UNIVERSITÀ
DI PAVIA

UNIVERSITY OF PAVIA
FACULTY OF ENGINEERING
DEPARTMENT OF ELECTRICAL, COMPUTER AND BIOMEDICAL ENGINEERING

MASTER'S DEGREE IN INDUSTRIAL AUTOMATION ENGINEERING, INDUSTRIAL TECHNOLOGIES AND MANAGEMENT

MASTER THESIS

# ACTIVE MEDICAL IMPLANTS - DEVELOPMENT OF HARDWARE AND SOFTWARE INTERFACES FOR LONG-TERM INSULIN DELIVERY

Candidate: Antonio Sabatini

Internal Supervisor: Prof. Chiara Toffanin
External Supervisor: M.Sc. Carlos Arteaga

A.Y. 2023/2024

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# Abstract

Nowadays, diabetes is a major global health challenge, with millions of people living with the disease and many others unaware they live with it. The number of people with type 1 diabetes is experiencing a major increase in recent years, and patients often face difficulties in maintaining adequate glycemic control.

Current therapies, which include the use of insulin through multiple injections or insulin pumps, require continuous blood glucose monitoring, but often do not provide optimal control. Patients must rely on frequent blood glucose measurements, calculation of carbohydrate intake, and self-regulation of insulin doses, which can be complex and a source of stress.

This thesis work is part of the MuSiC4Diabetes project, an innovative initiative uniting seven European partners focused on the development of an unobtrusive continuous Multi-Metabolite monitoring system for a physiological care of insulin-treated diabetes. This project involves the development of an innovative implantable insulin delivery pump with the goal of improving the management of type 1 diabetes.

The pump will provide an accurate deliverance of insulin directly into the patient's body. It will be connected to a Multi-Metabolite (MM) sensor that monitors blood glucose, ketone, and lactic acid levels in real time, providing patients with useful information for managing their needs. This integration enables timely response and personalized treatment via an innovative control algorithm, helping to reduce the risk of hypoglycemia, hyperglycemia and other complications associated with diabetes.

This thesis work is focused on the design and development of the software and hardware part of the insulin pump system. In particular, the interfaces of two applications were created: the first connected to the MM sensor and the pump, which allows users to visualize data through interactive graphs showing the levels of the three Multi-Metabolites and insulin in the body; the second is needed by engineers to manage the pump via Bluetooth connection.

On the hardware side, the printed circuit board has been designed and developed for the pump's electronics, which controls the implantable system and facilitates the Bluetooth connection to an external device used daily: a phone.

In summary, the work aims to provide practical and innovative tools to improve the quality of life for people with type 1 diabetes, contributing to more effective management of the disease and a reduction in associated complications. The research conducted in the MuSiC4Diabetes project, represents an important step toward a future where the management of diabetes and the quality of life of people will be enhanced.

# Prefazione

Al giorno d'oggi, il diabete rappresenta una delle principali sfide sanitarie a livello globale, con milioni di persone che convivono con questa malattia e molte altre che non sanno di esserne affette. Il numero di persone affette da diabete di tipo 1 sta avendo un importante incremento negli ultimi anni, e i pazienti spesso devono affrontare difficoltà nel mantenere un controllo glicemico adeguato.

Le terapie attuali, che includono l'uso di insulina tramite iniezioni multiple o pompe insuliniche, richiedono un monitoraggio continuo della glicemia, ma spesso non garantiscono un controllo ottimale. I pazienti devono fare affidamento su misurazioni frequenti della glicemia, sul calcolo dei carboidrati assunti e sull'auto-regolazione delle dosi di insulina, che può essere complesso e fonte di stress.

Il presente lavoro di tesi si inserisce nel progetto MuSiC4Diabetes, un'iniziativa innovativa che unisce sette partner europei, focalizzata sullo sviluppo di un sistema di monitoraggio continuo e non invasivo dei multimetaboliti per la cura fisiologica del diabete trattato con insulina. Il progetto prevede lo sviluppo di una pompa impiantabile innovativa per l'erogazione di insulina, con l'obiettivo di migliorare la gestione del diabete di tipo 1.

La pompa fornirà un'erogazione accurata di insulina direttamente nel corpo del paziente. Essa sarà collegata a un sensore Multi-Metabolita (MM) che monitora in tempo reale i livelli di glicemia, chetoni e acido lattico, offrendo ai pazienti informazioni utili per la gestione dei loro bisogni. Questa integrazione consente una risposta tempestiva e una personalizzazione del trattamento attraverso un algoritmo di controllo innovativo, contribuendo a ridurre il rischio di ipoglicemie o iperglicemia, e altre complicanze associate al diabete.

Nel lavoro di tesi, l'attenzione si concentra sulla progettazione e sullo sviluppo della parte software e hardware del sistema della pompa di insulina. In particolare sono state create le interfacce di due applicazioni: la prima collegata al sensore MM e alla pompa, che permette agli utenti di visualizzare i dati attraverso grafici interattivi che mostrano i livelli dei tre Multi-Metaboliti e di insulina in corpo; la seconda è invece necessaria agli ingegneri per gestire la pompa tramite connessione bluetooth.

Sul lato hardware, è stato progettato e realizzato il circuito stampato per l'elettronica della pompa, che controlla il sistema impiantabile; tramite questa parte si realizza il collegamento Bluetooth a un dispositivo esterno usato quotidianamente: un telefono.

In sintesi il lavoro ha l'obiettivo di fornire strumenti pratici e innovativi per migliorare la qualità della vita delle persone con diabete di tipo 1, contribuendo ad una gestione più efficace della malattia e a una riduzione delle complicanze associate. La ricerca svolta nel progetto MuSiC4Diabetes, rappresenta un passo importante verso un futuro in cui la gestione del diabete e la qualità della vita delle persone saranno migliorate.

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# Introduction

In recent years, autoimmune diseases have become increasingly important in the global public health landscape. These diseases are characterized by an altered response of the immune system, which no longer recognizes certain tissues of the body as its own and attacks them, generating often irreversible damage. Among autoimmune diseases, Type 1 Diabetes Mellitus (T1DM) emerges as one of the most critical and widespread conditions, with a significant impact on patients' daily lives.

Type 1 diabetes is a chronic disease characterized by the destruction of pancreatic beta cells, which are responsible for the production of insulin, a hormone essential for glucose metabolism. In the absence of replacement therapy, T1DM inevitably leads to severe and life-threatening complications. Currently, insulin therapy is based on the infusion of exogenous insulin, either through multiple daily injections or the use of insulin pumps, which, although effective, have limitations in terms of comfort and accuracy.

However, despite advances in medical technology, the management of T1DM remains complex and subject to multiple variables: diet, physical activity, stress, and individual variability in insulin sensitivity. Continuous blood glucose monitoring to maintain glycemic levels within an optimal range and adjustment of insulin doses require constant effort for the patient, with a not insignificant impact on quality of life, both in physical and psychological terms.

This is the context for MuSiC4Diabetes, a European project funded by the Pathfinder program of the European Innovation Council. The project aims to develop a closed system that integrates an automated implantable pump for insulin delivery and a Multi-Metabolite (MM) sensor, enabling dynamic and real-time regulation. The latter represents an evolution of traditional monitoring systems, being able to measure blood glucose, lactate and ketone body levels (the latter, indicators of physical activity and risk of ketoacidosis, respectively). These data are processed by an intelligent control algorithm, which calculates the patient's insulin requirements in real time, improving the accuracy and timeliness of therapy.

This thesis work is part of this ambitious initiative and aims to develop hardware and software interfaces for the management of the implantable system. The work is divided into the following chapters:

- Chapter 1- Background: provides an in-depth overview of the medical and technological context in which this thesis is set. Initially, a general overview of autoimmune diseases is presented, which is followed by a detailed analysis of the epidemiology of diabetes mellitus, with a focus on T1DM. The progressive increase in incidence globally, current methods of diagnosis and treatment, and major complications related to suboptimal glycemic control are discussed. The state of the art of current technologies for glycemic monitoring and insulin delivery is also reviewed, analyzing their advantages and limitations still present in today's solutions, such as the need to announce meals.
- Chapter 2- Project and Method: the MuSiC4Diabetes project, within

which this thesis work is located, is introduced. Its partners involved, objectives and system architecture are described. It goes into detail about the first phase of the work performed, focusing on the design and implementation of the first version of the Analog Pump Driver (APD V1) electronic module. The main hardware components are presented.

- Chapter 3- Results: results obtained during the thesis work are reported. The second version of the APD is presented, developed with the aim of improving the efficiency of the system and integrating its functionality, especially with the introduction of Bluetooth communication, which is essential for remote control of the device.

  In parallel, the software development of the two mobile applications made through the Flutter framework is described. The first, called MM Sensor App, is intended for patients and allows the visualization of data from the Multi-Metabolite sensor, including blood glucose, lactate, ketones, and the data of active insulin in the patient's body, data from the pump. The second, PumpApp, is aimed at technicians and allows precise control of pump operating parameters via Bluetooth interface.

  These results demonstrate the technical feasibility of the system and represent a first step toward full integration of the modules into an innovative implantable medical device.

- Chapter 4- Conclusion and Outlook: the chapter highlights how the developed integrated system represents a significant advance in diabetes management, potentially improving the quality of life of patients with T1DM. The chapter highlights the importance of the proposed innovative solutions, their alignment with global health initiatives, and the contribution of the work to improve therapy.

# Chapter 1

# Background

## 1.1 Worldwide impact of autoimmune diseases

Autoimmune Diseases (ADs) are influenced by a combination of genetic and environmental factors. These factors affect the quality of immune system cells, impairing their ability to distinguish between healthy tissues and foreign agents[7].

Genes play a crucial role in determining the predisposition of the immune system to recognize certain antigens (markers that signal to the body that something is foreign), thereby targetting cells that may be mistakenly considered foreign and therefore, become targets of an immune attack.

In other words, the immune system, misidentifies healthy tissues in our body, and erroneously attacks them. Despite numerous studies [8], in this area, predicting the onset of an autoimmune disease remains unknown.

These diseases affect a significant portion of the worldwide population, nearly 4% of individuals are affected by more than 80 different types of ADs. It has been observed that women are more likely to develop these diseases than men. This prevalence may be due to hormonal or genetic differences in the X chromosome. Among the most well-known autoimmune diseases are diabetes mellitus and celiac disease [8, 9].

These conditions can manifest with complex and variable symptoms; understanding such diseases, which require individualized and multidisciplinary approaches, is a significant challenge for medicine.

Autoimmune organ damage is mediated by T cells, a type of white blood cells that recognize and attack body cells that they perceive as foreign, contributing to autoimmune diseases as in Type 1 Diabetes Mellitus (T1DM) and multiple sclerosis. Antibodies, such as antibodies against beta cells, are also produced in these diseases [7, 8].

The T1DM also known as insulin-dependent diabetes mellitus, results from the autoimmune response against beta cells in the pancreas and is characterized by a total absence (or near absence) of insulin production.

## 1.2 Diabetes overview

### 1.2.1 Incidence

Diabetes mellitus is a chronic disease characterized by an increase in blood glucose concentration, commonly known as glycemia. It has emerged as one of the most prevalent and rapidly expanding health conditions globally, with forecasts indicating that by 2045, approximately 690 million adults will be impacted (more than 50% increase compared to 2017) [10].

The patients suffering from diabetes are steadily increasing and diabetes is no longer a condition exclusive to developed countries; its prevalence is growing especially in middle-income countries, thus shaping up as a global health priority.

According to The Lancet [11], more than 800 million adults worldwide currently suffer from diabetes. The quantity of patients has increased more than four times since 1990. Considering that more than 90 percent of diabetics suffer from Type 2 Diabetes Mellitus (T2DM), this figure highlights the increase in obesity, exacerbated by sedentary lifestyle and economic hardship. India and China account for the majority of this population, with over 200 and 140 million cases respectively [11].

In many areas, lack of effective policies to promote healthy lifestyles and limited access to a high quality healthcare system hinder the prevention and treatment of diabetes, particularly for the most modest segment of the population. By 2022, due to widespread prevalence in low-income countries, nearly 450 million adults aged 30 years and older were untreated, with 90 percent of these living in low-income settings.

Diabetes and its complications place a significant burden on the finances of individuals and their families, as well as on national economies. T1DM can be treated by delivering a precise dose of insulin depending on the glucose concentration in the body, nevertheless, due to its high production costs, it is not accessible to all patients [12, 11].

In response, Member States of the World Health Organization (WHO) have listed diabetes as one of the four priority NonCommunicable Diseases (NCDs), along with cardiovascular disease, cancer, and chronic respiratory disease [13].

WHO has established global targets for diabetes management to be achieved by 2030, including that 80 percent of people with diagnosed diabetes should have good glycemic control.

However, studies suggest that this significant increase of patients who suffer from diabetes is attributable to several factors: aging population, earlier diagnosis, and increased survival rate among people with diabetes. As a result, mortality has decreased significantly in all age groups [12].

### 1.2.2 Disease description

Diabetes is a disease that occurs when the body fails to use the insulin it produces (a hormone that regulates blood sugar), or when the pancreas does not produce enough of it, causing blood glucose concentrations to rise.

Glucose, carried by the bloodstream and regulated by the hormone insulin, is distributed throughout the body, and is used by cells to produce energy needed to carry out vital functions, such as cell multiplication, tissue repair, or muscle movement. In the absence of insulin, blood glucose concentration rise leading to a metabolic stress within the cells that are forced to continuously produce energy leading to its collective failure and an eventual tissue damage [10].

This disorder alters carbohydrate, fat, and protein metabolism. This is the result of insulin imbalance, which can manifest through insulin resistance or inadequate secretion. In the absence of adequate insulin action, metabolism undergoes alterations, preventing the regular utilization of glucose by cells.

The human body then adapts to conditions of sugar scarcity by activating alternative metabolic pathways to ensure sufficient energy intake, for instance some of the stored fat is converted to acetoacetic acid, which is used by tissues as an alternative energy source to glucose. This mechanism is particularly relevant in contexts of prolonged fasting or low-carbohydrate diets, where fat mobilization becomes essential for the maintenance of vital functions [10, 14].

Diabetes can be classified into various clinically distinct forms:

1. Type 1 Diabetes Mellitus (T1DM)

2. Type 2 Diabetes Mellitus (T2DM) [14]

3. Other types: may result from specific genetic defects in beta-cell function or insulin action, pancreatic diseases, or medications. For example gestational diabetes or pancreatic diseases [15].

The disease is usually diagnosed only when specific symptoms occur; major diabetes associations are moving to raise awareness of the importance of early diagnosis in order to prevent serious complications. In particular, the American Diabetes Association (ADA) and the International Diabetes Federation have listed the main symptoms in the hope that those who experience them will seek medical attention (See Figure 1.1).

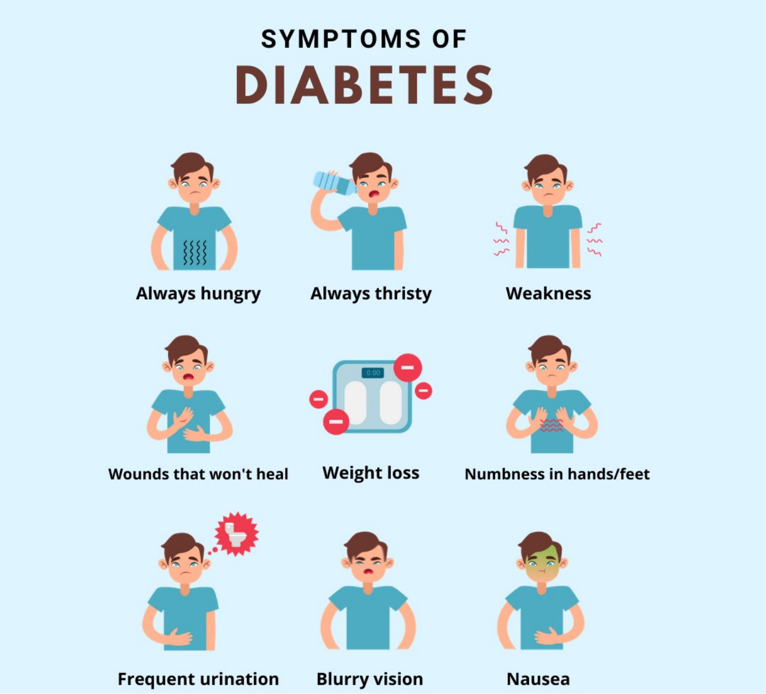


Figure 1.1: Diabetes symptoms [1]

So the most relevant symptoms are polyuria, polydipsia, extreme hunger, unusual weight loss, increased fatigue, irritability. Although these symptoms are often evident in patients with type 1 diabetes, it is not known how specific they are for the initial diagnosis of type 2 diabetes [16].

It is estimated that half of all patients with diabetes are unaware of their disease and are therefore more prone to develop diabetic complications. In addition to the evaluation of symptoms, which are not always evident (especially in type 2 diabetes), the diagnosis of diabetes is based on a series of chemical tests performed on urine and blood samples. In particular, urine ketone and glucose values are analyzed, as well as blood glucose levels, plasma insulin concentration and autoantibodies.

### 1.2.3 Complications and glucose control

Complications of diabetes are common among diabetic patients and impact their life quality and, when not adequately treated, may result lethal. These are divided into microvascular and macrovascular, with the former having a much higher prevalence than the latter.

Microvascular complications include nephropathy, neuropathy, and retinopathy, while macrovascular complications include cardiovascular disease, stroke, and peripheral arterial disease [15].

To prevent these complications, diabetics must keep blood glucose in a certain range throughout the day. In a healthy individual, blood glucose concentration is tightly controlled, usually between 80 and 100 mg/dL in the fasting person, between 120 and 130 mg/dL during the first hour after a meal. Feedback systems for blood glucose control quickly bring the glucose concentration back to the control level, within two hours after a meal. In contrast, in a fasting state, the liver supplies the glucose needed to keep blood glucose steady [14].

For a diabetic patient, the glucose concentration should be around 70 mg/dL and 180 mg/dL. Values below or above this concentration are considered hypo-or hyperglycemia, respectively. The latter value represents the blood threshold for the appearance of glucose in the urine [14].

The concentration of glucose in the bloodstream can be classified in two:

- Hypoglicemia: it occurs when blood glucose levels are in the 50-70 mg/dL range. This condition often happens after an overdose of insulin or after intense physical activity. It is essential that the patient ingest sacharose to restore blood sugar levels. If the blood glucose drop to 20-50 mg/dL, there is a high risk of loss of consciousness and hypoglycemic coma.

- Hyperglycemia: it occurs when values are over 180 mg/dL. Values over 180 mg/dL maintained for a prolonged period of time can cause nausea, thirst, and in severe cases coma caused by ketoacidosis. Without an insulin dose, hyperglycemia can progress to diabetic ketoacidosis and then a possible coma condition [14].

In Figure 1.2, three postprandial trends are shown. The graphs represent the glucose concentration levels (mg/dL) over time. The trend in green show normal glucose levels in a healthy person. The next trend in blue represents a person with high glucose concentration in blood but not yet diagnosed as diabetes. Finally the red graph depicts the graph of a person with diabetes.

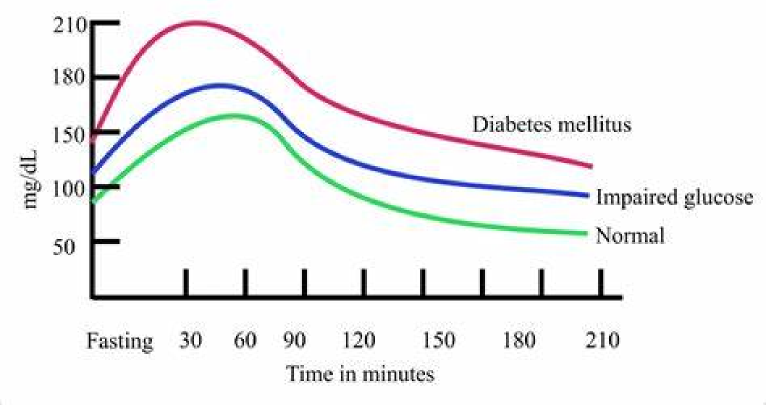


Figure 1.2: Curves for diabetic and healthy patients [2]

To keep blood glucose levels in the established range, numerous technologies have been developed over the years (Section 1.4).

### 1.2.4 T2DM overview

Also known as non-insulin-dependent diabetes mellitus, T2DM is the most common among individuals, affecting about 90-95% of diabetic patients. This condition is caused by reduced tissue sensitivity to the effect of insulin, a phenomenon known as insulin resistance. T2DM appears to be more common than T1DM; in most cases the onset of this disease occurs after the age of 30, often between the ages of 50 and 60 years, and develops gradually. This type of diabetes generally begins with a so called insulin resistance, where the insulin hormone couples to a determined receptor on the surface of the cell, nevertheless the cell doesn't respond, leading to an insulin resistance.The pancreas may gradually reduce insulin production or eventually stop producing it. The main risk factor is obesity and a sedentary and unhealthy lifestyle [15].

For people with T2DM, a balanced diet and exercise is strongly recommended to promote weight loss and reverse insulin resistance. If the strategy fails, there are several treatment options, for example, drugs to increase insulin sensitivity or, in some cases, the administration of insulin [14].

## 1.3 Type 1 Diabetes

T1DM is an autoimmune disease characterized by the destruction of pancreatic beta cells, which are responsible for insulin production.

In Figure 1.3, the main difference between a healthy and a diabetic subjet is shown. On the left hand-side, the insulin is produced from the pancreas, facilitating the transport of glucose to the body's cells. On the other hand, the lack of insulin production due to the destruction of beta cells, prevents glucose from being transported effectively, causing the concentration of glucose in the bloodstream to rise [17].

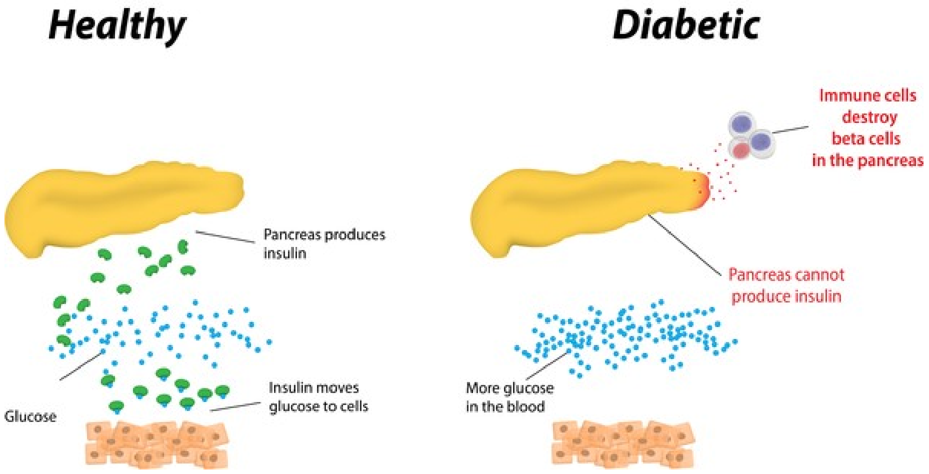


Figure 1.3: Comparison of healthy and diseased pancreas [3]

The T1DM can develop unexpectedly, over several weeks or months, and manifests itself through three main symptoms:

1. Increased blood glucose levels;
2. Increased utilization of fat for energy;
3. Depletion of protein in the body.

The patient with T1DM is characterized by an insulin-dependency. This hormone influences a balanced metabolism of carbohydrates, fats and proteins, thus allowing physiological functioning to be as normal as possible.

Currently there is no cure for T1DM; however, through effective insulin delivery, a healthy diet, and physical activity the patient can control T1DM. Currently, the only possible therapy is exogenous administration of synthetically produced insulin. Patients must therefore undergo lifelong insulin therapy [14].

Insulin is taken mainly by injections into the subcutaneous tissue, from which it then spreads to the whole body.

There are different types of exogenous insulin used in treatment, each with specific characteristics and different times of action; Table 1.1 shows the most commonly used types [18]:

Table 1.1: Insulin types

| **Type of Insulin** | **Administration** | **Onset of Action** | **Peak Action (max hypoglycemic effect)** | **Duration of Action** |
|---|---|---|---|---|
| **Ultrarapid** | Just before meals | 10-15 minutes | 30 minutes | 3-5 hours |
| **Rapid** | About 30 minutes before meals | 30 minutes | 1-2 hours | 6-8 hours |
| **Long-acting** | Once a day | 1-2 hours | No defined, long release | Up to 48 hours |

Currently, there are two main treatment modalities for T1DM: multi-injection therapy and the use of patches.

In multi-injection therapy, patients usually supplement, according to their specific physiological needs, long-acting insulin (or basal insulin) with injections of ultrarapid or rapid insulin given before meals, thus administering multiple injections throughout the day.

Insulin intake varies for each patient depending in their insulin sensitivity, defined as the ratio of insulin to carbohydrates.

In addition, insulin sensitivity is influenced by several factors, including each individual's insulin resistance, physical activity, stress, or the presence of viral infections. Insulin sensitivity in cell membranes is affected by the presence of lactate. Lactate is a metabolite produced under conditions of low oxygen supply, as occurs during intense physical activity. Therefore, having information about lactate levels in tissues optimizes and makes insulin dosing more accurate and effective. At the same time, it can also vary at different times of the day: for example, in the morning, due to the release of certain hormones, blood glucose tends to rise more easily [19].

Therefore, the diabetic patient should regularly monitor blood glucose levels throughout the day and should perform, for each meal, a count of the carbohydrates in the food in order to assess how much insulin to inject.

Traditionally, the glycemic goal for patients with T1DM is an A1C (glycated hemoglobin) value of 7.0 or less; glycated hemoglobin is a value that respects average blood glucose concentrations over the past three months [4]. Other hypotheses about the onset of T1DM have been proposed, including the influence of viral infections, autoimmune disorders, or stress as a trigger, but there are no firm assessments of the cause of the onset of the disease [17].

Nowadays, the epidemiology of T1DM remains unknown, as does the prevention and treatment of the disease. However, for just over a decade, new technologies have been developing to help patients in the daily management of the disease.

## 1.4 Actual Diabetes control systems

Current therapy for T1DM is based on daily insulin administration in relation to food intake and supplementation of daily activities such as exercise. Many advances have been made in insulin formulation and diabetes technologies, including glucose monitoring and insulin delivery methods.

### 1.4.1 Blood glucose monitoring systems

For patients with T1DM, continuous monitoring of blood glucose throughout the day is essential. Until the 1970s and 1980s, the measurement of glucose concentration was through urinalysis; later, there was a shift to capillary blood testing, which allowed more timely and targeted monitoring. However, in addition to the need of finger-pricking several times a day, they did not guarantee recognition of all the risky events of hypo/hyperglycemia, the cause of major long-term and short-term complications [20].

Throughout the last decade, the first wearable sensors were introduced in the market. They enable a Continuous blood Glucose Monitoring (CGM system) through 'real-time' measurements at the interstitial level. This technology has evolved over the last years, increasing their accuracy, response time without the need of extracting blood samples that affected the quality of life from patients.

CGM devices consist of a sensor, a transmitter (often integrated into the sensor itself), and a receiver. The sensor is inserted under the skin via an automated device, and is immersed in the interstitial fluid. The sensor emits a small electric current in response to glucose oxidation, and the transmitter (battery-operated or rechargeable) sends signals to the receiver (electronic device or an app on the cell phone). Through the receiver, the patient can view glucose data in real time, updated every five minutes and with a physiological delay of about five minutes due to diffusion between the plasma and the interstitial space, where the sensor in inserted [20].

The subcutaneous sensor needs to be replaced every 3-14 days, and an implanted sensor version is also available, to be replaced every 6 months. For glycemic control, monitoring functions, such as the rate of change of glycemic levels, trends, and alarms of hypoglycemia or hyperglycemia, are also essential. Furthermore, it provides diabetes teams with new tools for interpreting glycemic data and profiles, helping to make optimal therapeutic choices.

The goals of these systems are to reach a normal concentration of glucose in the body (normoglycemia) and avoid hypoglycemia episodes, allowing normal daily activities. Sensors are an important aid in this respect; despite this, the lancing device remains the most accurate method of measurement [21].

### 1.4.2 Insulin pumps

As mentioned in Section 1.3, insulin can be administered with multinjection therapy, or with a pump with or without a catheter (known as a patch-pump), which injects insulin depending on the patient's glucose levels. Until a few years ago, it was possible to use the sensor for glycemic control and, separately, the pump to inject the necessary insulin. However, recently the so-called 'Artificial Pancreas' has been introduced to the market, which not only allows for improved glycemic control and decreased episodes of severe hypoglycemia, but also brings benefits in terms of quality of life [4]. It represents an evolving closed-loop blood glucose control system with the goal of replacing the endocrine function of the pancreas, which is impaired in patients with diabetes, particularly in the case of T1DM. The device integrates a pump for automatic infusion of insulin based on the current blood glucose measured by the CGM device and additional information provided by the patient in order to compute the optimal therapy through a control algorithm. [4].

The main components, connected wirelessly, are:

- A subcutaneous sensor for continuous blood glucose reading, shown in Figure 1.4 (first panel).
- An insulin delivery pump, consisting of a refillable insulin cartridge, a pumping mechanism, and a programmable user interface; based on the carbohydrate intake and glucose in the body the pump injects a certain amount of insulin, as shown in Figure 1.4 (third panel).
- A control algorithm, a key element that determines the amount of insulin to be infused subcutaneously based on the recorded glucose value. The two most widely used algorithms are PID (Proportional-Integral-Derivative) and MPC (Model Predictive Control).

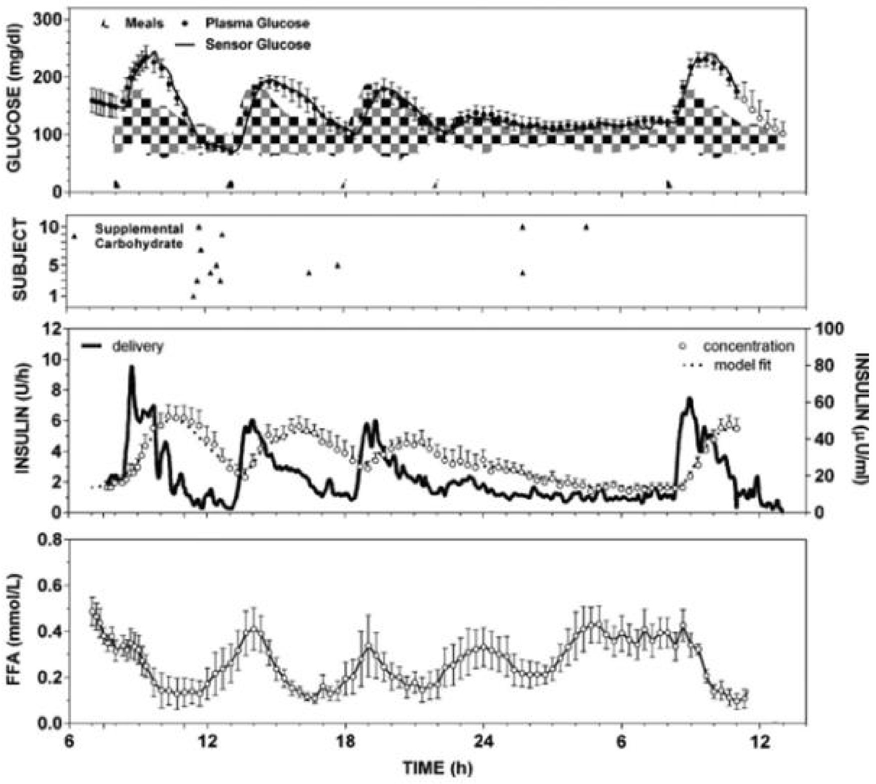


Figure 1.4: Glucose, carbohydrate, insulin and Free Fatty Acids (FFA) averaged over ten subjects, illustrating the performance of a PID closed-loop algorithm [4]

Most artificial pancreas devices require meal announcement, that is, an estimate of the carbohydrates to be consumed; thus the device calculates the dose of insulin needed based on the patient's insulin-carbohydrate sensitivity.

A significant example of development in this field is the Minimed 780G system, made by Medtronic. This system operates in two modes:

1. Manual mode: the device can detect episodes of hypoglycemia and suspend insulin delivery if necessary. In addition, the amount of

basal insulin is pre-programmed by the user.

2. The system automatically adjusts basal insulin delivery every five minutes, adapting to real-time blood glucose levels.

It is important to note that both systems still require boluses (i.e. insulin to be administered at mealtime) to be announced, based on an estimate of the amount of carbohydrate intake. However, these devices offer better nighttime glycemic control and reduced risk of hypoglycemia [4, 22].

We classify pumps into three types based on their delivery mechanism, as detailed in the following.

### Conventional pump

The insulin pump is a small, compact digital device that delivers fast-acting insulin through a small catheter inserted into the subcutaneous tissue. This catheter is attached to the skin by an adhesive and must be replaced periodically. In most pumps, the infusion set connects to the pump via a cannula, where the injected insulin passes through (as shown in Figure 1.5). The user programs customized doses for continuous basal insulin delivery, thus covering all 24 hours of the day. Common examples of conventional pumps are the Medtronic 630G, Tandem.

Figure 1.5: Conventional pump connected with CGM sensor [5]

### Patch Pump

To improve user comfort, so-called patch pumps have been developed. These are pumps without a cannula and attached directly to the skin by an adhesive. They are usually smaller and easier to use, but require more frequent replacement, on average every 2 to 3 days.

In addition, they present a greater risk of clogging of the insulin inside the tube and the possibility of air bubble formation, which can compromise the amount of insulin injected. Because of their smaller size, they also require more energy. Through its feedback system, it can communicate directly with the sensor and a handheld device, allowing for changes in settings and data visualization. An example of a patch pump is the Omnipod device (shown in Figure 1.6), which communicates with the Dexcom CGM sensor.

Figure 1.6: Patch pump, example of Omnipod [6]

### Implantable micropumps

An implantable insulin pump is a pump that remains in the intraperitoneal cavity, an area rich in blood vessels that promotes efficient insulin uptake. The use of this type of pump has been made possible by the development of programmable devices that deliver insulin via an intraperitoneal (IP) catheter; instead, the pump itself is implanted in the abdominal wall.

The model currently in use is the Medtronic-MiniMed MIP-2007, which has been in use since 2000 and has a battery life of 7-10 years (shown in Figure 1.7). Its delivery options are similar to those of external pumps and programmable via a communicator. In addition, the insulin used has a higher concentration of 400 IU/mL (Insuplant) [23].

Figure 1.7: The implantable pump Minimed

## 1.5 Bluetooth

The main control systems, and thus the sensors and pumps described in Section 1.4, use Bluetooth to ensure their services. Bluetooth is a wireless communication technology that has revolutionized interaction with electronic devices, becoming fundamental to everyday life. Introduced in the 1990s, it enables data transmission over short distances, eliminating the need for cables or connectors. Today it can be found in a wide range of devices, from headsets to cell phones, from computers to wearables, facilitating file synchronization or music playback and general communications between various gadgets [24].

In the field of health, Bluetooth has opened new frontiers, enabling a smoother communication between medical devices and monitoring tools. Devices such as smartwatches and blood pressure monitors use this technology to transmit data to smartphones and dedicated apps. This facilitates continuous monitoring of health conditions and sharing vital information by sharing it with medical professionals.

Bluetooth use in dedicated diabetes equipment is particularly relevant. Devices such as glucose meters now integrate this technology to automatically send blood sugar level data to a receiver or app on the phone. This functionality gives users more precise control over their condition, improving their quality of life. The synergy between technology and health is an important step toward a future in which disease management will be increasingly accessible [25].

## 1.6 Flutter as a technology for cross-platform development

In recent years, the development of mobile interfaces for medical device management and monitoring has become increasingly central. The choice of development framework is crucial to ensure efficiency, portability, and a consistent user experience across different platforms.

Flutter was adopted for the development of mobile interfaces for the MuSiC4Diabetes system.

Flutter is an open-source framework developed by Google for creating mobile, web and desktop applications from a single code base. It uses the Dart programming language and offers a wide range of predefined Widgets. Widgets in Flutter are the fundamental elements of the user interface. They represent the different parts of the interface, such as buttons, text, images, layouts, frames, and other visual components. Widgets can be:

- Stateless Widgets: They are used to construct parts of the interface that remain static.
- Stateful Widgets: They are used to build interactive interfaces that can respond to events, such as user clicks, sending or updating data.

In addition to customizable widgets, Flutter's main features include:

- High Performance: code is compiled natively, then turned into machine code that can be executed directly by the device's processor.
- Hot Reload: This feature allows developers to immediately see changes made to the code without having to restart the app.
- Cross-platform support: this allows iOS, Android, web, and desktop apps to be created from a single code base [26].

## 1.7 Quality of Life

T1DM significantly affects the lives of patients and requires complex daily management, leading to a significant impact not only on the affected person, but also on their relatives. This involves physical, psychological, social, and economic aspects, making it essential to adopt a healthy lifestyle to avoid complications. Managing diabetes requires careful diet control, regular exercise, continuous blood glucose monitoring, and insulin injections. Quality Of Life (QOL) is a concept defined by the WHO as 'an individual's perception of his or her position in life, the concept of the culture and value systems in which he or she lives, and in relation to his or her goals, expectations, standards and concerns' [27].

Several factors can influence the QOL of a subject with T1DM. Among them, objective characteristics related to the disease, such as glucose measurement, glycated hemoglobin (average blood glucose level in the last three months), complications and age of onset, are of primary importance [27].

In addition, QOL is influenced by acceptance of the disease and the difficulties associated with its management. Recent studies show that adults with T1DM report that hypoglycemia episodes impair sleep quality, productivity at work, driving safety and limit social interactions. During an episode of hypoglycemia, many patients encounter difficulties to speak or respond adequately to daily activities. Moreover, due to hypo- or hyperglycemia, fatigue and difficulty while concentrating may also appear.

Thanks to the development of new technologies, such as sensors for continuous blood glucose monitoring, or pumps for automatic insulin pumping, the management of the disease has improved dramatically in recent years. Despite the advances in technology, its appearance and functionalities, it also impacts other aspects regarding the QOL, such as changes in the lifestyle of the patient (psychological and social), and the affordability of the system (economical) [28].

# Chapter 2

# Project and Method

## 2.1 MuSiC4Diabetes

MuSiC4Diabetes is a European project launched on 1.10.2023 and funded by the Pathfinder program of the European Innovation Council (EIC). The project unites seven partners from four European countries and aims to improve the quality of life of people with type 1 diabetes, through improvements in management technology, prioritizing portability.

The 7 participants in the project are Indigo Diabetes in Belgium, the Centre Hospitalier Universitaire de Montpellier in France, the European Research and Project Office, FIDAM GmbH, and Fraunhofer Institute for Electronic Microsystem and Solid-State Technologies EMFT in Germany, and the University of Padua and the University of Pavia in Italy. The project focuses on improving substance monitoring and insulin transport through the development of an intelligent device that integrates Multi-Metabolite sensors and high-precision insulin delivery pumps.

The sensor is able to measure glucose concentration, lactate (physical activity marker), ketones and 3-$\beta$ OH-butyrate (ketoacidosis marker). These measurements are done at cell intersticial fluid, thanks to the optical properties of the metabolites described before.

Lactate is a metabolite produced under conditions of low oxygen supply, as occurs during intense physical activity. Insulin sensitivity in cell membranes is affected by the presence of lactate. Therefore, having information about lactate levels in tissues optimizes and makes insulin dosing more accurate and effective.

A new Multi-Metabolite control algorithm will consider these three parameters simultaneously allowing for quick and precise actions: based on this data, a micropump that will be also implantable will deliver the insulin needed to meet the patient's needs [29].

This system thus integrates three key components that communicate with each other: a sensor system, a control algorithm, and a pump system. As shown in Figure 2.1 there are different phases to make this system effective:

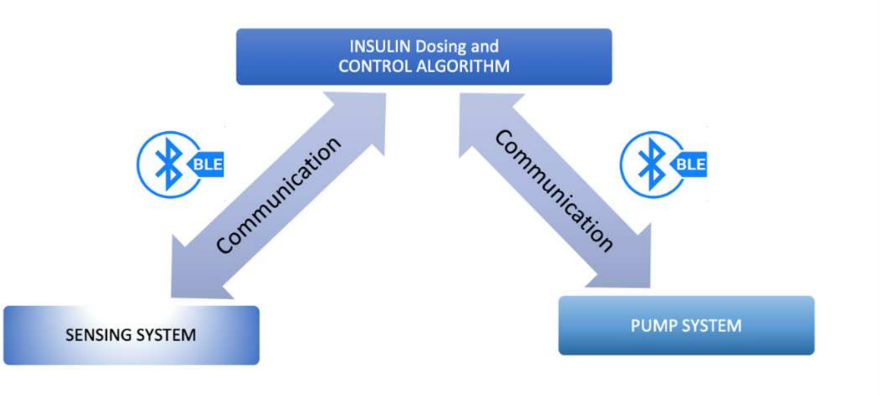


Figure 2.1: Modules of the closed loop implantable system

- Sensing System: measures the three metabolites in the interstitial fluid and correlates them with real-time levels in the blood.

- Communication Protocol: data collected by the sensors are transmitted wirelessly via Bluetooth Low Energy (BLE) to an external processing unit. BLE was chosen for its low power consumption and device compatibility.
- Processing Unit: it uses algorithms such as machine learning and neural networks to interpret sensor data. It predicts future insulin needs based on historical data, calculating the optimal doses to keep glucose within a target range.
- Silicon micropump: Controlled by the processing unit, it delivers the calculated insulin dosage.

The micropump, in order to maintain modest size, will incorporate insulin with a higher concentration.

The project has six primary objectives:

- The implantable device should have a battery life of 8 years and a one-year insulin refill cycle, transforming diabetes therapy from an intrusive process to a discreet and continuous way;
- Development of a long-term MM sensor without the need for calibration, used with an algorithm for precise measurement and prediction of glucose, lactate and ketone levels;
- Creation of a high-precision implantable insulin delivery system connected to the MM sensor;
- New MM data models will be analyzed to optimize the timely control

action of the device;

- The project collects testimonies from diabetes patients to identify areas where the project can reduce disease-related stress;
- Clinical and animal validation of the system components will be performed ß [29].

### 2.1.1 State of Art

In the previous section the working principle has been described. Their interrelation can be summarized in Figure 2.2. The Work Package 3, aims to develop the dosing delivery system. It consists of a silicon micropump that can withstand a high back pressure and a ultra-low leakage rate ($0.1\ \mu l/h$). This is achievable thanks to a new safety-valve feature designed and under development at Fraunhofer-EMFT in Germany.

The actual technology described in Section 1.4.2 are powered by an integrated battery, therefore the electronics including the pump driver and its connectivity module should be as low-power consuming as possible. Thanks to the electrical properties of the micropump, it is possible to predict or detect bubbles in the system.

This feature is called Self-Sensing, that positively impacts the precision of a dose delivery. The system must be able to communicate to the end-user to appreciate the status of the insulin delivery system (implant) and the MM sensor. The modular intercommunication is achieved thanks to an app. The institute development engineers have already begun with the new micropump driving module that consists of different submodules described in Subsection 2.2.1 . Regarding the optical sensor from Indigo, they provided a board where simulated data points are sent via Bluetooth in order to start the app development [29].

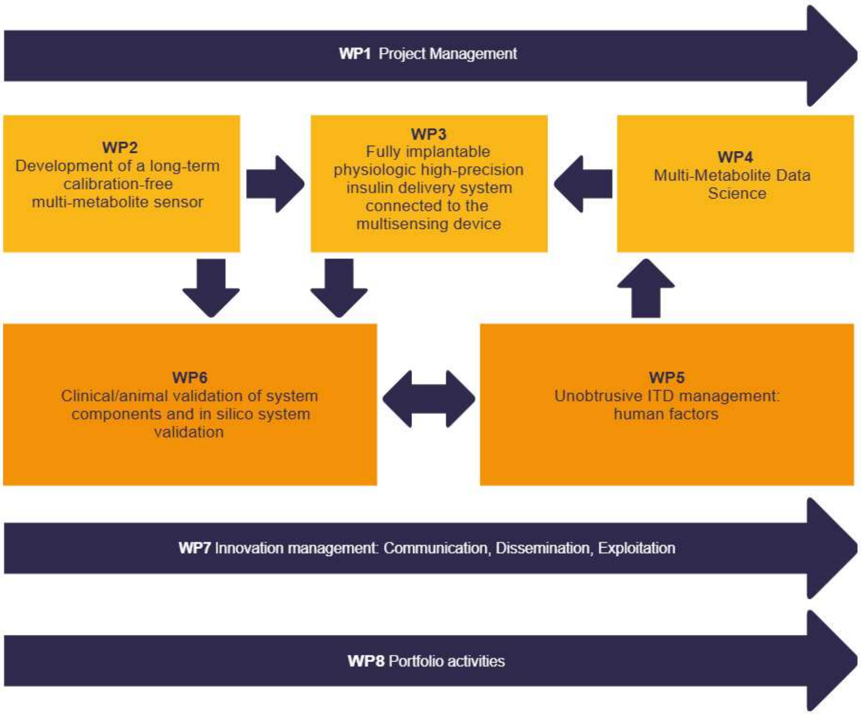


Figure 2.2: Work packages of the project

The new electronic development is called Analog Pump Driver (APD) and it consists of changes that are not present in the used electronics, called Micropump Driver (MPD). These changes involve the addition of the following modules: battery management, pump actuation, wireless communication with the sensors, and the control panel outside the body (from which the application requirements, such as pump actuation, or energy management, are managed). It can be used to regulate the delivery of insulin by the pump and any changes in pressure, voltage and speed.

Additionally, the system interacts via Bluetooth with a smartphone, where a dedicated interface is being developed to control the pump.

## 2.2 Materials and Method

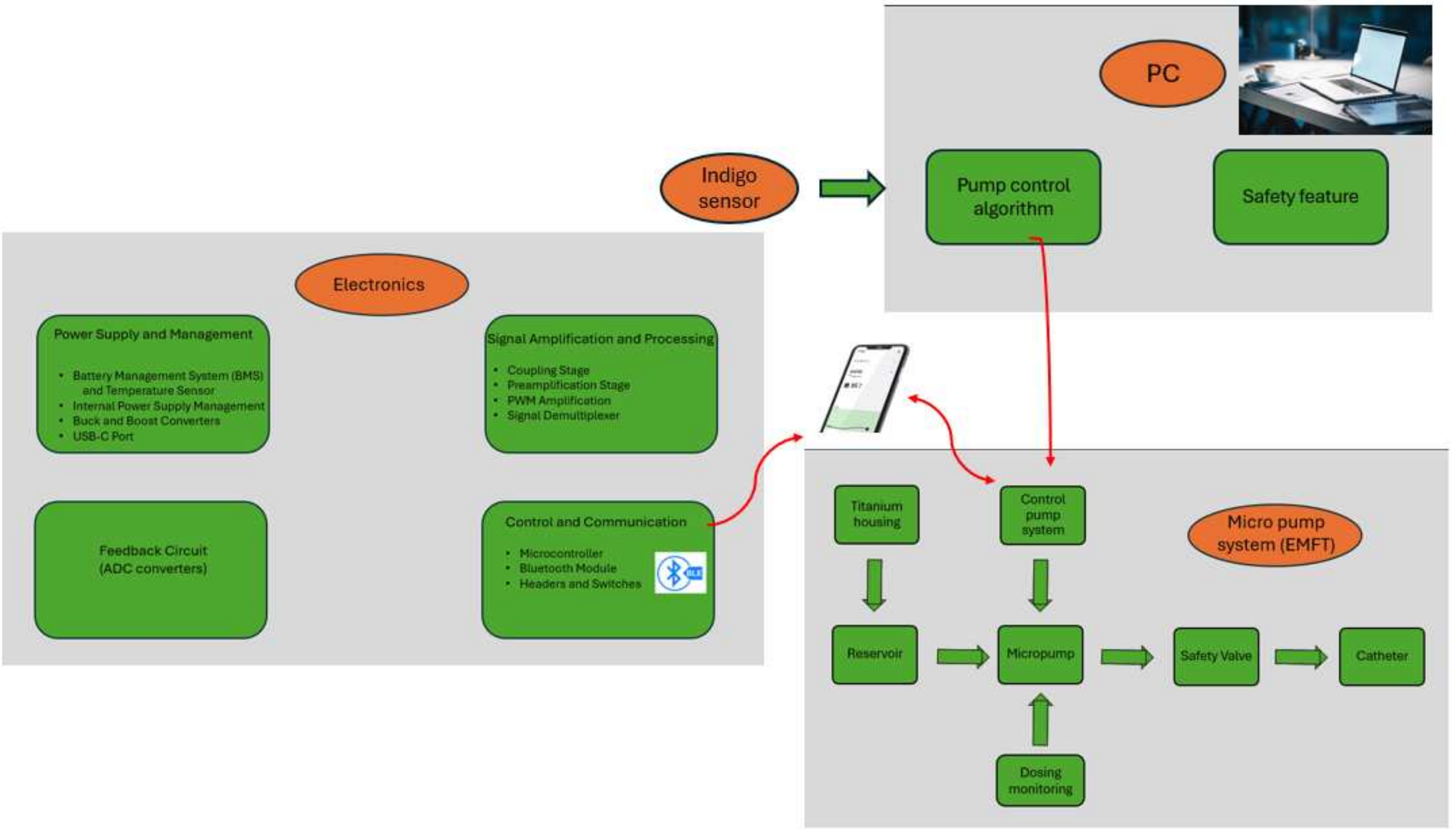


Figure 2.3: Functional Diagram of WP3

As shown in Figure 2.3, the electronics part includes numerous electronic components designed using Altium Designer software.

# Altium Designer

Altium Designer is an electronic design software used for creating circuit diagrams and Printed Circuit Board (PCB) layouts in a fully integrated environment, this allows users to manage the entire design process without having to switch between applications. It combines multiple features, including 3D design, which enables detailed and realistic design visualization and avoids pre-production errors, simulation of circuit behavior, and library management; the latter allows users to create, edit, and manage electronic components.

### 2.2.1 Analog Pump Driver (V1)

Figure 2.4 and Figure 2.5 show the PCB of the first version of the APD, respectevely the top side and the bottom side. Next, all the modules on the PCB are described.

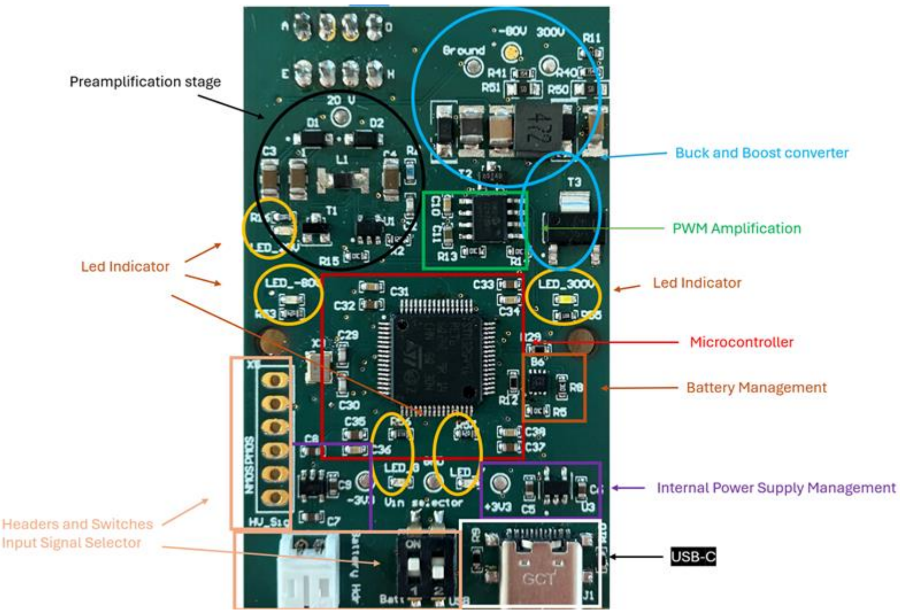


Figure 2.4: PCB Top Part

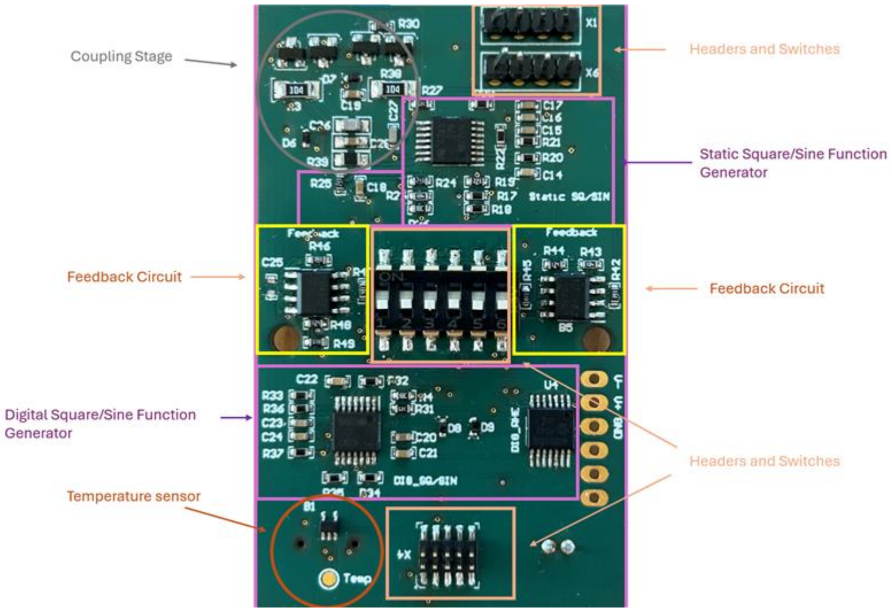


Figure 2.5: PCB Bottom Part

**Battery Management System (BMS) and Temperature Sensor** A new battery management system is implemented to surveil the battery and ensure the board power supply. The Integrated Circuit (IC) features include battery management with temperature monitoring, providing a complete solution for monitoring the implant's battery. The IC measures the battery cell voltage and provides a State Of Charge (SOC). A micro-controller communicates with the IC through the I2C protocol and has alert pins to signal abnormal conditions, such as critical voltage levels. The SOC is negatively impacted by the temperature, therefore the IC features an internal compensation model where the temperature has to be measured periodically. The temperature sensor is intended to be placed close to the battery in case it doesn't feature its temperature output.

**Preamplification Stage** Circuit designed to steps up the input voltage. It provides a stable voltage to power subsequent stages. The output voltage of 20V goes into the Buck and Boost Converters (BBC) circuit.

**Buck and Boost Converters** The circuit represents a circuit of DC-DC converters used to adjust the circuit voltage. The buck converter reduces the input voltage from +20V to -80V; it operates through a square wave, which drives the MOSFET from the converter; the MOSFET is a switch which turns on and off rapidly. The average voltage at the output is regulated with a MOSFET, a diode and a capacitor. The relationship between the input voltage Vin and the output voltage Vout is given by: $V_{out} = D \cdot V_{in}$, where D is the duty cycle of the switch. The boost converter increases it from +20V to +300V. It also works through a MOSFET, an inductor, a diode and a capacitor. When the switch is closed (On), the inductor stores energy; when the switch is open (Off), the stored energy is released by increasing the output voltage. The relationship between Vin and Vout is given by $V_{out} = \frac{V_{in}}{1-D}$

Through BBC the pump supply voltage can be adjusted to high and low voltages. This makes it possible to regulate the inlet and outlet of the micropump.

**Microcontroller** The microcontroller manages circuit operations by executing programmed code. In particular, it is used to read analog signals from sensors, such as temperature and to monitor the feedback voltage for BBC. Timers are used to control the switching of MOSFET switches in BBC and pins to control the status of LEDs. An oscillator that generates a periodic signal is used to synchronize the internal operations of the microcontroller. The pin headers are used to flash the program in the microcontroller and monitors the output signals of it.

**USB-C Port** The USB-C connector is a versatile port for data transmission and power.

**Internal Power Supply Management** It consists of two power management (ICs): a voltage regulator and a supply inverter. It is designed to provide stable and regulated voltages to various electronic components in the device, stabilizing the power supply. The voltage regulator converts the highest input voltage to 3.3V output voltage, suitable for the system. The supply inverter converts a positive voltage into negative voltage.

**Static Square/ Sine function generator (20Hz)** This represents a static function generator that produces square and sine waves at 20 Hz. The circuit includes an Operation Amplifier (OpAmp) whose outputs are connected to different components to obtain the desired waveforms; the latter has four OpAmp channels. The output signals are defined through the use of resistors and capacitors, used to compensate and stabilize the signals, defining their frequency and amplitude, and diodes to improve signal quality.

**Digital Square/ Sine function generator** It represents a digital function generator that produces square and sinusoidal signals. It consists of a microcontroller that handles the signal generation, but unlike the Static square, they are digitally produced waveforms.

**Coupling Stage** The circuit allows the low voltage signal to be safely transferred to higher voltage (from 3.3V to 20V, tension used in BBC). The integrated OpAmp manages the input signal and can handle both positive and negative signals. The circuit uses multiple supply voltages, including +3.3V,-3.3V,+300V and -80V, indicating that the circuit is designed to work with high-voltage signals. Resistors limit the current, diodes protect the circuit from surges and ensure that the current flow moves in the right direction, and finally capacitors help in preserving the signal integrity.

**Led indicator** Different colored LEDs were used to indicate the different states of the system. The blue LED indicates a voltage of 20V, the red LED of 30V, and the white LED of 300V. Then there is a green LED and a yellow LED used as debug. Resistors are used to limit the current flowing through the LED. Via the General Input and General Output (GPIO) pins, they are connected to the microcontroller, which controls their power on.

**Input Signal Selector** It handles multiple signal sources in the system. It allows easy changing the power supply from the USB to the battery. Via the DIP Switch it selects one of the input signals (square or sine, analog or digital), only the signal corresponding to the activated switch reaches the output.

**Headers and Switches** It represents a connecting interface for signals and controls, used for their management and monitoring.

**Feedback Circuit** It is designed to monitor and regulate high voltages (+300V and -80V) using an analog-to-digital converter. It maintains voltages in a specific range and ensures that readings are accurate and reliable.

**PWM Amplification** The circuit amplifies the Pulse Width Modulation (PWM) signal to control power devices.

As a result, the APD1 handles pump and voltage management, and temperature monitoring. It has an I2C for communication with ICs, generates square and sinusoidal signals for control, and uses LEDs as status indicators for pump parameters and conditions. It includes switches to select the power source (USB or battery) and amplification stages to enhance the output signal.

Although the first APD V1 version represented a valuable starting point for system development, some limitations emerged that necessitated a design revision geared toward improving efficiency and greater integration with other system components.

In particular, the absence of a module for wireless communication prevented remote control of the device, making interaction possible only through wired connections. In addition, some initial circuit solutions, such as static generation of activation signals, were inflexible for use in real clinical settings, where greater adaptability and precision is required.

For these reasons, the second version of the circuit was designed (see Section 3.1), with the aim of optimizing power management, reducing power consumption, improving signal controls, and, most importantly, introducing Bluetooth Low Energy (BLE) communication, a key element for system operation in implantable mode.

The changes introduced enabled greater compatibility with the requirements of the MuSiC4Diabetes project and formed the basis for subsequent developments presented in Chapter 3.

# Chapter 3

# Results

## 3.1 Analog Pump Driver (V2)

### 3.1.1 Features

The second version of the Analog Pump Driver (APD V2) represents a significant evolution from the initial version, not only functionally, but also structurally.

One of the first evidences is the reduction in the physical dimensions of the printed circuit board, from 65mm x 40mm in the V1 version, to 45mm x 40mm in the V2 version. This reduction is particularly important with a view to integrating the device into implantable medical environments, where compactness and efficiency is a major requirement.

Compared with the first version of the PCB, which featured a 4-layer signal configuration, the second version of the Analog Pump Driver (APD V2) adopts a more advanced 6-layer signal structure. This architecture was designed to improve functional separation between different signal types (such as high-frequency lines, power supplies, debug interfaces, and analog signals), enhancing signal integrity, reducing electrical noise, and enabling more efficient thermal management.

The PCB developed for APD V2 integrates a vertically symmetrical stackup composed of signal and dielectric layers, which not only improves mechanical stability and electrical performance but also supports higher component density, more accurate signal routing, and optimized interconnection between modules.

We distinguish six main signal layers: top layer, high frequency layer, voltage supply, Debug/USART, GPIO/DAC/ADC, bottom layer. They are responsible for transporting electrical signals between components. Layers dedicated to specific lines are used: the layer for high-frequency signals to better control signal quality, the layer reserved for power supply traces, the layer dedicated to debug and serial communication signals, and the layer reserved for general purpose I/O lines.

Among the signal layers are five dielectric layers, which act as insulators, reducing the risk of unwanted capacitive-inductive coupling.

Additionally, two solder masks are added (Top/Bottom), they protect against oxidation and short circuits during soldering. Finally, the Overlays (Top/Bottom) provide visual cues useful for assembly and maintenance of the device, such as identification of components and connections.

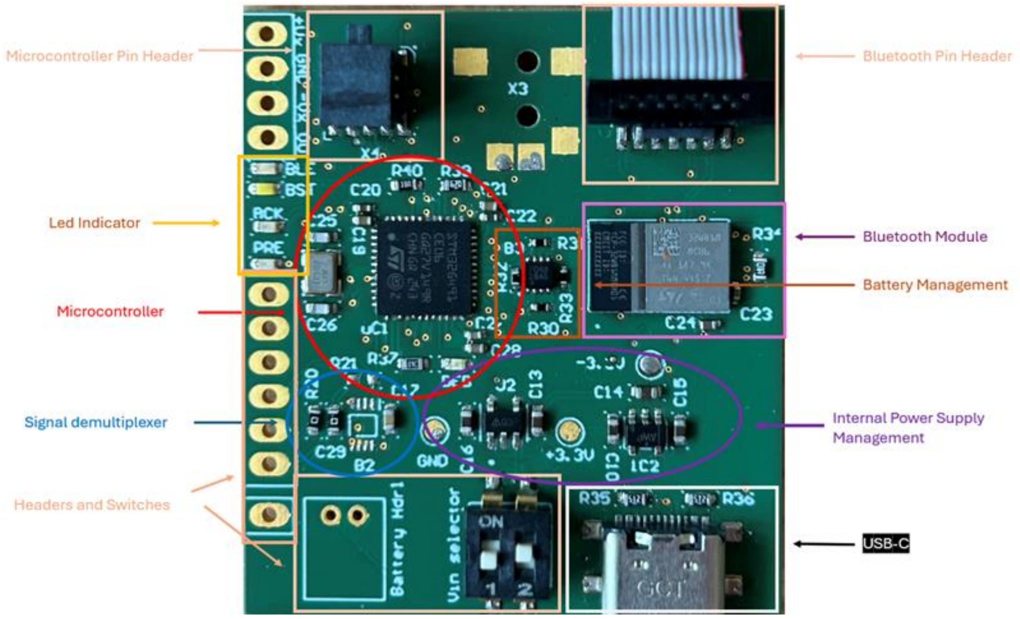


Figure 3.1: PCB V2 Top Part

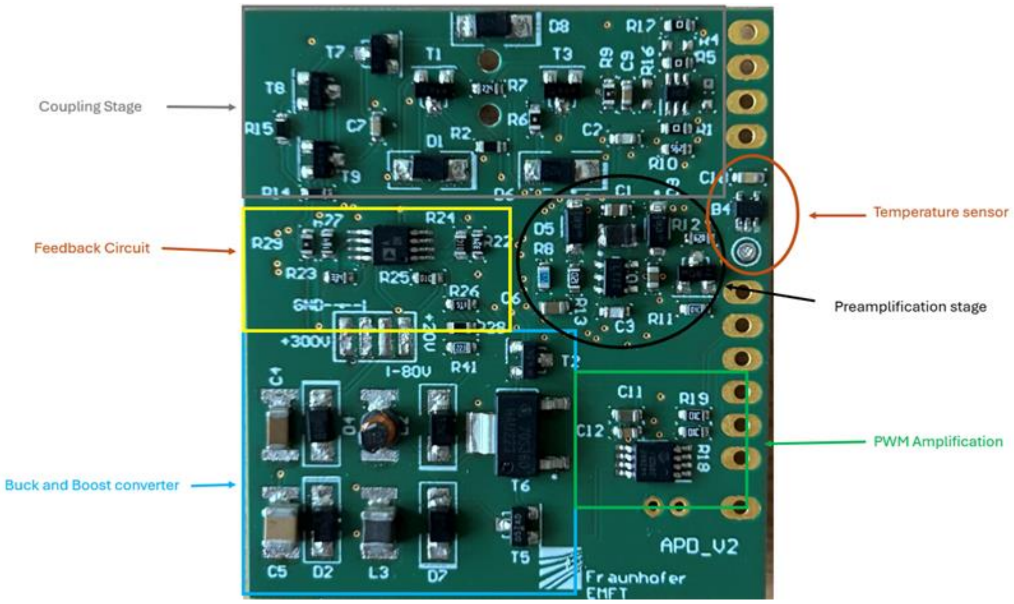


Figure 3.2: PCB V2 Bottom Part

In terms of the circuit structure, several changes have been made. The new PCB is shown in Figure 3.1 and Figure 3.2. In particular, a Bluetooth module was added for data transmission. There is also a new Coupling Stage, this new circuit offers the possibility to drive asymmetrical signals to drive the micropump using BJT transistors and an operational amplifier. It had been implemented for testing the coupling stage with symmetrical signals coming from the micro-controller.

A new Feedback Circuit has been designed: while in APD V1 focused on amplification of analog signals, in the new circuit there are no longer two OpAmps. There is an analog-to-digital converter (DAC) which generates waves, and an additional DAC channel is used to have a reference voltage in the ADC.

The Static Signal Generators have been removed and in APD signals are generated using the DAC via the microcontroller.

Hence the microcontroller generates analog signals such as the sine function, square function and rounded function for control applications, and uses the UART (Universal Asynchronous Receiver-Transmitter) to communicate with the Bluetooth module described above. A MOSFET and diode were added in the Boost Converter to control more efficiently the power consumption and to improve signal quality.

**Bluetooth Module** It consists of an IC that integrates an antenna and is designed for wireless communication applications, with data transmission and reception.

It incorporates BLE capabilities, enabling low-power wireless communications, ideal for wearable devices. UART communications are used to interface with the microcontroller. The circuit includes a LED that can be used to indicate the status of the bluetooth module (e.g., paired, connection active) and an antenna for transmitting and receiving bluetooth signals and to communicate with the external host device.

It has a pin header to flash the program and to appreciate events related to connection/disconnection, data transmission and reception. This information is sent to the computer for debug purposes.

BLE is the communication technology used in the project. In general, this type of technology is aimed at new applications in low-power healthcare.

It enables data transmission over short distances, reducing power consumption compared to traditional Bluetooth technology; consequently, BLE is ideal for battery-powered devices that need to operate for long periods, such as the micropump developed in the MuSiC4Diabetes project.

In this thesis work, it is used to establish the connection between smartphone and MM sensor, as well as smartphone - micropump. Each BLE device is structured into one or more services, each of them represents a set of related functionalities, called characteristics. For example, in the case of the MM sensor, the service dedicated to continuous monitoring of Multi-Metabolites includes three main characteristics, for measuring glucose, for lactate, and for ketones.

Each service and characteristic are defined by a Universally Unique Identifier (UUID), a unique identifier used to distinguish services and features from each other. UUIDs are defined in hexadecimal format and can be as long as 128 bits.

The app development was done through Flutter, described in Section 1.6, a framework for creating cross-platform applications using the Dart programming language.

Thanks to its customizable widgets, Flutter was particularly suitable for applications that require real-time updates, responsive interfaces, and interactions with external devices via Bluetooth. During the development of the two interfaces, in addition to the Flutter platform, a smartphone wired to the platform was used so that any changes made could be verified instantaneously.

The results obtained with the implementation of the two applications are presented below: MM Sensor App (Subsection 3.2.1) and PumpApp (Subsection 3.2.2).

**Signal Demultiplexer** It is useful in signal management where several input signals need to be routed to a common output based on external control.

## 3.2 App Development

The systems interconnection must be achieved using the Bluetooth protocol. The app interface must be coded in order to communicate with the mock sensor (board) from Indigo, so that the patient can appreciate their metabolites concentration in the bloodstream. The board sends preprogrammed data points and behaves as a the real MM system. Therefore an app development is necessary.

Among the circuit components, the Bluetooth module receives and transmits information to the microcontroller to manage the circuits mentioned in Subsection 3.1. The communication is through commands. It enables the transmission of signals and data between the mobile device and the system, facilitating the insulin delivery.

Specifically, as mentioned earlier, one of the aims of the project was to develop a patient app through which to receive and read data from the MM, thus glucose, lactate, and ketones, and to command the implantable insulin delivery system through bluetooth connection.

### 3.2.1 MM Sensor App

The first App developed was called MM Sensor App, its main interface is shown in Figure 3.3 using some in silico data. The app is designed to manage communication with the mock MM, allowing the display of glucose, lactate, and ketone levels. It was developed with the goal of simplifying diabetes management for patients, allowing them to independently monitor their values and understand how to intervene based on these data. In the context of this thesis, the mock sensor simulates real data of the metabolites.

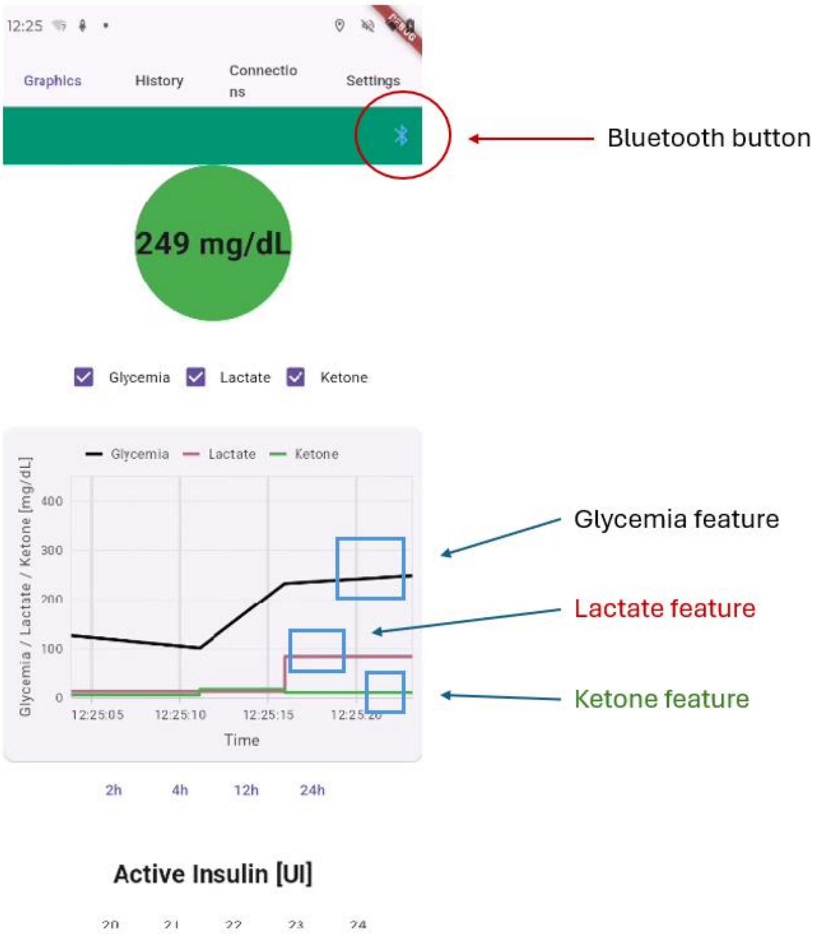


Figure 3.3: MM Sensor App, MM Graphics

The first objective was to establish a connection between the application and the Bluetooth module. After implementing the code needed to connect to BLE, a button was added on the application interface that, when pressed, searches for devices available for Bluetooth connection. Initially, the button is presented with a red color; once pressed, the button with the bluetooth icon turns green while searching for a device to establish connection and finally blue once connected as shown in Figure 3.3.

The application is organized into several frames or tabs, the main ones shown are ‘Graphics’ (see Figure 3.3) and ‘History’, where statistics related to glycemic levels, a signal of particular importance for people with diabetes, are displayed.

Next, the code was integrated with the UUID service, which is responsible for the transmission of data related to blood glucose, lactate and ketones. Thanks to this connection, the green icon displays the updated blood glucose value every time data is received from the sensor, expressed in mg/dL.

An additional functional aspect developed in the application concerns adjusting the frequency of transmission of data received from the MM sensor. Specifically, the user has the ability to configure the frequency with which the sensor transmits new data for each metabolite.

This feature introduces a degree of flexibility that can be adapted to different clinical scenarios. For example, in the configuration shown in Figure 3.3, the sensor is set to transmit data every 5 seconds. However, this transmission frequency can be changed to reduce power consumption or adjust the amount of incoming data; moreover, in a real case, the concentration of the three metabolites undergoes visible changes in longer time intervals.

A toolbox enables the possibility to appreciate the graphs in real time, allowing users to see concentration graphs of glucose, lactate and ketones. Users have the option of viewing one, two or all three graphs simultaneously.

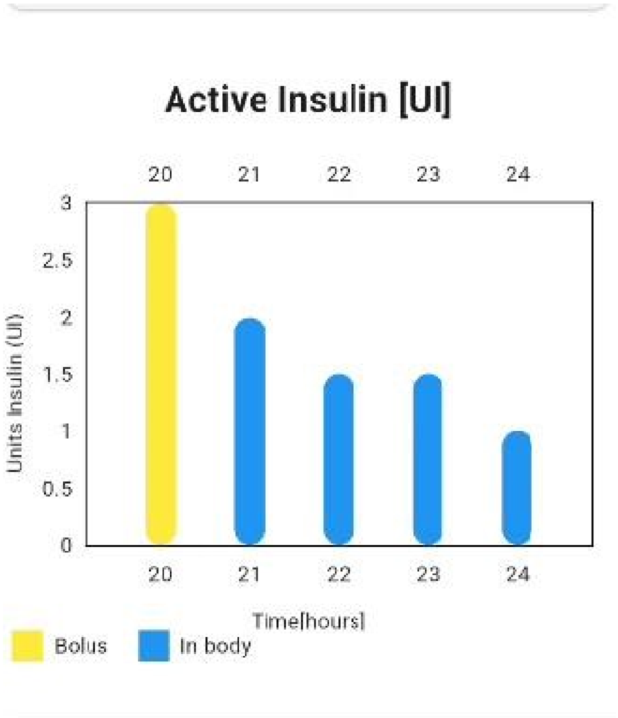
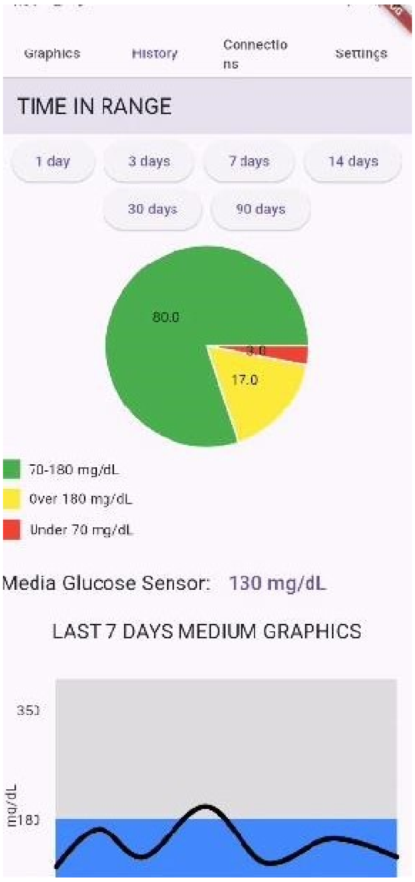


Figure 3.4: MM Sensor App, Active Insuline

Figure 3.4 shows the bottom of the first screen of the app, visible by scrolling down. This graph is generated through the Bluetooth connection with the implantable device, here the units of active insulin within the patient's body is displayed in real time as well. In the graph, the bolus administered by the pump is shown in yellow, while the insulin in circulation in the hours following the bolus is shown in blue.



Media Glucose Sensor: 130 mg/dL

Figure 3.5: MM Sensor App, Time in Range, time in optimal blood sugar range

Figure 3.5 shows the pie chart of Time in Range (TIR), which represents the time that blood glucose values remain in the optimal range for a diabetic, between 70 mg/dL and 180 mg/dL. A larger ‘green’ area indicates a higher TIR for the user. This figure can be calculated over a range from one day to 90 days by pressing the dedicated button. Besides being useful for the user, the TIR is also very important for the treating physician, as it gives a more accurate picture of the patient’s health status.

Below, the trend of the patient’s last week’s blood glucose curve is shown, where the blue area represents the TIR. This graph allows both patient and physician to identify any need for changes in therapy to optimize glycemic control.

In general, the application is particularly useful for patient therapy management because of its connections with the MM sensor and implantable pump.

It provides a tool for autonomous monitoring of glucose, lactate, and ketone levels by patients. However, there are additional aspects that could improve the user experience and better meet patients' information needs regarding device implantation. These features could be integrated into the application interface in future updates.

First, the integration of customizable notifications for critical events, such as hypo or hyperglycemia, could offer immediate support, thus helping to improve patient safety. The inclusion of a food diary, allowing meals and physical activity to be recorded, would also be useful in correlating glycemic data with daily habits.

Another crucial aspect to consider is the creation of a support system for communication with physicians. The ability to generate detailed reports to share with health professionals could improve the quality of care and provide adequate treatments. This functionality could be implemented through another frame in the interface.

In addition, an information section on connected implantable devices will soon be added, including sensor charge status, pump battery level, and overall performance.

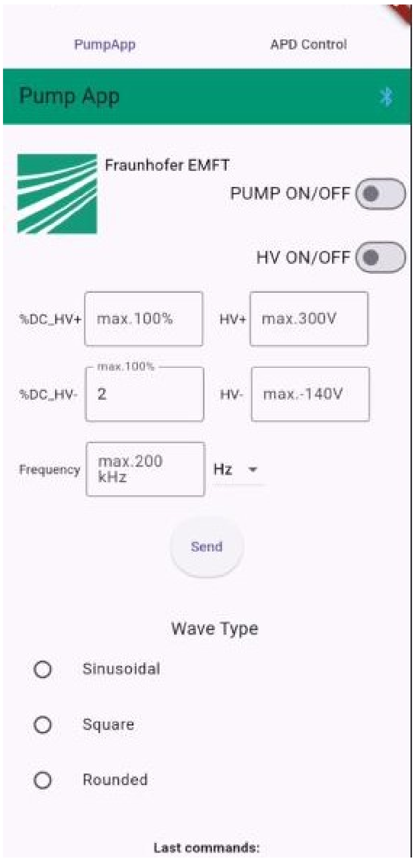
However, at the moment there is still no control of the plant on the app, which needs to be implemented; therefore, the corresponding service and characteristic for bluetooth implant-app connection need to be created. For the bluetooth connection, while waiting for the sensor with real data, a bluetooth module that simulates the values of the concentrations of the three metabolites was used.

Such information would enable patients to better manage their device and prevent any health risk.

By implementing these improvements, the App could become an even more powerful ally in disease management.

### 3.2.2 PumpApp

Subsequently, a new application called ‘PumpApp’ was developed (see Figure 3.6). The app handles communication with the electronics of the hardware device. The ‘PumpApp’ interface is an innovative application designed to control and manage a pump operating in a high-voltage system. This application was developed to enable engineers to precisely monitor and adjust pump settings, thus ensuring efficient and safe operation.



%DC_HV- 2

Figure 3.6: Pump App

Each time the user interacts with the app interface, a specific command is generated and sent through Bluetooth to the IC integrated in APD V2. These commands are designed to control different aspects of pump operation and are critical to the proper management of the system.

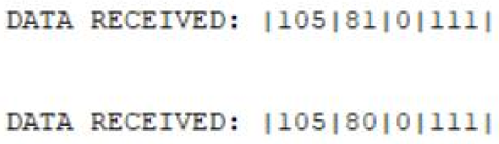
When commands are received by the microcontroller, it performs specific actions, such as turning power supplies and pump settings on or off, ensuring that operations are carried out properly. The BLE acts as an intermediary between the app and the device, allowing commands to be transmitted and operational data to be returned in real time.

Specifically, concatenation is performed, so each command is anticipated by an input index and an output index. The indexes are combined with the command and with its parameter. They are then interpreted in the microcontroller, which modify a certain functionality in the board, accordingly. The input and output indexes are coded to indicate the beginning and end of a command.

Below are the main components and functions of the interface and related representations of the commands and how they are sent.

- **Bluetooth Settings:** Once the application is opened, the interface presents a question, “Do you want to turn on the Bluetooth?” Users are given two options, “Yes” and “No.” The ability to turn on Bluetooth is crucial for connecting the app with external devices, enabling remote control of the pump and sending commands remotely.

- **Pump Control:** The interface offers two main switches to manage pump operation:
  - ’PUMP ON/OFF’ : this switch allows the pump to be turned on or off. This allows the operator to quickly manage the operating conditions of the pump, reacting to any need. When the user presses the button to turn the pump on, a command defined on flutter in hexadecimal, is automatically sent. In contrast, when the user presses the button to deactivate the pump, the command changes again (see Figure 3.7). Both commands are anticipated and followed by the indexes mentioned above.



```
DATA RECEIVED: |105|81|0|111|

DATA RECEIVED: |105|80|0|111|
```

Figure 3.7: First line Pump ON, Second line Pump Off

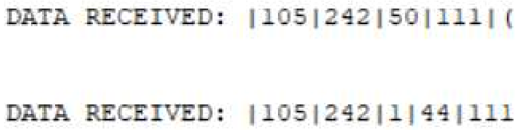
- ’HV ON/OFF’ : a second switch that enables or disables the pump’s high-voltage power supply. This control is critical for the safety of the system, since high voltage is required for pump operation in certain modes. Just as with the PUMP ON/OFF Switch, the user also receives two separate values, for the high voltage ON command and for the high voltage OFF command. In Figure 3.8 High Voltage is ON, and consequently the LEDs are also ON to signal High Voltage.

Figure 3.8: PCB at High Voltage Led ON

- **Control Parameters:** Below the main controls, the interface has several input fields that allow the user to set the pump's operating parameters:
  - Percentage $\%DC^{+}_{HV}$: this input field allows the user to set the positive Duty Cycle (DC) of the pump up to a maximum of 100%. DC is a parameter that affects the pump's operating efficiency, it ensures a certain voltage level is reached. Via Bluetooth the input index is received, the command defined for positive DC, followed by the value entered in the text box (between 0 and 100), and finally the output value.
  - $HV+$: it allows the user to set the positive high voltage, with a limit value of 300V, beyond which the pump could be damaged. This parameter is critical for optimizing pump performance in applications requiring high power. Via Bluetooth, in the case where the value entered is less than 256, the input index, the command, the value entered in the text box, and the output index are received (see Figure 3.9). A byte can contain values from 0 to 255, if the number is greater than 255 there is a need to use two bytes.

    The code handles the value as two bytes, More Significative Byte (MSB), which represents the upper part of the number (the most significant digits) and Less Significative Byte (LSB), which represents the lower digits of the number. To check whether the most significant bit is active, and thus the number is greater than 255, the "masking" technique is used.

By converting these two digits into a binary value and placing them side by side, the value actually entered in the text box is obtained. The example of 300, in binary value corresponding to 0001 0010 1100, divided into 1 (MSB) and 44 (LSB), 0001 and 0010 1100, respectively, is shown in the figure 3.9.



```
DATA RECEIVED: |105|242|50|111|(

DATA RECEIVED: |105|242|1|44|111
```

Figure 3.9: First line example 50V, Second line example 300V

- Percentage $\%DC^{-}_{HV}$: similar to the previous one, it allows the negative DC to be set, also with a maximum value of 100%. It represents the percentage of time working at high negative voltage.Then the input index is received, the command, and later the output index.
- $HV-$: it allows the negative high voltage to be set, with a limit value of -140V. In this case a positive value is entered in the text box. The pump recognizes that it is coming from the negative High Voltage text field because of the command. In this case, since the threshold value is 140, masking is not needed. The input index, command and output index will be sent to the pump via bluetooth.
- Frequency: input field to set the operating frequency of the pump, with a maximum value of 100kHz. It determines the

operating speed of the pump, affecting system performance. A ComboBox has been created to choose the unit of measurement of frequency, whether Hz or kHz; depending on the choice, the respective command for frequency, the value entered in the text box, and sequentially "10, 0 " if the value entered is in Hz (hence $10^0$ ) or "10, 3" if the value entered is in kHz (hence $10^3$) are sent in addition to the input and output signals.

- **Send Button:** "Send" button allows the user to send entered parameters via Bluetooth connection. It activates the changes made to the pump settings, allowing real-time operation to be checked. The separation of this button helps prevent accidental sends.

- **Wave Type:** Finally, the interface offers a selection for the type of wave to be used in pump operation. The user can choose from three options: Sinusoidal, Square, Rounded. For each wave chosen, in addition to the input and output signals, a different command is sent.

Currently, the "High Voltage" field is not used in daily pump operations. In fact, the main functionality that allows the output voltage to be adjusted is the duty cycle. Through the duty cycle the flow of the pump can be changed.

However, in the future, it is planned to review and modify the "High Voltage" field to better suit operational needs and test the new micropump. This transition will ensure better management of the pump.

The main goal of the app is to provide a simple and intuitive interface for controlling the micropump. Unlike the MM Sensor App, which is specifically designed for the MuSiC4Diabetes project, the Pump App is designed to be used with a wide range of pumps, not limited to the silicone pump used in our project. This allows for greater versatility in the application.

Currently, the PumpApp is used to test the micropump. In the future, as the control algorithm is developed, it will be possible to reduce the need for manual testing. Currently, input is transmitted from the cell phone via Bluetooth; in the future, it is planned to also receive input from the micropump to the app, further improving the interaction between the devices.

The intent is to integrate functionality and commands related to other modules of the electronic part, such as battery management, temperature and pressure monitoring, into the app.

In a future update, the battery charge could be displayed and could be useful for tests on the future implant. Through reading the values detected by the temperature sensor and the pressure sensor, the temperature and the pression can be analyzed; two boxes could be implemented through which the desired value could be displayed, ensuring proper pump operation and avoiding overheating.

In summary, “PumpApp” not only enhances the interaction between the operator and the system, but also offers the ability to customize and control the electronic of the pump. Through well-defined commands and efficient communication management, the application represents a significant step forward in medical device control technology, helping to ensure effective pump operation in high-voltage systems.

# Chapter 4

# Conclusion and Outlook

The thesis work addressed a highly relevant topic: the management of type 1 diabetes through the MuSiC4Diabetes project. The objective was to create an integrated system for monitoring and administering insulin.

The practical experience gained during the project demonstrated how it is possible to improve the quality of life for patients affected by this disease through the implementation of an implantable insulin pump connected to a Multi-Metabolite sensor.

From the research conducted, the following key points emerged:

- **Development of software and hardware interfaces:** software interfaces have been developed for two main applications: one for patients to view metabolic data interactively; the second for engineers to manage the pump via Bluetooth connection. This development facilitates the testing and monitoring of electronics and in a future may help in the regulation of insulin delivery.

- **Bluetooth communication integration:** The circuit board developed in the thesis work enables communication via Bluetooth with the dedicated app. This functionality facilitates a friendly interaction between the patient and the devices, allowing the patient to monitor blood glucose levels as well as lactate and ketone levels in real time. Thanks to this connection, patients can actively manage their condition, accessing vital information easily and directly.

- **Quality of Life:** the developed system not only aims to improve glycemic control, but also has a significant impact on patients' quality of life by reducing the stress associated with the daily management of diabetes.
- **WHO recognition:** It is important to note that the WHO has recognized diabetes as a major global health challenge, highlighting the need to develop innovative solutions for its management. In particular, the results obtained from the thesis work, and the MuSiC4Diabetes project more generally, align with the goals outlined in the 2030 Agenda. This work indicates that we are well on our way to facilitating the control of diabetes, thus helping to improve the quality of life of people with this disease.
- **Future developments:** this work represents an important step toward a future in which diabetes management will be more intelligent and less invasive. It is expected that the results obtained will provide an important basis for further research and development in the field of medical technology.

# Bibliography

[1] Manal Mortady Hamed. Antidiabetic activity of medicinal plants. pages 151–165.

[2] Glucose concentrations. https://labpedia.net/diabetes-mellitus-carbohydrate-and-glucose-metabolism-insulin-and-glucagon/.

[3] Aboul Ella Hassanien, Sameer Anand, Ajay Jaiswal, and Prabhat Kumar, editors. *Innovative Computing and Communications*. Lecture Notes in Networks and Systems. Springer Nature Singapore, Singapore, 2024.

[4] Thomas Peyser, Eyal Dassau, Marc Breton, and Jay S. Skyler. The artificial pancreas: current status and future prospects in the management of diabetes. *Annals of the New York Academy of Sciences*, 1311:102–123, 2014.

[5] Nucleusmedicalmedia. https://nmal.nucleusmedicalmedia.com/treatment-options-for-type-1-diabetes/view-item?itemid=6055.

[6] Omnipod. https://www.omnipod.com/en-ca.

[7] P. Marrack, J. Kappler, and B. L. Kotzin. Autoimmune disease: why and where it occurs. *Nature medicine*, 7(8):899–905, 2001.

[8] Lifeng Wang, Fu-Sheng Wang, and M. Eric Gershwin. Human au-

toimmune diseases: a comprehensive update. *Journal of internal medicine*, 278(4):369–395, 2015.

[9] Gunjan Nautiyal, Isha Sharma, Parijat Pandey, and Shiv Kant Sharma. Autoimmune diseases: Recent insights on epidemiology, pathogenesis, and prevalence rate. In Khalid Raza and Surender Singh, editors, *Artificial Intelligence and Autoimmune Diseases*, volume 1133 of *Studies in Computational Intelligence*, pages 33–58. Springer Nature Singapore, Singapore, 2024.

[10] Joanne B. Cole and Jose C. Florez. Genetics of diabetes mellitus and diabetes complications. *Nature reviews. Nephrology*, 16(7):377–390, 2020.

[11] Bin et Al. Zhou. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *The Lancet*, 404(10467):2077–2093.

[12] World Health Organization. https://www.who.int/news/item/13-11-2024-urgent-action-needed-as-global-diabetes-cases-increase-four-fold-over-past-decades.

[13] World Health Organization. Global report on diabetes.

[14] John E.Hall. *Guyton and Hall Textbook of Medical Physiology*.

[15] Anjali D. Deshpande, Marcie Harris-Hayes, and Mario Schootman. Epidemiology of diabetes and diabetes-related complications. *Physical therapy*, 88(11):1254–1264, 2008.

[16] Nathaniel G. Clark, Kathleen M. Fox, and Susan Grandy. Symptoms of diabetes and their association with the risk and presence of diabetes: findings from the study to help improve early evaluation and management of risk factors leading to diabetes (shield). *Diabetes care*, 30(11):2868–2873, 2007.

[17] Mark A. Atkinson, George S. Eisenbarth, and Aaron W. Michels. Type 1 diabetes. *The Lancet*, 383(9911):69–82, 2014.

[18] Roberto Toni. Tipi di insulina e suoi analoghi a 100 anni dalla scoperta. *L'Endocrinologo*, 22(1):63–67, 2021.

[19] Kirstine J. Bell, Alan W. Barclay, Peter Petocz, Stephen Colagiuri, and Jennie C. Brand-Miller. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. *The Lancet Diabetes & Endocrinology*, 2(2):133–140, 2014.

[20] Nelly Mauras, Larry Fox, Kimberly Englert, and Roy W. Beck. Continuous glucose monitoring in type 1 diabetes. *Endocrine*, 43(1):41–50, 2013.

[21] Alvin C. Powers. Type 1 diabetes mellitus: much progress, many opportunities. *The Journal of clinical investigation*, 131(8), 2021.

[22] Minimed. https://www.medtronic-diabetes.com/de-de/minimed-780g-system.

[23] Mohammad Towhidul Islam Rimon, Md Wasif Hasan, Mohammad Fuad Hassan, and Sevki Cesmeci. Advancements in insulin

pumps: A comprehensive exploration of insulin pump systems, technologies, and future directions. *Pharmaceutics*, 16(7), 2024.

[24] Bluetooth. https://www.bluetooth.com/.

[25] William Saltzstein. Bluetooth wireless technology cybersecurity and diabetes technology devices. *Journal of diabetes science and technology*, 14(6):1111–1115, 2020.

[26] Flutter. https://flutter.dev/.

[27] Mi-Kyoung Cho and Mi-Young Kim. What affects quality of life for people with type 1 diabetes?: A cross-sectional observational study. *International journal of environmental research and public health*, 18(14), 2021.

[28] Hannah Chatwin, Melanie Broadley, Mette Valdersdorf Jensen, Christel Hendrieckx, Jill Carlton, Simon Heller, Stephanie Amiel, Bastiaan de Galan, Norbert Hermanns, Katharina Finke-Groene, Jane Speight, and Frans Pouwer. 'never again will i be carefree': a qualitative study of the impact of hypoglycemia on quality of life among adults with type 1 diabetes. *BMJ open diabetes research & care*, 9(1), 2021.

[29] Music4Diabetes Project. https://music4diabetes.eu/.

# Acknowledgements

I thank all the people who made the completion of my master's degree possible.

Firstly, sincere thanks to Professor Toffanin, my academic supervisor, for her constant support and for guiding me toward the completion of my master's degree. Her guidance and encouragement were crucial in achieving this accomplishment.

Thanks to Fraunhofer and Sebastian for giving me the opportunity to work in such a challenging environment and project. My experience in the company has been fundamental to my professional and personal growth.

Special thanks to my internal supervisor Carlos, whose support was precious during my journey as a student worker. His availability and expertise contributed significantly to the success of my work.

Finally, special thanks go to my family, Irene and friends. Their unconditional love and support have guided me along this path, providing me with motivation and strength in difficult times.