glucose and its basal value,

A (n*n), B(m*n), E(I*n), and C(1*n) denote matrices characterizing the process dynamics derived from the glucoregulatory system that will be detailed in the next section. N denotes the prediction horizon.

Considering the disturbances sequence:

$$D(k) = [d^T(k), d^T(k+1), \dots\dots\dots, d^T(k+N-1)]^T \text{..... (19)}$$

And an input sequence prediction:

$$U(k) = [u^T(k|k), u^T(k+1|k), \dots\dots\dots, u^T(k+N-1|k)]^T \text{..... (20)}$$

Beginning with the initial condition x(k|k) = x(k), the temporal progression of the state is generated by simulating the model (18) in a forward direction over N sampling time intervals. Consequently, the evolution of the state is produced as below:

$$X(k+1) = [x^T(k+1|k), x^T(k+2|k), \dots\dots\dots, x^T(k+N|k)]^T \text{..... (21)}$$

Given u(k+i|k) and x (k+i|k), i∈N, the input and state at time k+i predicted at time k. An optimization problem is used to determine the control input to be applied to the plant. This optimization is led by a predefined cost function to be minimized, for instance,

$$\text{J(X (k), U (.), k) } = \sum_{i=0}^{N-1} \|x(k+i|k) - x_{ref}(k+i)\|_Q^2 + \|u(k+i|k) - u_{ref}(k+i)\|_R^2 \text{.....}$$

(22)

X_{ref} (k) and u_{ref} (k) represent the states and inputs references at time k, respectively.

$$U_{ref}(k) = \left[u_{ref}^T(k), u_{ref}^T(k+1), \dots\dots\dots, u_{ref}^T(k+N-1)\right]^T \text{..... (23)}$$

$$X_{ref}(k) = \left[x_{ref}^T(k), x_{ref}^T(k+1), \dots\dots\dots, x_{ref}^T(k+N-1)\right]^T \text{..... (24)}$$

Note that Q and R are positive symmetric definite matrices.

The primary goal is to pick the optimum control sequence U* (k) that achieves the following:

$$U^*(k) = \arg \underbrace{min}_{U} J(\text{X(k), U(.), k}) \text{ ..... (25)}$$

$$\text{S.t} \begin{cases} X_{k+1} = Ax_k + Bu_k + Ed_k \dots\dots\dots\dots N-1 \\ y_k = CX_k \dots\dots\dots\dots N \end{cases}$$

Finally, upon the determination of the control input and following the receding horizon approach, only the initial item of the optimal control sequence is applied to the plant. It is

presented as $u^0(k)= u^*(k|k)$. The optimization process is then repeated at each sampling time k as presented in **Figure III-1.**

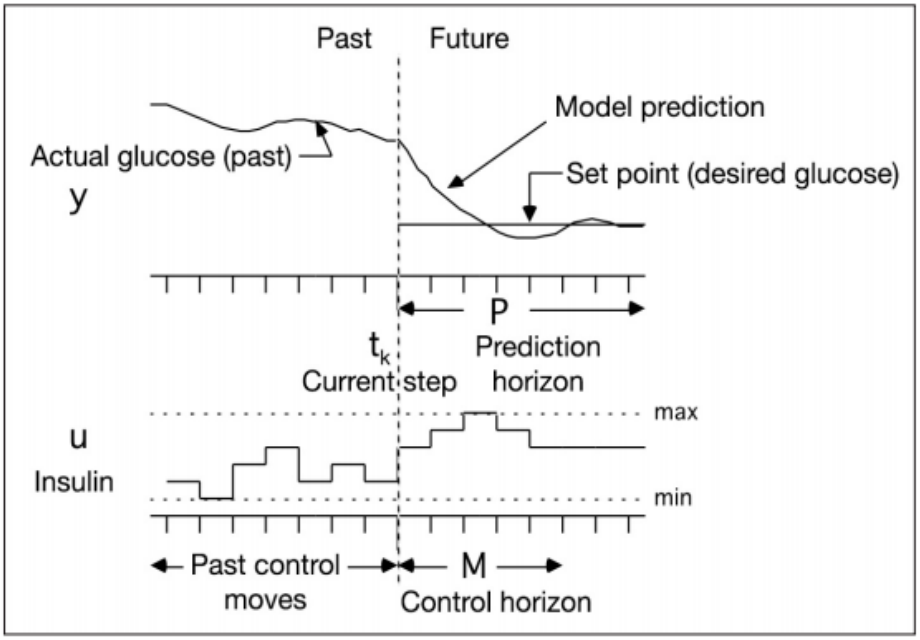


Figure III- 1: Fundamental concept of LMPC.

In the optimization problem, it is feasible to incorporate inequality constraints on input and state variables. The cost function given by (eq. 22) can be improved by associating a weight with the state prediction at the horizon N. Consider the quadratic cost function to accomplish this modification.

$$J(X(k),U(.),k) = \sum_{i=0}^{N-1} \left\| x(k+i|k) - x_{ref}(k+i) \right\|_Q^2 + \left\| u(k+i|k) - u_{ref}(k+i) \right\|_R^2 + \|x(k+N|k)\|_P^2 \text{..... (26)}$$

$$\text{S.t} \begin{cases} X_{k+1} = Ax_k + Bu_k + Ed_k \\ z_k = CX_k \end{cases}$$

Where P is the unique nonnegative solution of the discrete-time Riccati equation:

$$P(k) = Q + A^T P(k+1)A - A^T P(k+1)B * ((R + B^T P(k+1)B)^{-1} B^T P(k+1)A \text{ ..... (27)}$$

The matrix P ∈ R^{n*n} is the weight associated with the term x(k+N|k), representing the predicted state at the horizon N. P takes the cost over an infinite horizon. By considering the horizon N, the predicted state path of the system dynamics can be expressed as:

$$X(k+1) = AX(k) + BU(k) + ED(k) \text{ ..... (28)}$$

The matrices A ∈ R^{nN*n}, B ∈ $R^{nN*mN,}$ and E ∈ R^{nN*IN} are derived via algebraic calculations. according to the specific control application, D (k) may be known, estimated, or unknown. In the case of unknown disturbance, If the disturbance input is unknown, the MPC algorithm must be tuned in a robust way using the Q and R parameters of equation (26) to ensure that the control performance is suboptimal yet safe. Thus, the cost (26) can be expressed as:

$$J(X(k), U(.), k) = \|U(k)\|_H^2 + 2\left(X^T(k)F_x^T + D^T(k)F_D^T - U_{ref}^T(k)R - X_{ref}^T(k)F_{x_{ref}}^T\right)U(k) \text{ ..... (29)}$$

Only the terms reliant on U(k) have been maintained with:

$$H = B^TQB + R,\ F_x = B^TQA,\ F_D = B^TQE, \text{ and } F_{x_{ref}} = B^TQ \text{..... (30)}$$

$$Q = \text{diag}(Q,\ldots..Q) \in R^{nN*nN}, \text{ and } R = \text{diag}(R,\ldots.,R) \in R^{mN*mN} \text{..... (31)}$$

Under the assumption of non-singularity of the matrix H, if the optimization problem does not include input and state constraints, the solution exists, is unique, and can be explicitly expressed as:

$$U^0(k) = H^{-1}(-F_xX(k) - F_DD(k) + RU_{ref}(k) + F_{x_{ref}}X_{ref}(k)) \text{ ..... (32)}$$

In contrast, when constraints are applied to the input or state variables, must be solved online using a quadratic programming optimizer, which is the case of our utilized approach.

3.2. LMPC approach :

Absorption of glucose from a meal is known to be faster than the effect of infused insulin, which can lead to hyperglycemic events [146]. However, the Model Predictive Controller allows us to integrate meal consumption (size, number of carbohydrates) into the model and

consider it as an external disturbance. By adopting this strategy, better postprandial glucose control is ensured [136, 141, 145]. Furthermore, constraints are imposed on the input and the input rate of movement to ensure that insulin infusion volume and speed are controlled [145].

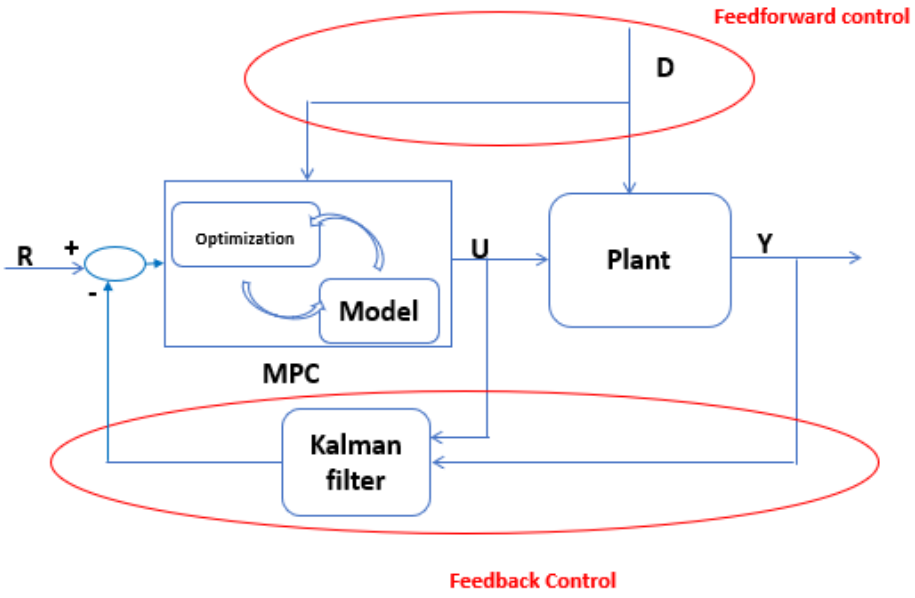


Figure III- 2: MPC basic structure

R, U, z, and D represent the reference value (desired glucose level), predicted amount of insulin (input control), measured interstitial glucose, and ingested meal, respectively. The utilized LMPC approach integrates both feedforward and feedback mechanisms as represented in **Figure III-2**.

Both of them are essential components that allow it to adapt to process variations, improving the system's reaction speed and robustness. Feedback is conventionally employed for tuning the dynamic behavior of the system, where the measured output (y) is utilized to enable the controller to respond to potential disturbances. On the other hand, feedforward is a system loop that transmits a known disturbance to the controller (ingested meal), enabling it to react rapidly while sustaining a more resilient measured output. Furthermore, the MPC model integrates Kalman Filters to forecast future glucose behavior according to prior insulin inputs. The

measured blood glucose level serves as feedback to correct the prediction, thereby enhancing the controller's performance [147, 148].

3.3. Glucoregulatory system (process) :

The glucoregulatory system is typically represented mathematically as a dynamic system. It is made up of four interconnected subsystems [149]. The first subsystem is concerned with the kinetics of insulin absorption, which involves the subcutaneous administration of insulin, followed by its assimilation into the bloodstream. The secondary subsystem is responsible for meal absorption, in which glucose is absorbed from the intestines and transported to the circulation. Both insulin uptake and meal-glucose assimilation from ingested carbohydrates have a significant impact on BG levels, representing plasma glucose kinetics. Furthermore, the interstitial glucose concentration represents delayed and noisy information in comparison to the plasma glucose concentration. This characteristic is observed in the interstitial glucose kinetics, and it's critical to take into account when analyzing glucose regulation in the body [149].

Various mathematical models that describe these four subsystems are proposed to be used in an AP system [150–154]. The most used ones are UVA/Pavoda and the Bergman minimal model. UVA/Pavoda is designed to simulate insulin secretion in response to changes in glucose levels within the body. It serves as a substitute for pre-clinical trials in the development of artificial pancreas systems because the UVA/Pavoda simulator can emulate meal challenges and includes a population of 300 in-silico subjects [155]. The UVA/Padova model has been updated to include the most recent advancements in glucose measurement devices, insulin analogs, and administration routes, as well as time-varying parameters that characterize intraday SI variability and the dawn phenomenon [156]. In addition, recent studies have provided new insights into the nonlinearities of insulin action, which have been incorporated into the UVA/PADOVA mode [157].

The Bergman minimal model, on the other hand, is another widely used mathematical model that describes glucose and insulin dynamics in the body [158]. Both of these models are effective in simulating the behavior of the human glucose-insulin system and have been utilized in the development and optimization of various AP systems.

The UVA/Pavoda model's complexity may make it difficult to implement, calibrate, and validate. Furthermore, the model's complexity requires more computers, making it difficult to execute and operate in real-time, especially in an AP system where speed and efficiency are crucial. The Bergman minimum model simplifies the glucose-insulin interaction, making it easier to understand. In our study, we employed a modified version of Bergman's minimal model.

Bergman Minimal Model:

The Bergman minimal model is a complex mathematical model that mimics glucose-insulin dynamics in the human body. It was developed by Dr. Richard I. Bergman in 1983 and has since become a benchmark model in the design of an AP system [159]. The Bergman minimal model is distinguished by a small number of parameters, which will be explored in the next section [159, 160].

Following an oral glucose perturbation, the Bergman minimal model offers an extensive model of the glucoregulatory system, which comprises two basic components. The first is responsible for variations in glucose levels, whereas the second explains the dynamics of pancreatic insulin production in response to glucose stimulation[160]. The relation between plasma insulin and plasma glucose is modeled by this model. Moreover, the subcutaneous glucose sensors, which measure the interstitial fluid glucose, are modeled by the interaction of two compartments [158]. The first compartment denotes the plasma glucose concentration, while the second depicts the concentration of glucose in the interstitial fluid. By combining these intricacies, the Bergman minimal model provides a sophisticated depiction of the numerous interactions within the glucoregulatory system as depicted in **Figure III-3**, making it a valuable tool for understanding glucose metabolism and developing diabetic treatment strategies.

The Bergman Minimal model utilized in this study comprises a set of five differential equations:

$$\frac{dG}{dt} = -P_1 (G + G_b) - X_{rG} + D_m(t) \quad \textbf{.....} \ \textbf{(23)}$$

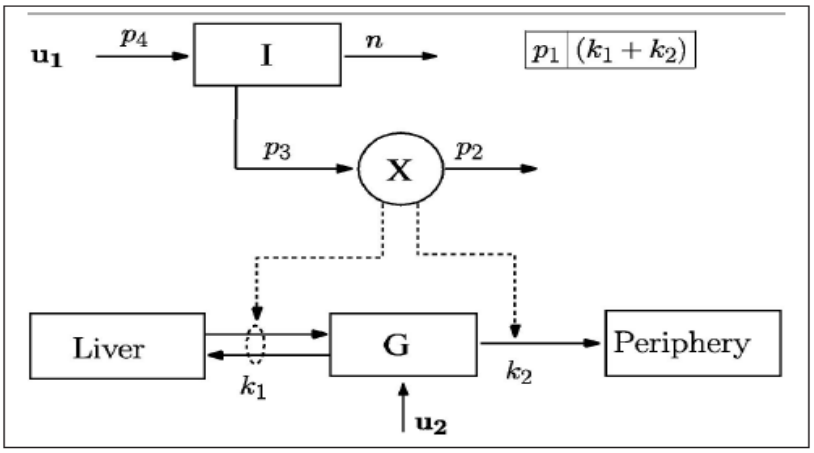


Figure III- 3: Bergman's Minimal Model' describing the glucose and insulin kinetics in an IVGTT study.

$$\frac{dX_r}{dt} = -P_2X_r + P_3\,(I - I_b) \text{ ..... (33)}$$

$$\frac{dI}{dt} = -nI + UV(It) \text{ ..... (34)}$$

$$\frac{dG_{sc}}{dt} = \frac{(G-G_{sc})}{5} - R_{utln} \text{..... (35)}$$

$$\frac{dD_m}{dt} = -\alpha D_m(t) \text{ ..... (36)}$$

With: A (n*n), B(1*n), E(1*n) and C(1*n) matrix system

$X \in R^n$

$U \in R$

$D \in R$

G (mg/dL) represents BGC in plasma. Xr (mU/L) signifies insulin concentration in the remote compartment, while I (mU/L) denotes insulin concentration in the plasma. Gsc (mg/dL), on the other hand, corresponds to glucose concentration on the subcutaneous layer. It is noteworthy that this state is the one that is measurable, approximates G and is affected by Dm (mg/dL/min), which represents the meal glucose disturbance.

Moreover, Ib (µU/ml) represents the basal insulin level, whereas Gb (mg/dl) is the basal BG level. p1 (min^{-1}) represents the insulin-independent rate constant of glucose absorption in muscles and liver, while p2 (min^{-1}) indicates the rate of decrease in tissue glucose uptake ability.

Additionally, p3 [(μU/ml) min^{-2}] reflects the insulin-dependent increase in tissue glucose uptake ability per unit of insulin concentration above the basal level. Finally, n (min^{-1}) represents the first-order degradation rate for insulin in the bloodstream. The time interval preceding the glucose infusion is t (min).

3.4. Linear MPC implementation :

Multiple MPC algorithm implementations exist, based on the model and objective function chosen[125, 126, 137, 143]. In our work, we used a Constrained Linear Model Predictive Controller (LMPC) law. Using the formulation of a Finite Horizon Optimal Control Problem (FHOCP) with specified control boundaries, this method accomplishes the definition of a control law able to consider multiple objectives. As described by Soru et al [145], LMPC employs a discrete linear model (plant) of insulin-glucose dynamics derived by discretization and linearizing the Bergman Minimal model (system of differential equations) around equilibrium points (basal values). The model's system equation, represented by x, is as follows:

$$x = \begin{bmatrix} G \\ X_r \\ I \\ G_{sc} \\ D \end{bmatrix} \rightarrow \dot{x} = \begin{bmatrix} \dot{G} \\ \dot{X_r} \\ \dot{I} \\ \dot{G_{sc}} \\ \dot{D_m} \end{bmatrix}$$

- u and d are the inputs U(t) and D(t), respectively, with the steady state point:

$$x_s = \begin{bmatrix} G_b \\ X_{br} \\ I_b \\ G_{bsc} \\ D_{bm} \end{bmatrix}, u_s = nI_b V_{I,} d_s = 0$$

The model may be expressed as follows, after linearization:

$$\dot{X} = \bar{A}X + \bar{B}U + \bar{E}D \text{..... (36)}$$

Where X represents the state vector. U represents the insulin injection input variable. D represents the meal consumption input variable.

And they are deviation variables: $X = x - x_s$, $U = u - u_s$, $D = d - d_s$

The partial derivatives of the model are represented by the matrices $\bar{A}$, $\bar{B}$, $\bar{E}$.

$$\bar{A} = \left.\frac{\partial f}{\partial x}\right|_{(x_s,u_s,d_s)}, \ \bar{B} = \left.\frac{\partial f}{\partial u}\right|_{(x_s,u_s,d_s)}, \bar{E} = \left.\frac{\partial f}{\partial d}\right|_{(x_s,u_s,d_s)}$$

Our system gives:

$$\bar{B} = \begin{bmatrix} 0 & 0 & \frac{1}{V_I} & 0 & 0 \end{bmatrix}^T$$

$$\bar{E} = [1 \quad 0 \quad 0 \quad 0 \quad -\alpha]^T$$

$$\bar{A} = \begin{bmatrix} -P_1 - X_b & -G_b & 0 & 0 & 1 \\ 0 & -P_2 & P_3 & 0 & 0 \\ 0 & 0 & -n & 0 & 0 \\ 0.2 & 0 & 0 & -0.2 & 0 \\ 0 & 0 & 0 & 0 & -\alpha \end{bmatrix}$$

To facilitate the application of the previous model (Bergman minimal model) in the LMPC, it will be transformed into a linear state space model with discrete time representation. Following the discretization steps, the resulting linear discrete state space model can be formulated as follows:

$$\begin{cases} X_{k+1} = Ax_k + Bu_k + Ed_k \\ z_k = CX_k \end{cases} \text{..... (37)}$$

With:

$$C = [0 \ 0 \ 0 \ 1 \ 0]$$

In the Bergman minimal model used: n= 12, these parameters are presented in **Table III-1**.

Table III- 1: Bergman Minimal model parameters values

Name	Value
P_1	0.028735 min^{-1}
P_2	0.028355 min^{-1}
P_3	5.035. 10^{-5}mU/L
n	5/54 min^{-1}
V_1	12 L
R_{utln}	0.7400 mg/dL/min
α	0.05
G_b	81.3 mg/dL
X_{br}	0
I_b	15 mU/L
G_{bsc}	G_b -5Rutln
D_{bm}	0

Now, the linear model predictive controller will be presented. **Figure III-4** depicts the fundamental concept of LMPC.

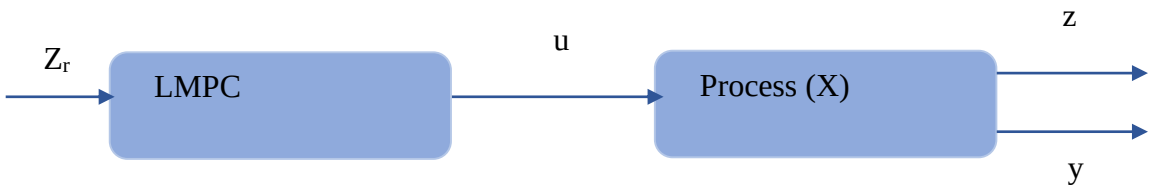


Figure III- 4: Fundamental concept of LMPC

Here, Z denotes the actual output, while y represents the measured output. The primary function of the controller is to manipulate the input, u, to achieve an output that is as close as possible to the specified setpoint, r. This fundamental control mechanism will be progressively expanded in this section, by incorporating various types of constraints, feedback, and feedforward. To that purpose, and to get the ideal profile of future insulin administration, the

difference between Z(k) and Z_{ref} (set-point) must be minimized as described in (eq. 22). This gives the following control problem, which is based on the use of least squares problem (the weighted 2-norm is used):

$$\underset{U}{\text{Minimize}} \quad J = \frac{1}{2}\sum_{k=1}^{N}\left\|z(k) - z_{ref}(k)\right\|_{Q}^{2} \text{..... (38)}$$

$$\text{S.t:}\begin{cases} X_{k+1} = Ax_k + Bu_k + Ed_k \\ z_k = CX_k \end{cases}$$

With: N: prediction Horizon

Q: output weight (diagonal matrice)

Z_{ref} : set-point (1,n)

U: input vector (1,n)

- **<u>Regularization:</u>**

the term $\Delta U_k = U_k - U_{k-1}$ is introduced to the optimization problem to reduce the variance between two successive steps in u, resulting in more smoother supply.

- **<u>Constraints design:</u>**

The design of constraints in the LMPC algorithm necessitates an understanding of physical limitations and boundaries about both the input (insulin injected) and output (measured glucose level). These constraints must be carefully factored in to ensure the efficacy of the algorithm [161].

a. <u>The input constraints :</u>

Physical restrictions are a major concern in the field of subcutaneous insulin pump technology. Specifically, the insulin infusion rate is subject to a non-negativity constraint, thereby establishing a lower bound on insulin levels. This limitation serves to limit the minimum amount of insulin that the controller may suggest. It is important to highlight that the aforementioned constraints apply to the minimum and maximum volumes of insulin that can be safely and effectively injected.

$$U_{min} \leq U_k \leq U_{max}$$

b. Constraints on input rate of movement:

To provide a more seamless control law, a particular constraint has been included to restrict the rate at which input constraints may fluctuate, the input movement rate u_k.

$$\Delta U_{min} \leq \Delta U_k \leq \Delta U_{max}$$

c. Output constraints:

The presence of output constraints ensures the output remains within the targeted range, thereby limiting the output. This means, that to prevent hyperglycemia or hypoglycemia occurrences, it was essential to establish boundaries, otherwise referred to as output limitations, on blood sugar levels. It should be noted that for all constraints, it is assumed that the boundaries remain constant at each time step k.

$$Z_{min} \leq Z \leq Z_{max}$$

In some cases, obtaining a solution to a quadratic function while adhering to pre-existing restrictions may be impossible. To address this, soft constraints are implemented to allow for boundary violations as necessary. In this scenario, the most straightforward method for loosening output limits is to introduce a new slack variable Ψk.

$$-\infty < Z - \Psi k \leq Z_{max}$$

$$Z_{min} \leq Z - \Psi k < +\infty$$

Ψk is chosen equal to zero if there is no necessity to violate the output constraints, otherwise,Ψk is set to be as small as feasible so that the output constraints are violated by the smallest amount possible.

- The final cost function is written as follows:

$$J(x(k), u(.), k) = \frac{1}{2} \sum_{k=1}^{N} \left\| z - z_{ref} \right\|_q^2 + \frac{1}{2} \|\Psi k\|_S^2 \Psi + S^T \Psi . \Psi k + \frac{1}{2} \sum_{k=0}^{N-1} \|\Delta uk\|_S^2$$

…….(39)

$$\text{S.t:} \quad \begin{cases} X_{k+1} = Ax_k + Bu_k + Ed_k \\ Z_k = CX_k \end{cases}$$

$$U_{min} \leq U_k \leq U_{max}$$

$$\Delta U_{min} \leq \Delta U_k \leq \Delta U_{max}$$

$$0 \leq \Psi k < \infty$$

$$-\infty < Z - \Psi k \leq Z_{max}$$

$$Z_{min} \leq Z - \Psi k < +\infty$$

With: $\Delta U_k = U_k - U_{k-1}$

s > 0: input weight

q > 0: output weight

S^{Ψ} : weight of soft constraint

Ψ : vector to soft the constraints

As we have a constrained model, The problem must be expressed as a quadratic programming problem to be easily solved using the quadprog function in MATLAB.

After control input generation and following the receding horizon method, only the U^0 is applied to the plant where: $U^0(k) = U^*(k/k)$. At each sampling time, the optimization process is then repeated.

3.5. Kalman filter :

The Kalman Filter is a Bayes filter variation that operates as a Recursive Bayesian Estimator, employed in the realm of minimizing the effects of noise in a given problem. The design of the Kalman Filter involves the introduction of Gaussian noise into the process and output of the linear system, as illustrated in **Figure III-5.**

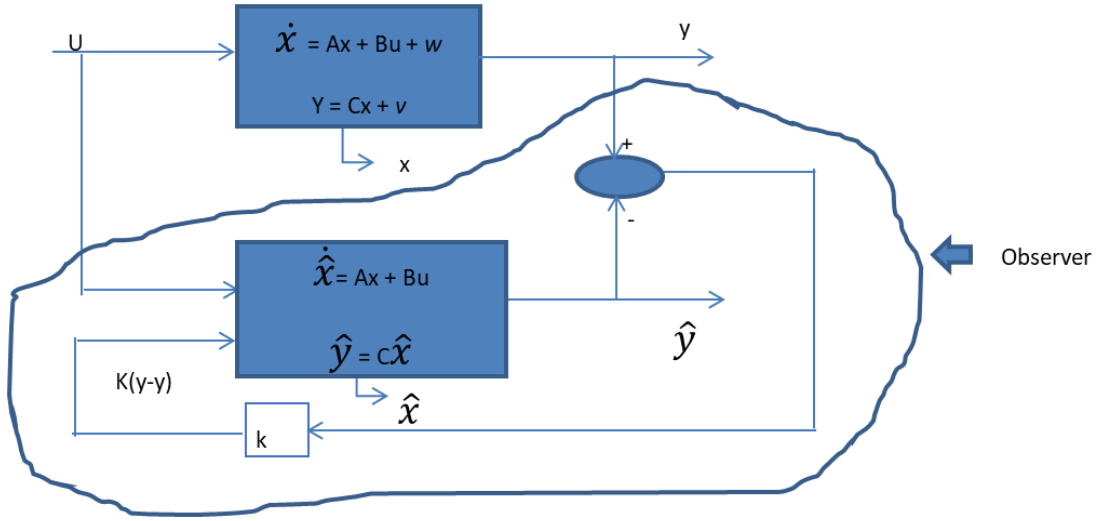


Figure III- 5: The structure of the Kalman filter estimator

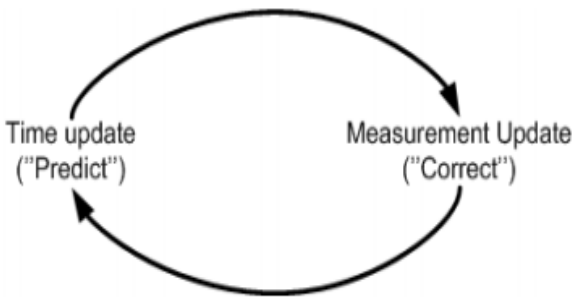
Where: w (μ, R) with $w \sim N(0,R)$ and v (μ , R) with $v \sim N$ (0,Q)

$$\begin{cases} x(k+1) = Ax(k) + Bu(k)Ed(k) + w \\ y(k+1) = Cx(k) + v \end{cases} \quad \text{..... (40)}$$

As a general rule, the state of the model, x(k), remains inaccessible, necessitating its estimation through the utilization of a Kalman filter. By leveraging the model's knowledge and prior insulin administration, the Kalman filter serves to augment the quality of information supplied to the LMPC algorithm. Particularly, the Kalman filter plays a pivotal role in updating the predicted glucose-insulin state, drawing from previous information about glucose, insulin, and carbohydrate intake.

Pseudo code:

1) KF (μ_t,$\sum_{t-1}$, U_t, Z_t)
2) $\bar{\mu} = A_t \mu_{t-1} + BU_t$



1) $\bar{\sum}_t = A_t \sum_{t-1} A_t^T + R_t$
2) $K_t = \bar{\sum}_t C_t^T (C_t \bar{\sum}_t \bar{C} + Q_t)^{-1}$
3) $\mu_t = \bar{\mu}_t + K_t (Z_t - C_t \bar{\mu}_t)$
4) $\sum_t = (I - K_t C_t) \bar{\sum}_t$
5) Return μ_t , $\sum_t$

With: A(n,n), B (n,1)and C(1,n), system matrices (A square matrix)

tx: the current state
$\hat{\dot{x}}_t$: The estimation of the state at time t
$\sum_t$: the covariance of the state estimated.
U_t: control input at time t
Z_t: sensor reading (CGM). The Measurement
K: Kalman gain

- $e_t = Z_t - C_t \bar{\mu}_t$

4. Results:

The different parameters that have been initialized are:

- Input constraints that restrict the rate of the insulin injected:

$$60 \text{ mg/dL} \leq z \leq 180 \text{ mg/dL}$$

$$0 \quad \text{mU/min} \leq u \leq 100\text{mU/min}$$

$$-16{,}7 \text{ mU/min} \leq \Delta u \leq 16{,}7 \text{ mU/min}$$

- An appropriate sampling time and horizon should be selected: N= 25, Ts = 8 min **[3].**

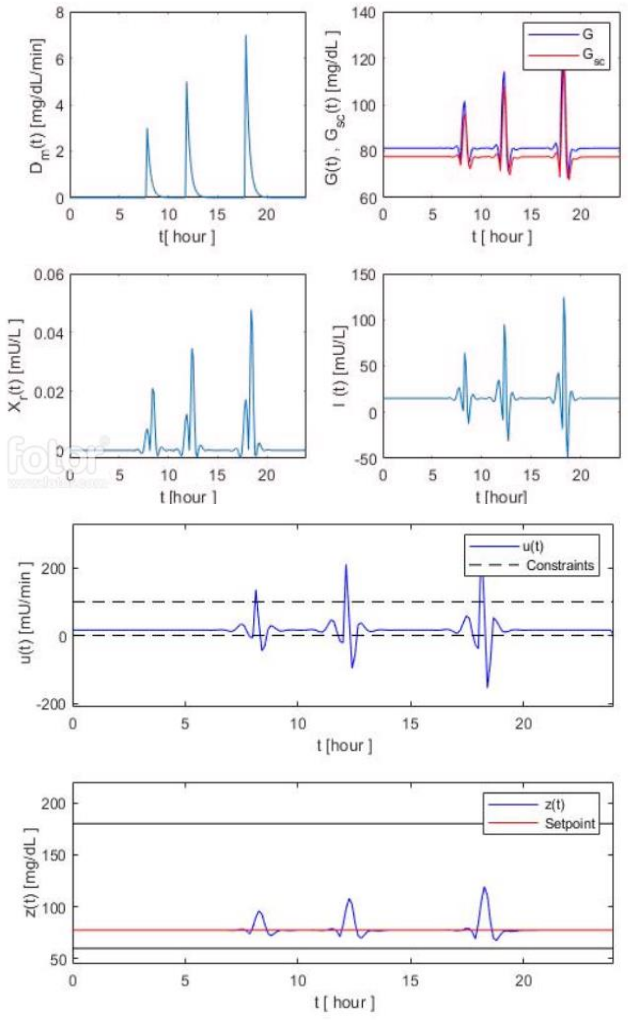
The evaluation of LMPC performance will be conducted through two scenarios. At first, the virtual patient is subjected to three distinct meals. In this case, an exploration of the impact of feedforward, measurement noise, and process noise will be undertaken, while also allowing for meal size variation across occasions. During this scenario, the controller's primary goal is to maintain the blood glucose level in the target range.

Using a feedforward technique, the controller may predict an increase in blood sugar levels caused by consuming a meal and administering insulin before it is eaten. This leads to a lower glucose level compared to not using feedforward. The strategy increases the likelihood that the patient will maintain a good control of postprandial glucose. As a result, feedforward will be used in all next simulations. Table III-2 presents the temporal distribution of meal ingestion events and their amount.

Table III- 2: The temporal distribution of meal ingestion events.

Time (hours)	D(t) (mg/min)
8	3
12	5
18	7

As the first experiment, and to highlight the necessity of constraint incorporation in the artificial pancreas, we simulate our system without constraints. **Figure III-6** and **Figure III-7** depict the evolution of the system with constraints and without it.



(a)

(b)

Figure III- 6: The evolution of the system without constraints of: a) the evolution of the state b) the evolution of insulin input and output.

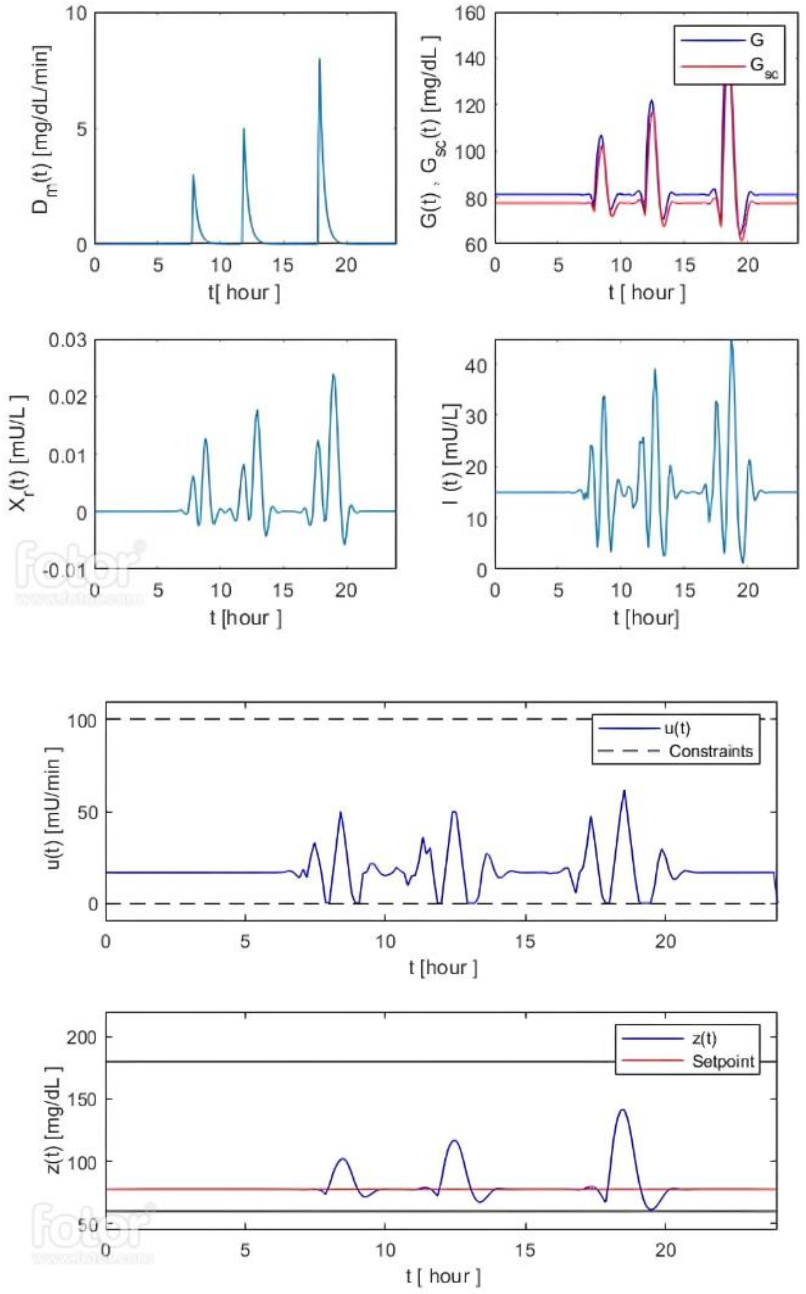


Figure III- 7: The evolution of the system with constraints: a) the evolution of the state b) the evolution of insulin input and output

The findings reveal the necessity of incorporating the constraints into an LMPC. In particular, shows instances of negative insulin delivery values (U(t)), which are incompatible with the physical reality of insulin infusion rates. Consequently, the implementation of input constraints within the model becomes a mandatory measure to ensure the controller operates within the insulin pump capabilities.

In the second experiment, we will evaluate the controller's capability to handle potential system disturbances coming from a variety of sources, such as the glucose concentration measurement sensor and unexplained physiological components in the Bergman minimum model. The system can be exposed to simulated disturbances, such as measurement noise (y) and process noise (x), to accomplish this goal. The controller's overall robustness and flexibility may be determined by studying how it reacts to various interruptions. **Figure III-8 (a)** shows the progression of the model's states, and **Figure III-8 (b)** shows a visual depiction of the scenario's inputs and outputs.

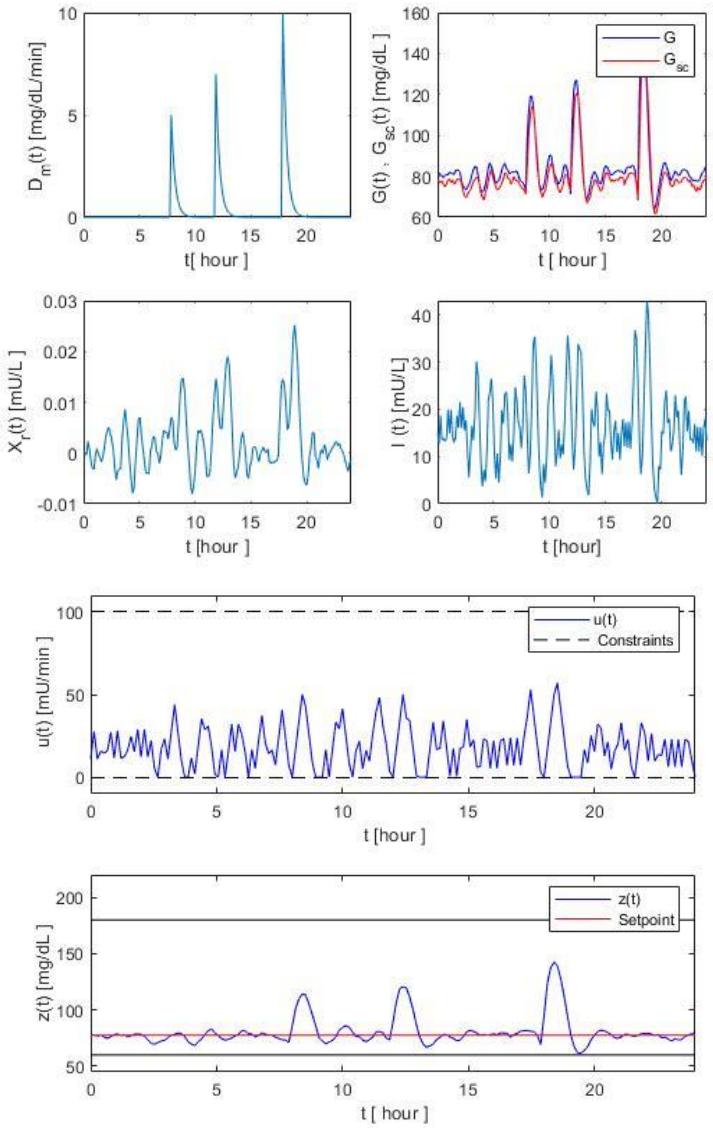


Figure III- 8: The evolution of the system with process and measurement noises, a) the state, b) insulin input and output

Comparing **Figures III-8 (a)** and **8 (b)** to **Figures III-7 (a)** and **7 (b)**, there is a noticeable rise in oscillations, indicating a more difficult management situation. However, the controller's effectiveness is still present as shown by the regular maintenance of blood glucose levels within the desired range. Noise could replicate physiological features that the model ignores.

In the third experiment, As shown in the following figure (**Figure III-9**), we added an insulin basal rate to the system to achieve a consistent insulin pump infusion rate. The results show that the controller performs better when both basal and bolus rates are used, as seen by the constant management of blood glucose levels within the established limits.

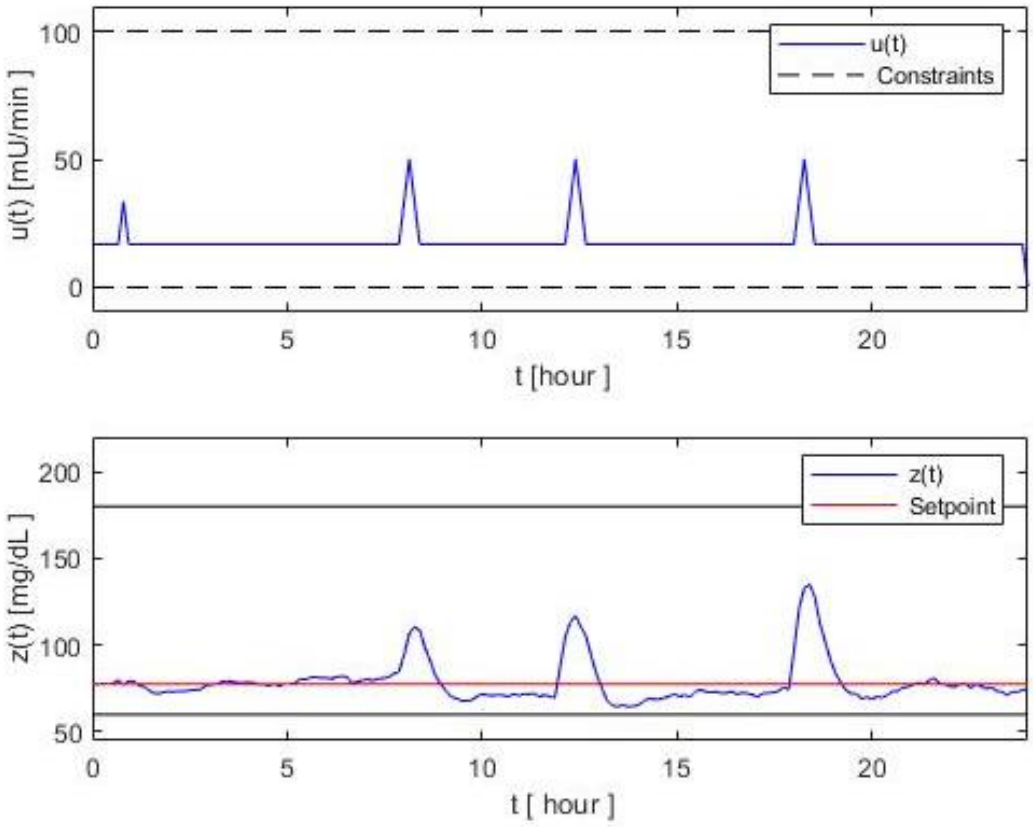
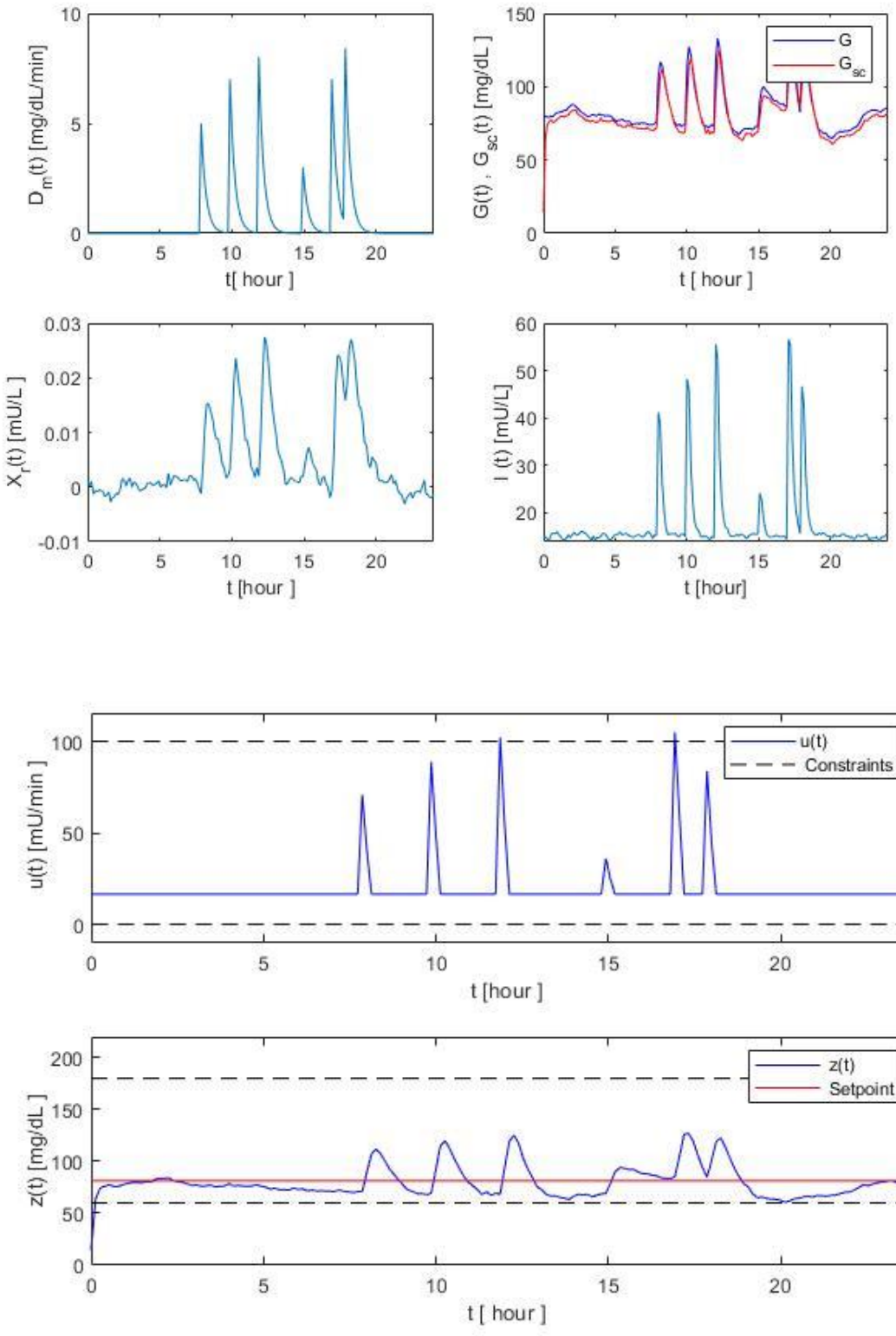


Figure III- 9: The evolution of states with process and measurement noise with basal and bolus injection.

In the fourth experiment, the simulation will be done with both measurement and process noise. However, using another scenario. Where the patient eats 6 random meals. **Figure III-10 (a)**, **and (b)**, illustrate the evolution of the state and the input/output respectively.



(a)

(b)

Figure III- 10: The evolution of the system, a) the states, b) insulin input and output

As shown, even with different numbers and sizes of meals, the controller developed manages to keep the blood sugar at the target range.

5. Conclusion:

The simulations conducted have demonstrated that the Constrained LMPC algorithm utilizing Bergman's minimum model performs exceptionally well in maintaining acceptable blood glucose levels for patients across different scenarios. It effectively manages measurement and process noise, which is crucial for the practical implementation of the system. Moreover, the incorporation of feedforward capability in the controller has shown significant benefits, enabling proactive planning for future meals and optimizing blood glucose levels. However, the real-world application of feedforward may be limited by the patient's ability to provide accurate information about their mealtimes and sizes

Despite this, an Artificial Pancreas system's control algorithm's effectiveness depends on a variety of factors, including the accuracy of the glucose measurement device, the patient's specific characteristics, and insulin sensitivity, and the algorithm's ability to adapt to changing circumstances and disturbances. By incorporating patient-specific data and considering individual preferences and requirements, the combination of machine learning and artificial intelligence approaches has recently produced amazing success in improving the performance of AP control algorithms. According to that, an adaptative predictive controller using machine learning is under development to create a sophisticated controller for better postprandial glucose.

Chapter

IV. Wireless Syringe Infusion Pump

1. Introduction:

The development of the Internet of Things (IoT) has created new possibilities for healthcare applications, including the ability to remotely monitor and control medical devices. One such application is the Intelligent, Wearable Infusion System based on Smartphone Application, which represents a significant advancement in the field of biomedical engineering and a crucial component in an AP system. This system utilizes IoT technology to enable microliter-precision insulin delivery, remote monitoring of patients' actions (insulin delivery and meal uptake), and real-time data analysis, all through a lightweight, wirelessly controlled syringe pump managed by a mobile application. Such a system can improve patient safety by providing real-time data to healthcare providers and alerting them to any potential issues.

This chapter focuses on the design and implementation of novel solutions for diabetes self-management. By leveraging the power of the IoT and mobile health technology, this system can significantly improve diabetes outcomes and enhance the overall quality of care. Following a brief overview of the existing SIPs and a discussion of the suggested solution. This chapter describes the methodology followed to develop a smart, wearable insulin infusion system, that operates based on a smartphone application. Hardware and software have both been considered. Then, we present the results obtained with their discussions. Finally, a conclusion was made about the impact of the Internet of medical things on diabetes self-management technologies.

2. Background :

Syringe infusion pumps (SIPs) are critically important medical devices that are utilized to deliver precise amounts of fluids, medicines, or nutrients intravenously to patients over prolonged periods. These electrical devices function by providing a steady rate of medication infusion, thereby mitigating the risk of errors during the administration of various medications, which is particularly crucial in the context of critical care patients [162, 163]. SIPs are employed to administer a wide range of medications, including chemotherapy for cancer patients, parenteral nutrition for patients with gastrointestinal disorders, insulin delivery for diabetic patients, analgesics for pain relief, and antibiotics for the treatment of infections. Moreover, SIPs are often used in ambulatory settings such as ambulator automobiles or helicopter

emergency medical services (HEMS), thus highlighting the importance of developing precise, lightweight, wireless, and wearable syringe pumps [164].

The need for such a device led to the development of several lightweight SIPs with high accuracy. One of these is the MicropumpTM (Micrel, Greece), which is a low-weight model (0.22 Kg), 10 times lighter than conventional SIP models. As presented in **Figure IV-1 (b),** this SIP model comprises both mechanical and electronic components [165, 166]. Another group has also introduced its SIP model, the Medfusion 4000, which is smart and wireless (**Figure IV-1 (a)**). However, despite its wireless and smart characteristics, this SIP model still contains a significant number of electronic and mechanical elements, making it relatively cumbersome [167]. Furthermore, both of these models are operated manually [166, 167].

(a) (b)

Figure IV- 1: (a) Medfusion® 4000 Wireless Syringe Infusion Pump, (b) Micropump (Micrel Medical Device).

Advancements in technologies in the field of smart, wearable sensors and IoMT like mobile health have paved the way for the creation of new medical solutions. In this work, we aim to investigate the potential use of these advancements to create a lightweight, wearable, and smart SIP that supports diabetic self-management. The presence innovation consists of eliminating most electronic components of SIP and replacing them with mobile health applications. Doing that, the infusion syringe pump became lightweight weighted, wirelessly controlled using a smartphone application. Furthermore, to support diabetes self-management, the application comprises an intelligent operation, which can determine the appropriate insulin amount needed to be injected before meal consumption. Practically, we focus on enhancing connectivity and applying Mobile health technology to address the challenges of remote control, big data

management, and achieving autonomy, robustness, and an intuitive, user-friendly interface for the miniaturization of the SIP.

3. Materials and methods:

The syringe infusion pump developed consists of a lightweight insulin injection system controlled via Bluetooth using a smartphone application. The wireless network provides better access for health providers by storing personal data such as the infusion history and BGL in the cloud. Furthermore, a calculator provides the smartphone application to determine the appropriate insulin rate needed to be injected for better postprandial glucose. The whole architecture of our system is presented in the synoptic diagram in **Figure IV-2**.

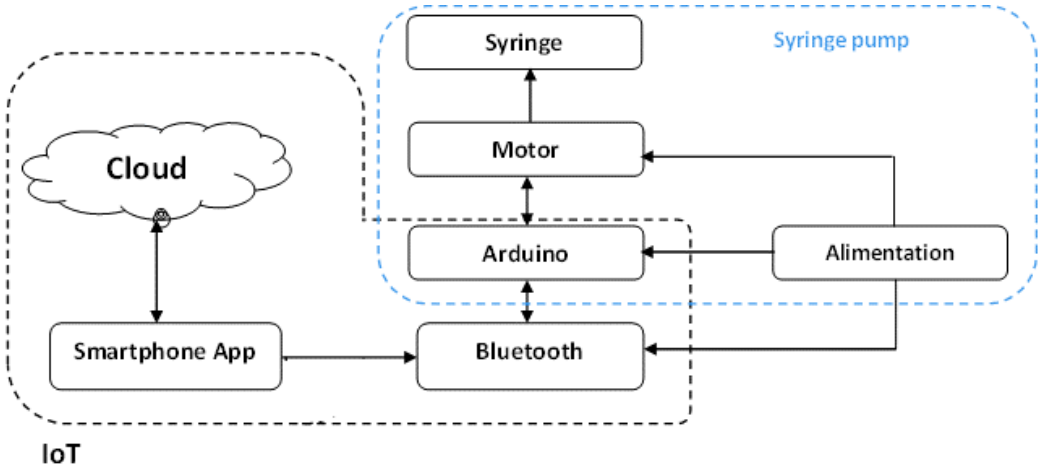


Figure IV- 2: Architecture of Intelligent IoT (I^2oT) Biomedical Wearable System based on Smartphone Application

a. Syringe Infusion Pump:

A syringe pump is a programmable pump that allows the injection of drugs into a patient, given the synoptic diagram, our design will be based on the main levels:

- **Mechanical part:** consists of pushing the piston using the rotary motion of a motor and a set of mechanical devices that transform this rotation into translational mechanical energy (gears, supports, nuts), and a body that carries the syringe (the case).
- **Electrical part (prevention):** this part includes a computer platform (microcontroller system) which makes it possible to manage the entire mechanism.

b. IoT system:

The IoT system is responsible for the wireless communication between the syringe pump and the external environment (smartphone app - cloud). It consists of three main parts:

- **Electric part:** where we can find the communication module (Bluetooth in our case) responsible for transmission and the reception of the data wirelessly, and the microcontroller (Arduino) to read the transmitted data and encrypt it to control the syringe accordingly.
- **The smartphone application:** responsible for various tasks such as remotely controlling pulse rate with micro-liter accuracy, by calculating the insulin dose appropriate.
- **Firebase platform (Cloud service)** where all the information including the BGC, and the insulin dose calculated will be stored. Such a system can improve patient safety by providing real-time data to healthcare providers and alerting them to any potential issues.

3.1. Hardware of the system:

- Endless screw: it is a cylinder comprising a helical groove (sometimes several), making it look like a threaded rod. Associated with a pinion, it constitutes a left gear (the two axes are not in the same plane), in which it behaves like a wheel with one tooth (or more, depending on the number of splines). This system is also sometimes called a worm and wheel.

Following the synoptic diagram, each part is a key element of our design, first, we will see the global definitions of each body.

3.1.1. Engine (motor):

One of the main components that make up the mechanics of the syringe pump is the motor. It allows linear movement of the piston of a syringe via a worm that rotates through a series of gears, allowing the correct movement of the piston to transfer the contained solution to the circulation of a patient. By definition, a motor is a component that converts electrical energy

into mechanical energy. In electronics, generally, there are three types of motors: direct current (DC) motor, servo motor, and stepper motor.

i) Direct current motor:

It is also called a Direct Current Machine (**Figure IV-3**). The DC motor is made up of two main parts: the rotor (part that rotates) and the stator (part that does not rotate or static). In electrical engineering, the stator is also called the inductor, and the rotor is called the armature[168].

Figure IV- 3: Direct current motor

ii) Servomotor:

This is, somewhat, a special motor (**Figure IV-4**), since it includes control electronics. The name comes from the Latin word *servus*, which means slave. Similar to DC motors, servo motors have an axis of rotation that sits in the center of the wheel. This axis of rotation is however hindered by a clamping system. Servomotors therefore have the advantage of being servo-controlled in an angular position. This means that the output axis of the servomotor will respect an orientation instruction that you send to it at its input[169].

Figure IV- 4: Servomotor

iii) Stepper motor:

Stepper motors are widely used in various industries for their precise control over rotational movements, by converting electrical pulses into mechanical rotation. These pulses determine the number of steps the motor will take and the direction of rotation. The presented moto in **Figure IV-5** combines the technology of both [169]. They are designed to provide accurate positioning and control, making them a popular choice in applications that require precise motion control, such as robotics, CNC machines, 3D printers, and automated systems.

Figure IV- 5: Stepper Motor

To justify our choice of engine, we had to make a comparison table (**Table IV-1**) [169]:

Note: the servomotor is not mandatory because the latter is limited in its movement, it is designed to work between 0° and 180° (without modification).

Table IV- 1: a comparison between the stepper motor and DC motor

	Advantages	Disadvantages
Stepper Motor	• Open loop operation (no regulation required) • No need for an incremental encoder • Precision of high steps • Existing linear stepper motors.	* More complex control electronics * Lower power for equal-size
DC Motor	• Easy speed adjustment • Simple electric control • High power for a small footprint	* Necessary regulation * Incremental encoder required * Linear rotary transformation required (belt, etc.)

For our application, the stepper motor is therefore advantageous compared to the DC motor and the Servomotor. Indeed, the precision of the steps as well as the fact that the regulation is not compulsory, are advantages for the realization of our system. The minimum angle of rotation for the stepper motor between two changes in electrical impulses is called a step. A motor is characterized by the number of steps per revolution (i.e., for 360°). Common values are 48, 100, or 200 steps per revolution. The principle of operation of stepper motors is based on the successive switching of the stator (or phase) windings. To do this, an electrical pulse is translated by a sequencer acting on switching electronics (drivers or power transistors) which distribute the polarities in the windings. A single switching causes a single step regardless of the duration of the pulse (greater than a minimum value).

The technical characteristics of the stepper motor:

The electronics driving a stepper motor can be divided into 3 functions:

- The motor power supply with its voltage, current, and power constraints to be dissipated. It's power electronics.
- The sequencer manages the chronology of the impulses.
- The oscillator.

Within our application context, the pm55l-048-hp69 stepper motor has been established as the most suitable option, given its potential to facilitate meticulous regulation of motor speed through precise calibration. The remarkable features of this stepper motor from the datasheet are presented in **Table IV-2.**

Table IV- 2: The motor datasheet.

Motor Size	PM55L-048	
Number of Steps per Rotation	48(7.5°/Step)	
Drive Method	2-2 PHASE	
Drive Circuit	UNIPOLAR CONST. VOLT.	BIPOLAR CHOPPER
Drive Voltage	24[V]	24[V]
Current/Phase		800[mA]
Coil Resistance/Phase	30[Ω]	5.5[Ω]
Drive IC	2SC3346	UDN2916B-V
Magnet Material	Ferrite plastic magnet (MSPL) Polar anisotropy ferrite sintered magnet (MS50) Nd-Fe-B bonded magnet (MS70)	
Insulation Resistance	100M[Ω] MIN	
Dielectric Strength	AC 500[V] 1[min]	
Class of Insulation	CLASS E	
Operating Temp	-10[°C] ~ 50[°C]	
Storage Temp	-30[°C] ~ 80[°C]	
Operating Hum.	20[%] RH ~ 90[%] RH	

3.1.2. Control card:

In order to be able to control our stepper motor, the use of a control card is essential. It must be at the same time simple (in programming), intuitive (understanding of operation), and above all small to occupy the least space possible. That's why we opt for the use of an Arduino MEGA card. It is a board based on the ATmega2560 microcontroller. There are several types of Arduino boards, all different from each other, among these boards, we can find those that are the most used according to their characteristics, which are: the Mega, Uno, Duemilanove, Leonardo, Mega Adk, and Nano. For our project, as we mentioned earlier, our choice was the

Arduino MEGA board because of its simplicity of operation and especially the number of pins available. As with any control card, the Arduino Mega consists of two main part hardware and software, described as follow:

i) Hardware:

ATmega2560 microcontroller (**Figure IV-6**) is an electronic card in the form of a flat, flexible, or rigid support, generally made of epoxy or fiberglass. It has electronic tracks arranged on one, two, or more layers (on the surface and/or internally). Each track connects one component to another, to create an electronic system that works and performs the required operations. This card is based on an ATMega microcontroller from the manufacturer Atmel and is characterized by the following main features [170].

- Power supply: via USB port or 5 Vdc regulated or 6 to 20 V unregulated
- Microprocessor: ATMega2560
- Flash memory: 256KB including 8KB for the bootloader
- SRAM memory: 8KB
- EEPROM memory: 4KB
- 54 I/O pins including 14 PWM
- Current per I/O: 40 mA
- 16 analog inputs
- Clock: 16 MHz
- Serial bus, I2C, and SPI
- Management of interruptions
- USB plug: mini-USB B
- Dimensions: 18.54 x 43.18mm

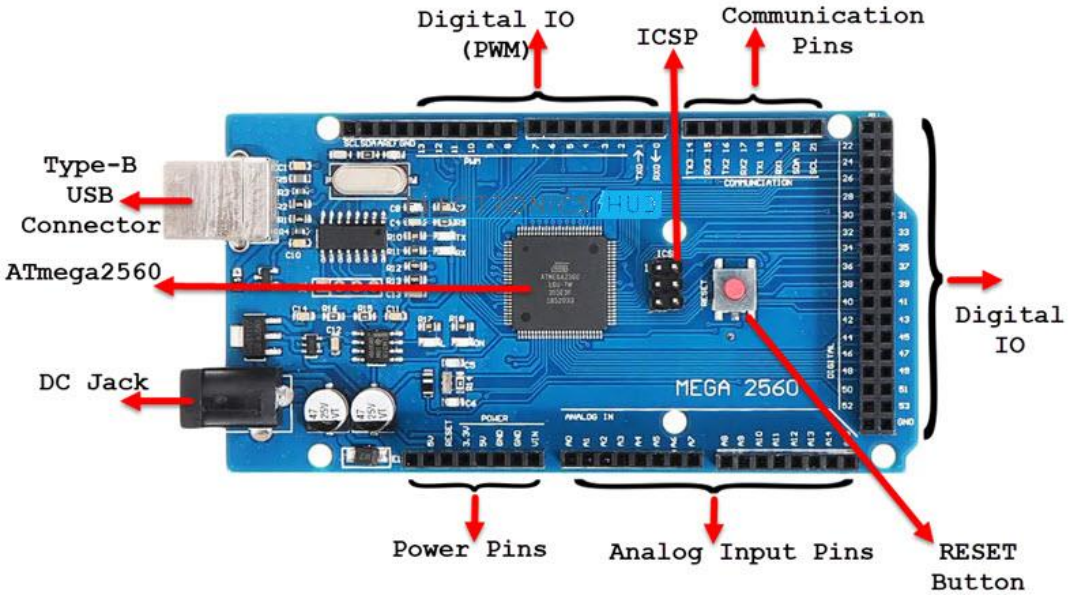


Figure IV- 6: Arduino MEGA 2560 board (front view).

i) Software:

The Arduino module programming software, depicted in Figure IV-7, is a Java-based application that is freely available and compatible with multiple operating systems. It functions as a code editor and compiler, and it can transfer the firmware and the program through the serial link (RS-232, Bluetooth, or USB depending on the module). This versatile software enables the transfer of firmware and programs via various serial communication interfaces, including RS-232, Bluetooth, or USB, depending on the specific module being used.

The programming language used is C++, compiled with avr-g++, and linked to the Arduino development library, allowing the use of the board and its inputs/outputs. The implementation of this standard language makes it easy to develop programs on Arduino platforms, for anyone familiar with C or C++.

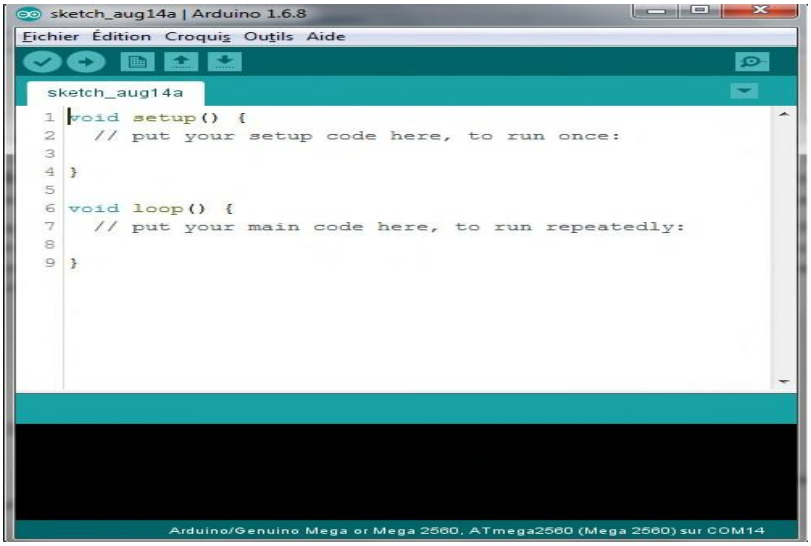


Figure IV- 7: Arduino software.

3.1.3. Power Control card (Arduino shield):

Now that we have specified the platform for driving the system as an Arduino board, it has become evident that the board does not possess the necessary electrical performance to operate a motor efficiently. When the motor begins to rotate, it generates significant interference that can produce voltage spikes far beyond the supply voltage. Additionally, the motor draws current far greater than what a digital output of an Arduino board can handle, capable of providing approximately 40 mA. To address these issues and regulate the direction and speed of the motors, an Arduino shield Rev3, depicted in **Figure IV-8**, is employed. This shield allows for the motor to be powered separately by a dedicated power source, which can reach up to 12v. The motor shield can control two DC motors or a stepper motor, with two separate channels provided for each. [171].

When connected to an external power supply, the motor shield can safely deliver up to 12V and 2A per motor channel (or 4A if channeled individually). Is worth noting that certain Arduino pins are perpetually utilized by the shield. By directing these pins, one can opt for a motor channel to activate, identify the motor polarity, set the motor speed (via PWM), stop and start motor operation, as well as monitor the current consumption of each channel [171].

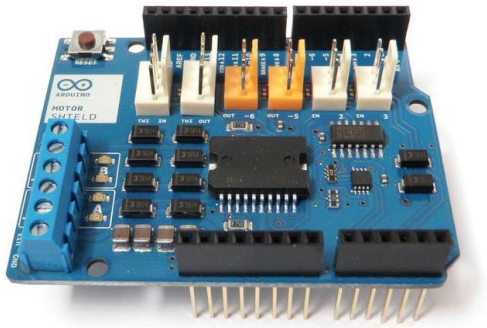


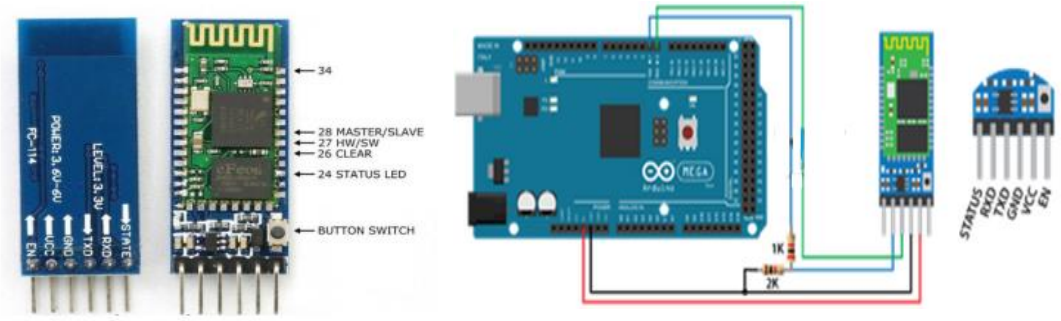
Figure IV- 8: Arduino shield Rev3.

3.1.4. Le module Bluetooth:

It is a hardware device that enables wireless communication between devices using a short-range wireless technology that uses radio waves to transmit data over short distances, typically up to 10 meters (30 feet) or so. Bluetooth modules come in various shapes and sizes and can be used for a wide range of applications.

After considering the availability of Bluetooth modules in the local market, we opted for the HC-05 module (**Figure IV-9 (a)**), which is a Bluetooth SPP (Serial Port Protocol) module. It can be paired with a smartphone, tablet, or other Bluetooth-enabled device to exchange data or control devices remotely. This module boasts extremely low energy consumption, limited range (within ten meters), low speed, economical pricing, and a compact form factor. Particularly, the HC-05 module has six pins and may be driven by either 5V or 3.3V [33]. Moreover, the module can be activated or deactivated, and its status (visible or non-visible) can be obtained from two additional pins [172, 173].

It is critical to add a voltage divider between the Arduino's Transmit Pin (which outputs 5 volts) and the Bluetooth module's Receive Pin (which only supports 3.3 volts) to avoid module damage, as shown in **Figure IV-9 (b)**. In contrast, the line between the Bluetooth module's Transmit Pin and the Arduino's Receive Pin may be linked directly. This is because the 3.3V signal from the Bluetooth module is strong enough for the Arduino Board to interpret as high logic [172, 173].



(a) **(b)**

Figure IV- 9: Module Bluetooth HC-05, b) Bluetooth connection with Arduino.

3.1.5. Feed (Alimentation):

To be able to make a good power supply for our device, we will need different elements that can simultaneously power our Arduino board, the stepper motor. The syringe pump is a device used in a hospital environment and whose operation must be permanent, even in the event of a power cut,

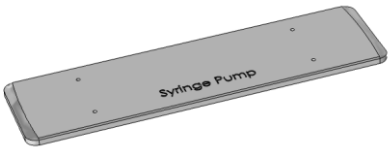
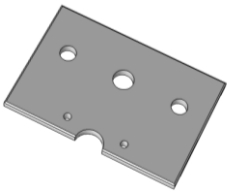
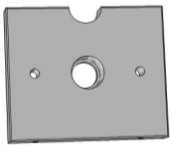
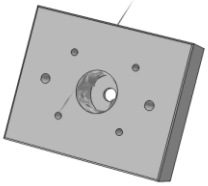
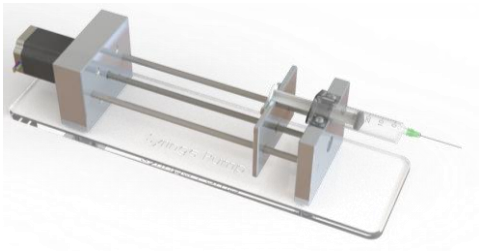
To do this, we will install a battery that will take over from the mains power supply as soon as a power cut occurs to this product. In order to be able to choose the type of battery used, we will need to do some tests on the device and know the different parameters such as the current, the supply voltage, and above all the most important, the duration of which the device must remain in operation.

3.1.6. Other components:

The diverse mechanical components used for the development of the syringe infusion system presented in **Table IV-3** were designed using COMSOL Multiphysics and have been fabricated using a 3D printer.

Table IV- 3: The 3D printer design

Designed parts	Specification

	The base
	The mobile part
	The fixed border 1
	The fixed border 2
	The final expected syringe driver

Conversely, the metallic components of the mechanical assembly comprise various fundamental elements **Table IV-4.**

Table IV- 4: The metallic components of the mechanical assembly.

	Trapezoidal screw
	Trapezoidal nut
	Linear shafts
	Bearings

The motor shaft is linked with the screw and the nut to enable linear displacement. The selection of the Trapezoidal screw and its length has been meticulously scrutinized, with the distance between the teeth being equivalent to the interval between two volume markings on the syringe.

3.2. Software :

3.2.1. Calibration of the syringe-driver:

The critical issue of calibrating the syringe driver necessitates particular attention to many key elements, such as the rotation of the stepper motor, the length of the Trapezoidal screw, and the size of the syringe. Firstly, we determine the distance relative to one rotation:

$$48 \text{ steps by rotation} \rightarrow 8\text{mm}$$

$$1 \text{ step} \rightarrow 0.16667 \text{ mm}$$

Then, because the calibration is produced by the Arduino code, we can add this equation to it and get an accurate motion relative to the syringe volume calibration.

3.2.2. Arduino code:

Incorporating the calibration equation into the Arduino program will result in precise motion concerning syringe volume calibration.

```
START
Include required libraries
Define pins for Bluetooth module
Define Stepper motor
Define calibration value in steps/mm and maximum dose in mm
    SETUP
        Set up communication with Bluetooth module
        Set Motor Speed
    END SETUP
    LOOP
        Wait for incoming commands from Bluetooth module
         Read incoming command and convert to integer value
        Check that dose is within range
        Calculate the number of steps required to move the motor the specified dose
        Move the motor forward the required number steps
   END LOOP
END
```

3.2.3. Smartphone application:

a. Calculator:

Before building the automatic infusion system, we investigate the impact of some specific parameters including carbohydrate consumption on the glucose level. As is known, the amount of insulin required before consuming calories is determined by several factors, including the subject's insulin sensitivity, the amount and kind of food ingested, and current blood glucose levels. For that reason, to precisely administer the appropriate insulin dosage, it is critical to work with a healthcare expert who can assist with a personalized insulin regimen.

A variety of formulae and algorithms are utilized to determine the best insulin dosage, taking into account different parameters. The carbohydrate counting method is one commonly employed technique, wherein the insulin dose is determined by the amount of carbs consumed during a meal or snack, as encapsulated in the insulin-to-carbohydrate ratio (ICR) formula.

- ICR = Total grams of carbohydrates per meal / Units of insulin needed to cover the carbohydrates.

The Insulin to insulin-carbohydrate ratio (ICR) is mathematically derived by dividing the aggregate amount of carbohydrates present in a given meal or snack by the corresponding insulin units required to cover those carbohydrates. For example, if an individual's ICR is 1:10 and they intend to consume a meal comprising 50 grams of carbohydrates, they would need: 5 Units of insulin needed to cover the carbohydrates [174]. This operation has been implemented in the smartphone application to provide the user with the appropriate insulin amount needed when taking a known meal or snack [175].

b. MIT application:

Apps Inventor, an advanced Artificial Intelligence software developed by MIT, represents Google's second iteration of its original App Inventor. This innovative software offers a web browser-based developmental environment that simplifies the challenging process of creating Android applications [173]. Programming is executed online, through a Mac, Linux, or Windows computer web browser. It is worth noting that a Gmail account is mandatory to access

the Internet, and data is stored on external servers. The App Inventor framework entails three fundamental stages as shown in **Figure IV-10;** firstly, the design of the User Interface (UI); second, the creation of programming algorithms that assemble blocks to construct the application's behavior; and lastly, the utilization of an emulator to test the program's functionality instead of a physical device

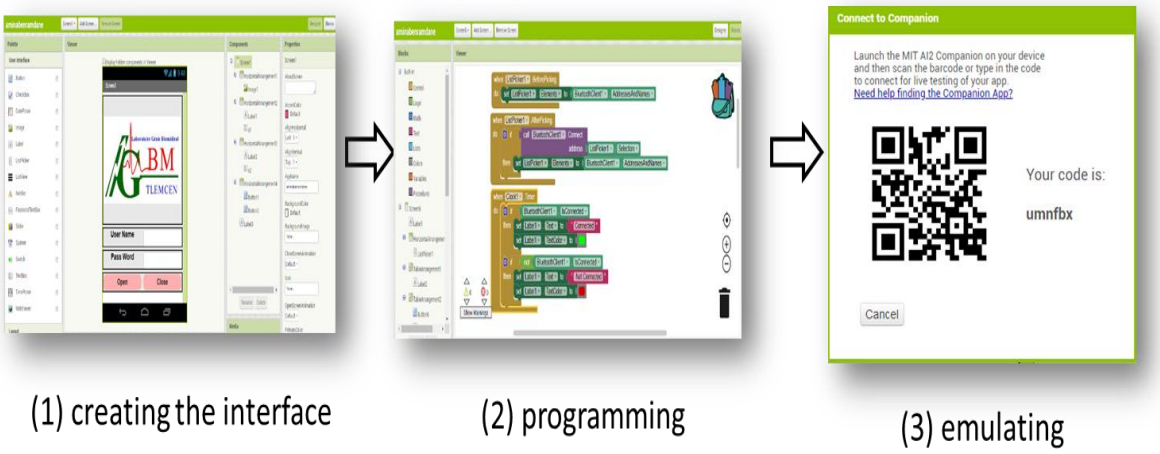


Figure IV- 10: The App Inventor framework.

The application's architecture consists of four distinct activities as shown in **Figure IV-11**, each of which is prioritized sequentially as follows:

1. Authentication via login to ensure optimal safety.
2. Integration with the Firebase platform to furnish a comprehensive interface for recording patient information.
3. An interface that facilitates the precise calculation of insulin dosage and its subsequent injection.
4. Authorization for Bluetooth connectivity and an autonomic injection interface.

Figure IV- 11: The structure of the App smartphone interface.

c. Firebase platform:

When the Send button is pressed, all patient-related data will be transferred to the Firebase platform, **Figure IV-12,** including, the amount of insulin calculated, the amount of carbs, and the time of the operation. Firebase platform is a subset of Google Cloud Platform projects that utilize the Firebase service, which is characterized by shared payment and project authorizations across all consoles, as well as the visibility of Firebase projects within the API Google and Google Cloud Platform consoles [173].

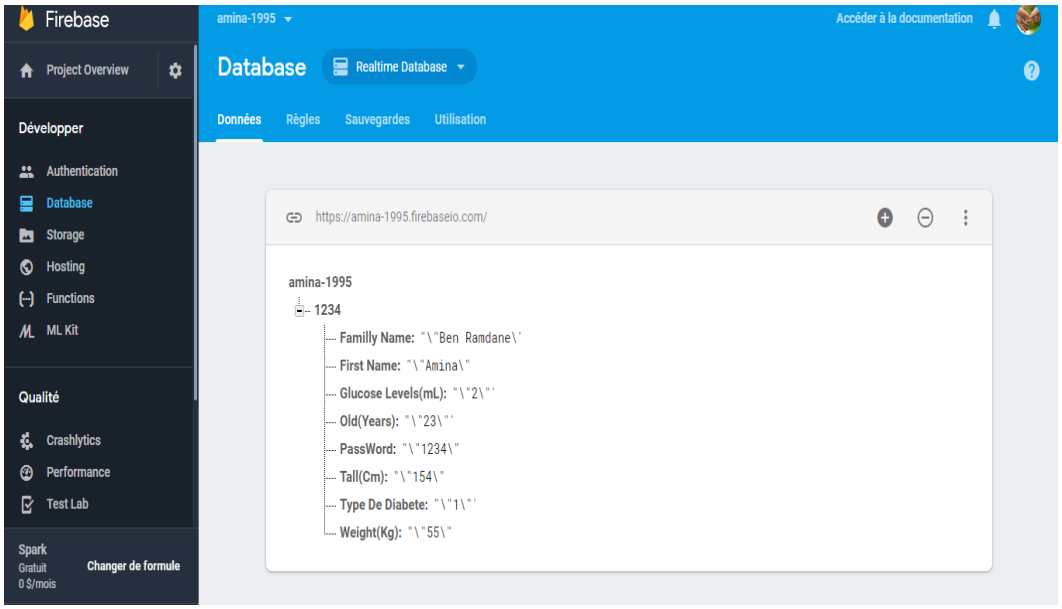


Figure IV- 12: Google Cloud Platform.

4. **Results and discussion**:

The flow rate must be determined using a digital microscope (PARALUX) in combination with a MATLAB application. We used the optical mounting approach to measure the flow rate. The data variables that will be taken into consideration include:

- The segment of the tube labeled "S,"
- The time interval between two successive motor steps "T1" (manipulated via the Arduino code),
- The distance traveled by the fluid or "D," and its corresponding travel time "T."

Certain parameters such as the distance D and the tube cross-sectional area denoted as "S" are held constant, while time T1 is allowed to vary. The resultant measurement is presented in **Table IV-5.**

Table IV- 5: The experimental measurements

Motor speed [mm/s]	Flow-rate [uL/min]
0.8	377.824
0.6	127.226
0.5	118.745
0.47	100.55
0.37	90.3492
0.33	83.1213
0.3	79.4153
0.28	76.492
0.25	45.3389
0.23	31.3271

Examining the Flow-rate measurement function concerning the motor speed curve reveals the presence of several linear fits as shown in **Figure IV-13**. We will select a specific interval that best serves our purpose. Following that, we will modify the Arduino code to replace the motor speed variable with the flow-rate variable. This will allow us to directly change the flow rate using a smartphone application.

The fluid flow rate validation range is set between 130 and 400 microliters per minute (uL/min). We then use App Inventor to compute the required insulin dose and send it to the SIP. A comparative assessment of the insulin dosage computed by the application and the actual amount measured at the SIP's output after the prescribed injection duration indicates a high degree of proximity between the two values, with a negligible margin of error not exceeding 5%.

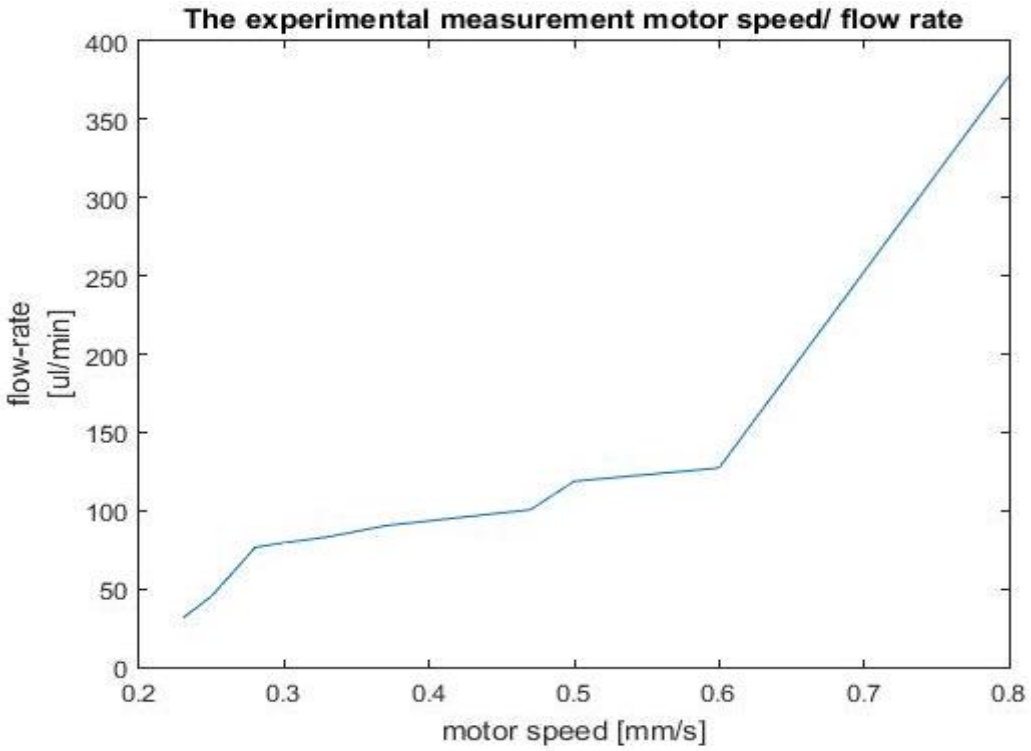


Figure IV- 13: The linear fit flow rate/motor speed.

Our experimental results indicate that the syringe infusion pump exhibits exceptional precision in micro-injection delivery. Furthermore, the incorporation of a smartphone application confers the necessary autonomy for efficient control. This seamless integration eliminates the need for cumbersome electronic components, such as a keyboard and screen, resulting in a significantly lighter SIP than models like the Medfusion 4000 or Micropump™. Additionally, unlike these models, our system enables wireless control through a simple interface, making it an intelligent Internet of Things (IoT) system. The integration of a glucose sensor (CGM) will further augment the intelligence of the entire biomedical system.

To sum up, through the employment of Bluetooth technology, a wireless network is established between a syringe pump and a smartphone application, thereby enabling comprehensive remote-control functionality. This technological solution not only facilitates enhanced access to healthcare, but also facilitates the recording of history, and its direct transmission to the Cloud. Consequently, the issue of inadequate physician supervision is effectively addressed. Furthermore, the incorporation of an intelligent calculator or algorithm plays a pivotal role in accurately determining the medication's flow rate and injection quantity.

Our current research focus involves enhancing the miniaturization of the syringe pump by implementing MEMS Nanofabrication technology. Specifically, we have integrated small piezoelectric membranes that consume minimal energy [176] within a biocompatible PDMS-based chamber. These membranes, easily fashioned using soft lithography as demonstrated in **Figure IV-14**, effectively contain and dispense drugs.

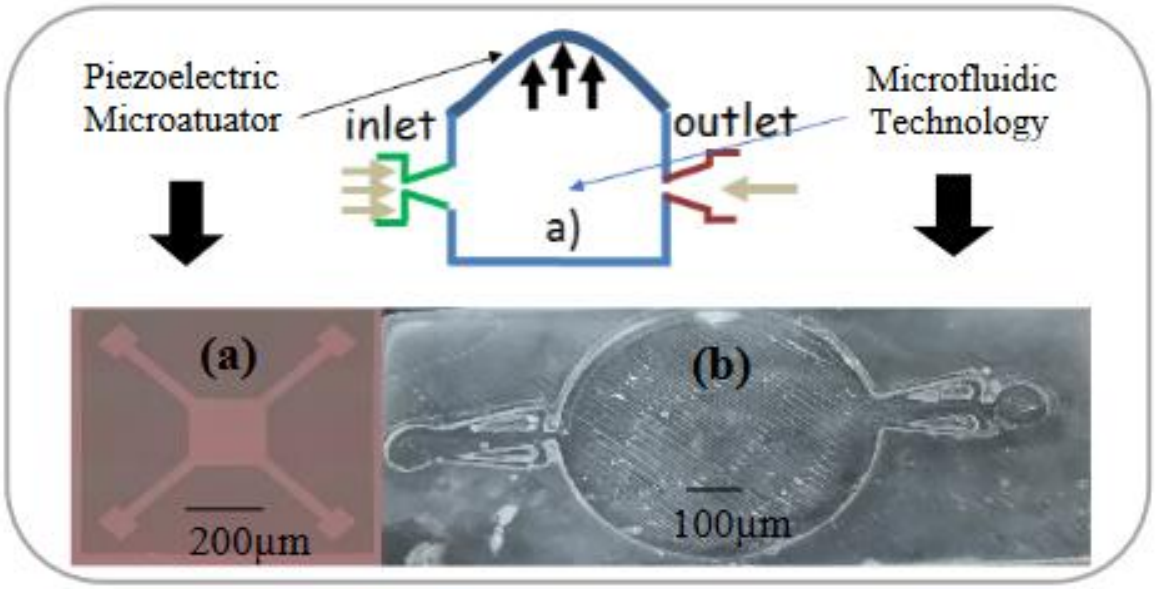


Figure IV- 14: Schematic of a micropump for drug delivery (a) optical photo of piezoelectric membrane fabricated by MEMS technology, and (b) optical photo of PDMS microfluidic circuit for insulin delivery fabricated by MEMS technology

5. Conclusion:

Our study presents a ground-breaking solution for a lightweight precise syringe infusion pump. By utilizing a smartphone application App Inventor, we have eliminated certain

electronic components, resulting in a lighter device that can be closely monitored by physicians. This innovation is particularly crucial for patients who require syringe infusion pumps in home or ambulatory settings or for the development of an AP system. The integration of smartphone technology has enormous potential to revolutionize healthcare delivery systems by enabling remote control, big data management, and leveraging diverse network communications protocols and modalities. The ubiquitous availability of mobile-based solutions further strengthens their potential to address outstanding healthcare challenges.

Looking ahead, we are actively developing a state-of-the-art biomedical patch that will utilize MEMS Nanofabrication technology methodologies and a monolithic integrated circuit.

Chapter

V. IoMT architecture for Artificial Pancreas using wearable ECG device

1. Introduction:

The practice of self-management is a critical component of diabetes management, and it has recently undergone a paradigm shift. In addition to enhancing treatment efficacy, self-management has become an essential driver of cost-effectiveness. According to a 2015 report by Goldman Sachs [3], the incorporation of the IoT in digital health has the potential to generate substantial savings, estimated to reach up to $305 billion. Notably, $200 billion of the total savings is attributed to the improved prevention and management of chronic diseases, with a particular focus on heart disease, asthma, and diabetes.

The emergence of self-management technologies owes much to the IoT concept. IoT platforms utilize wearable sensors to facilitate diabetes management by continually monitoring physiological signals such as glucose levels, calorie intake, and physical activity that can influence blood glucose levels. Systems that provide patients with real-time feedback and give doctors and patients decision-making tools have produced better results than traditional blood glucose self-monitoring [177].

It is pertinent to note that the artificial pancreas qualifies as an IoT system, given its incorporation of wearable sensors, wireless connectivity, and data processing that is contingent on the control algorithm [178, 179]. As research efforts continue to focus on integrating additional physiological signals into the AP system, progress toward a completely functional AP system is warranted. The significance of data format standardization and the interoperability of mobile devices with current clinical infrastructure is highlighted by the exponential rise of data collection, analysis, and transmission that involves both patients and healthcare practitioners.

In this chapter, we will examine cutting-edge IoT technologies that enable significant progress toward total diabetes self-management. We will additionally present an innovative IoT platform design for a diabetes self-management system that uses a wearable ECG device to continuously monitor blood sugar.

2. Background:

2.1. Commercial Artificial Pancreas systems provided by IoT platform:

The current landscape regarding Internet of Things (IoT) platforms dedicated to diabetes self-management technologies is quickly increasing and progressing [180]. Several corporations and institutions are actively developing IoT platforms tailored [180, 181], while others are focused on producing more generalized IoT platforms with the potential to be customized for use in AP systems [182, 183]. In terms of commercial-specific IoT platforms for AP systems, some examples include Medtronic's MiniMed 630G system, Tandem's t: slim X2 insulin pump with Basal-IQ technology, and Dexcom System [178]. As the example presented in **Figure V-1**, The system uses a CGM to monitor BG and an insulin pump to autonomously regulate BG levels in DM patients. The system is controlled by a mobile app that communicates with the CGM and insulin pump via Bluetooth. The appropriate amount of insulin for a patient is determined by the app via the use of a control algorithm, and based on the patient's current BGC and other features [178].

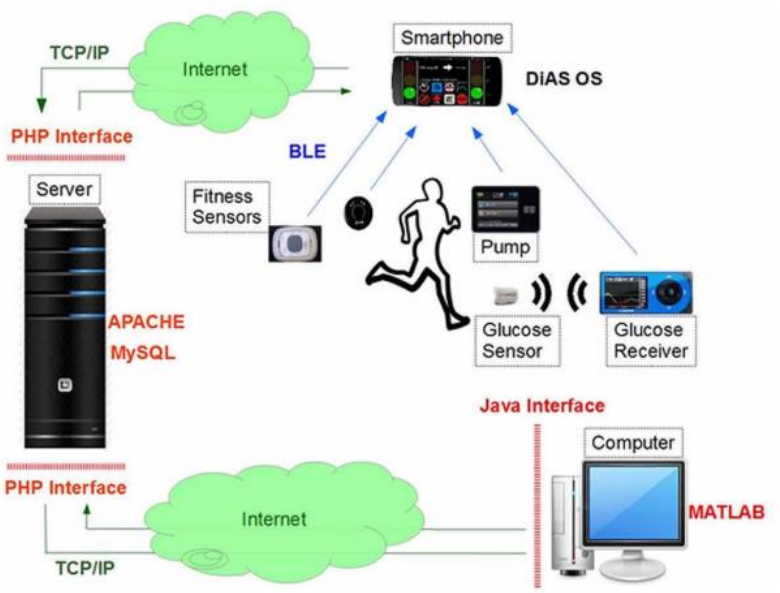


Figure V- 1: Artificial pancreas system with Mobile Device: Diabetes Advisory System (DiAs)

Several additional hybrid closed-loop (HCL) systems are currently being put through clinical trials and are anticipated to be released for commercial use within the coming years. Furthermore, the diabetes community “Do-It-Yourself (DIY)” has created a closed-loop code, which is utilized by numerous diabetes patients to construct custom closed-loop devices. These DIY closed-loop systems leverage publicly accessible CGMs and insulin pumps, along with an open-source algorithm that is executed via a mobile application to automate the administration of insulin [184, 185].

2.2. The impact of AI on the artificial pancreas and diabetes self-management system:

Artificial intelligence has a significant impact on the development and improvement of the artificial pancreas, providing new and innovative approaches to improve glucose control for individuals with diabetes. Machine learning algorithms can be trained on large datasets of glucose levels acquired from CGMs, insulin dose histories, and other physiological data to identify patterns and predict future glucose levels. This information can be used to help the artificial pancreas make more informed decisions about insulin dosing, improving glucose control, and reducing the risk of hypoglycemia.

Furthermore, AI can be used to optimize the performance of the artificial pancreas using advanced control algorithms. These algorithms can dynamically adjust insulin delivery in real time according to the current BG, ensuring that insulin dosing is tailored to the individual's needs [186, 187].

2.3. Revolutionizing Diabetes Care: The Emergence of IoT-Based M-Health Systems:

Recent advancements in information and Communication Technologies (ICT) and inventive biosensors permit a real-time, and full-scale diagnosis of a patient's condition. This set of technologies enabled the introduction of things to the internet. On the other hand, new emergent technologies such as Big Data, Cloud Computing, offer a new perspective in DM management by enabling the incorporation of Machine Learning (ML) and AI into such IoT systems. IoT-based M-health technologies let patients self-manage their chronic diseases, decreasing healthcare system traffic and expense.

Successful execution of such a platform's structure necessitates a comprehensive of the unique characteristics and specifications of the IoT project, as well as the ability to leverage advanced technologies and methodologies to deliver optimal outcomes [181]. This section explains how this is accomplished by enumerating the various IoT-based M-health solutions for diabetic self-management, providing illustrations followed by a comparative analysis.

A. Web-Based Services and Sensors:

This new approach supports the remote management of diabetes and involves the utilization of a web-based service that establishes cost-effective, and global communication between the patient's device and their web portal. This service facilitates a real-time updating of the patient's personal information, medication reminders, and blood glucose levels [188]. Whenever there is an increase in blood sugar levels, a phone call or SMS message is automatically sent to the patient's physician. It provides them with access to timely and effective care, regardless of their geographic location, while also reducing the burden on healthcare providers and improving overall patient outcomes. The diagram in **Figure V-2**. Describe an example of Web Based Services and Sensors process [188].

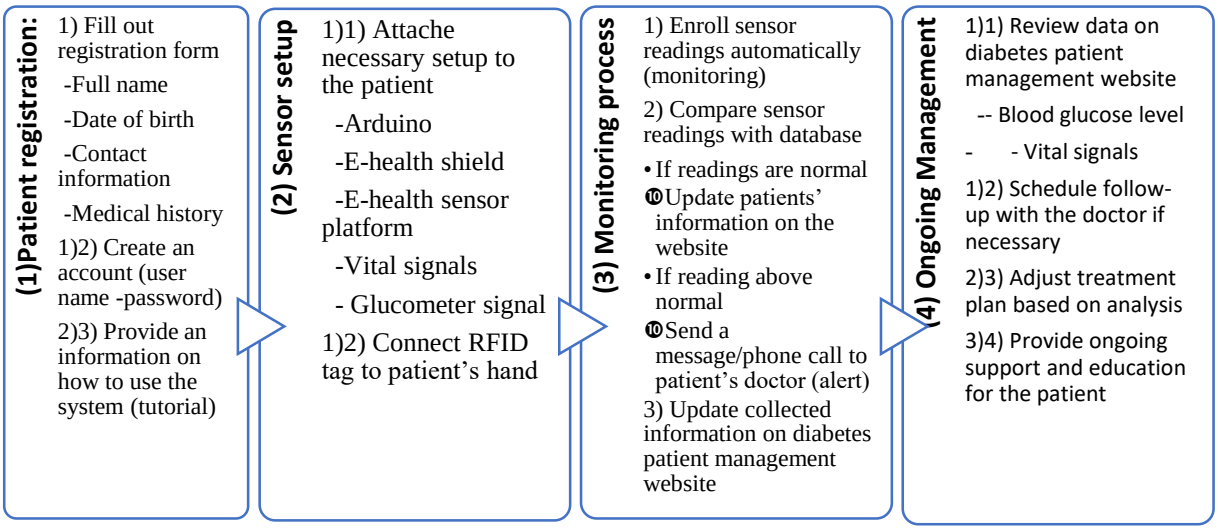


Figure V- 2: Diagram for Web Based Service and sensor process

There exist many universal Web-Based Services and Sensor platforms, such as Glooko, Tidepool, Carelink, and Diasend. Their capability to download data from multiple medical devices has significantly enhanced the operational efficiency of clinics. While most devices require manual downloading, certain devices can already be accessed by mobile applications, such as Dexcom, Freestyle Libre, and T-slim. These last have the added advantage of establishing an automated and continuous link with the hospital account, thereby eliminating the need for a computer [189, 190].

B. Robot Assistant in Management of Diabetes Based on the Internet of Things:

The present framework introduces an e-health platform that employs humanoid robotics to facilitate a multidimensional strategy of care for diabetes management. It applies IoT to a web-centric paradigm by leveraging operative web-based protocols for accessing, managing, and controlling physical layer objects. The foundation of the technological platform is policy-aware Internet of Things objects with the essential design characteristics [191]:

- Awareness: It is fundamental to the system, as it enables an in-depth understanding of the degree to which patients' activities conform to their unique treatment strategies. In turn, this comprehension enables the system to effectively monitor and manage the medical data of patients, ensuring optimal outcomes.
- Representation employs an ensemble of rules to analyze the data and extracts helpful summary information. It includes BG patterns, insulin dose estimation, and patient categorization based on the characteristics of their health conditions.
- Interaction, which exploits the patient's accumulated electronic health record data.

This e-health infrastructure consists of two elements: capillary networks and a web-based Disease Management Hub (DMH). Bluetooth is utilized to connect biosensors and humanoid robots that are part of the networks. The robot functions as a link between the patient's sensors and the DMH via a wireless local area network (Wi-Fi) that is connected to the current network structure (internet) [191, 192].

A DMH dashboard reveals a one-page summary of the patient’s medical profile and links to all the platform's most important applications, including the treatment plan, dialogue wizard,

diabetes diaries, and BG patterns, among others. Specialist physicians write the conversations, which are stored in a DMH dialogue library and accessible to caregivers. This collection's dialogues may be tailored to each patient's requirements and sickness treatment. During the discourse, the automaton may communicate with the DMH server to transmit information between both local and remote databases. **Figure V-3** shows the system architecture [191].

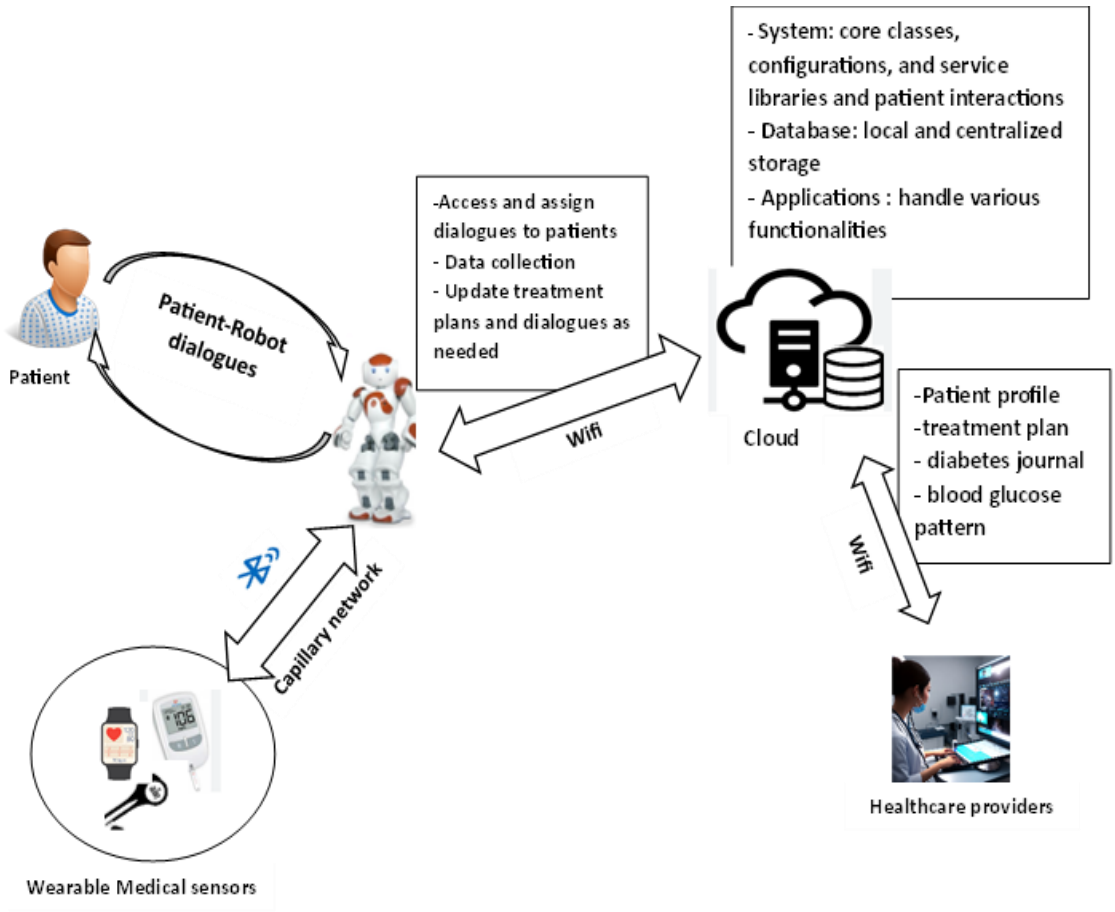


Figure V- 3: Abstract view of Robot Assistant in the Management of Diabetes Based on the Internet of Things.

C. Smartphone-Based m-Health System:

Mobile health (mHealth) is a type of e-health that involves the utilization of mobile devices to support public health and medical practices. The deployment of healthcare delivery systems through IoT and smartphone technology has the potential to impact healthcare significantly [153]. Numerous mobile applications exist to promote self-management, lifestyle changes, and

adherence to medications. These applications provide tele-management and consulting services for diabetes, allowing healthcare professionals to monitor their patients remotely and provide advisory services [193]. The platform as described in **Figure V-4** comprises [181]:

biomaterial: The patient layer produces data and triggers the system outputs (via medical decisions). Variables include motion, epidermis, blood, and other physiological alterations.

Sensors: The input data for the whole system is provided by various IoT-connected sensors. The ability to remotely configure and control these sensors via the Internet has enabled the development of numerous monitoring applications and technical frameworks.

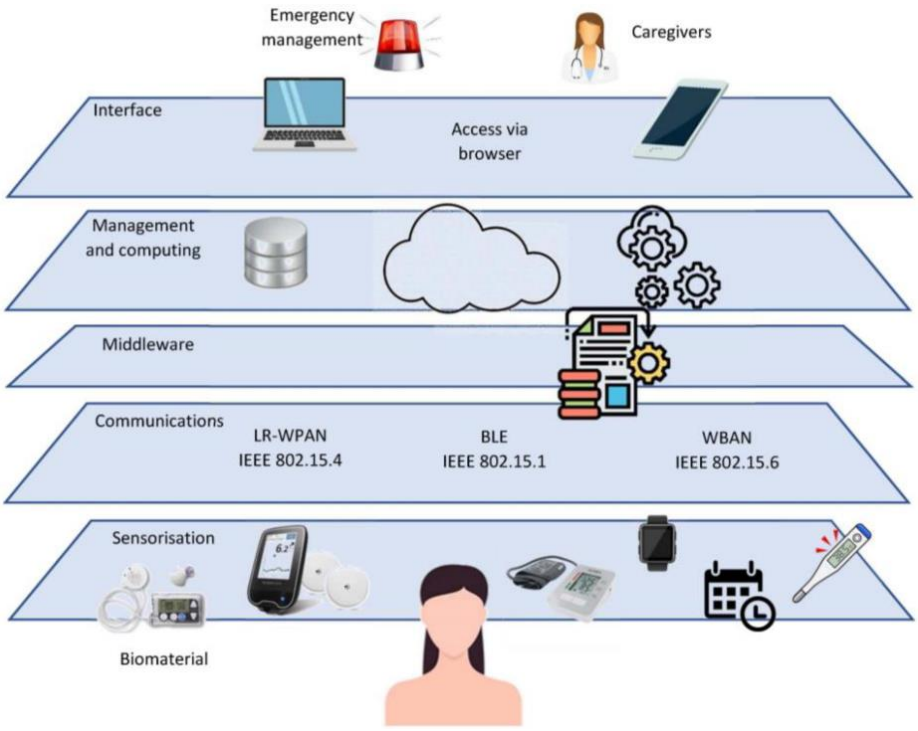


Figure V- 4: IoT-Architecture for Smartphone-Based m-Health System.

Communications: permit data penetration (transmission) across different layers. All sensors must provide different communication channels for a seamless connection. There are two kinds of networks, the first is a Local Area Network (LAN). consist of the communication between sensors and smart gateway devices such as smartphones/tablets. This kind can be done using Wi-Fi, 5G, ZigBee (or 6LowPAN), and BLE, which serve for short-range communication. The

second type of network is the Wide Area Network (WAN), which enables data transmission over longer distances. This network typically utilizes the internet.

Middleware: it is necessary to manage heterogeneous sources of data and seamlessly integrate devices and networks within the sensors and communication layer. The middleware enables the conversion of data from diverse sources into a standard language. This standardization of data is critical for ensuring that all data can be effectively processed and analyzed by the system

Management and computing: This layer performs data analysis, BG prediction, and treatment strategy selection. This is the location where the data processing algorithms are situated. Ubiquitous smartphones and pervasive Cloud computing are required to avoid problems caused by Internet disruptions and battery failure.

Interface layer: Browser-based system access, Android app, and Appel app allow a smartphone or computer to remotely modify the patient's or healthcare professionals' settings. The previous layer must have forecast BG levels as well as optimal insulin input, and other data which can be presented to the patient in this layer for approval or modification.

As an example, Dario (Appel-iOS, Android) [194]: developed by Tyto Innovation Ltd, is a self-management application designed for individuals with both T1DM and T2DM. The app allows users to track various aspects of their condition, and it analyzes the data to offer personalized recommendations for insulin dosing, meal planning, and physical activity to improve diabetes management. The Dario Blood Glucose Monitoring System is designed to work in conjunction with the app, allowing patients to measure their BG levels utilizing a smartphone-connected glucose meter. The system has been used in a multi-center setting and has shown a better outcome[195].

D. An IoT-Based Personal Device for Diabetes Therapy Management in Ambient Assisted Living (AAL):

The blood sugar levels of a patient are affected by a variety of factors; therefore, managing diabetes medication in AAL settings, such as nursing homes for the elderly or for diabetic patients, can be a difficult task. Several circumstances, such as disease, therapy, stress, exercise, medications, and dietary adjustments, can cause sometimes hazardous fluctuations in BG levels

making it unpredictable. Consequently, a personal care device will require accurate insulin calculation capabilities. Therefore, a personal device has been designed to assist with insulin treatment dose calculation and to take into account a greater number of variables [182, 196].

This system demonstrates an IoT-based personal diabetes management device. This approach aims to develop cutting-edge mobile assistance services that take into account more insulin therapy-related factors. Aiming to minimize hyperglycemia and hypoglycemia incidences, as well as the associated risks. The device supports 6LoWPAN communication to link the personal device with a home gateway [193]. The RFID identification is used to load the patient's profile from the personal health card, and a color touch screen to interact with the patient. In addition, this personal device is augmented by a glycemic index information system that consists of over 2,600 indexed products and is expanding, a desktop application that enables nurses and physicians to set up and review a patient's health card, and an application layer based on AI to define an adaptive insulin therapy for the patients. **Figure V-5** depicts the system's entire architecture.

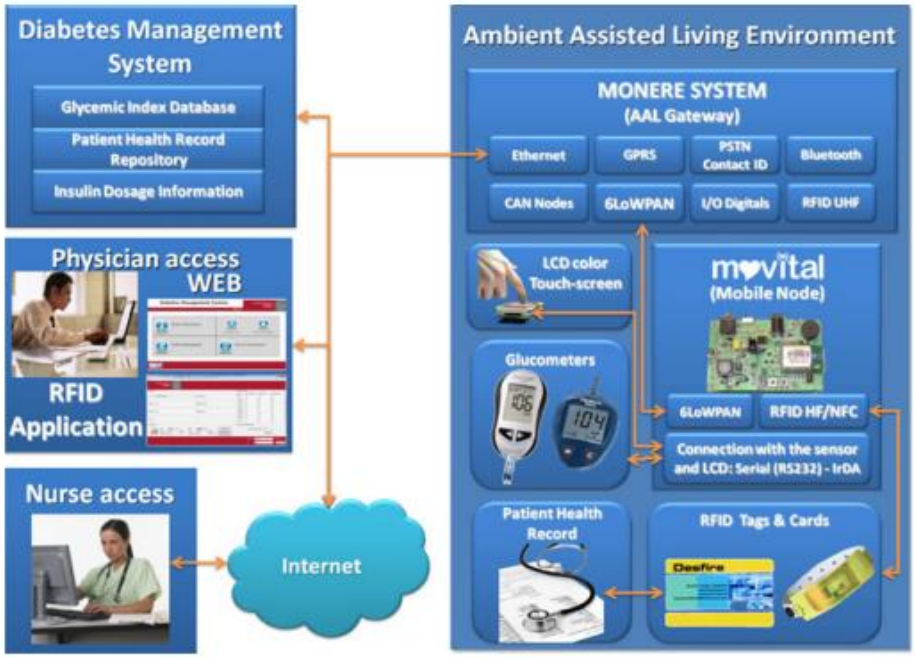


Figure V- 5: Architecture diagram for AAL system

E. Context-Aware-m-Health system:

The system facilitates two-way communication between patients and healthcare professionals. Patients are empowered to update their measured blood glucose values in the system database, with inconsistencies in the recorded readings being monitored by healthcare professionals. **Figure V-6** shows that the Context-Aware-m-Health system comprises several components, including a General Packet Radio Service (GPRS) glucometer, a Blood-Glucose Monitor (BGM) that collects patient data, and which consist of a telecare android and iOS application. This item facilitates communication between patients and healthcare professionals, physicians, and caregivers. Cloud server utilized to track updated values. The system also incorporates an Abnormal Blood Glucose Detection (ABLD) module and a Proactive Notification Module (PNE). In general, the GPRS BGM device collects BG values at various intervals (before/after meals, morning, etc.), which are subsequently uploaded to the Cloud server using the GPRS protocol and XML format[197].

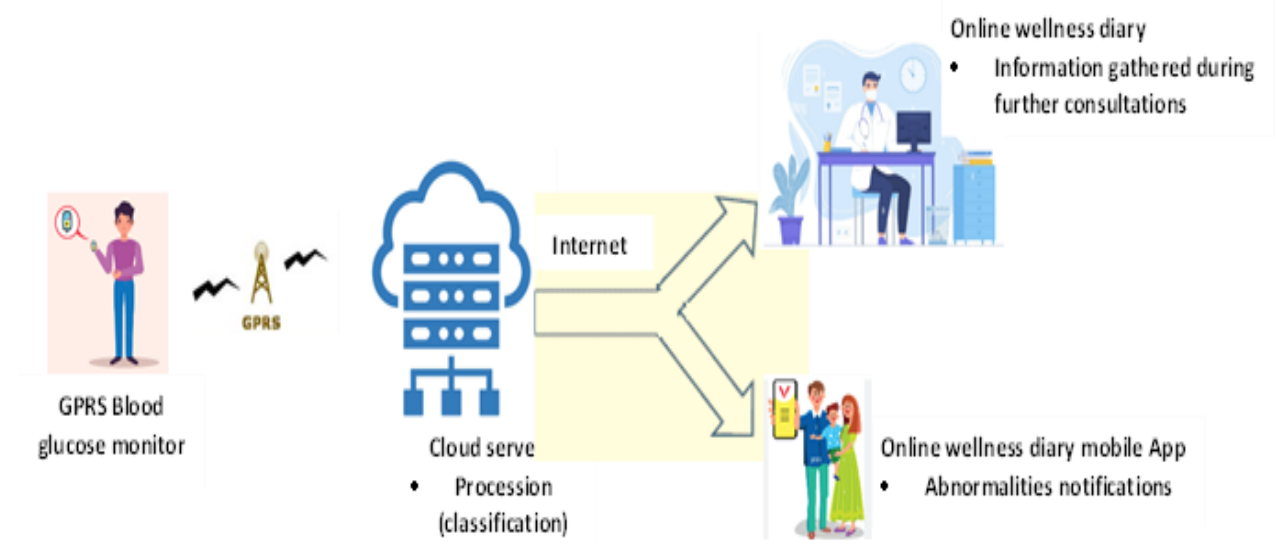


Figure V- 6: IoT architecture for Context-Aware m-Health system

Comparative study between cases A-B-C-D-E:

To select the most suitable IoT architecture for our proposed system, which is based on the real-time detection of BG level using a wearable ECG device, a detailed comparison of previously cited approaches [198] has been compiled in **Table V-1**.

Table V- 1: Comparison of different diabetes management IoT systems

System	Web Based Service	Robot-Assisted	Smartphone assisted	Personal Device In AAL	Interactive M-health Service
Cost	Low	High	Medium	Medium	Medium
Security	Insecure	Secure	Secure	Secure	Secure
Complexity	Low	High	Medium	High	Medium
Protocols used	GPRS	GPRS, Bluetooth	GPRS/LTE, Bluetooth-Wi-Fi	6LoWPAN, GPRS	GPRS, XML, MQTT
User control Over the System	No	No	yes	No	yes
Flexible	No	yes	yes	yes	yes
User interaction with the system	No	yes	yes	yes	yes

3. The proposed IoMT framework for artificial pancreas:

We have decided, based on the current state of the art, to develop a Smartphone-Based m-health System that employs a ubiquitous ECG device for continuous monitoring of blood glucose value. In recent years, the ECG has been predominantly utilized in cardiology to aid in the diagnosis and monitoring of cardiac disease. Smartwatches, bracelets, and bracelets are currently available as ECG wearable devices. Apple Watch Series 4 generates a single-lead electrocardiogram using electrodes and it is approved by the Food and Drug Administration

(FDA) to detect atrial flutter [199]. Other devices authorized by the FDA are used to detect ECG and HR. Zephyr-BioHarness 3, Kardiac Mobile from AliveCorCompany, and CompletTM (Omron+Alive Cor) are not the only devices on the list [87]. People must utilize the technologies they have already employed to monitor their blood glucose levels. By incorporating the previous methods adopted in Chapter 2 for BG measurement based on ECG signals, and the LMPC developed in Chapter 2 to determine the insulin amount needed, a new IoT architecture for artificial pancreas technologies that support diabetes self-management can be established.

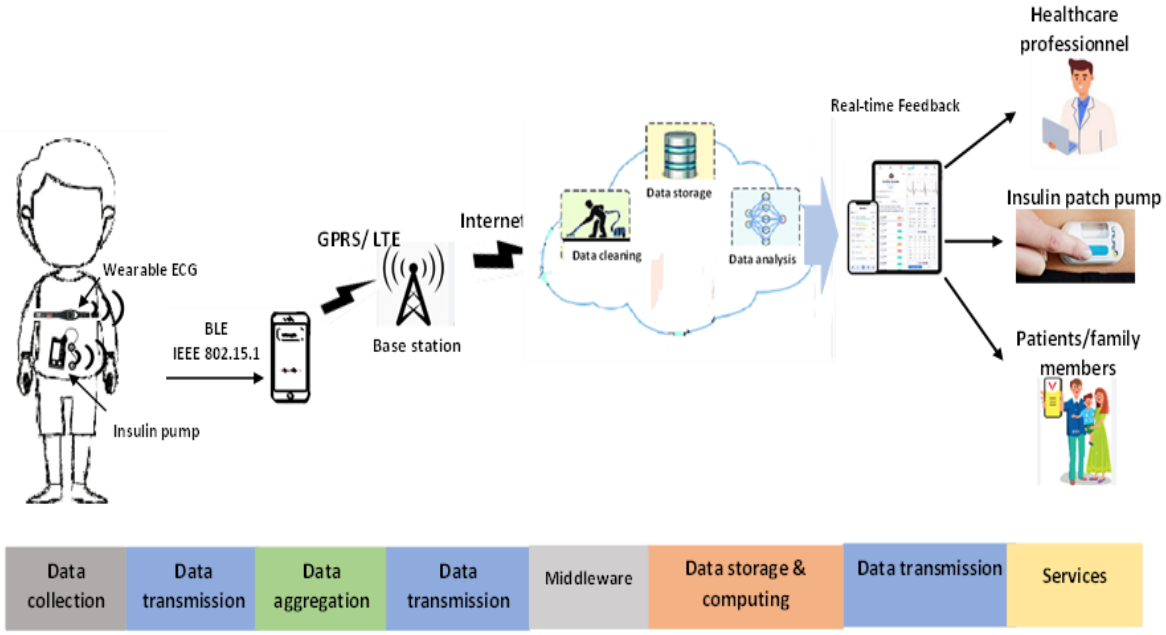


Figure V- 7: IoMT architecture for our artificial pancreas system

The development of an intelligent diabetes self-management system which is in our work an artificial pancreas system (closed loop system) that utilizes the electrocardiogram (ECG) signal to monitor blood glucose concentration necessitates the integration of diverse hardware, software, and cloud components within an IoT infrastructure. It is imperative to design a robust and comprehensive architecture that prioritizes data security, reliability, and scalability while ensuring seamless interoperability between the various components [200]. **Figure V-7** The proposed IoT system is represented as an abstract view. The exhibited IoT-based platform seeks to facilitate diabetes self-management via remote monitoring and individualized mobile

feedback. The platform encompasses a physical objects layer, a network layer, and a health portal layer that performs remote data collection, processing, and monitoring based on individual patient treatment plans.

3.1.Physical-Objects Layer:

This layer enables communication among humans and device objects, and between objects themselves. It entails a Wireless Body Area Network (WBAN), which is comprised of multiple medical sensors (wearable ECG monitor, insulin pump) and a mobile device. All the above gadgets communicate using Bluetooth. The smartphone (gateway) serves as the master Bluetooth node for a piconet of medical sensors and as a link between this layer and the health portal applications. Moreover, it functions as the patient's entry point to the platform. The latency required for data transmission varies based on the type of data being transmitted. In the context of our study, we are utilizing an ECG signal for real-time blood glucose monitoring. Extensive literature reviews suggest that a latency of up to 2 to 4 seconds is deemed acceptable.

Comparatively, BLE is a more energy-efficient option than 6LoWPAN. This is attributed to the reduction in advertising channels from 16 to 3, which simplifies scanning and necessitates a standby period before data transfer [201]. Furthermore, the connection time is faster and automatic during scanning, enabling connection and transmission within 3 milliseconds. The BLE top current is below 17.5 mA. This low power requirement of the BLE technology makes it possible to use small coin cell batteries as a power source, which is critical for designing a compact system.

The WBAN in our application can consist of two or more devices: a wearable ECG device and an insulin pump are presented as indispensable components in this project and they are defined as different kinds of objects: the insulin pump is an actuator, whereas the wearable ECG device is a sensor.

The actuators (insulin pump): It can be activated to release the amount of insulin calculated by the MPC model according to the BG estimated using ECG features. On the other hand, it can be deactivated in low BGC cases. The insulin pump must be connected to the gateway (smartphone). It is imperative to ensure that the actuator is equipped with the necessary functionality and features to enable precise and accurate regulation while adhering to the

highest standards of safety and reliability. As mentioned in Chapter 4, a member of our team "Slami Ahmed" is working on a patch pump using MEMS technologies.

3.2.Network Layer :

Long-distance connectivity between the physical layer and the Web health portal is representative of the network layer. It uses GPRS or LTE wireless protocols. A fundamental component of the platform is the Internet, which is regarded as an existing global networking infrastructure for communication and data exchange.

3.3.The application layer :

The application layer (Cloud Layer), which situated on top of the Internet. It allows interaction between physical layer objects and other entities, such as healthcare professionals, hospitals, and other systems. By leveraging an IoT Cloud, computational tasks that require significant processing power such as ML and AI algorithms can be carried out on powerful servers, thereby lightening the load on smart devices [20]. The Cloud computing service layer is of paramount importance in the IoMT healthcare system wherein all data is meticulously processed, stored, and analyzed. **Figure V-8** depicts the operations that can be carried out in the Cloud layer for our application. This platform can be conveniently hosted on a public Cloud, such as Amazon Web Services (AWS), Microsoft Azure, or Google Cloud Platform (GCP) [202], which offers a broad spectrum of services and features suitable for developing IoT solutions. Alternatively, to ensure enhanced security, the Cloud platform can also be hosted on a private Cloud, which can be an optimal choice for organizations that need to comply with stringent data privacy and security regulations. The subsequent section elaborates on some Cloud service specifics

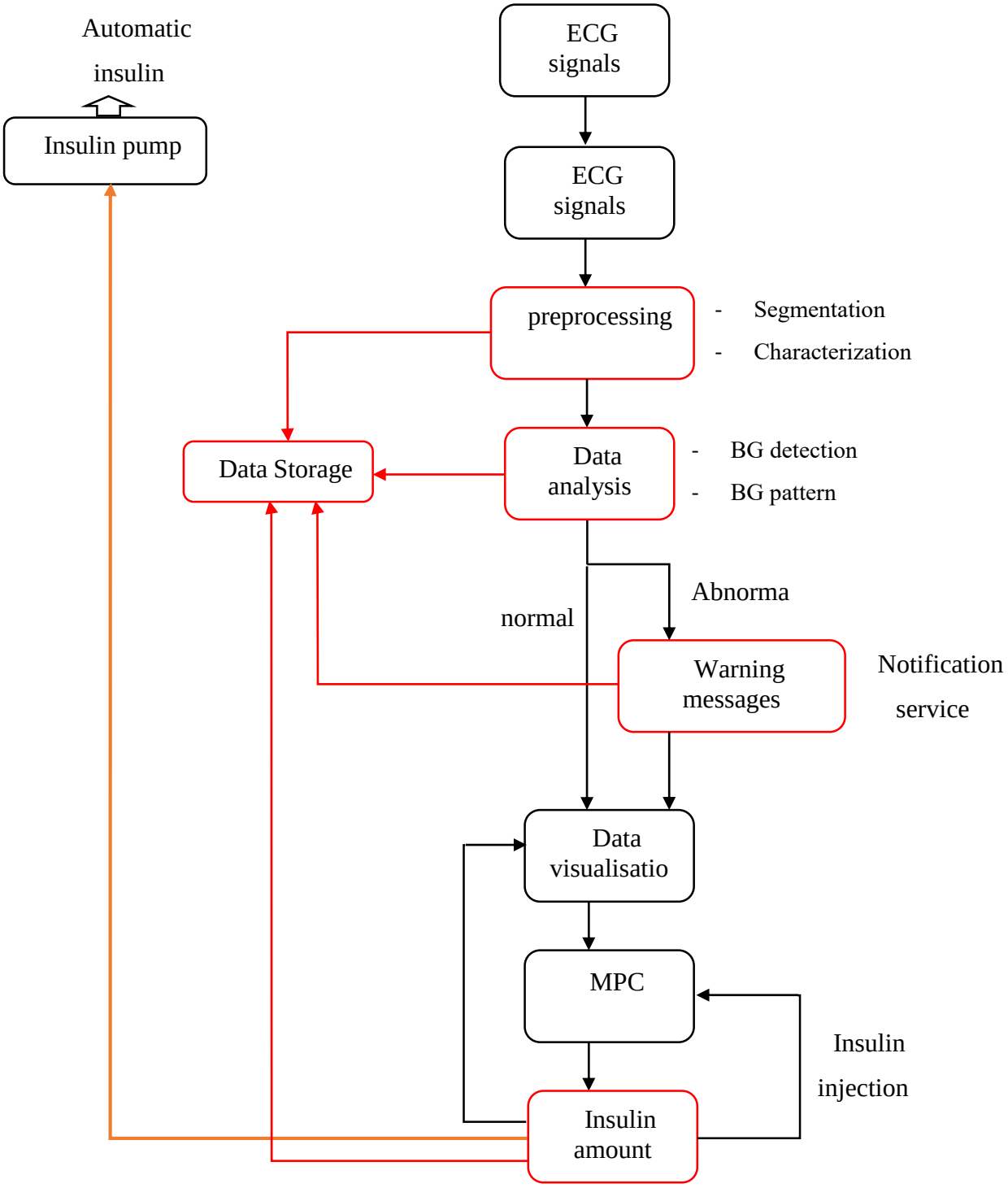


Figure V- 8: Diagram for the operations carried out in the Cloud

a. Data Storage:

In the context of the IoT, data storage is a critical component of the Cloud platform. The platform is required to store vast amounts of data collected from sensors, which can be achieved through the utilization of a database management system, such as MySQL or MongoDB [203]. The database can be hosted on the Cloud platform itself or a separate server, depending on the specific requirements and constraints of the IoT project. Continuous monitoring of ECG signals is characterized by a big volume, so, it is imperative to ensure that the chosen database management system is capable of handling the volume, velocity, and variety of data generated by the IoT devices in a reliable, scalable, and secure manner.

b. Data processing:

This is required to extract vital insights and meaningful information from the data collected by the sensors. This is achieved through the application of sophisticated ML algorithms, specifically, artificial neural networks, which are adopted in Chapter 2 for ECG segmentation. The algorithms can be trained on annotated ECG data to enable accurate extraction of the different ECG features needed for accurate BGC. It is important to ensure that the selected ML algorithms are suitable for the specific requirements and characteristics of the IoT project, and can deliver reliable, accurate outputs.

c. Data analysis:

This step also includes sophisticated algorithms based on ML. The algorithm is utilized to determine the BGC based on the previous ECG features extracted as described in chapter 2. Another algorithm is utilized to determine the severity of the estimated BG level (normal or abnormal) to provide a real-time warning message defining the case (hypoglycemia or hyperglycemia). This will make the patient act quickly and prevent a critical situation. On the other hand, the developed MPC algorithm in Chapter 3, must be included in this step, to determine the appropriate infusion insulin rate needed according to the actual BG estimated. another algorithm can be added to perform other tasks such as the suggestion of carbohydrate/snack intake (if BG is too low) and other regimen propositions.

3.4.User interface (Data visualization) :

In the context of the IoT ecosystem, the user interface enables users (patient/family members, doctors, nurses) to visualize and interact with the data collected by the sensors and analyzed by the Cloud. This critical component can be implemented through the development of a mobile and/or web application that provides a comprehensive display of the blood glucose concentration in real time, along with the provision of real-time alerts (warnings) in the event of abnormal readings. It is essential to ensure that the user interface is intuitive, user-friendly, and capable of delivering a seamless experience to the end-users. Additionally, the user interface should be designed in a manner that is compatible with the specific requirements and limitations of the IoT project.

4. Issues and challenges:

The Internet of Things has the potential to provide medical professionals access to important data that may lead to better patient outcomes; nevertheless, several obstacles are preventing its widespread use in the healthcare industry.

Security Concerns/Privacy Issues/ Legal Regulatory and Rights issues: With a growing number of interconnected devices in the market and more to come, it's important to prioritize security policies. Poorly secured IoT devices can be exploited by cyber attackers and used as entry points to harm other devices in the network, resulting in the loss of personal data and decreased trust in internet-connected devices. To prevent such scenarios, it's essential to prioritize the security, resilience, and reliability of internet applications. Furthermore, the wide variety of devices that are linked to one another presents a multitude of security concerns, yet there are no legislative rules in place that address such vulnerabilities. In addition, the constant connection of IoT devices to the internet increases the possibility of tracking and surveillance by government and private agencies. Leading to a privacy issue [204].

Inter-operability standard issues: In the most optimal setting, all the networked Internet of Things devices should communicate with one another and share information. The reality of the situation, on the other hand, is intrinsically more complicated and is dependent on several tiers of communication protocol stacks connecting the relevant equipment [204].

5. Conclusion:

In recent years, the medical sector has been revolutionized by IoT technologies, which have facilitated real-time and remote monitoring by connecting various objects. Moreover, the integration of AI and ML has endowed these objects with intelligent capabilities, enabling them to provide accurate diagnoses regarding the patient's health status. In this chapter, we have proposed an intelligent IoMT platform that utilizes a smartphone application for an artificial pancreas. This platform employs a wearable ECG device as a continuous glucose monitor, instead of the commercially available CGMs. Additionally, it utilizes a model predictive controller to determine the appropriate insulin rate required for each patient, based on their calculated BGC. The proposed architecture has been carefully designed to meet the requirements of our application. Bluetooth Low Energy has been selected as the primary mode of connectivity between the objects (insulin pump, wearable ECG device, and smartphone) in WBAN. GPRS and/or LTE have been dedicated to the transmission and reception of data (ECG signals, insulin rates, alarms, and recommended treatments) between the smartphone and the internet, where the Cloud is located. The Cloud is responsible for processing, analyzing, and storing the data using AI and ML. It enables seamless interaction between the different components and other entities, such as healthcare professionals, hospitals, and other systems, while also automating the entire system.

This novel intelligent IoMT architecture for the artificial pancreas, based on the use of the ECG signal, represents a significant achievement, as we have successfully presented all the necessary components of this architecture.

General Conclusion

The Internet of Things (IoT) has the potential to connect physical and virtual objects through communication capabilities, providing data collection, management, and other services. Research is currently being conducted on the use of IoT in mHealth applications, with a particular focus on ubiquitous personal diabetes self-management. In the current digital era, with the availability of Cloud computing, AI, and ML technologies, a new accurate autonomous concept of medical applications has emerged. This thesis adopts these various technologies to build a novel diabetes self-management system.

Diabetes is a widespread disease that poses a significant threat to global health, highlighting the urgent need for medical solutions to alleviate the strain on healthcare services. By leveraging the aforementioned technologies, there has been a significant paradigm shift in diabetes self-care management. Nowadays, it is regarded as an indispensable aspect of diabetes management, not only for its potential to enhance treatment efficacy but also as a pivotal factor driving cost-effectiveness.

A successful diabetes self-management system must ensure that the blood glucose level is always within the normal range. For that, the system must provide a real-time BG monitoring service, an insulin rate calculator coupled with an autonomous injection system. Additionally, the system must provide alert and advisory services to prevent potentially life-threatening scenarios. Furthermore, to reduce the burden, these previously mentioned services need to be remotely monitored by healthcare administrators. In this context, we can find the artificial pancreas.

This thesis proposes a novel architecture for an intelligent IoMT health system for diabetes self-management, particularly an artificial pancreas. The system is composed of three different parts:

1. A novel approach for continuous glucose monitoring based on ECG signal:

In this part, we validated two different methods for BGC estimation based on ECG features. The first method utilized linear mathematical equations that employed 3 ECG features. It has been applied to 4 patients over numerous days, demonstrating a strong linearity between Real BG and Calculated BG, yielding RMSEs of 0.23 and 0.24, respectively, for equation 1 and

equation 2. The finding may introduce novel avenues for physiological modeling. Nevertheless, it should be noted that this method necessitates calibration each time there is a remarkable change in the BGC range. Despite this limitation, the results achieved are quite satisfactory, making the method very promising.

To overcome the calibration issue noted in the first method, we utilized ML to estimate the blood glucose concentration in the second method, specifically an artificial neural network. Our Algorithm models enabled us to estimate blood glucose concentration with an accuracy of 98%. In the second method, seven ECG features have been employed. Furthermore, the two methods have employed a convolutional neural network to accurately segment the different features needed in the studies. The features have been segmented with an accuracy of 94%.

The widespread availability of portable devices equipped with electrocardiogram (ECG) acquisition capabilities has made them accessible to a broad spectrum of individuals. These devices are affordable, non-invasive, simple to use, and durable, making them ideal for integration into an artificial pancreas as a wearable sensor for continuous glucose monitoring. This feature and the findings of our work render the device highly attractive to individuals living with diabetes or pre-diabetics.

2. An intelligent algorithm (model predictive controller) to predict the insulin rate required for maintaining the blood glucose in the normal range:

The MPC algorithm has been adopted in this part to estimate and predict the insulin rate needed to maintain the blood glucose in the normal range, avoiding hyper- and hypoglycemia episodes. After a deep comparative study, the MPC model has been confirmed to be suitable to be implemented in an AP architecture because it can incorporate different constraints (input-output). Additionally, it can support various numbers of inputs, such as the actual BGC, meal consumption, and other physiological signals that can impact the BGC. The adopted model (MPC) has been confirmed in simulation studies and has given promising results in handling different scenarios. According to the findings, the proposed algorithm gives better postprandial glucose control by delivering a continuous basal insulin rate and bolus rate in the case of meal consumption.

3. An IoMT-platform architecture based on a Smartphone application connects the different devices and permits remote monitoring:

In this part, we proposed a novel IoMT architecture for an AP system that contains the two previously cited parts. An IoT-based platform designed to facilitate diabetes self-management through remote monitoring and personalized mobile feedback. The platform consists of a physical objects layer, a network layer, and a health portal layer, which performs data collection, processing using ML and AI, and monitoring based on ECG signal. The physical objects layer involves wireless communication between medical sensors and mobile devices (BLE), while the network layer connects the physical layer to the web health portal through GPRS or LTE. The health portal layer interfaces the various objects of the physical layer to other objects, including healthcare professionals and hospitals, through a Cloud computing service layer. The platform also includes data storage and a user interface for data visualization. We emphasize the importance of ensuring that the platform is reliable, scalable, and user-friendly and that the machine learning algorithms used for ECG data analysis and insulin rate calculation are suitable for the specific requirements and characteristics of the IoT project. Remote health monitoring technologies are revolutionizing the healthcare business and enhancing people's lives. They also raise new questions concerning the privacy and security of users' medical data. For that, a deep study in this context must be conducted to finalize or propose an IoT platform, followed by the realization of the entire system.

In future work, the wearable device with the proposed algorithm will be evaluated in actual clinical trials to further investigate the performance of software and hardware in real-world settings and modify the functions and GUIs according to user feedback. Considering miniaturization, it is possible to deploy the prediction algorithm in other IoMT wearable devices with the collaboration of manufacturers, such as CGM and insulin pumps, to provide on-device decision support.

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