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STUDY AND DEVELOPMENT OF MACHINE LEARNING ALGORITHMS FOR THE IMPROVEMENTS OF CONTINUOUS GLUCOSE MONITORING SYSTEMS PERFORMANCE IN PEDIATRIC PATIENTS

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If the sun don't shine on me today
and if the subways flood and bridges break
will you lay yourself down and dig your grave
or will you rail against your dying day

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Chapter 1

Introduction

Autoimmune diseases happen when the body's natural defense system fails to differentiate its own cells from the foreign cells and mistakenly attacks the healthy ones. Type 1 diabetes (T1D) is the most widespread autoimmune disease [1]. T1D is also called juvenile due to the fact that it attacks mainly children and adolescents. T1D, insulin-dependent diabetes mellitus, is a disorder in which the body cannot produce enough insulin or cannot absorb the proper amount of it, causing the increase in glucose level in the blood. Diabetes is a serious, long-term condition with a major impact on the lives and well-being of individuals, families, and societies and sort of half a billion people are living with diabetes worldwide and the number is projected to increase by 25% in 2030 and 51% in 2045 [2].

Several therapeutic options for those who suffer from T1D exist and they include multiple daily injections of rapid acting insulin with meals as well as continuous subcutaneous insulin infusion via an insulin pump [3]. Nevertheless, a complete metabolic normalization is not possible yet, which can provoke heterogeneous complications. Therefore, researchers are mainly focused on the improvement of the aforementioned solutions to develop an artificial pancreas (AP) that can imitate the real one in all its functions.

1.1 Patophysiology of diabetes

The energy source that allows cells to complete all their functions is glucose. It could be utilized immediately or be stored in the liver as glycogen; thus, this means that glucose should be removed from the blood and driven to specialized cells at the liver to be stored. This mechanism is made possible thanks to insulin, a peptide hormone produced by β-cells of the pancreas, specifically at the Langerhans' islets. But from where do we obtain glucose? From the diet. After a meal, carbohydrates get hydrolyzed in the intestine into simple monosaccharides causing an increase in postprandial glycaemia that reaches its peak after 90-120 minutes; most of the glucose in released by the liver after 4 hours while only a small percentage (30%) is immediately used. A key role is also played by the kidneys that are capable of removing through micturition the exceeding quantity of glucose (above the threshold of 180 mg/dl).

Insulin is produced as a response to the increase of glucose level in the blood and can work in two modes:

1. *Basal insulin*: also known as long-acting insulin, it keeps glycaemia low and constant through the day and between meals.

2. *Postprandial or bolus*: it is activated due to the glycaemic peak after food intake.

Insulin deficiency or the lack of sensibility to its action are two mechanisms that lead to the diabetes. In particular, we can distinguish into:

1. **Type 1 diabetes**: Also known as insulin-dependent or juvenile diabetes. It is characterized by the destruction of pancreatic beta cells, which eventually leads to absolute insulin deficiency (type IV hypersensitivity). Most cases are due to autoimmune-mediated β-cell destruction (type 1a), while a minority of cases are due to idiopathic destruction or β-cell exhaustion (type 1b) [3]. Although type 1 diabetes is usually diagnosed in childhood, 84% of people with type 1 diabetes are adults. An estimated 5-15 % of adults diagnosed with type 2 diabetes actually have type 1 diabetes or latent autoimmune diabetes in adults (LADA) [4]. A lifetime of insulin injections is required to partially resolve it.

2. **Type 2 diabetes**: It is characterized by insulin resistance and an inadequate response to compensatory insulin secretion [5]. Historically, T1D has been and remains the most common form of diabetes in children and adolescents, although type 2 diabetes (T2D) is increasingly diagnosed during adolescence, mainly affecting those in their 30s and 40s [3] who suffer from obesity or a sedentary life.

Another form is the **gestational diabetes mellitus** (GDM): it is the most frequent metabolic disturbance during pregnancy. The risks of multiple serious perinatal complications are increased in women with GDM, including gestational hypertension, pre-eclampsia, polyhydramnios. After the birth, the gestational diabetes disappears but women that have been affected by it should undergo screening in the postnatal period to exclude overt diabetes or impaired glucose tolerance [6].

In this thesis, we will deal with Type 1 Diabetes.

1.2 Etiology of diabetes

In medicine, it's fundamental to know the cause or set of causes of a disease or condition. The etiology factors that lead to T1D can be found mainly in autoantibodies, genetic and environmental factors [1]. In depth:

- *Autoantibodies*: They are screened in infants with a mother or a father affected by T1D in order to improve the target of environmental and genetic factors [7]. The 90% of the β-cells are destroyed after the first year of age and before the symptomatic stage [1]. Furthermore, patients with the HLA-DR4-DQ8 haplotype have the higher frequency of insulin autoantibodies [7].

- *Genetics*: T1D can be defined as a polygenically inherited disease [1]. The gene variants at human leukocyte antigen (HLA) are responsible for more or less 60% of T1D cases and about 50 others small variants contribute to increasing to 80% the percentage of correlation between genetics and T1D expression [4].

- *Environmental*: Environmental factors include diet as well as regional toxicity differences [1]. Diet includes breast feeding and diversity among diets like the intake of

cereal or meals rich in vitamin D [4]. The chemical toxins include nitrites, nitrates, N-nitroso compounds, and polychlorinated biphenyls, which damage β-cells through immunological pathways [1] but they need to be further analyzed.

- *Epigenetics*:it is a term used to define what is beyond genetics, and it acts as a mediator for environmental risk factors. As such, these changes are stable and alter heredity due to changes in the chromatin without DNA sequence changes. DNA methylation is the most commonly detected risk factor associated with the secretion of insulin in the body [1].

Some other factors can be added to the previous list like gender and geographical origin. It is interesting to evaluate that unlikely the most widespread autoimmune diseases that disproportionately affect females, on average girls and boys are equally affected with T1D in young populations [8]. Moreover, urbanization has tremendously affected trends in the incidence of diabetes (279.2 million in urban centres compared with 145.7 million in rural settings) [9]. Similar trends have been observed also in those countries which are adopting a 'western lifestyle' [10]. Another interesting factor is etnicity: it has been demonstrated that a clustering of genetic defects or polymorphisms may determine the predisposition of some individuals to develop insulin resistance and therefore predispose to diabetes. The clustering of polymorphisms predisposing some ethnic groups to insulin resistance may have developed as a genetic advantage in populations such as the Hispanics or Asians [10]. According to the $thriftygenehypothesis$ [11], predisposition to insulin resistance may have protected individuals during period of food deprivation by reducing muscle utilization of glucose and favouring glucose utilization in organs such as the brain [10].

1.3 The Diagnosis

Early diagnosis of the disease enables doctors to intervene immediately, reducing the likelihood of future complications. The more diabetes goes untreated, the worse the health of the patient will be. Polyuria, polydipsia, and weight loss are common in children with type 1 diabetes and about one-third have diabetic ketoacidosis. The incidence of type 1 diabetes in adults may be more variable, and they may not have the typical symptoms seen in children [12]. Patients who are subsequently diagnosed with T1DM may experience increased thirst and urination, fatigue, lack of energy, unexplained bacterial and fungal infections, delayed wound healing, blurred vision, and numbness or tingling in the hands and feet. Therefore, as soon as the above symptoms appear, a diagnosis and follow-up are required [13]. Diagnostic criteria are based on the following measurements [14]:

1. Fasting blood glucose (at least 8 hours) $>$ 200 mg/dl,

2. Random glycaemia (regardless of the moment of day) $>$126 mg/dl,

3. Glycaemia during load curve (OGTT) at doses of 75 g glucose, greater than 200 mg/dl.

1.4 Psycho-physical complications

1.4.1 The physiological complications

The discovery of insulin in 1922 allowed diabetes to be considered as a treatable disease but is still associated with considerable medical, psychological, and financial pressure [15]. Diabetes-related physical complications are classified as long- and short-term ones and achieving normoglycaemia is an important therapeutic goal for patients with type 1 diabetes, especially to avoid complications [16].

Hypoglycaemia is the major obstacle to glycaemia control for many patients and an inadequate caloric intake, excessive insulin dosage, and mediocre preparation for physical activity can be annovereted among the causes of this condition [17]. An episode of severe hypoglycaemia predisposes the individual to further episodes, as a result of downgraded regulatory responses to repeated hypoglycaemic events [18]. Hypoglycaemic events are associated with adverse effects on cognitive function [19] and are associated with 4–10% of type 1 diabetes-related deaths [15].

Hyperglycaemia is a dangerous condition, too. Diabetic ketoacidosis is an acute metabolic complication of diabetes provoked by high blood glucose concentration, hyperketonemia, and metabolic acidosis. It's frequent among T1D patients rather than T2D and occurs in a condition of severe insulin deficiency. Hyperglycemia, due to lack of insulin, causes osmotic diuresis leading to marked loss of water and electrolytes in the urine and symptoms of it are nausea, vomiting and abdominal pain and can progress to brain edema, coma and death.

Individuals with type 1 diabetes have a ten-times higher risk for cardiovascular events (eg, myocardial infarction, stroke, angina, and the need for coronary-artery revascularisation) than age-matched nondiabetic populations [20]. These complications consist of microvascular and macrovascular disease, which account for the major morbidity and mortality associated with T1D [17]. In depth:

1. **Diabetic nephropathy**: it's the most common cause of renal failure in the developed world [17]. Diabetic nephropathy consists of glomerular sclerosis and fibrosis caused by the metabolic and haemodynamic alterations of diabetes mellitus. It manifests as slowly progressive albuminuria, with worsening of hypertension and renal failure.

2. **Diabetic neuropathy**: refers to a complex group of conditions falling into two major categories: focal and generalized [21]. The focal neuropathies include the mononeuropathies such as carpal tunnel syndrome, palsy of the peroneal nerve or of the third cranial nerves. Diabetic sensorimotor polyneuropathy is by far the most common generalized neuropathy among the neurologic complications of diabetes [21]. Peripheral neuropathy, in conjunction with peripheral vascular disease, can lead to skin ulceration of the lower limbs, poor healing and gangrene, amputation or the development of the diabetic foot [17].

3. **Diabetic retinopathy**: it's a long-term complication of diabetes that affects the eyes. It is caused by damage to the blood vessels of the tissue in the light-sensitive part of the eye, the retina. It can develop in anyone with type 1 diabetes and type 2 diabetes.

4. **Cardiovascular diseases**: Macrovascular complications of type 1 diabetes include atherosclerosis and thrombosis in the heart, peripheral arteries, and brain. The risk of

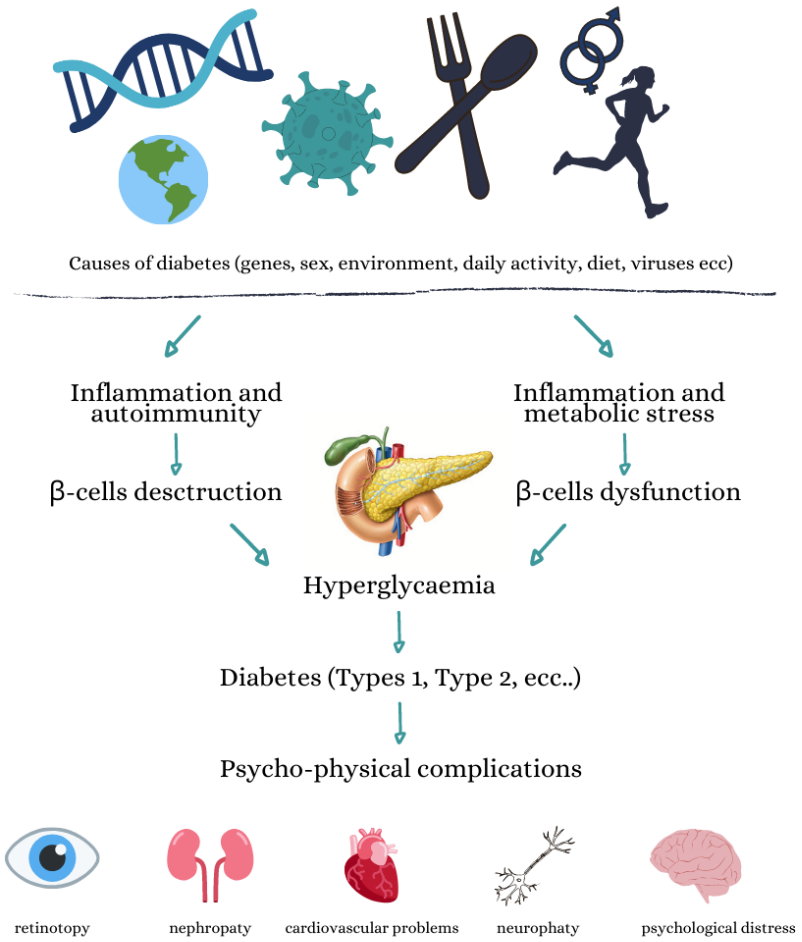


Figure 1.1: Phatophysiology, etiology and complications of diabetes

cardiovascular complications does not appear to be as attenuated by intensive blood sugar control [15]. The relative risk of cardiovascular disease in type 1 diabetes can be as much as 10-fold greater than that in non-diabetic individuals [17].

1.4.2 The psychological complications

The onset of a chronic disease like diabetes can be complex to face, especially at a tender age, and the patients will have to develop control strategies for T1D and their general psycho-physical well-being. A wide variety of factors, like peer group influences, importance of body image, less parental oversight, greater risk-taking, and fear of hypoglycaemia, represent a central challenge in the management of diabetes in children and adolescents [22], emphasized by the physiological, social and emotional changes which occur between child-

hood and adulthood [23]. Therefore, researchers have focused attention on the psycho-social concomitants of type 1 diabetes particularly in children and teenagers, but also in adults.

Depression, anxiety, and general psychological distress, diabetes-related emotional distress, a stress condition specifically resulting from concerns and worries about diabetes and its management, are common in people with diabetes [24].

The management of diabetes is an aspect that seriously affect the daily life of young patients. In fact, they generally feel that others do not understand them and cannot imagine what it is like to have diabetes. They said they felt lonely about their illness and wished more people knew and understood about it. They are all eager to meet and talk to someone who can understand them [25]. Additionally, they feared that poorly regulated diabetes would impact their future health or that they would die at an early age [25]. Young women mainly suffer of the psychological aspects of this pathology: nearly a quarter of teenage and young adult women with type 1 diabetes have either a full-blown (about 10%) or sub-threshold (about 14%) eating disorder, and that such disorders are associated with insulin omission to control weight through induced glycosuria, poor glycaemic control, and early onset of diabetes-related complications [26].

Continued efforts to integrate diabetes management into social life demonstrate the importance of social support for adolescents [25]. Support from strong peer relationships is especially important. Research supports that peer relationships are important for social development and self-esteem, especially during adolescence.

Mindfulness interventions to alter psycho-social stressors have also been tested in people with diabetes. They have been found to have psychological benefits in multiple studies, reducing symptoms of depression, anxiety, and diabetes distress in people with diabetes [27].

In Figure 1.1 can be seen a recapitulatory scheme of the patophysiology, etiology and complications of T1D.

1.5 The Therapy

People with diabetes require systematic and ongoing treatment planned by a professional medical team. The primary goal of treatment is to maintain blood sugar within the normative range, and the secondary goal is to implement an appropriate lifestyle, including proper eating habits and physical activity. Thus, the foundations of diabetes care are therapeutic education, nutrition, exercise, and medication. Smoking cessation is also important because it is a risk factor for chronic complications of diabetes, but it also makes controlling blood sugar difficult.

The discovery of insulin in 1922 was clearly the most important therapeutic event in the history of type 1 diabetes. However, exogenous insulin replacement therapy does not always provide the metabolic modulation necessary to avoid one or more disease-related complications. As a result, diabetes management in modern countries often involves the use of insulin analogs and mechanical techniques such as insulin pumps and continuous glucosemeters to improve treatment of T1D [16].

For what concern insulin injection, its dosage depends from subject to subject based on their daily life and habits. There are different types of insulin, based on their functions:

- **Basal and postprandial**: while the first one, administered formerly every 24 hours, has a long action period and is used to maintain the glycaemia between one meal and another as constant as possible, the second one, which is also known as short-acting

insulin, because it's employed in response to food input, through an injection that comes ahead, during or after a trial to mimic the hormonal postprandial response [4].

- **Premixed**: it unites, in prefixed rates, basal and postprandial insulin and is used by subjects that refuse to do further than two injections in one day, but it isn't flexible, therefore it isn't recommended [28].

- **Concentrated**: it's a special type of basal insulin that's concentrated 2 to 5 times more than the common one and is used on cases that have high insulin resistance or that are particularly overweight, demanding more than 200 units per day [28].

Therapeutic training involves imparting knowledge beyond insulin doses alone and helps manage all aspects of the disease as effectively as possible. It is taught to patients and their families by doctors and nurses, as well as other professionals such as nutritionists and psychologists. The education of young people with diabetes and the development of their awareness and expertise is critical for their adherence to treatment. Therefore, improving this education is necessary to increase its consistency, because despite the widespread availability of effective therapies, adolescents affected by T1D remain less adherent to treatment compared with other pediatric age groups and do not adhere is associated with glycemic control and increased risk of morbidity and premature death. Non-pharmacological treatments are necessary for efficient monitoring of every aspect of the illness and, mainly, for the prevention of possible complications that could worsen the general health of the patient.

Over the years, the patient's diet was restricted, demonizing certain foods, especially those high in carbohydrates. Today, fortunately, consumable foods are no longer imposed and diabetics can eat freely, of course paying attention to the amount and type of carbohydrates, proteins and fats, to choose the correct insulin dose, and to try to follow a sensible and healthy diet. Various studies have shown, for example, that our Mediterranean diet is a solid choice for achieving a healthy lifestyle [29, 30].

Physical activity is clearly necessary for people with diabetes because it increases the body's insulin response, increases the use of glucose by muscles, and helps improve overall health by increasing HDL (the so-called good cholesterol) and lowering arterial pressure [31]. Exercise must be regulated along with insulin doses and meals to avoid metabolic disturbances, hypoglycemia and hyperglycemia, and must never be forced [32].

1.6 Glyceamic control: past, present and future of glucose monitoring

Blood glucose must be regularly monitored through tests and HbA1c analysis performed on the same patient to prevent complications from developing or worsening.

Traditionally, the primary method of blood glucose monitoring in diabetic patients has been self-monitoring of blood glucose (SMBG), but there is no clear consensus on the frequency of sample collection, which varies from 4 to 10 times per day in insulin-dependent diabetic patients [33]. This variation reflects differences in activity levels, lifestyle, insulin injection schedules, and agreements between physicians and patients [34]. However, few patients adhere to a strict SMBG regimen to delay the onset and progression of diabetic

complications, including retinopathy, nephropathy, and neuropathy that can lead to amputation [33]. However, intensive insulin therapy has its limitations, including an increased incidence of hypoglycemia and the need for frequent SMBG testing [35].

Current T1D treatments focus on balancing exogenous insulin and food intake while incorporating daily activities such as exercise and sleep. Significant advances have been made in insulin formulation and diabetes technology, including insulin delivery methods and blood glucose monitoring [36]. Diabetes technology is a term used to describe "the hardware, devices, and software that diabetics use to control their blood sugar levels, prevent diabetic complications, reduce the burden on diabetics, and improve their quality of life" [37]. More specifically, diabetes technology includes insulin delivery and blood glucose monitoring devices, such as insulin syringes, pens, and glucose meters, as well as newer devices and software, such as insulin pumps, continuous glucose monitoring (CGM), mobile apps, smart pens, and remote medical. While we often think of technology in terms of novel devices used to treat diabetes, its introduction has also evolved models of healthcare delivery [37].

Among the most advanced technologies, today the interstitial constant glucose monitoring systems (CGMs) stand out. They represent the modern alternative to the standard glucometer. They are composed by:

1. a glycaemic sensor usually implanted in the most adipose subcutaneous area of the abdomen or the arms,

2. a monitor that allows to read and show the values of glucose in the interstitial fluid in real-time (CGM real-time) or postponed (CGM offline),

3. a transmitter that allows the communication between the first two parts (through a wire or Bluetooth technology), sending data on the plasma glucose concentration[1].

These devices must get calibrated using glucose measurements in the capillaries: the sensor performs measurements every 5/10 seconds and computes an average value every 5 minutes that it then sends to the monitor. In the past, the accuracy of this type of sensor was the major problem as it had to be calibrated various times by the patient through standard glycaemic controls. Adherence to and frequency of CGM use over time has been a particularly important aspect of the associated reduction in HbA1c. More frequent CGM use in all age-groups has been associated with greater HbA1c reduction from baseline to 6 months [35].

CGMs can join the “open-loop” or “closed-loop” systems:

- Open-loop: coupled with multiple daily insulin injections or a subcutaneous insulin pump with the patient's input.

- Closed-loop: systems that incorporate a long-term functional implantable sensor device directed at normalizing blood glucose levels and an insulin pump.

The concept of closed-loop glucose control has been present since the 1960s [38] but the approach was not feasible until much more recently. The availability of smaller and reliable insulin pumps, the emergence of accurate and reliable continuous glucose monitoring systems, and the access to secure and safe wireless communication technologies made the

[1] `https://www.dexcom.com/g6-cgm-system`

development of wearable closed-loop systems possible. These systems delivered small automated correction boluses when glucose was predicted to exceed a pre-defined level, but did not modulate insulin delivery continuously. Systems were shown to improve time in target range overnight without increasing time in hypoglycaemia in both children and adults [39].

Different kinds exist, each with a different self-management level:

- **Insulin infusion suspension due to hypoglycaemia**: Instead of sending an alert to the patient and/or their family, the insulin infusion is automatically paused whenever the blood sugar level falls below a certain threshold.
- **Predictive insulin infusion suspension due to hypoglycaemia**: It predicts before a drop in blood sugar occurs by examining trends in blood sugar levels.
- **Hypo- and hyperglycaemias' minimizer**: It acts as a dual control, operating within a range of values below which hypoglycemia occurs and above which hyperglycemia occurs. The system blocks the infusion until the first of these two thresholds is exceeded, and instead activates it until the second is reached.
- **Hybrid**: It works well at night but not so well during the day. Basal control is provided by the pump, but the postprandial injection is in the patient's hand.
- **Double hormone**: the insulin pump is able not only to inject insulin but glucagon too. The latter is the main hormone for the response to hypoglycaemia as it stimulates hepatic glycogenolysis (which is to say the release of glucose by the liver) [32]

CGM has developed and evolved as a new tool for diabetes management. CGM sensors have revolutionized real-time glucose concentration monitoring, enabling applications that were not feasible before their introduction, such as AP systems [40]. Diabetes requires intensive management to normalize blood sugar to avoid short- and long-term complications, health care costs, and premature death [34]. What will the treatment for T1D be within 10 or 20 years? This will be determined by weighing the benefits, sustainability, negative impacts, safety, convenience, personal preferences and financial costs of these evolving options. As treatments in each category continue to improve, the "standard" of other competing treatments will rise, and the best treatments may change [36].

In Figure 1.2 the history of diabetic devices and future improvement of this technology are represented. Specifically, (A) represents current insulin delivery tools and glucose measurement tools (B) that have been adapted into glucose management options that are available or are emerging in practice (C), including partially automated basal insulin delivery. Fully automated insulin delivery that will not rely on the user to manually prompt mealtime insulin doses and will adapt to conditions such as physical activity will require multiple components (D). In (D), blue arrows indicate technological advances, and red arrows indicate pharmacological advances.

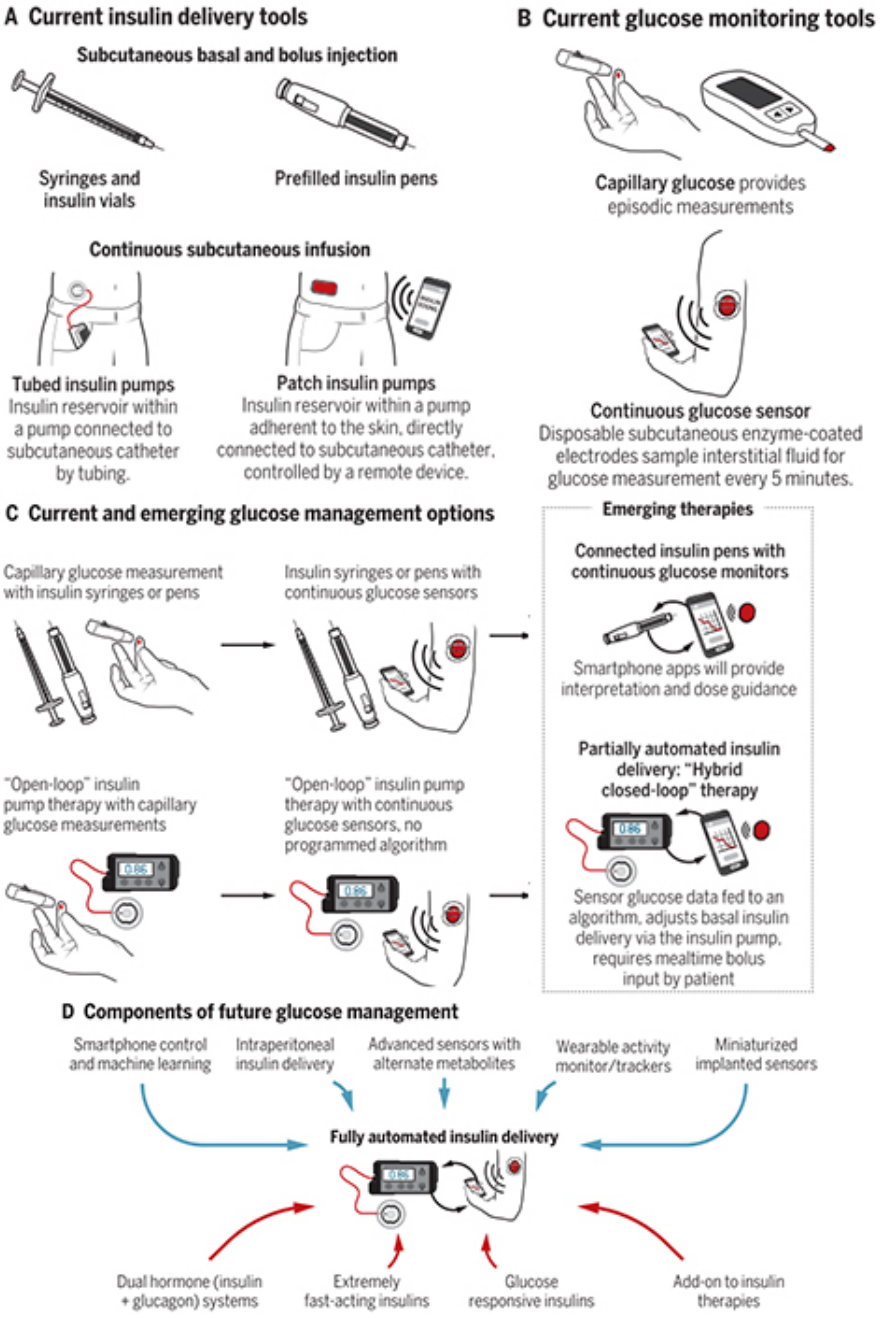


Figure 1.2: Diabetic devices and their future improvements for T1D management [41]

Chapter 2

State of the art

The SMBG devices are used for the traditional home glucose monitoring: it consists of small drop of blood collected by the patient 3-4 times per day, put on a fingerstick to instantaneously measure the blood glucose concentration [42].

Nowadays, CGM sensors have been introduced which can measure almost-continuously (e.g. every 5 min) glucose concentration in the subcutaneous tissue [43]. Diverse researches have shown that a continuos monitoring make progresses in diabetes management and therapy, significantly reducing both hyperglycemia and hypoglycemia episodes [44].

The integration of CGMs with continuous subcutaneous insulin infusion devices (insulin pumps) has led to the development of algorithmically controlled pumps that suspend insulin delivery if hypoglycemia levels are predicted within the next 30 minutes, as well as hybrid closed-loop systems that can be set up to both deliver insulin to prevent hypoglycemia; it can also automatically provide additional insulin to correct hyperglycemia. Treating T1D with these devices is fast becoming the standard of care [45].

Contemporary, together with hardware improvements, the challenges of the AP are gradually being addressed with the development of advanced algorithmic strategies [46] to improve the devices' performance as well as possible personalize the algorithms. The advantages of machine learning illustrates a promising path towards the resolution of the aforementioned problems and challenges, as has been recently recognised and reported by [46] .

This thesis tries to figure out solutions to improve the management of diabetes using a CGM sensor by DexCom and an insulin pump by Tandem™ Diabetes Care. Although, an important aspect that will be stressed out is the optimization of features' choices and which machine learning approaches fit better for the purpose of this thesis and, therefore, can help the clinician to personalize and initialize the previously mentioned insulin pump.

2.1 The blood glucose monitoring: DexCom G6®

Blood glucose concentrations in diabetics can undulate significantly throughout a day, and lead to serious consequences, as previously stated, including kidney failure, strokes, heart attacks, high blood pressure, blindness and coma.

The emergence of glucose sensors has provided patients the ability to self-monitor BG levels so as to manage insulin levels, and thus control the mortality of diabetes mellitus [47].

According to Chen et al. [47], there are three generations of glucose biosensors [47]:

- the first-generation is based on the use of the natural oxygen and the production-detection process of hydrogen peroxide.

- the second-generation sensors employ a non-physiological electron acceptor to shuttle electrons and thus solve the oxygen deficiency.

- The design of the third-generation glucose sensors aims to get rid of the leachable artificial mediators and even the glucose enzyme.

The current gold standard glucose biosensors are invasive, and CGM systems still suffer from many limitations, such as inflammation and bio-fouling [48]. On the other hand, non-invasive procedures are becoming more popular because they have more high sensitivity and better patient compliance [49].

The ideal sensor should be able to provide reliable real-time, continuous monitoring of glucose fluctuations throughout the day with high selectivity and speed for extended periods of time under tough conditions.

In this context, the G6 sensor by DexCom had been proposed. In 2006, the Dexcom SEVEN, the first real-time continuous glucose monitoring system, was approved by the FDA [47]. Since then, a lot of steps forward have been made. G6 sensor is the latest version available and it consists of [1]:

- An automatic applicator (one-touch applicator) that can easily insert a small sensor under the skin.

- The sensor and transmitter, a slim sensor that continuously measures glucose levels just below the skin and sends data wirelessly to a display device via a transmitter.

- Display device: it's compatible with a smart device or touch screen receiver that displays real-time blood glucose data, such as mobile apps or insulin pumps.

The G6 sensor is the one compatible with and accepted by the Tandem™ t:slim X2™ insulin pump. It is calibrated directly inside the factory, so it does not require any blood withdrawal from the fingertip.

Successful management of diabetes requires a near-continuous awareness of the factors that influence blood glucose levels and the complex interplay between dietary habits, physical activity, and medication. For children in particular, strategies must also involve parents and caregivers to monitor and treat diabetes. The extent to which patients and their families seize the opportunity to address diabetes may be an important predictor of long-term health and psycho-social outcomes [50].

Thus, CGM devices are considered to be the ideal candidate for the next generation products to replace the currently used portable glucosemeters [49].

2.2 The insulin pump: Tandem™ t:slim X2™

Latest options in the treatment of type 1 diabetes have enabled the commercialization of an artificial pancreas that can be better described as a feedback loop for insulin delivery.

[1] `https://www.dexcom.com/it-IT`

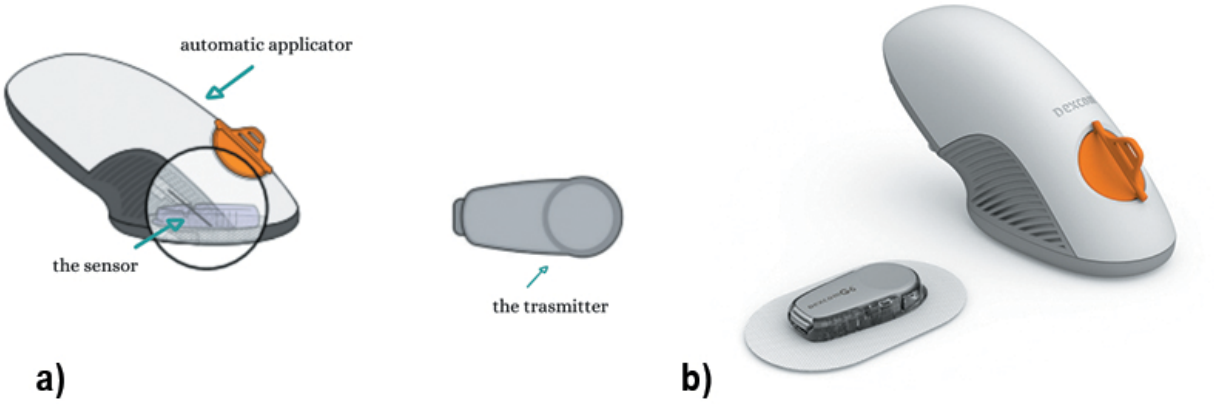


Figure 2.1: a) Schematic representation of insertion device, sensor and transmitter. b) DexCom G6® device.

The goal of these systems is to minimize or prevent short- and long-term complications of diabetes and to reduce the daily burden of diabetes management [51].

The development of CGMs in the early 2000s led to major advances in insulin pump technology, and its integration with insulin pumps pushed to the growth of insulin control algorithms that allow dynamic insulin delivery in response to current glucose trends [52].

The t:slim X2™ insulin pump by Tandem™ is an example of it and it's the one whose data is used in this work. It is an example of a hybrid closed-loop system. Closed-loop artificial pancreas technology uses a control algorithm to automatically adjust insulin delivery according to data acquired by subcutaneous sensors [53].

Fully automated closed-loop systems should not need an announcement about meals or physical activity. It has been shown in several studies [54–56] that a fully automated system improves blood sugar control and reduces hypoglycemia. However, given the delays currently associated with subcutaneous insulin delivery, ideal glycemic control after an unannounced meal is not feasible [51]. Therefore, a hybrid system that requires user-requested boluses at mealtime and when needed is a functional and commercially widespread approach for children, adolescents, adults at home and pregnant women [57,58]. Although the prospects for complete closed glycemic control have improved significantly [59], combination therapy is currently the best option for the management of T1D.

Tandem™'s t:slim X2™ insulin pump[2] is composed of (2.2) :

- the insulin pump.
- a 3 mL (which is the equivalent of 300 units of insulin) cartridge.
- a compatible infusion set.

It is equipped with a color touchscreen in shatterproof glass allowing patients to easily view all the necessary functions on the display. The pump delivers up to 300 units of insulin in a

[2] https://www.tandemdiabetes.com/docs/default-source/product-documents/t-slim-x2-insulin-pump/aw-1005628_c_user-guide-tslim-x2-control-iq-7-4-mgdl-artwork.pdf?sfvrsn=18a507d7_140

Source: `https://www.tandemdiabetes.com/products/infusion-sets`

Figure 2.2: Tandem™'s t:slim X2™ insulin pump and one of its compatible infusion sets

cartridge in basal or bolus insulin mode (requires change every 48 to 72 hours depending on patient usage).

The t:slim X2™ pump can be upgraded to provide automatic and personalized insulin dosing, allowing the system to adjust insulin delivery 30 minutes in advance based on CGM sensor readings and blood glucose predictions. However, because it is a hybrid closed-loop system, this feature cannot replace the patient's own active diabetes management.

One of the innovations of the Tandem™'s t:slim X2™ insulin pump is the ability to remotely update the insulin pump's software, using the Tandem Device Updater, to incorporate advanced technologies onto the pump as they become available.

When combined with its Control-IQ™ technology and the compatible CGM system, the whole set can be referred to as 'system' and the pump acts as a sensor receiver, getting data every 5 minutes.

The patient can create up to six Personal Profile but only one can be active at a time and for each of them 16 different time segments can be set. When a Personal Profile is generated, the patient can set any or all of the following Timed Settings:

- Basal Rate (BR): is the background supply of a chemical or process. As it applies to diabetes, the basal rate is the rate at which an insulin pump infuses small, "background" doses of short-acting insulin. It can be set inside specific ranges reported in the user guide.
- Carb Ratio, also known as insulin-to-carbohydrate ratio (ICR): it's the grams of carbohydrate covered by 1 unit of insulin.
- Carbohydrates setting: it can be set as ON or OFF.
- Target BG: ideal BG level, measured in mg/dL.
- Correction Factor, also known as insulin sensitivity factor (ISF): it's the amount of blood glucose that is lowered by 1 unit of insulin;

These settings are then used by the pump to calculate the right delivery of basal insulin and correction boluses. If Control-IQ™ technology is active, some of the previous settings cannot be personalised.

2.2.1 Control-IQ™ technology

Following FDA approval in December 2019 [3], the Control IQ algorithm is available in the U.S. in 2020 for those 14 and older. This hybrid closed-loop system uses a model predictive control algorithm originally implemented on the DiAS platform, an ultra-portable artificial pancreas research platform developed by the University of Virginia, for closed-loop control of blood glucose in home studies of T1DM patients [60].

The Control-IQ technology is the most advanced software available in the t:slim X2 pump. It uses a model predictive control (MPC) algorithm that is capable to predict future glucose levels based on CGM data and, subsequentially, automatically adjusts insulin doses, keeping the blood glucose levels inside the normal ranges [52]. Deeply on its functioning, the system use a plug-and-play architecture of different subsystems to enable for different situations in which glycemic control is fundamental [61]. The algorithm is realized using a series of safety modules to diminish hypoglycemia risk and other reduction modules to avoid hyperglycemia adjusting the basal rate as well as automated boluses [52]. Another distinguishable feature of this algorithm is that it gradually intensify control overnight, lowering the algorithm target to obtain blood glucose levels around 100–120 mg/dL by the morning [62]. To do its work, the system requires BR, ISF and ICR settings to appropriately modulate insulin delivery and it does not have any adaptive learning.

These Personal Profile settings must be configured in order to use Control-IQ™:

- Correction factor.
- Carb ratio.
- Target BG.
- Carbohydrates settings should be in mode ON.

Additionally, the weight and total daily insulin must be set by clinicians. The latter is decided by the doctor's own experience and on some general guidelines on continuous subcutaneous insulin demand related to patients age [63].

So, the ratio behind the algorithm's functioning is the following:

- If the predicted CGM value is in the range previously mentioned, the pump will continue to deliver insulin according to rate set in the Personal Profile.
- The algorithm will constantly diminish the insulin rate to avoid hypoglicaemia, if the predicted value is at or below the target range in 30 minutes in the future. Control-IQ™ is also capable to reduce or completely suspend the basal delivery when it predicts a lowering of blood glucose levels.

[3] `https://www.nsmedicaldevices.com/news/tandem-slim-x2-insulin-pump/`

- If hyperglycaemia is forecast, it progressively augments the insulin delivery rate. After the maximum rate of insulin delivery has been reached, Control-IQ™ stops increasing the insulin delivery rate. Individual Correction Factor setting, the total daily insulin estimated by Control-IQ™ algorithm and the active insulin in the organism after a bolus delivery are the parameters used to compute the maximum insulin rate.

    - If the algorithm predicts a value above 180 mg/dL 30 minutes in the future and the pump is increasing the insulin delivery or is delivering the maximum quantity, the 60% of the total correction bolus will be automatically injected to decrease to 100 mg/dL the target glucose value. The automatic bolus is computed based on the estimated CGM values and the correction factor annotated in the personal profile setting. This process occurs once every 60 minutes and the duration between boluses and the delivered percentage is conceived to avoid undesirable decrease of glucose level. The maximum amount of insulin that an automatic correction bolus will deliver is 6 units.

The user is responsible for delivering bolus doses for meals by entering the total grams of carbohydrates to be consumed into the bolus calculator. Sleep mode should be scheduled through days, specifically start and end time, but it can also be activated manually. Another possible manual activation is the one of the Exercise mode.

While using Control-IQ™, the user should only inject insulin provided by and through the pump.

Studies and trials showed a reduction in hypo- and hyperglycaemia: these results demonstrate that Control-IQ™ is safe and efficient [64].

Control-IQ™ technology is not recommended for those who use less than 10 units of insulin per day and that weigh less than 24,9 kilograms due to the requirement for a safe running of the algorithm. Moreover, it should not be used on children under the age of 6 years old. Additionally, the technology also limits the basal rate to 3 units/hour when the pump doesn't receive a CGM reading for 20 minutes and it shuts off when the sensor session ends.

While using Control-IQ™, the user should only inject insulin provided by and through the pump.

2.3 From Glycated Hemoglobin to Time in Range

As already explained in section 2.1, continuous glucose monitoring is playing a key role in the management of type 1 diabetes, mainly in children and adolescents. This tool is used to guide the person with diabetes and caregivers when striving for optimization of glycaemic control. Coupled with an insulin pump, this system is capable of maintaining the glucose levels inside specific ranges to avoid any complications, using a parameter called Time in Range.

But before this, which was the parameter used to diagnose and keep under control diabetes? The glycated hemoglobin (HbA1c). The HbA1c values reflect the average glucose concentrations in the blood over the past three months. Therefore, the glycated hemoglobin allows to know if the glycaemia has exceeded the "guard" levels in people with diabetes or at risk of becoming one. Biochemically, HbA1c is formed through a process called glycosylation, in other words when a sugar molecule binds to the hemoglobin contained in red blood cells, proportionally to glycaemia. HbA1c is less effective than normal hemoglobin for

oxygen transport. Furthermore, glycation of hemoglobin is a major cause of organ damage during diabetic disease.

However, not all HbA1c measurements provide results that match the BG values measured by the patients themselves and this could be due to some diseases that can affect erythrocyte life, such as anemia [65]. Still, the glycated hemoglobin remains a good parameter for the patients to supervise their glycaemic values. The HbA1c value is also used to assess the efficacy of new drugs for improving BG control in clinical studies as well as to keep an eye on the incidence and progression of cardiovascular complications [65].

Since the development and massive usage of the aforementioned technologies, a new parameter that can fit better the their requirements had to be found. This is why, in February 2019, an international panel of physicians, researchers and individuals affected by T1DM with expertise in CGM met at the Advanced Technologies & Treatments for Diabetes (ATTD) Congress [66] to convene on consensus recommendations leading to the formulation of guidelines expressing the ranges of desired blood glucose levels which compose the time in ranges.

The metric includes three key CGM measurements made of percentage of readings and time per day spent in these ranges [66]:

- within target glucose (TIR), inside the range 70-180 mg/dL,
- below target glucose range (TBR), below 70 mg/dL,
- above target glucose range (TAR), above 180 mg/dL.

Ideally, all diabetics have blood glucose levels consistently within the target range (TIR of 100%); however, with currently available treatment options, TIR of up to 70% are realistic. In depth (Figure 2.3):

- TIR should be more than 70% of the daily readings and, during this time, blood glucose levels should be between 70 and 180 mg/dL,
- TBR should be less than 4% of the daily readings when blood glucose levels are between 54 and 70 mg/dL and less than 1% when they are below 54 mg/dL,
- TAR should be less than 25% of the daily readings when blood glucose levels are between 180 and 250 mg/dL and less than 5% when they are above 250 mg/dL.

Recent evidence suggests that 80-90% TIR can be achieved by avoiding hypoglycemia or severe hyperglycemia events primarily using automated insulin delivery systems, in everyday conditions [65].

In conclusion, it can be stated that TIR doesn't share the same time limitations as HbA1c and has the ability to provide instant feedback on a changed insulin regimen. This information enables people with diabetes to optimize food intake and exercise, make informed treatment decisions regarding meal timing and insulin dose correction, and, more importantly, respond in a timely and appropriate manner to mitigate or prevent the condition acute glycemic events. Therefore, TIR may work as a more understandable daily metric compared to HbA1c, as a study proposed by Petersson et al. on children and adolescents suggests [68]. In addition to reflecting the daily experiences of people with diabetes, recent evidence advises that TIR itself can predict future risk of diabetes complications like retinopathy [69] and cardiovascular diseases [67].

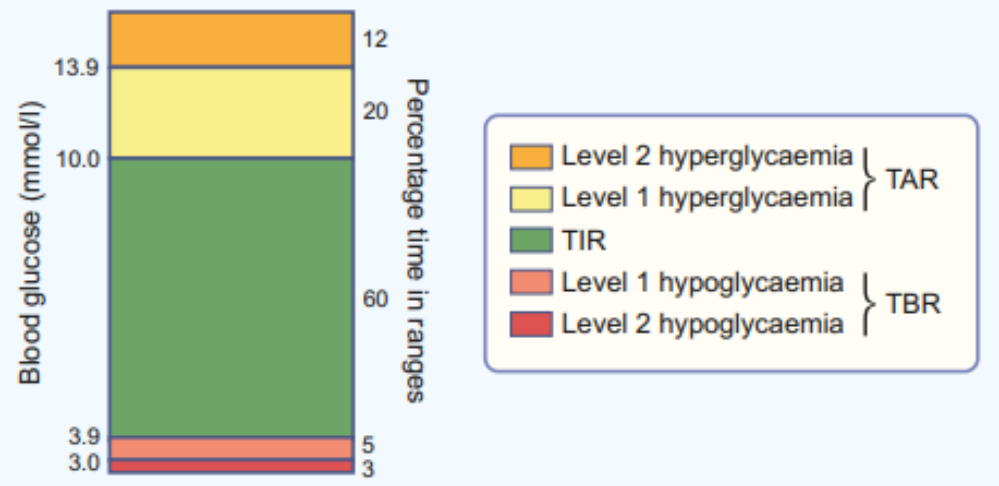


Figure 2.3: Stacked bar representation of time in ranges [67].

2.4 Algorithms to improve closed-loop systems

Children and adolescents with type 1 diabetes who use non-automated insulin delivery strategies often fail to achieve target blood glucose levels in the real world. Over the past decade, however, technological advances in various aspects of insulin delivery have had a particularly important impact on clinical diabetology, as reported in section 2.2.

The introduction of a changing automated closed-loop insulin delivery system with algorithms that help minimize hypoglycemia and control hyperglycemia. These systems cannot fully automate diabetes management, but will motivate patients to strive to maximize blood sugar control [70]. This new technology can also help parents of young children, since they are responsible for daily T1D cares including insulin bolusing and a carbohydrate estimation. From the study conducted by Patton and colleagues [71], young children, like adolescents, adhered to individual pump behaviors, but showed some variability in their adherence to hyperglycemia. Thus, targeting pump behaviors in young children and adolescents may have the potential to optimize glycemic control.

Technological innovations have revolutionized the treatment of type 1 diabetes. Although technological advances can potentially improve diabetes outcomes, maintenance of target glycemic control, at the present time, remains largely dependent on patient and family motivation, competence, and obedience to daily diabetes care requirements. The greatest impact in the future will come from combining these pharmacological solutions with existing automated insulin delivery methods that integrate insulin pumps and glucose sensors. These systems will use algorithms enhanced by Machine Learning [41].

Recently, Machine Learning has become popular with its growing applications, specially in diabetes researches. Despite this, most of the studies are focused on the implementation and upgrade of blood glucose predictions algorithms [72] and only in the latest years is becoming widely used for the optimization of hypo- and hyperglycaemia situations and insulin pumps improvements.

The bibliographical research to assess the latest enhancement in this field was based on articles published within the range 2017-2022, since the artificial intelligence has become predominant in the academic world, especially in the health management.

For example, in 2017, an artificial pancreas method consisting of a CGM system, an insulin pump, and an adaptive control algorithm attempted to find an effective way to control blood sugar and insulin levels [73]. The main goal is dynamic iterative and patient-centric optimization to create this will produce good results in the simulation. In the same year, Herrero et al. [74] proposed a new technique that can automatically adjust the pre-prandial insulin bolus used by the insulin pump to compensate for the delay in subcutaneous insulin absorption, thereby avoiding the initial postprandial hyperglycemia, and achieving a TIR of 77.5% and 89.5% of adolescents and adults passed the computer test. Toffanin et al. [75] suggest an automatic approach based on the so-called Run-to-Run (R2R) strategy, which adjusts the insulin therapy based on the performance measured during the previous run, usually the day before the current one, using CGM measurements. Through the UVA/Padova simulator, they obtained a significal increase in the percentage spent in the range 70–180 (p-value < 0.001) with a reduction of the time spent below 70 mg/dl. A year later, Cappon et al. [76] published a preliminary study showing the potentiality of using Neural Networks for the personalization and optimization of the meal insulin bolus calculation which brought to a small but statistically significant ($P < .001$) reduction of blood glucose risk index.

In 2019, Seo et al. [77] propose a ML algorithm for predicting postprandial hypoglycemia, since it's still a challenge due to extreme glucose fluctuations that occur around mealtimes. The authors went through four machine learning models with a unique data-driven feature set: a random forest (RF), a support vector machine using a linear function or a radial basis function, a K-nearest neighbor, and a logistic regression. Among them, the RF model showed the best performance with the average sensitivity of 89.6%, the average specificity of 91.3%.

In 2020, Askari et al. [78] proposed an adaptive and predictive control framework that combines disruption prediction and pattern learning based on subject historical data and subsequent predictions. They achieved it 84.4% of the time and had no events of hypoglycemia or hyperglycemia. That same year, Colmegna et al. [79] tested control laws with linear parameter changes on a computer, with the ultimate goal of minimizing user intervention, focusing on moderate-intensity exercise.

A work proposed by Tyler et al. [80], a K-nearest-neighbours decision support system (KNN-DSS) was used to identify causes of hyperglycaemia or hypoglycaemia and determine necessary insulin adjustments from a set of 12 potential recommendations. The algorithm achieves an agreement with board-certified endocrinologists of 67.9% when validated on real-world human data allows for early identification of dangerous insulin regimens and may be used to enhance glycaemic outcomes and prevent life-threatening complications in people with T1D.

In 2021, several studies have been produced about this argument. Noaro et al. [81] proposed machine learning based model, based on multiple linear regression (MLR) and least absolute shrinkage and selection operator (LASSO), to improve the calculation of mealtime insulin boluses in T1D therapy using CGM data in UVa/Padova T1D simulator environment. The results show that the error for bolus calculation was reduced to 0.86 U vs 1.45 U in literature findings as well as hypoglycemia incidence from 44.60–45.01% of literature methods to 35.93%. Dave et al. [82] present a machine learning model for probabilistic prediction of hypoglycemia in 30- and 60-minute time horizons based on CGM datasets. The model showed good results in predicting hypoglycemia with >91% sensitivity for 30- and 60-minute prediction horizons while maintaining specificity >90%. Model performance was also highest for nocturnal hypoglycemia with a 95% sensitivity circa.

For what concern the parameters' optimisation of an insulin pump, there are no published papers or articles focused. Few of them have been found but they all represent a first approach to the subject. For example, the work proposed by Chow and collegues [83] provides a new formula developed by regression analysis of clinical data in insulin pump therapy for patients with type 1 and 2 diabetes in order to determine the starting basal rates of insulin infusion. Another interesting work is the one carried on by Nimri et al. [84] in which they tested whether frequent insulin dose adjustments guided by an automated artificial intelligence-based decision support system is as effective and safe as those guided by physicians in controlling glucose levels: they obtained great results since the glucose control was statistically non-inferior to those held by the physicians.

Chapter 3

Materials and Methods

The main purpose of this work is to optimize the choice of parameters set by the clinicians to improve the usage of the Control-IQ algorithm, with the ultimate goal of enhancing the patients' TIR.

The medical team sets up the algorithm by entering BR, ICR, and ISF variables. It is difficult for an inexperienced physician to choose the most effective values, especially the first two. In addition, ISF affects the quality of life of patients with diabetes and therefore should be prioritized when optimizing.

The desired outcome is an algorithm that automatically outputs optimal values, manually tuned by clinicians to standardize the introduction of Control-IQ and increase its effectiveness. To this end, data from insulin pumps is used in machine learning methods to gain insightful information about the relationship between measurements and settings, making improvements feasible.

Therefore, the experimental work was divided into two parts: the first part looked for the connection and relationship between insulin and blood glucose, and the second part looked for their connection with the parameters set by clinicians for the Control-IQ.

3.1 Dataset

Patients are required by the clinicians at Ancona's pediatric Ospedale Salesi to upload their DexCom G6® sensor and Tandem™'s t:slim X2™ insulin pump data on the Diasend[1] platform.

The hospital gave us data coming from the website after having removed any personal information (for privacy reasons) belonging to the subjects, except for their year of birth and sex, from their files.

Firstly, all the 48 patients registered on the platform were examined to individuate the candidates for this study. For all of them, the main interest was on blood glucose level, insulin injections, carbohydrates intake and pump settings. A time range of 180 days was considered and this become another discriminating factor to choose the perfect subjects. Not all subjects have the same months covered. Nevertheless, as the main intent was to create a dataset with the most continuous data possible, participants were selected according to

[1] `https://www.diasend.com/`

Demography			
Patient ID	Year	Patient ID	Year
Sub1	2010	Sub11	2010
Sub2	2004	Sub12	2008
Sub3	2006	Sub13	2007
Sub4	2008	Sub14	2011
Sub5	2008	Sub15	2003
Sub6	1990	Sub16	2013
Sub7	2003	Sub17	2003
Sub8	2008	Sub18	2003
Sub9	2008	Sub19	2009
Sub10	2011	Sub20	2014

Table 3.1: Patients' demography. First column display their assigned ID, while the second column displays their year of birth.

the continuity of the period of the year. Thus, patients with fragmented glycaemic and/or insulin values upload were discarded.

Out of the remaining subjects, only the ones who had uploaded ingested carbohydrates quantities were chosen, thus discarding 10 of them. In the end, out of the initial 48 patients, only 20 of them were considered to be of interest.

Thus, 20 subjects compose the analysed dataset: 15 of them are females, while 5 are males. In Table 3.1 can be seen the year of birth for each patient.

The next move was to examine the information downloaded from the Diasend platform. Two files were considered:

1. an Excel file, composed of five sheets with data about:
   (a) glycaemic values in mg/dL and the date and time at which they have been received by the pump, coming from the sensor.
   (b) blood glucose values in mg/dL along with the date and time in which they were recorded by the DexCom G6® sensor (that measures values every 5 minutes).
   (c) insulin consumption in U/h for basal and in U for bolus, bolus setting, carbohydrate consumption in grams and the associated date and time. In addition, the total amount of basal and bolus injections in U is displayed at the end of each day.
   (d) pump settings;
   (e) events recorded by the pump, such as change in basal rate, insulin cartridge inserted or sleep activity initiation.

2. a PDF file, reporting the comparison of 8 of the most recently uploaded pump settings coming from the days in which users uploaded their data on the Diasend platform and highlighting the differences. Since some limitations of the platform and the wide time range considered, not all the information were visible on this file. Fortunately, a drop-down menu on Diasend gives the possibility to explore the settings for a specific day in a specific time interval. Because of this, some patients were discarded for the pump setting analysis but this will be explained deeply later in section 3.3.2.

3.2 Pre-processing

The downloaded raw data coming from the Excel and PDF file were manipulated in order to create a starting database useful for our purpose. In detail:

- from the Excel file, only information about date, time, glycaemic values, basal, bolus and carbohydrates quantities were selected. Due to fact that the timestamps for insulin and glycaemic values are different, two excel sheets were organized: the first one with timestamps and glycaemic values and the second one with timestamps, basal, carbohydrates and bolus information.

- from the PDF file, each Personal Profile, thus time segments, ICR and basal values, of each change were transposed on a Excel file to be later used for the pump settings' analysis. As a consequence of the lack of ISF values, this parameter wasn't considered during the study.

Now, a complete description of the steps followed for the pre-processing is provided for both parts of this thesis. This work has been done on Google's Colaboratory, working in Python.

3.2.1 Pre-processing of glycaemic and insulin data

To prepare the data for being analysed, glycaemia and insulin pieces of information had to be comparable. In fact, as already explained in Section 3.1, the frequency at which blood glucose levels and insulin velocities and injections are recorded are different. For this reason, data have been homogenized.

Thus, the following points were followed:

1. firstly, after the conversion of date and time into a datetime object, all the minutes were rounded to the nearest multiple of five minutes. This was made in order to easily compare these values in the next steps.

2. secondly, all the duplicated values of date and time values were removed. This part was necessary because, after a quick investigation of the raw data, it has been noted that in some patients multiple time rows, all equal among them, were saved and associated with different values of glycaemia or basal rate. Therefore, to eliminate every possible errors that could affect the subsequent analysis, these values were removed and only those paired with the highest values were kept. To do so, the *groupby* function of Pandas' library was used.

3. lastly, since the discrepancy between glycaemic and all the insulin data in terms of time instants, the *merge_ asof*[2] [3] function was used. This is similar to a left-join except that we match on nearest key rather than equal keys. Our key is the 'time' (date, hours and minutes) and the ratio behind its functioning is to compare the value in the right data frame (B, time column of insulin data) with the one on the left (A, time column of glycaemic data), and if there is no perfect match, it takes the previous one and it merges them, by attaching the values of B to the comparable times of A. It is also possible to choose a latency (in seconds) to be tolerated: in this case, since blood glucose levels are measured every 5 minutes by the DexCom G6® sensor, the time delta for the "tolerance" parameter was set at 299 seconds (less than 5 minutes).

   At the end of this step, some empty cells were generated in the columns related to the insulin data and they were filled with zeros. There's physiological explanation behind this procedure: generally speaking, no values recorded mean that no injections have been programmed by the algorithm. In fact, the algorithm does not leave the original BR, set by the clinician, because it has predicted serious hypoglycemia in the next 30 minutes, suspending insulin delivery. Thus, since these new empty cells are created after the merging and that in that specific time instant the algorithm didn't plan an injection, they were filled with zeros.

After this process, the clean data was saved in a new Excel file with a single merged time column, glycaemic and insulin values (basal rate, bolus and carbohydrates). The first dataset is ready for the Machine Learning step.

3.2.2 Pre-processing of insulin pump data

The work on the pump settings was done for only 12 subjects. This choice was done based on the balance of their basal data, the content of their settings' changes, if they were using Control-IQ or not, and the availability of data, otherwise if it was possible to download the same data belonging to the same period.

For the pump settings' analysis a similar pre-processing has been followed. Point by point:

1. at the beginning, to match the glycaemic values and time instant with the different pump settings, the merge of both information was made. The procedure is similar to the one depicted in point 3 of 3.2.1. The same key and tolerance value were used.

2. in the second place, the Personal Profile data were written, thanks to a fully automatic algorithm, to the right position and time slot, accordingly to the information acquired from the original PDF. In this way, it has been obtained a file with time, glycaemic data, ICR and target basal rate.

[2] https://pandas.pydata.org/pandas-docs/version/0.25.0/reference/api/pandas.merge_asof.html

[3] https://towardsdatascience.com/how-to-merge-not-matching-time-series-with-pandas-7993fcbce063

3.3 Modelling

In this section, definitions and explanations of the Machine Learning (ML) modelling methods and the steps followed in the pump settings' analysis used in this work are presented.

3.3.1 Machine Learning approaches

This section reports the definitions and explanation of the machine learning modelling approaches used in this work.

Logistic Regression (LR), Random Forest (RF) and Zero-inflated regressor (ZIR) were chosen as ML algorithms for our purpose. For all of them, basal insulin and glycaemic info were used but the manipulation were different according to the algorithms purpose, that is classification for the first two models, and regression for the last one.

Firstly, the focus was on a classification model able to tell if the Control-IQ™ algorithm decided to either change the basal rate or not based on the analysis of the 1 and 0 labels, respectively injection or not. For this reason, LR and RF were implemented. But, due to the nature of the dataset, some adjustmets had to be done to further generalize our approach. In fact, since the insulin rate often goes to zero to avoid hypoglycemic situations, the database is strongly unbalanced on zero. This is an issue that can affect the performance of the model, causing difficulty in learning to classify the minority class. Thuse, it requires more effort to achieve balanced levels of performance in classification.

Moreover, it was necessary to use a model capable of distinguishing the different meanings behind these values. Thus, the ZIR model, that include both classification and regression steps, was implemented because it was able to satisfy our requirement.

It is possible to visualize the idea behind the whole conceptualization in Figure 3.1

In the following pages, a deep explaination of how these algorithms work is provided.

Logistic regression

Logistic regression estimates the probability of an event occurring, such as voted or didn't vote, based on a given dataset of independent variables. Since the outcome is a probability, the dependent variable is bounded between 0 and 1. Thus, the logistic regression is used when the dependent variable is categorical [4]. The ultimate goal of this approach was to compute if Control-IQ™ decided to change the insulin rate or not based on info coming from glycaemic values and carbohydrate intake.

By using the module called statsmodels[5], a logistic regression model was built, through the Logit(y,X) function where y is the column of 0 and 1s of the basal file and X is constituted by data coming from glycaemic and carbohydrate info.

In the example of logistic regression applied to the glycaemia file where the columns for the 6 previous basal levels were added, the logistic regression equation was:

[4] https://www.ibm.com/topics/logistic-regression

[5] https://www.statsmodels.org/stable/index.html

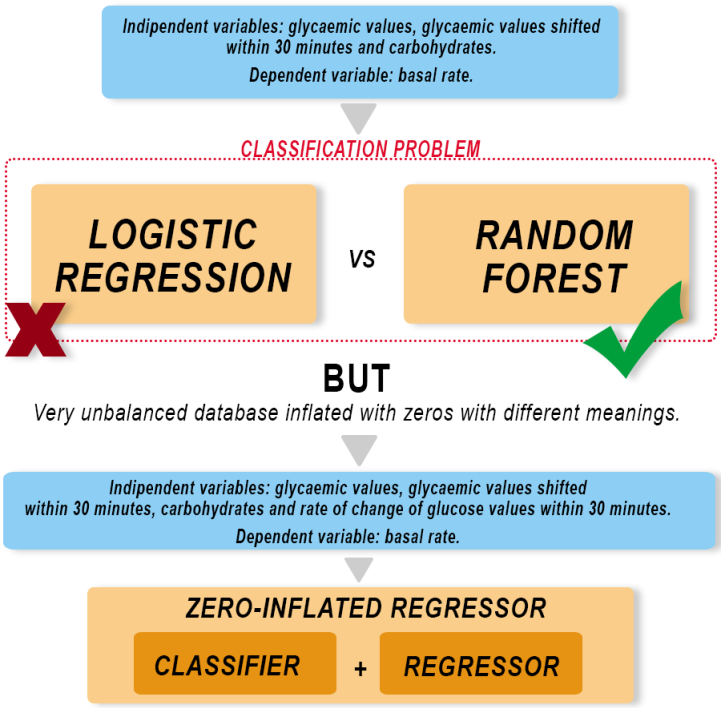


Figure 3.1: Block diagram representing the data analysis approach followed in this study.

$$Pr(y=1|X) = \frac{exp(\beta_0 + \beta_1 Glycemia + \beta_2 Carbs + \beta_3 Glyc_{tminus1} + \beta_4 Glyc_{tminus2} + \beta_5 Glyc_{tminus3} + \beta_5 Glyc_{tminus4} + \beta_6 Glyc_{tminus5} + \beta_7 Glyc_{tminus6})}{1 + exp(\beta_0 + \beta_1 Glycemia + \beta_2 Carbs + \beta_3 Glyc_{tminus1} + \beta_4 Glyc_{tminus2} + \beta_5 Glyc_{tminus3} + \beta_5 Glyc_{tminus4} + \beta_6 Glyc_{tminus5} + \beta_7 Glyc_{tminus6})} \tag{3.1}$$

where $Glycemia$ indicates the glycaemic recorded values, $Carbs$ indicated the carbohydrates recorded intake and from $Glyc_{tminus1}$ to $Glyc_{tminus6}$ indicates the recorded glycaemic values within 30 minutes.The addition of these 6 time-shifted columns was done based this strategy: Control-IQ™ predicts the glycaemic trend of the following 30 minutes, meaning that the basal velocity of each row where it is present is based on the blood glucose level recorded 30 minutes prior, which is to say 6 glycaemic measurements prior. The empty cells generated by this process were removed.

By using the open-source library Scikit-learn[6] and its functions, for each patient, the model was fitted and the script computed its accuracy (see Eq. 3.2), its predicted values, its confusion matrix, its precision ($Prec$, see Eq. 3.3), recall (Rec, see Eq. 3.4) and F1-score ($F1$, see Eq. 3.5) and its receiver operating characteristic (ROC) curve and area under it.

Here are reported the equations of the used metrics [85], where TN represents the true

[6] `https://scikit-learn.org/stable/modules/generated/sklearn.linear_model.LogisticRegression.html`

negatives, FP represents the false positives, FN represents the false negatives and TP represents the true positives:

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{3.2}$$

$$Prec = \frac{TP}{TP + FP} \tag{3.3}$$

$$Rec = \frac{TP}{TP + FN} \tag{3.4}$$

$$F1 = \frac{2 * Prec * Rec}{Prec + Rec} = \frac{2 * TP}{2 * TP + FP + FN} \tag{3.5}$$

Random Forest

The Random Forest approach was used in an attempt to improve the performance of the Logistic Regression.

The RF algorithm picks N random records from the dataset and builds a decision tree based on them, repeatedly for the chosen number of trees wanted by us (in this case, 200 trees) and each tree predicts the category to which the new record belongs and then the latter is assigned to the category that wins the majority vote.

The RF algorithm presents some interesting advantages: it is not biased because there are multiple trees and each one is trained on a subset of data, it is stable and it works well even when data has missing values or it has not been scaled well.

By using the open-source library Scikit-learn[7] and its functions, the RandomForestClassifier functions was implemented.

Firstly, the algorithm was fed with the same dataset used for the LR but, due to the huge amount of data, the model did't perform well. Probably, the dataset wasn't organized in suitable way for the Random Forest. Thus, the ri-organization consisted in:

- firstly, the randomization of all values was made to avoid that samples were taken from the same days or weeks.
- as we have previously stated, the database is strongly imbalanced. So to allow the Random Forest algorithm to correctly classify the zeros and ones, a personalized percentage for each patient was computed based on the amount of 0 and 1. According to the results, they were split for the training and testing phases.
- lastly, after the two matrices were completed, all the rows had been randomized again.

[7] `https://scikit-learn.org/stable/modules/generated/sklearn.ensemble.RandomForestClassifier.html`

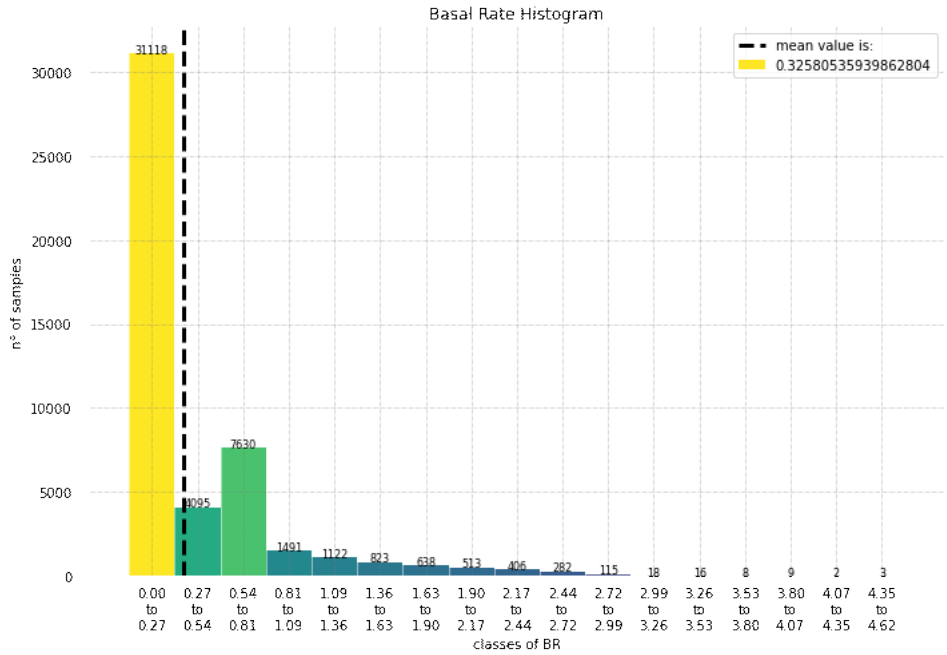


Figure 3.2: Histogram representation of distribution of basal values for subject 3

Always through the same library as before, $Prec$, Rec and $F1$, the accuracy, balanced accuracy and the confusion matrix were computed. Here it is reported the formula of the balanced accuracy, an important metric for imbalanced database.

$$Acc_B = \frac{TP + TN}{2} \tag{3.6}$$

Zero-inflated Regressor

Our dataset has an unusually high amount of zero targets in it and they have different meanings (an example in Figure 3.2): fistly, they can be associated with no injection by the insulin pump because the glycaemic curve is in the ranges or to avoid hypoglycaemia; secondly, they can be generated after the merge to line up insulin and blood glucose data.

Thus, we have to work with the so called zero-inflated dataset, and this constitute a problem for any model because they can be deflected by such behavior, including linear regression, support vector machines, and also neural networks. The probability that any of these models will output a zero is quite small.

An estimator that solves problems related to zero-inflated datasets is the Zero-inflated Regressor (ZIR) and the idea behind it is quite simple. In fact, it is based on (Figure 3.3):

- a classifier C: its task is to find if the target is zero or not.
- a regressor R: its task is to output a (usually positive) prediction whenever the classifier indicates that the there should be a non-zero prediction.

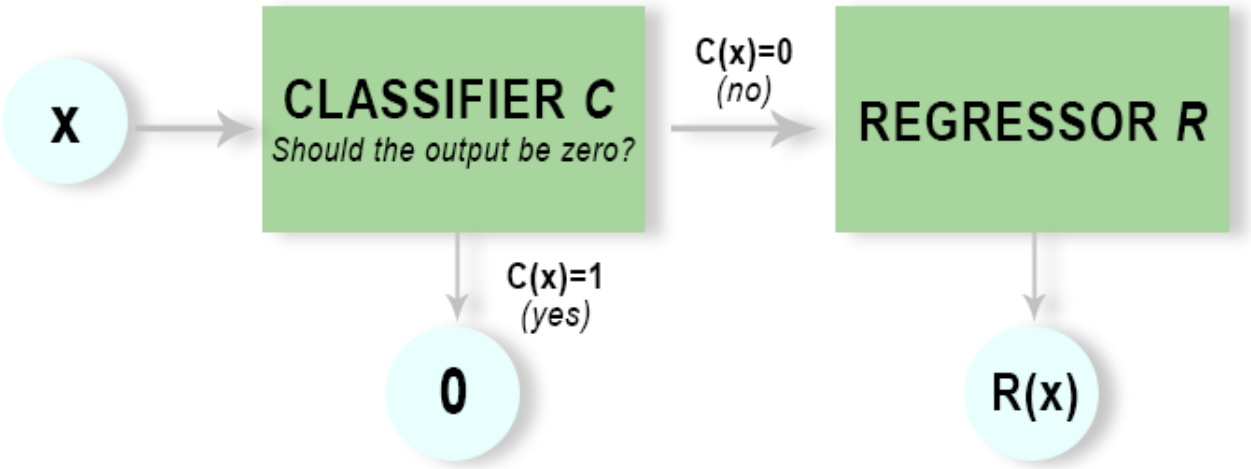


Figure 3.3: Schematic representation of how the Zero-inflated Regressor works.

The regressor is only trained on examples where the target is non-zero, making it easier to focus. When predicting, first ask the classifier if the output should be 0. If it is, output zero. Otherwise, ask the regressor for its prediction and print it.

This is a meta-model, i.e. a model that consists of other models, thus aggregating both classification and regression steps. The great thing is that it can be plug in any classifier and regressor, according to the requirement of the study.

By using the module called sklego.meta library[8], a ZeroInflatedRegressor model was implemented, combining different kindS of classifiers and regressors. Among the classifiers, Random Forest classifier, Gradient Boosting and Extra Tree classifier were chosen while for the regression analysis Random Forest regressor, Multivariate Linear regression and Extra Tree regression were implemented.

Gradient Boosting classifiers are a group of machine learning algorithms that combine many weak learning models together to create a strong predictive model. Decision trees are usually used when doing gradient boosting and they are becoming popular because of their effectiveness at classifying complex datasets. The main objective of Gradient Boosting classifiers is to minimize the loss, or the difference between the actual class value of the training example and the predicted class value.

Extra Trees algorithm (Extremely Randomised Trees) is an ensemble learning method essentially based on decision trees. Like Random Forest, Extra Trees Classifier randomises specific decisions and subsets of data to minimise overlearning of data and overfitting. ExtraTrees, like Random Forest, builds multiple trees and splits nodes based on random subsets of features, but with two key differences: it does not bootstrap observations (i.e. random sampling without replacementis performed) and it splits nodes according to random splits,

[8] `https://scikit-lego.readthedocs.io/en/latest/meta.htmll`

not the best splits. In terms of computational cost and hence execution time, the Extra Trees algorithm is faster. This algorithm saves time because the whole procedure is the same, but it randomly selects the split point and does not calculate the optimal point.

The combination used are the following:

1. Random Forest classifier and Multivariate Linear Regression: they have been used in our previous study, obtaining good results in terms of accuracy. Thus, we want to test them in this new combined approach.

2. Gradient Boosting with both Random Forest Regression and Multivariate Linear Regression: due to its capability and efficacy of working with elaborate database, it was paired with these two regression model that have been previously successfully used and that their reliability has been founded and demonstrated in several studies [77].

3. Extra Tree Classifier and Regression: since it is similar to the Random Forest approach, it has been selected to evaluate its goodness in terms of computational speed and accuracy compared to the aforementioned Random Forest.

At the very beginning, the same predictors used for the RF and LR were considered but the results were unsatisfying. Thus, the number of independent variables was incremented by adding three new features: the differences between 10,20 and 30 minutes delayed glucose values. This decision was based on some considerations made by the clinicians and some findings in the literature [82], reporting that the rate of glucose changes is an important descriptor to consider for the overall glycaemic control.

Here are reported the equations of the used metrics [85];

$$MAE = \sum_{i=1}^{D} |x_i - y_i| \tag{3.7}$$

$$MSE = \sum_{i=1}^{D} (x_i - y_i)^2 \tag{3.8}$$

$$RMSE = \sqrt{\frac{1}{n} \Sigma_{i=1}^{n} \Big(\frac{d_i - f_i}{\sigma_i} \Big)^2} \tag{3.9}$$

$$R^2 = 1 - \frac{\text{sum squared regression}}{\text{total sum of squares}} = 1 - \frac{\sum (y_i - \hat{y}_i)^2}{\sum (y_i - \bar{y}_i)^2} \tag{3.10}$$

180-days time in range			
Patient ID	TIR	Patient ID	TIR
Sub3	83.24%	Sub14	69,31%
Sub4	72,20%	Sub15	49,84%
Sub5	89,25%	Sub16	68,13%
Sub7	62,48%	Sub17	86,27%
Sub8	42,73%	Sub18	77,50%
Sub13	92,20%	Sub20	69,29%

Table 3.2: Patients' TIR computed for the total 180-days period.

3.3.2 Pump settings' analysis

First thing first, for all the 12 subjects, a Python algorithm was applied to calculate their TIR, based on the clinicians' guidelines [66]. This step was done to have a general view of the trend of the TIRs for each patient. The results are visible in Table 3.2.

Data analysis was done based on the settings' changes for each subject. All of them had changes in either BR or ICR over different date intervals and with a different number of parameters' settings. The overall changes of the parameters created different date intervals regarding BR and/or ICR changes for each subject in which different time intervals of interest could be studied. Among the 13 patients, two of them had always kept the same BR and ICR parameters for all the 180 days. These differences will be underlined in the following sections.

By working on time masks coded in Python, computations were conducted, on a Colab notebook, only applied to the data linked to the date intervals of interest and to the time intervals of interest. Several approaches have been followed, in particular:

1. Approach A: for each date interval and each time slots, TIRs were computed in order to investigate the overall glycaemic control during the day. Also TIRs for lunch and dinner time were computed to compare the adherence to the target threshold. the different time masks were based on both the basal rate and insulin-to-carbohydrate ratio changes. The subjects' meal TIRs (lunch: 11:30-15:00 and dinner 18:30 - 23:00) were computed for each of their different date intervals. This was done to analyse how the combination of changes of the parameters perform, meaning how well they control blood glucose levels keeping them inside the guidelines' thresholds [66]. These mealtime intervals were based on the metabolic regulation of food intake both in healthy and diabetic individuals [86, 87] and on clinicians' experience. This preliminary approach was performed only on those subjects who have kept the same time segments in each Personal Profile change (5 subjects).

2. Approach B: TIRs were calculated in three diverse time periods (11:00-12:30, 12:30-14:00 and 14:00-16:00) to assest if the insulin pump's setting were good enough to

avoid postprandial spikes. The same was done for the dinner time, considering three other time segmets (18:00-19:30, 19:30-21:00, 21:00-23:00).

This analysis was mainly focused on understanding which parameters influence the most the glycaemic control after the meal ingestion in order to define a standard for the postprandial spikes and see how the insulin pump control works in this condition. In fact, it is normal for the level of glucose in the blood to rise a small amount after eating, even in people who do not have diabetes. However, if the rise is too high, it can affect your quality of life today and contribute to serious health problems down the road. Even though after-meal blood glucose spikes are temporary, several spikes a day, day after day, can raise the HbA1c level, and a high HbA1c level has been shown to raise the risk of long-term diabetes complications.

In a person who doesn't have diabetes, eating foods containing carbohydrate causes two important reactions in the pancreas: the immediate release of insulin into the bloodstream, and the release of a hormone called amylin. The insulin starts working almost immediately (to move glucose out of the bloodstream and into cells) and finishes its job in a matter of minutes. The amylin keeps food from reaching the small intestine too quickly. As a result, the moment blood glucose starts to rise, insulin is there to sweep the incoming glucose into the body's cells. In most cases, the after-meal blood glucose rise is barely noticeable. On the contrary, in people with diabetes, the timing is all fouled up: rapid-acting insulin that is infused by a pump at mealtimes takes approximately 15 minutes to start working, 60–90 minutes to "peak," or reach maximum effectiveness, and four hours or more to finish working. Meanwhile, amylin is either produced in insufficient amounts or not at all, so the movement of food from the stomach to the intestines is not slowed the way it should be. As a result, food digests even faster than usual. This combination of slower insulin and faster food can cause the blood glucose level to rise quite high soon after eating. Once the mealtime insulin finally kicks in, the high is followed by a sharp drop. The exact timing of a high blood glucose spike can vary from person to person and meal to meal. The differences between the healthy and pathological management of glucose levels is shown in Figure 3.4.

Thus, it is essential to know the exact time of food ingestion to examine all these factors in a reliable way. Unfortunately, we haven't notes about it, we have therefore individuated the just presented three time slots based solely on the aforementioned studies, on the clinicians knowledge about the topic, and on our hypotheses.

Moreover, the standard deviation of the difference between the actual basal rate and the target insulin flux set by the clinician and the mean glucose values for the range 14:00-16:00 and 21:00-23:00 of all the different periods were calculated in order to assert how the insulin pump parameters work to keep blood glucose levels inside the guidelines' thresholds.

3. Approach C: a preliminary analysis of the overnight control has been conducted. In fact, the majority of the subjects have setting changes in the interval between 00:00 and the 06:30, allowing us to investigate how good the settings perform while circadian rhythms influence the subjects' glucose metabolism. Circadian rhythms are fundamental biological processes that allow organisms to predict and adjust to changes in the environment due to the 24-hour rotation of the earth on its own axis [89]. These

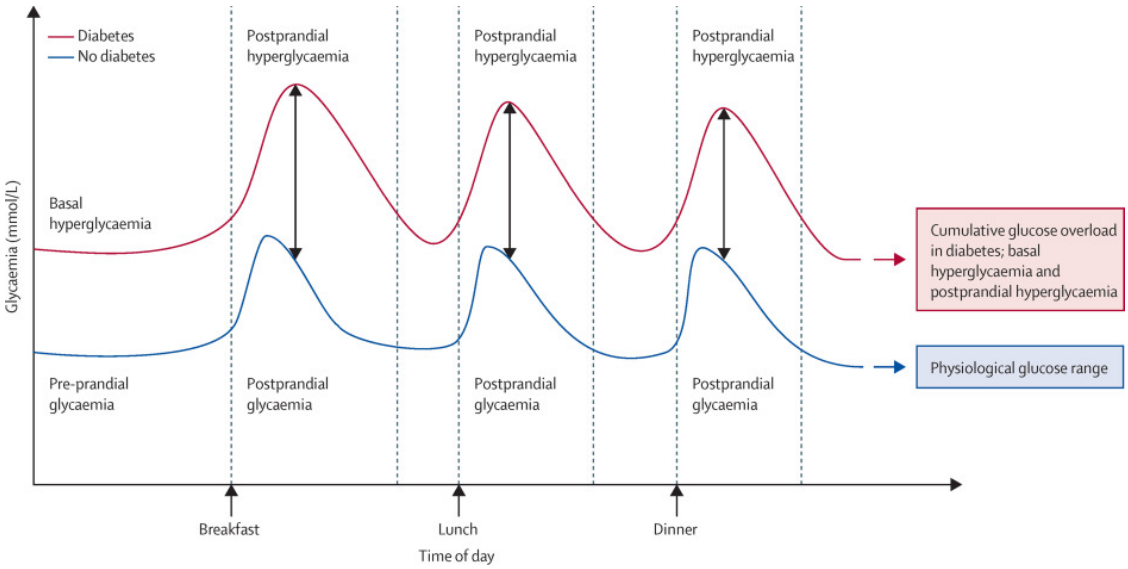


Figure 3.4: Postprandial spikes in healthy and diabetic patient [88]

rhythms are synchronised by the circadian clock, which temporally organises chemical, molecular and psychological processes based on light and dark cycles. Numerous studies [90–93] have demonstrated that individuals affected by T1D have less insulin sensitivity during the second half of the night, leading to higher insulin dosage, even in absence of external influences like physical activity and food intake. This phenomenon is called the The term "dawn phenomenon", first introduced in 1981, describes a spontaneous hyperglycaemia or increased insulin requirement to maintain normoglycaemia in the early morning hours, without nocturnal hypoglycaemia (Figure 3.5). In patients with T1D, the dawn phenomenon did not occur predictably, posing a major challenge for blood glucose management.

The analysis was performed on time slot from 00:00 to 06:30, when the night profile is activated; the end point was chosen accordingly with the clinician experience on the matter and on the guidelines founded in the manual of Tandem t:slim X2 [9]. In fact, the offset of night control is "premature" compared to the actual awakening time: this is done to gradually pass from the nocturnal settings to the daily ones without unexpected changes or glycaemic peaks.

Furthermore, two additional time slots were individuated: from 00:00 to 03:30 and 03:30 to 06:30, the latter one to investigate the response of the Control-IQ technology to the dawn phenomenon. For each of them, TIRs were computed, always considering the several periods defined previously and based on the setting changes, but the ranges were modified based on the pump settings for the night control: the hypoglycaemia falls in the range from 0 to 112.5 mg/dL, normoglycaemia from 112.5 ro 120 mg/dL and hyperglycaemia from 120 mg/dL and over. Further, the hours spent in each of these states were calculated.

[9] https://www.tandemdiabetes.com/docs/default-source/product-documents/t-slim-x2-insulin-pump/aw-1006509_b_user-guide-tslim-x2-control-iq-7-4-mgdl-ita-artwork_web.pdf?sfvrsn=18a507d7_196

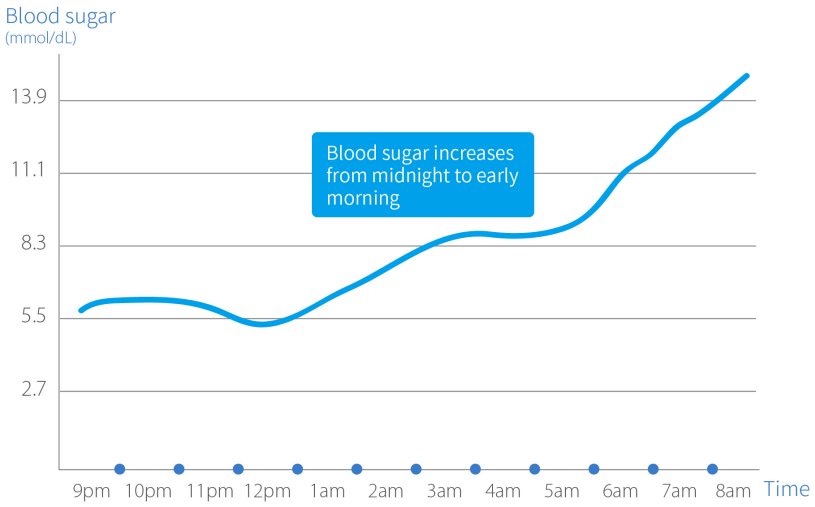


Figure 3.5: Representation of the "Dawn Phenomenon"

The following equation has been used for the computation of standard deviation:

$$SD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i - \bar{x})^2} \tag{3.11}$$

Chapter 4

Results

In this section, results obtained with different Machine Learning approaches, described in Chapter 3 are reported.

Firstly, results achieved by mean of Logistic Regression are presented: confusion matrix, *Prec*, *Rec* and $F1$ *values* and *ROC* curves.

It then reports the results from the Random Forest: confusion matrix, *ROC* curves and, again *Prec*, *Rec* and $F1$ *scores*.

Then the results coming from the Zero-inflated Regressor are shown in terms of MAE, MSE, $RMSE$ and R^2.

Finally, it gives the result of the pump setup analysis, for each approach described in Chapter 3, which is the TIRs computed for every time interval of interest.

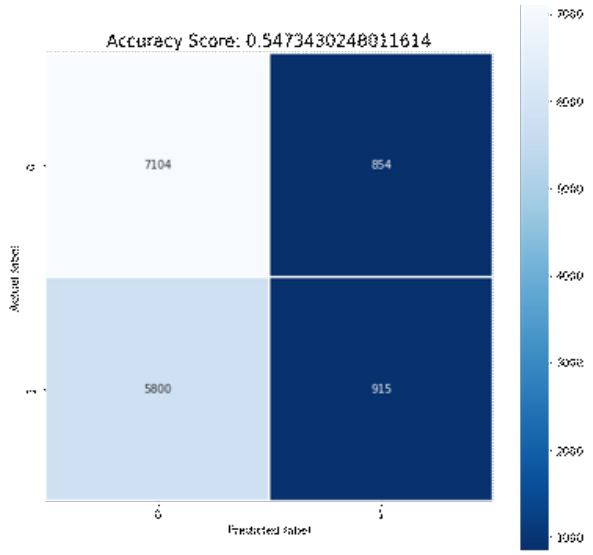
In Chapter 5 the proposed results will be deeply discussed.

4.1 Logistic Regression

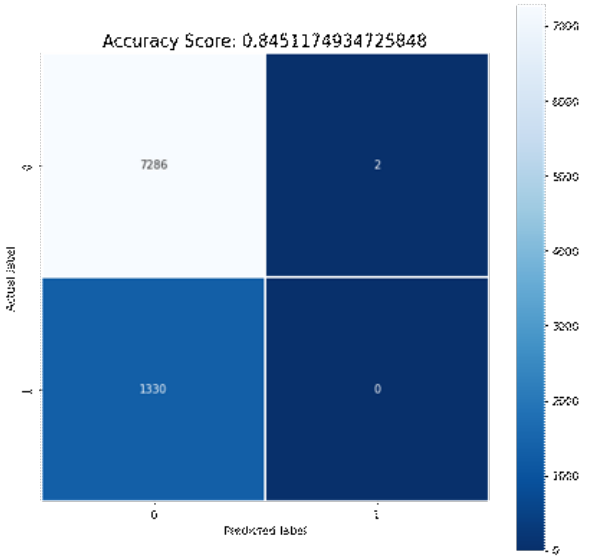
In this section, results coming from Logistic regression approach, described in Subsection 3.3.1, are reported. This algorithm showed a discred success in managing glycaemic data and its performance has improved, compared to our previous study in which the glycaemic columns reporting the blood glucose levels in the 2 previous columns were added, considering the new 6 time-shifted columns that have been added to the predictors' matrix. Normalisation was tested to verify if results could be improved but resulted in minuscule and negligible variations.

Figures 4.1,4.2, 4.3,4.4 and 4.5 display the confusion matrix of each subject. The number on the first square (first row and column) represents the true negatives (TN), the second square (first row and second column) represents the false positives (FP), the third square (second row and first column) represents the false negatives (FN) and the fourth square represents the true positives (TP). Above each matrix, the accuracy score is reported.

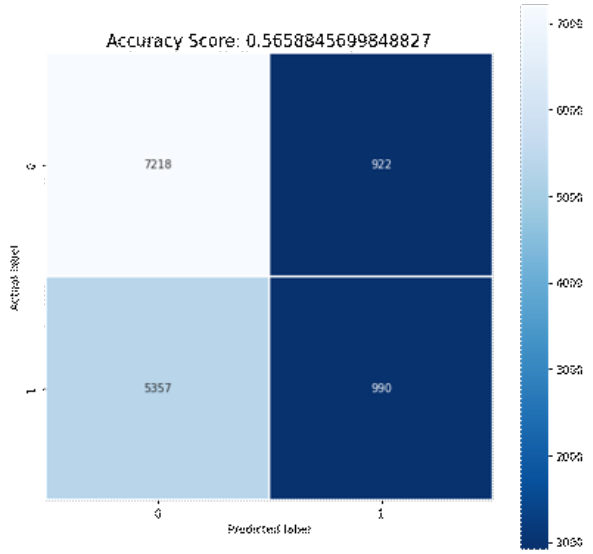
Regarding ROC curves, only the best one are displayed for space-saving reasons. Figure 4.6 shows the plots for subjects 3, 5, 6, 10, 16 and 17 respectively. Table 4.1 displays the *Prec*, *Rec* and $F1$ values for the two labels 0 and 1 for each subject.



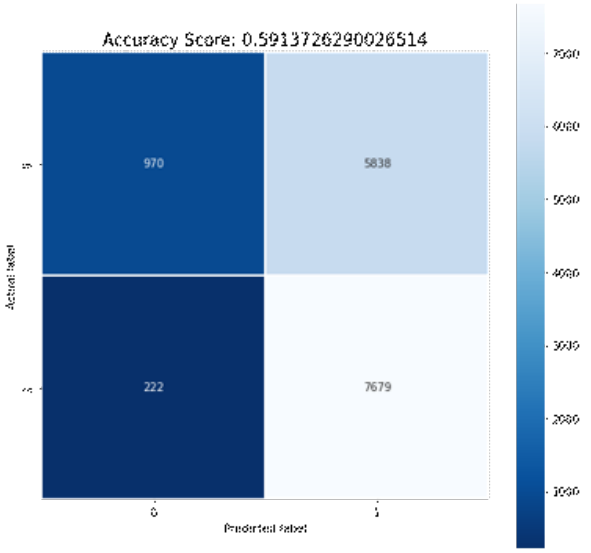
(a) Confusion matrix table resulting from the logistic regression on basal data for Subject 1.



(b) Confusion matrix table resulting from the logistic regression on basal data for Subject 2.

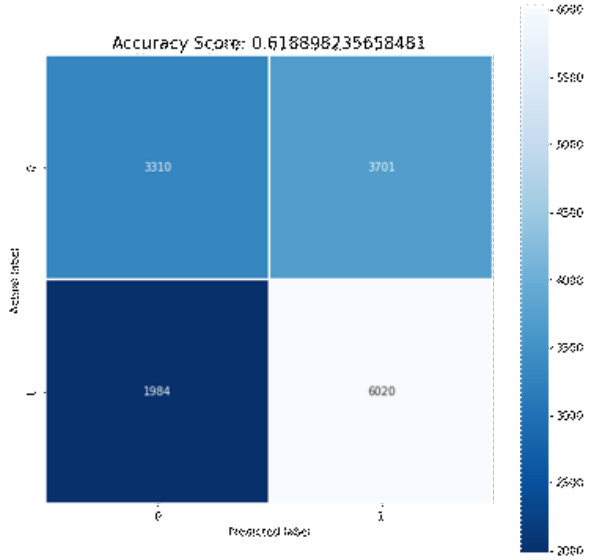


(c) Confusion matrix table resulting from the logistic regression on basal data for Subject 3.

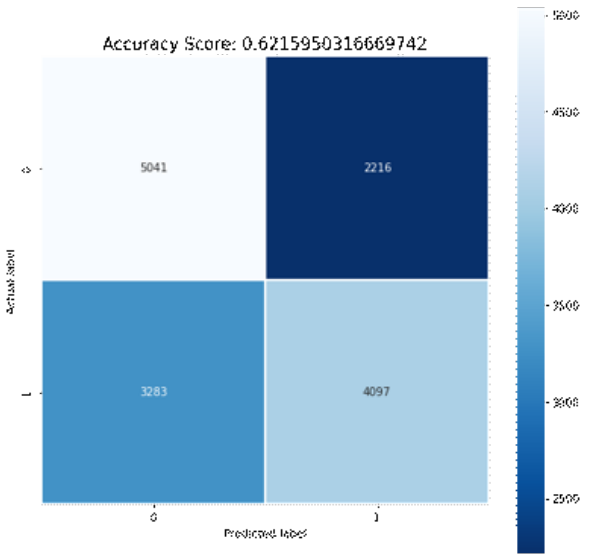


(d) Confusion matrix table resulting from the logistic regression on basal data for Subject 4.

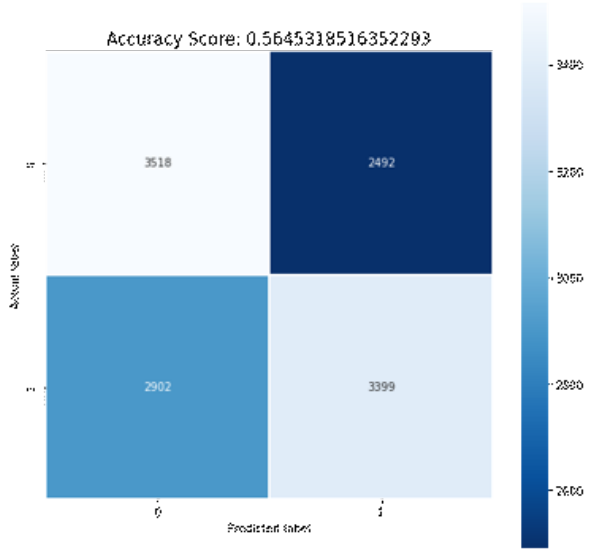
Figure 4.1: Confusion matrices resulting from the logistic regression on basal data for subjects 1, 2, 3 and 4.



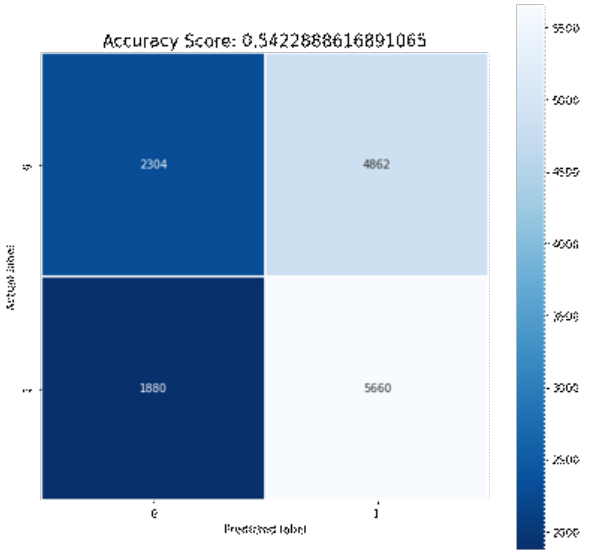
(a) Confusion matrix table resulting from the logistic regression on basal data for Subject 5.



(b) Confusion matrix table resulting from the logistic regression on basal data for Subject 6.

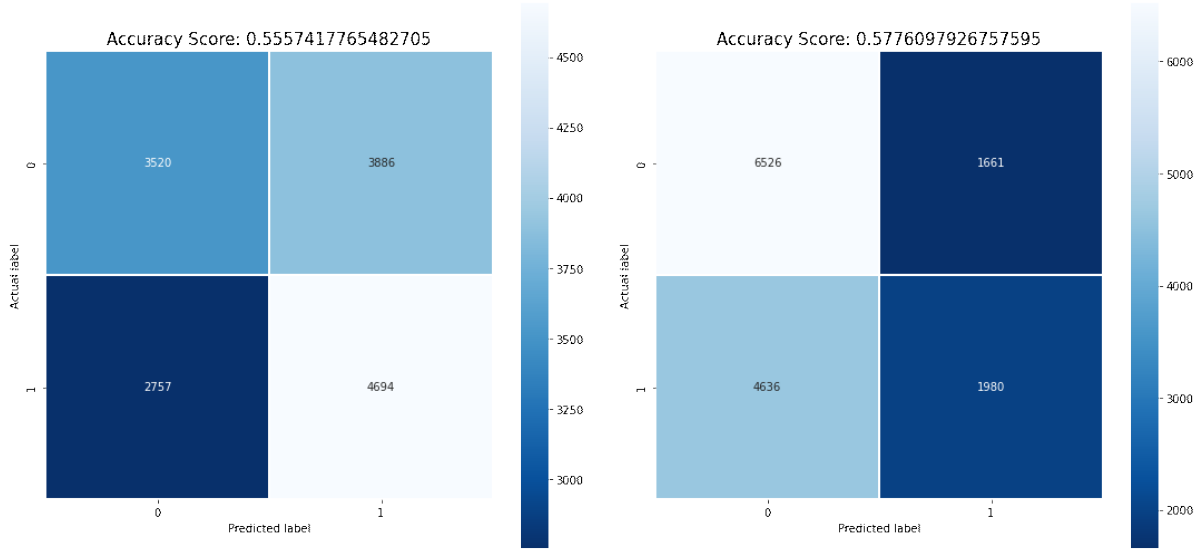


(c) Confusion matrix table resulting from the logistic regression on basal data for Subject 7.



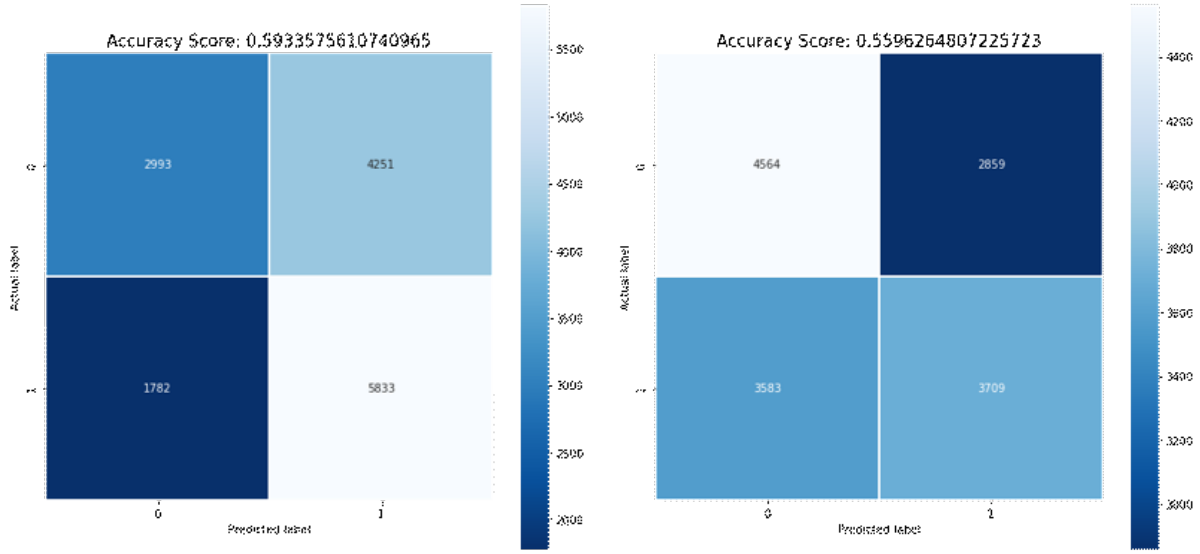
(d) Confusion matrix table resulting from the logistic regression on basal data for Subject 8.

Figure 4.2: Confusion matrices resulting from the logistic regression on basal data for subjects 5, 6, 7 and 8.



(a) Confusion matrix table resulting from the logistic regression on basal data for Subject 9.

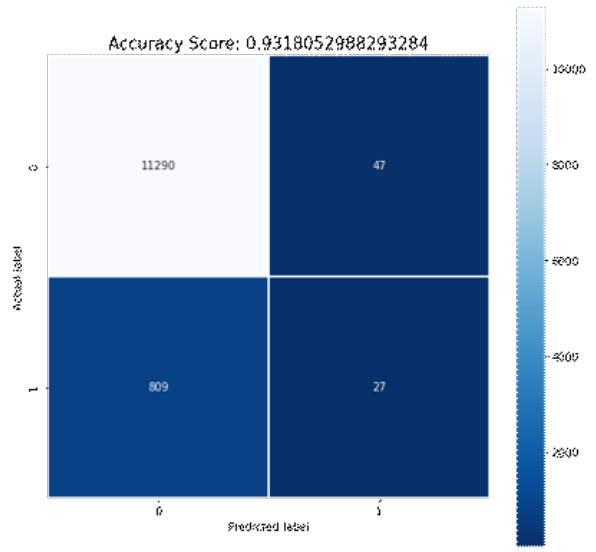
(b) Confusion matrix table resulting from the logistic regression on basal data for Subject 10.



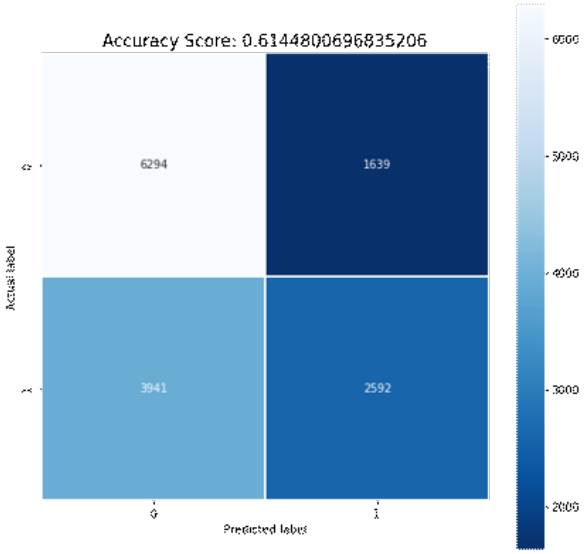
(c) Confusion matrix table resulting from the logistic regression on basal data for Subject 11.

(d) Confusion matrix table resulting from the logistic regression on basal data for Subject 12.

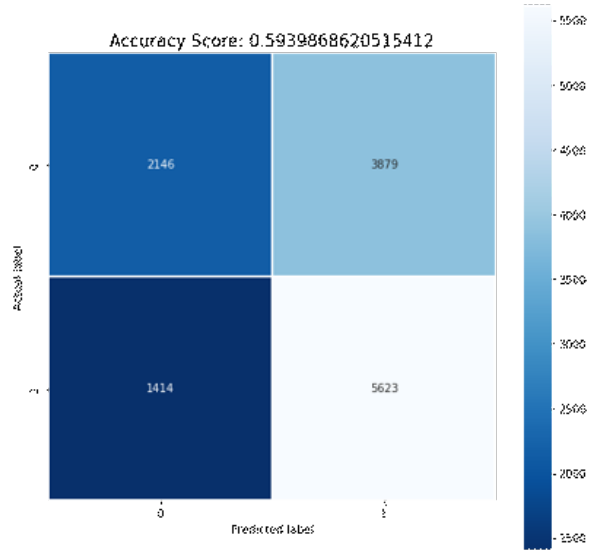
Figure 4.3: Confusion matrices resulting from the logistic regression on basal data for subjects 9, 10, 11 and 12.



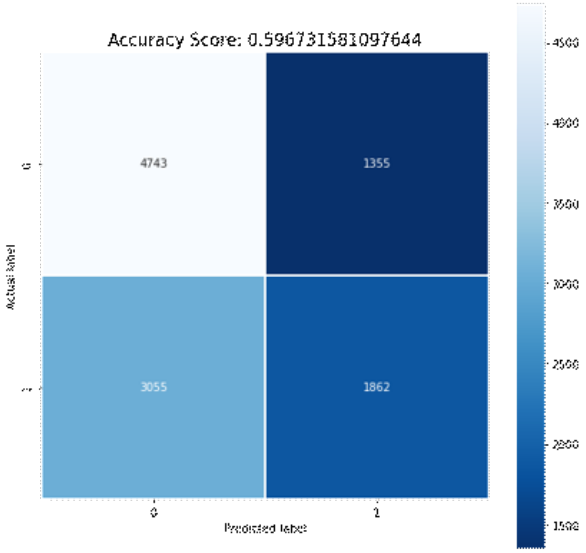
(a) Confusion matrix table resulting from the logistic regression on basal data for Subject 13.



(b) Confusion matrix table resulting from the logistic regression on basal data for Subject 14.

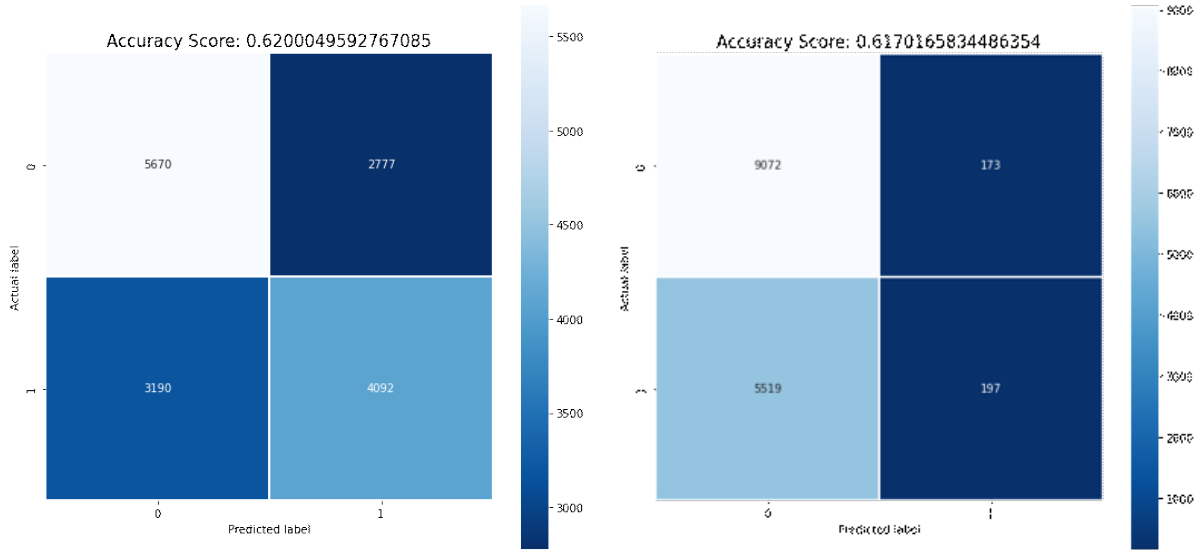


(c) Confusion matrix table resulting from the logistic regression on basal data for Subject 15.



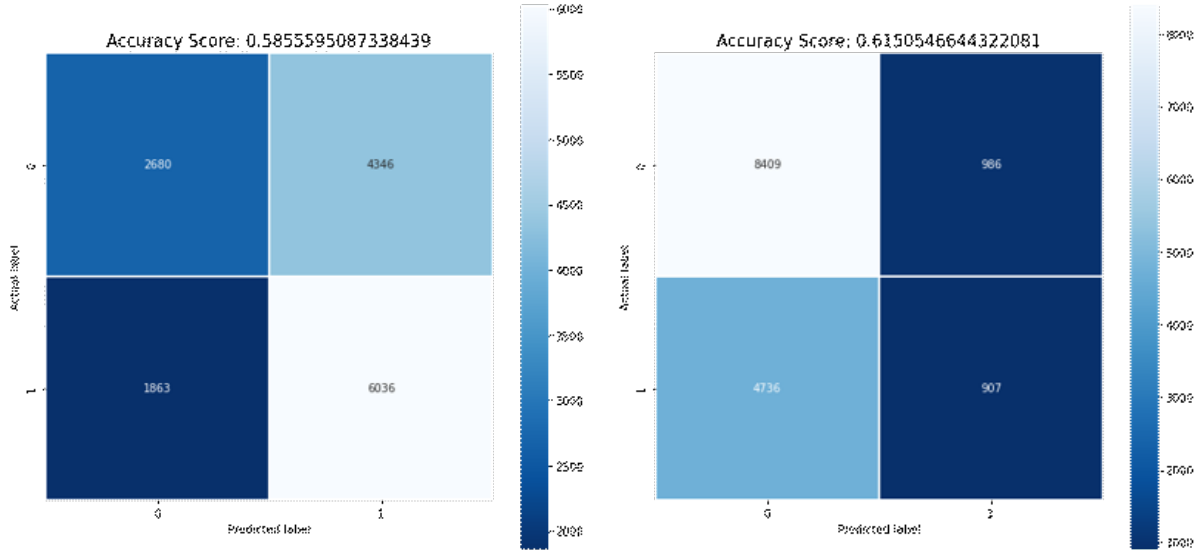
(d) Confusion matrix table resulting from the logistic regression on basal data for Subject 16.

Figure 4.4: Confusion matrices resulting from the logistic regression on basal data for subjects 13, 14, 15 and 16.



(a) Confusion matrix table resulting from the logistic regression on basal data for Subject 17.

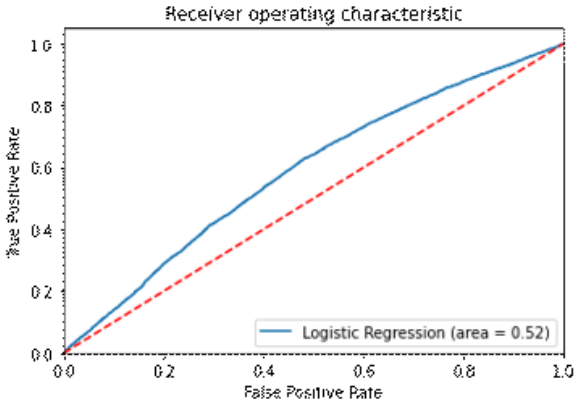
(b) Confusion matrix table resulting from the logistic regression on basal data for Subject 18.



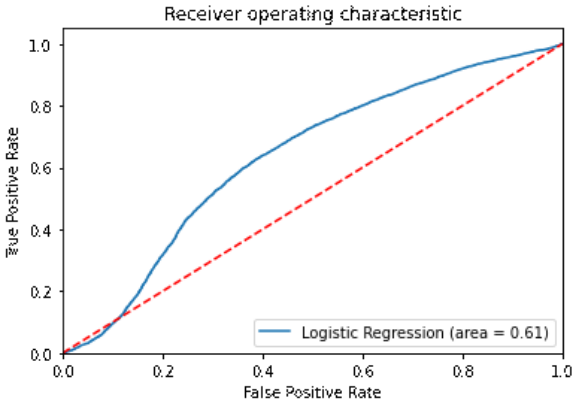
(c) Confusion matrix table resulting from the logistic regression on basal data for Subject 19.

(d) Confusion matrix table resulting from the logistic regression on basal data for Subject 20.

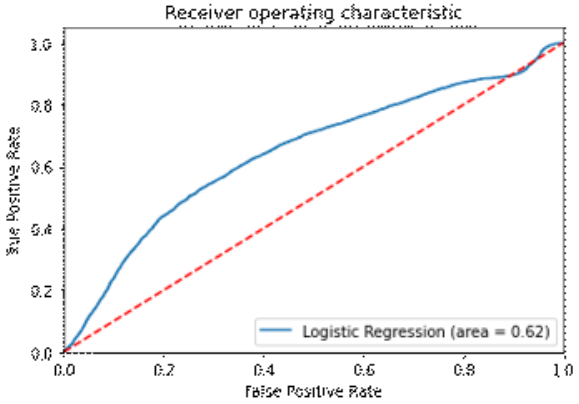
Figure 4.5: Confusion matrices resulting from the logistic regression on basal data for subjects 17, 18, 19 and 20.



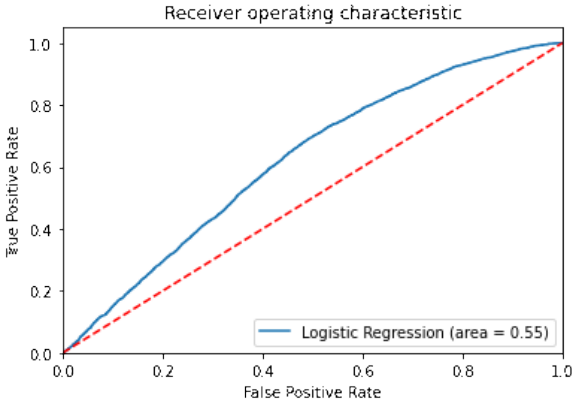
(a) ROC curve for subject 3.



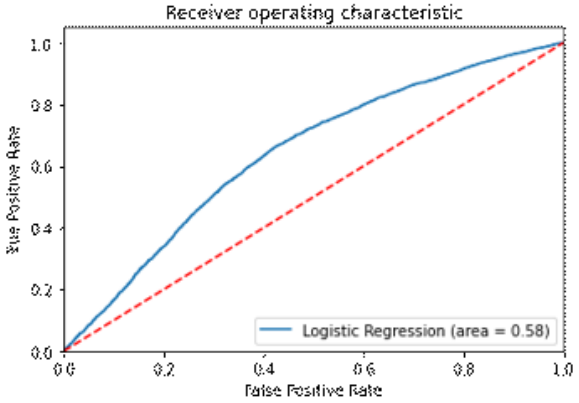
(b) ROC curve for subject 5



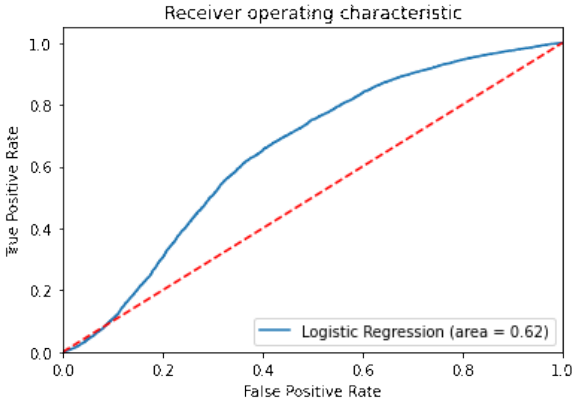
(c) ROC curve for subject 6



(d) ROC curve for subject 10



(e) ROC curve for subject 16



(f) ROC curve for subject 17

Figure 4.6: Plot for the ROC curve and area resulting from the logistic regression on basal data for subjects 3,5,6, 10,16 and 17.

Table 4.1: Metrics of the results coming from the logistic regression. The values for Precision ($Prec$), Recall (Rec) and F1-score ($F1$) for labels 0 and 1 are reported.

ID	Label	$Prec$	Rec	$F1$
Sub 1	0	0.59	0.89	0.62
	1	0.52	0.40	0.22
Sub 2	0	0.85	1.00	0.92
	1	0.00	0.00	0.00
Sub 3	0	0.57	0.85	0.70
	1	0.52	0.16	0.24
Sub 4	0	0.81	0.14	0.24
	1	0.57	0.97	0.72
Sub 5	0	0.63	0.47	0.54
	1	0.62	0.75	0.60
Sub 6	0	0.61	0.69	0.65
	1	0.65	0.56	0.60
Sub 7	0	0.55	0.59	0.57
	1	0.58	0.54	0.56
Sub 8	0	0.55	0.32	0.41
	1	0.54	0.75	0.63
Sub 9	0	0.56	0.48	0.51
	1	0.55	0.63	0.59
Sub 10	0	0.58	0.80	0.67
	1	0.54	0.30	0.39
Sub 11	0	0.63	0.41	0.50
	1	0.58	0.77	0.66
Sub 12	0	0.56	0.61	0.59
	1	0.56	0.51	0.54
Sub 13	0	0.93	1.00	0.96
	1	0.36	0.03	0.06
Sub 14	0	0.61	0.79	0.69
	1	0.61	0.40	0.48
Sub 15	0	0.60	0.36	0.45
	1	0.59	0.80	0.68
Sub 16	0	0.61	0.78	0.68
	1	0.58	0.38	0.46
Sub 17	0	0.64	0.67	0.66
	1	0.60	0.56	0.58
Sub 18	0	0.68	0.98	0.76
	1	0.53	0.03	0.06
Sub 19	0	0.59	0.38	0.46
	1	0.58	0.76	0.66
Sub 20	0	0.64	0.90	0.75
	1	0.48	0.16	0.24

4.2 Random Forest

This section reports the results coming from the Random Forest procedure defined in Subsection 3.3.1. Normalisation was also tested to verify if results could be improved but enhancements have been obtained.

Figures 4.7,4.8, 4.9,4.10 and 4.11 display the confusion matrix of each subject. The number on the first square (first row and column) represents the true negatives (TN), the second square (first row and second column) represents the false positives (FP), the third square (second row and first column) represents the false negatives (FN) and the fourth square represents the true positives (TP). Above each matrix, the accuracy score is reported.

Regarding ROC curves, only the best one are displayed for space-saving reasons. Figure 4.12 shows the plots for subjects 3, 5, 7, 10, 16 and 17 respectively.

Table 4.2 displays the $Prec$, Rec and $F1$ values for the two labels 0 and 1 for each subject. Instead, Table 4.3 reports the values of the balanced accuracy, the arithmetic mean of sensitivity and specificity. Its use case is when dealing with imbalanced data, i.e. when one of the target classes appears a lot more than the other, like ours.

4.3 Zero-inflated Regressor

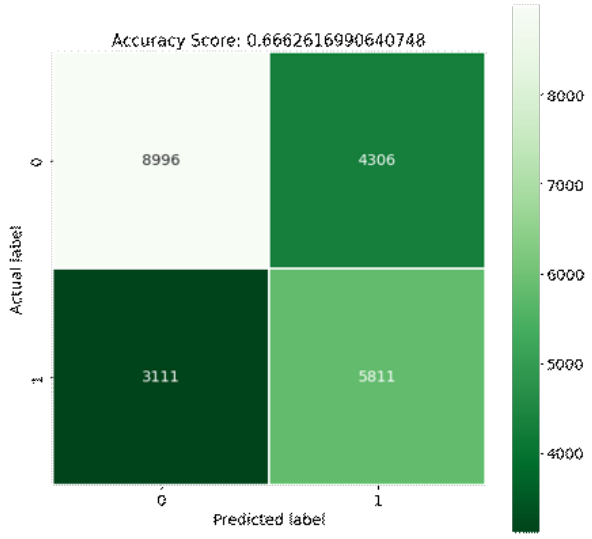
This section reports the results coming from the Zero-inflated regressor procedure defined in Subsection 3.3.1.

As previously stated, this procedure was chosen to manage the heavy unbalanced dataset and the huge amount of zeros generated by the sensor.

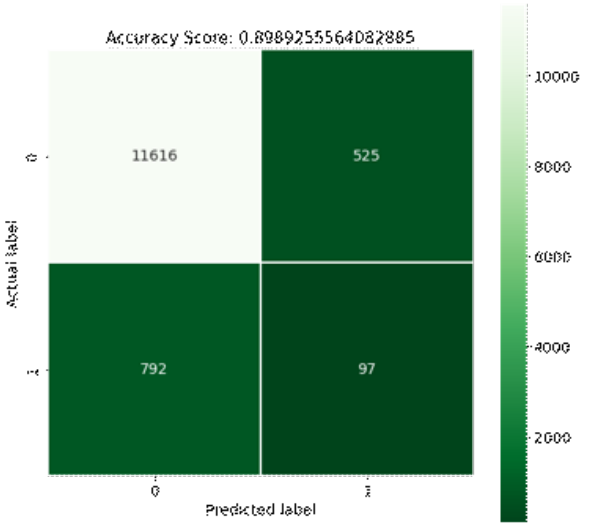
Firstly, the Zero-inflated regressor was applied to the same dataset of the Logistic regression and Random Forest, in which the glycaemic columns reporting the blood glucose levels in the 6 previous rows were added. Due to the mediocre and insufficient performance of the model, four additional predictors were added, such as the rate of change of glucose levels within 5,10,20 and 30 minutes. The outcomes are satisfactory compared to the previously even though they are not as acceptable as we expected.

Normalization was performed but it hadn't improved the results, thus, they will not be reported here.

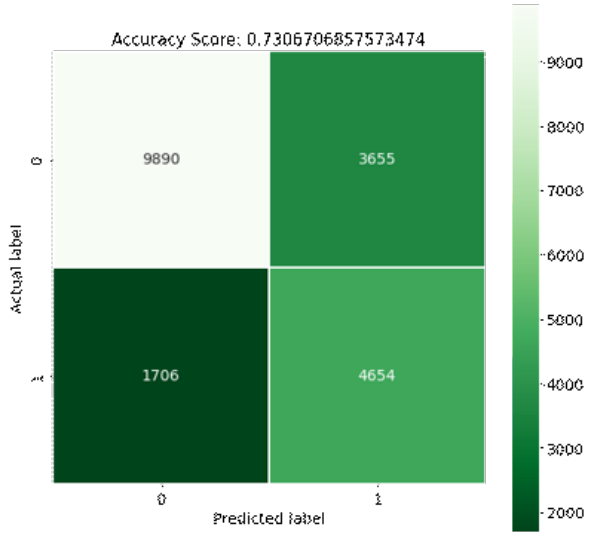
The Table 4.4 presents the metrics of the results coming from the Zero-inflated regressor approach. It displays the MAE, MSE, $RMSE$ and R^2 values for each subject and for each of the four combinations described in Subsection 3.3.1. The acronyms stands for: RF isRandom Forest Classifier, MLR is Multivariate Linear Regression while GB and EXTRA TREE stands for Gradient Boosting and Extratrees classifier and regressor, respectively.



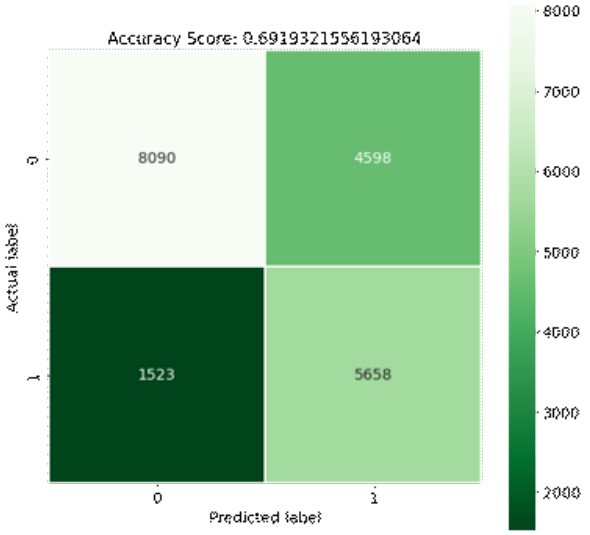
(a) Confusion matrix table resulting from the random forest on basal data for Subject 1.



(b) Confusion matrix table resulting from the random forest on basal data for Subject 2.

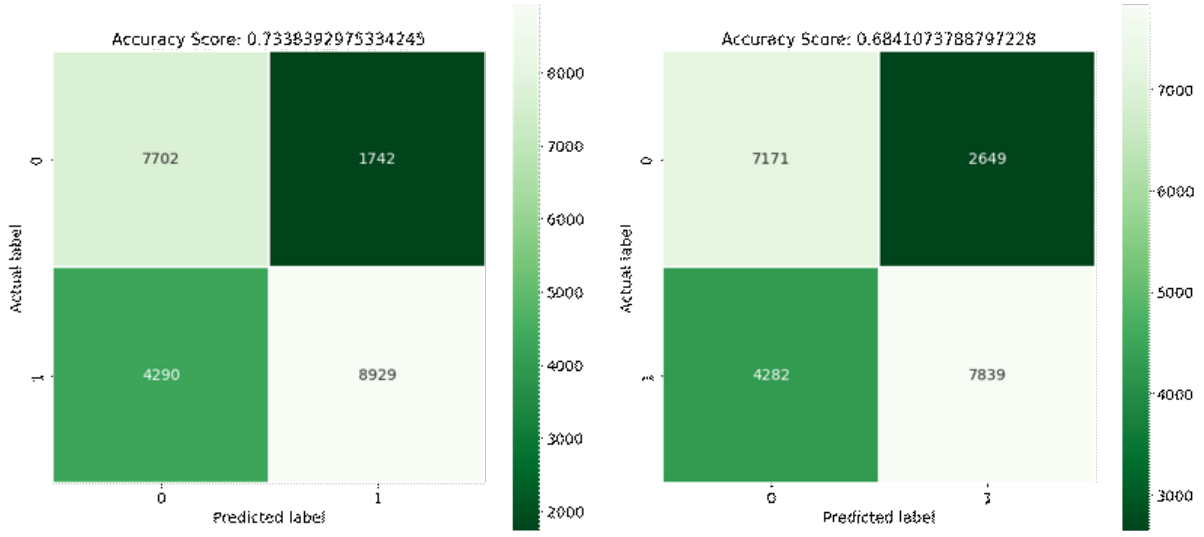


(c) Confusion matrix table resulting from the random forest on basal data for Subject 3.



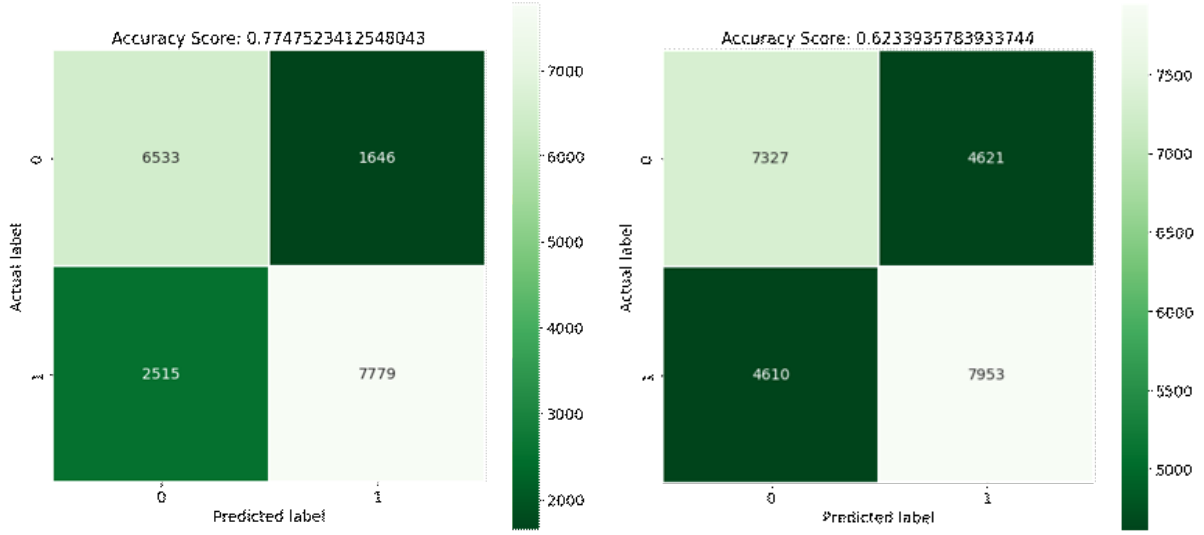
(d) Confusion matrix table resulting from the random forest on basal data for Subject 4.

Figure 4.7: Confusion matrices resulting from the random forest on basal data for subjects 1, 2, 3 and 4.



(a) Confusion matrix table resulting from the random forest on basal data for Subject 5.

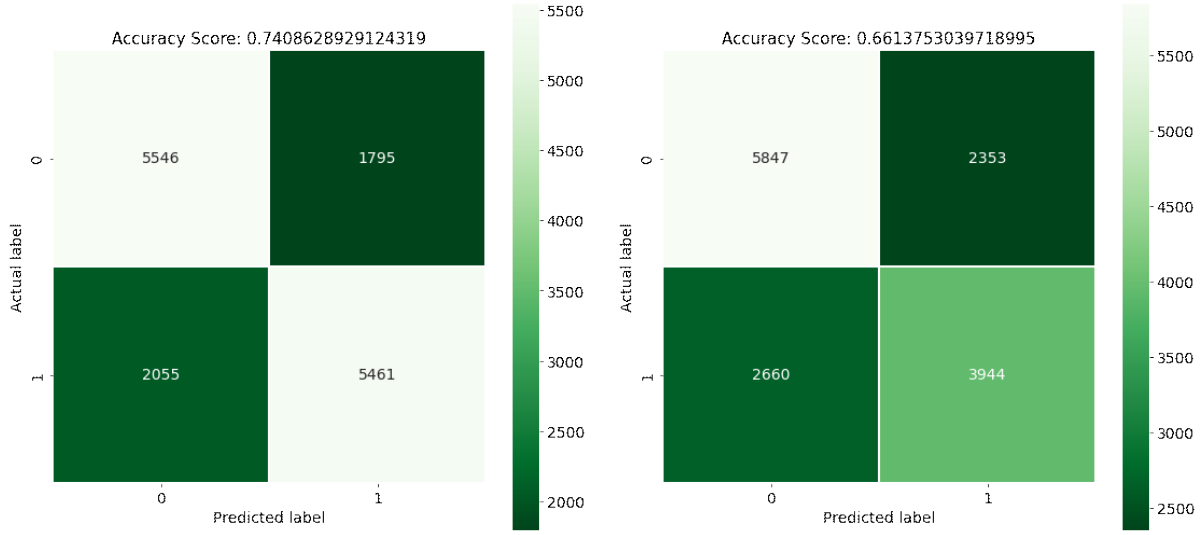
(b) Confusion matrix table resulting from the random forest on basal data for Subject 6.



(c) Confusion matrix table resulting from the random forest on basal data for Subject 7.

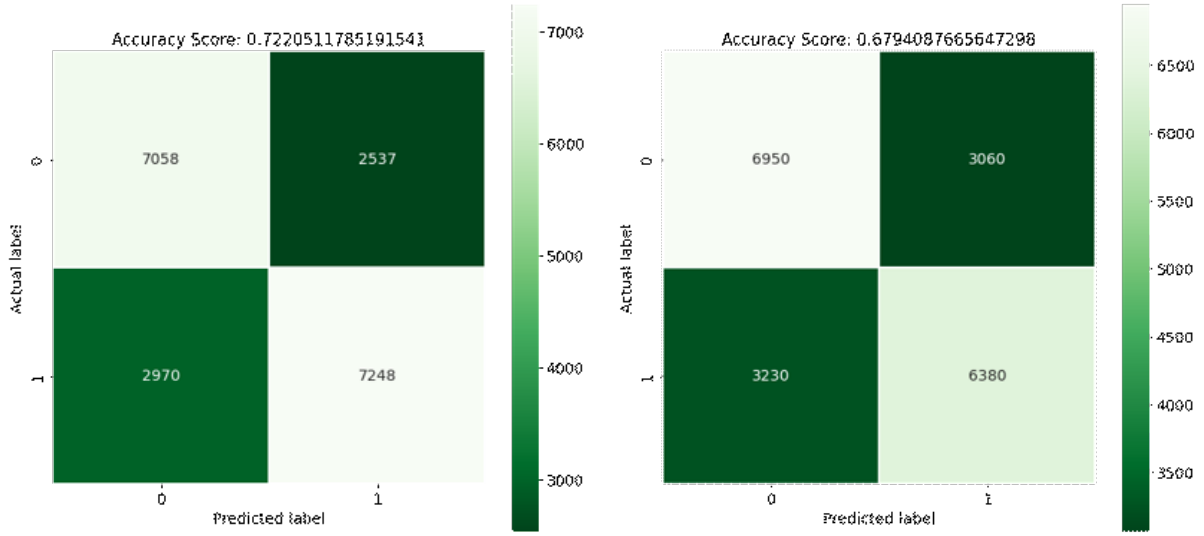
(d) Confusion matrix table resulting from the random forest on basal data for Subject 8.

Figure 4.8: Confusion matrices resulting from the random forest on basal data for subjects 5, 6, 7 and 8.



(a) Confusion matrix table resulting from the random forest on basal data for Subject 9.

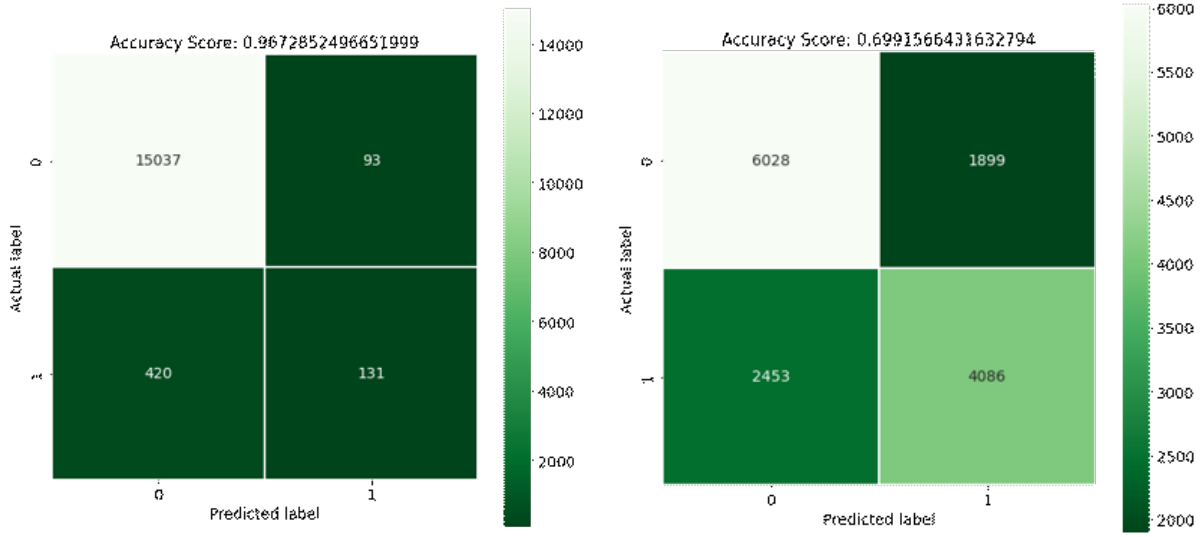
(b) Confusion matrix table resulting from the random forest on basal data for Subject 10.



(c) Confusion matrix table resulting from the random forest on basal data for Subject 11.

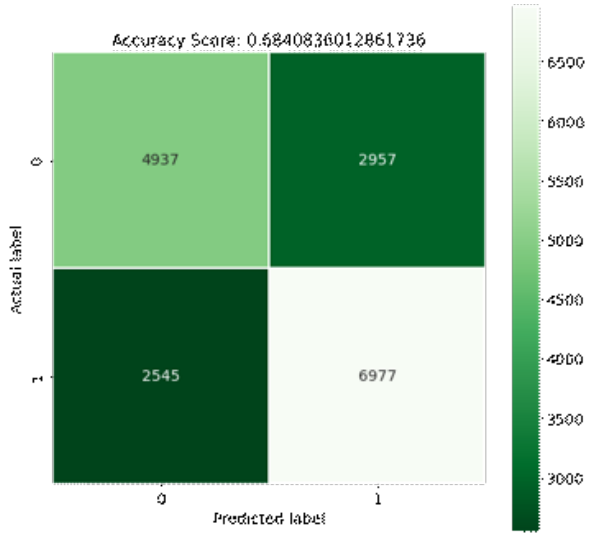
(d) Confusion matrix table resulting from the random forest on basal data for Subject 12.

Figure 4.9: Confusion matrices resulting from the random forest on basal data for subjects 9, 10, 11 and 12.

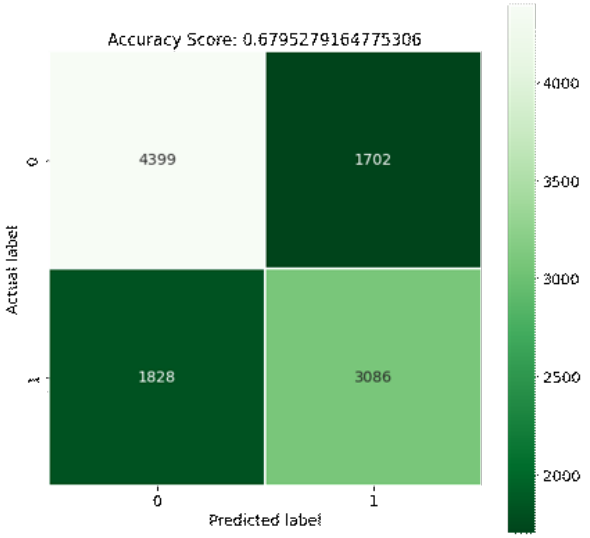


(a) Confusion matrix table resulting from the random forest on basal data for Subject 13.

(b) Confusion matrix table resulting from the random forest on basal data for Subject 14.

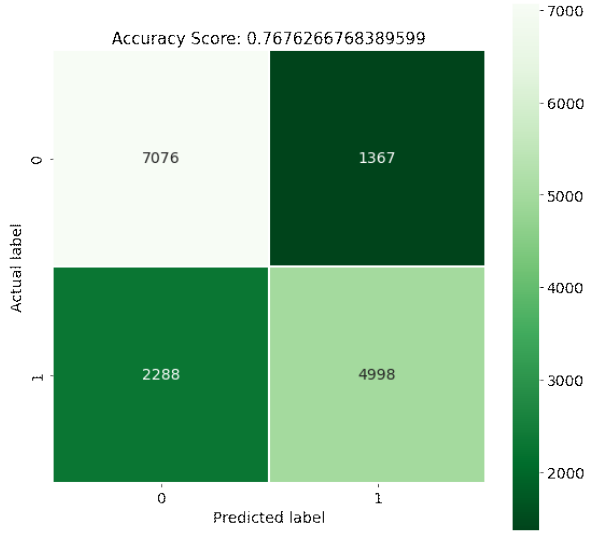


(c) Confusion matrix table resulting from the random forest on basal data for Subject 15.

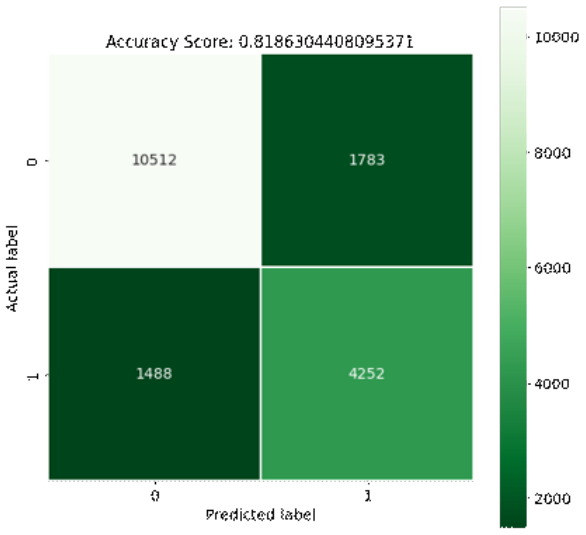


(d) Confusion matrix table resulting from the random forest on basal data for Subject 16.

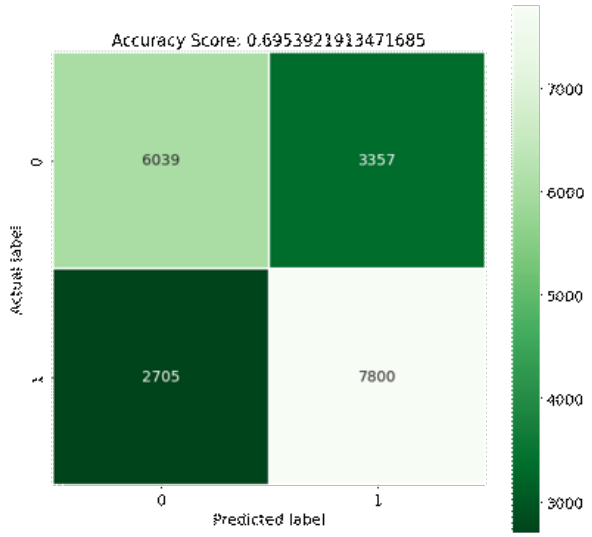
Figure 4.10: Confusion matrices resulting from the random forest on basal data for subjects 13, 14, 15 and 16.



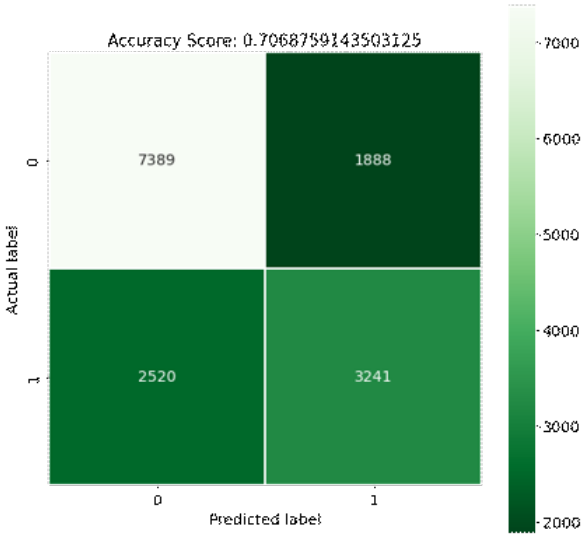
(a) Confusion matrix table resulting from the random forest on basal data for Subject 17.



(b) Confusion matrix table resulting from the random forest on basal data for Subject 18.

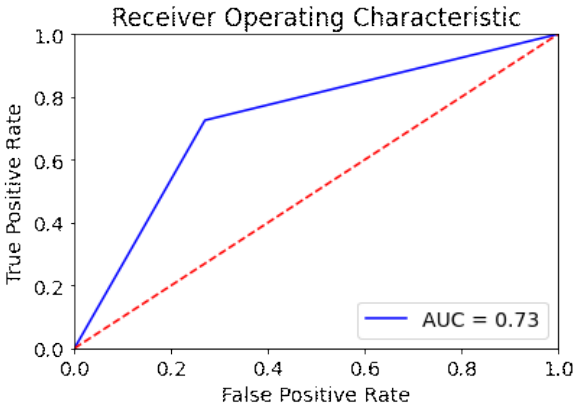


(c) Confusion matrix table resulting from the random forest on basal data for Subject 19.

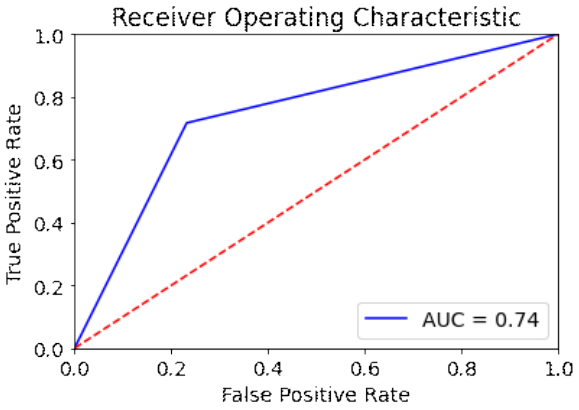


(d) Confusion matrix table resulting from the random forest on basal data for Subject 20.

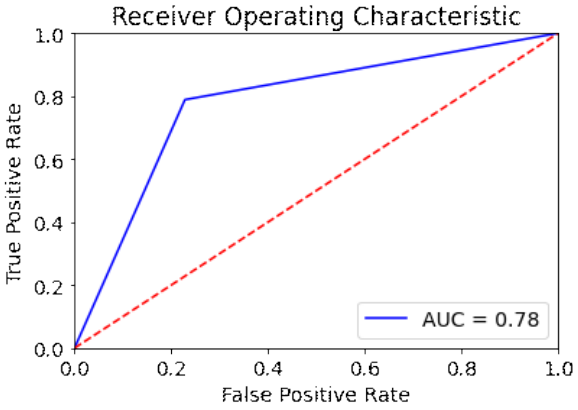
Figure 4.11: Confusion matrices resulting from the random forest on basal data for subjects 17, 18, 19 and 20.



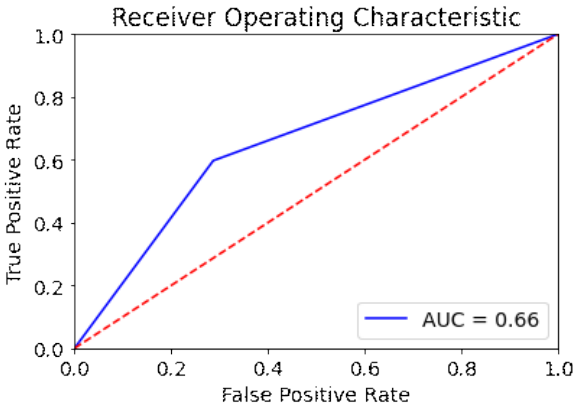
(a) The random forest ROC curve for subject 3.



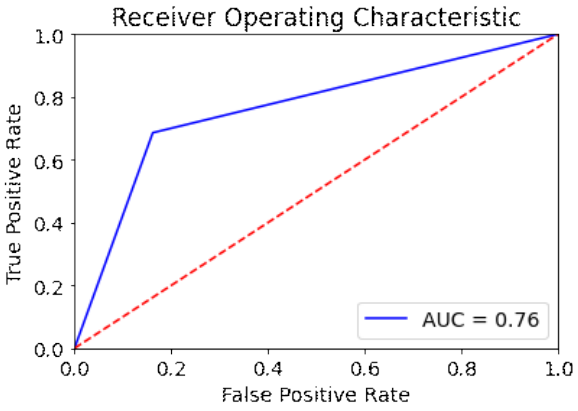
(b) The random forest ROC curve for subject 5



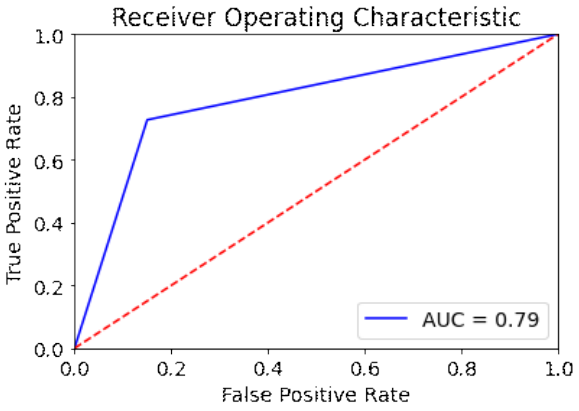
(c) The random forest ROC curve for subject 7



(d) The random forest ROC curve for subject 10



(e) The random forest ROC curve for subject 17



(f) The random forest ROC curve for subject 18

Figure 4.12: Plot for the ROC curve and area resulting from the random forest on basal data for subjects 3,5,7, 10,17 and 18.

Table 4.2: Metrics of the results coming from the random forest. The values for Precision ($Prec$), Recall (Rec) and F1-score ($F1$) for the two labels 0 and 1 are reported.

ID	Label	$Prec$	Rec	$F1$
Sub 1	0	0.74	0.68	0.71
	1	0.57	0.65	0.61
Sub 2	0	0.94	0.96	0.95
	1	0.16	0.11	0.13
Sub 3	0	0.85	0.73	0.79
	1	0.56	0.73	0.63
Sub 4	0	0.84	0.64	0.73
	1	0.75	0.79	0.65
Sub 5	0	0.64	0.82	0.72
	1	0.84	0.68	0.69
Sub 6	0	0.63	0.73	0.67
	1	0.75	0.65	0.69
Sub 7	0	0.72	0.80	0.76
	1	0.83	0.76	0.79
Sub 8	0	0.61	0.61	0.61
	1	0.63	0.63	0.63
Sub 9	0	0.73	0.76	0.74
	1	0.50	0.73	0.75
Sub 10	0	0.69	0.71	0.70
	1	0.63	0.60	0.61
Sub 11	0	0.70	0.74	0.72
	1	0.74	0.71	0.72
Sub 12	0	0.68	0.69	0.69
	1	0.68	0.66	0.67
Sub 13	0	0.97	0.99	0.69
	1	0.58	0.24	0.34
Sub 14	0	0.71	0.76	0.73
	1	0.68	0.62	0.65
Sub 15	0	0.66	0.63	0.64
	1	0.70	0.73	0.72
Sub 16	0	0.71	0.72	0.71
	1	0.64	0.63	0.64
Sub 17	0	0.76	0.84	0.79
	1	0.79	0.69	0.73
Sub 18	0	0.88	0.85	0.87
	1	0.70	0.74	0.72
Sub 19	0	0.69	0.64	0.67
	1	0.70	0.74	0.72
Sub 20	0	0.75	0.80	0.77
	1	0.63	0.56	0.68

Table 4.3: Balanced accuracy computer for each patient for the random forest classification

Balanced Accuracy			
Patient	Acc_B	Patient	Acc_B
Sub1	0.66	Sub11	0.72
Sub2	0.53	Sub12	0.67
Sub3	0.73	Sub13	0.61
Sub4	0.71	Sub14	0.69
Sub5	0.74	Sub15	0.67
Sub6	0.65	Sub16	0.67
Sub7	0.77	Sub17	0.76
Sub8	0.62	Sub18	0.79
Sub9	0.73	Sub19	0.69
Sub10	0.65	Sub20	0.67

Table 4.4: Metrics of the results coming from the zero-inflated regressor. The values for MAE, MSE, $RMSE$ and R^2 values for each combination are reported.

ID	Metrics	RF+MLR	GB+MLR	GB+RFR	EXTRA TREE
Sub 1	MAE	0.40	0.37	0.36	0 .40
	MSE	0.53	0.0.53	0.53	0.56
	$RMSE$	0.73	0.72	0.73	0.75
	R^2	0.10	0.10	0.10	0.10
Sub 2	MAE	0.28	0.27	0.27	0.28
	MSE	0.74	0.74	0.74	0.77
	$RMSE$	0.86	0.86	0.86	0.86
	R^2	0.10	0.10	0.10	0.10
Sub 3	MAE	0.26	0.32	0.29	0 .26
	MSE	0.26	0.26	0.25	0.26
	$RMSE$	0.51	0.51	0.50	0.51
	R^2	0.21	0.16	0.21	0.21
Sub 4	MAE	0.40	0.38	0.37	0 .38
	MSE	0.40	0.39	0.39	0.45
	$RMSE$	0.68	0.62	0.62	0.67
	R^2	0.17	0.17	0.20	0.20
Sub 5	MAE	0.25	0.31	0.28	0 .25
	MSE	0.25	0.24	0.23	0.25
	$RMSE$	0.50	0.49	0.48	0.50
	R^2	0.24	0.23	0.28	0.23

Sub 6	MAE	0.32	0.31	0.30	0 .32
	MSE	0.25	0.20	0.20	0.25
	$RMSE$	0.50	0.45	0.44	0.50
	R^2	0.19	0.22	0.25	0.20
Sub 7	MAE	0.56	0.59	0.53	0 .52
	MSE	1.00	0.89	0.83	0.99
	$RMSE$	0.10	0.94	0.90	0.99
	R^2	0.23	0.20	0.25	0.26
Sub 8	MAE	0.36	0.42	0.40	0 .37
	MSE	0.36	0.29	0.29	0.37
	$RMSE$	0.60	0.54	0.54	0.60
	R^2	0.10	0.10	0.10	0.10
Sub 9	MAE	0.49	0.45	0.42	0 .46
	MSE	0.77	0.66	0.65	0.75
	$RMSE$	0.87	0.81	0.80	0.87
	R^2	0.10	0.10	0.10	0.10
Sub 10	MAE	0.42	0.38	0.39	0 .42
	MSE	0.47	0.40	0.40	0.49
	$RMSE$	0.68	0.63	0.63	0.70
	R^2	0.10	0.11	0.12	0.11
Sub 11	MAE	0.56	0.59	0.53	0 .52
	MSE	1.00	0.89	0.83	0.99
	$RMSE$	0.1	0.94	0.90	0.99
	R^2	0.23	0.20	0.25	0.26
Sub 12	MAE	0.51	0.49	0.48	0 .50
	MSE	0.75	0.67	0.67	0.75
	$RMSE$	0.86	0.82	0.82	0.85
	R^2	0.10	0.10	0.11	0.10
Sub 13	MAE	0.10	0.10	0.10	0 .10
	MSE	0.10	0.10	0.10	0.10
	$RMSE$	0.10	0.10	0.10	0.10
	R^2	0.20	0.18	0.19	0.18
Sub 14	MAE	0.34	0.33	0.32	0 .32
	MSE	0.35	0.31	0.30	0.35
	$RMSE$	0.59	0.56	0.55	0.59
	R^2	0.22	0.22	0.25	0.22
Sub 15	MAE	0.74	0.69	0.67	0 .71
	MSE	1.00	0.80	0.80	0.99
	$RMSE$	1.00	0.80	0.80	0.99
	R^2	0.11	0.15	0.18	0.14
Sub 16	MAE	0.31	0.27	0.27	0 .30
	MSE	0.26	0.21	0.21	0.25
	$RMSE$	0.51	0.46	0.46	0.50
	R^2	0.12	0.13	0.14	0.14
Sub 17	MAE	0.41	0.42	0.40	0 .41
	MSE	0.67	0.67	0.66	0.71

	$RMSE$	0.82	0.82	0.80	0.84
	R^2	0.10	0.10	0.10	0.12
Sub 18	MAE	0.27	0.27	0.25	0 .25
	MSE	0.29	0.27	0.26	0.30
	$RMSE$	0.54	0.52	0.51	0.55
	R^2	0.20	0.18	0.21	0.21
Sub 19	MAE	0.33	0.32	0.30	0 .33
	MSE	0.31	0.26	0.26	0.32
	$RMSE$	0.56	0.51	0.51	0.57
	R^2	0.10	0.10	0.10	0.10
Sub 20	MAE	0.30	0.34	0.33	0 .30
	MSE	0.30	0.27	0.27	0.30
	$RMSE$	0.54	0.52	0.52	0.54
	R^2	0.12	0.10	0.10	0.12

4.4 Pump settings' analysis

This section reports the results coming from the pump settings' analysis approaches defined in Subsection 3.3.2. In primis, results coming from the approach A are reported, so those showing TIRs computed during meal time and during each time segments of each date interval. Lastly, results computed during Approaches B and C, regarding the after-meal spikes and night control, are proposed.

4.4.1 Approach A

The results about the TIRs trend during the different periods are depicted in Figure 4.13 while the TIRs computed during lunch and dinner time are reported in the following list[1]:

1. Subject 4:
   (a) Lunch time: PP1=74,42%, PP2=69,18%, PP3=61,08% and PP4=66,95%
   (b) Dinner time: PP1=53,08%, PP2=50,65%, PP3=66,18% and PP4=55,45%
2. Subject 5:
   (a) Lunch time: PP1=89,13%, PP2=82,69%, PP3=83,77% and PP4=88,88%
   (b) Dinner time: PP1=88,18%, PP2=83,87%, PP3=84,51% and PP4=88,81%
3. Subject 15:
   (a) Lunch time: PP1=34,98%, PP2=36,27%, PP3=29,85%, PP4=38,44% and PP5=22,34%
   (b) Dinner time: PP1=58,16%, PP2=45,93%, PP3=30,14%, PP4=42,09% and PP5=19,32%
4. Subject 18:

[1]The abbreviation PP stand for Personal Profile, thus PP1, for example, means that we are considering the period 1 with that Personal Profile setting

(a) Lunch time: PP1=79,88% and PP2=70,70%

(b) Dinner time: PP1=76,88% and PP2=71,00%

5. Subject 20:

(a) Lunch time: PP1=60,42%, PP2=62,61%, PP3=51,23%, PP4=60,28% and PP5=48,16%

(b) Dinner time: PP1=58,20%, PP2=62,61%, PP3=51,80%, PP4=46,29% and PP5=48,32%

Figure 4.13: TIRs trends for subjects 4, 5, 15, 18 and 20, from top to bottom and from left to right.

4.4.2 Approach B

The results regarding TIRs calculated in three diverse time periods for lunch and dinner time, as explained in Subsection 3.3.2, are reported. The analysis focused primarily on understanding which parameters had the greatest impact on postprandial glycemic control in order to define criteria for postprandial spikes and to understand how insulin pump control performed in this setting.

Tables 4.5,4.6, 4.7,4.8, 4.9,4.10, 4.11, 4.12, 4.13, 4.14, 4.15 and 4.16 show the TIRs, together with the the standard deviation (SD) of the difference between the actual and target basal rate and the mean glucose value (MGV) computed for the third slot, for both lunch and dinner. Pre meal stands for the time segment of 11:00-12:30 and 18:00-19:30, meal time means 12:30-14:00 and 19:30-21:00 slots while for after meal the time ranges 14:00-16:00 and 21:00-23:00 have been considered.

Table 4.5: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 3

Period	Pre meal	Meal time	After meal
PP1	98,53%	96,43%	88,10%
PP2	89,68%	95,23%	83,83%
PP3	77,46%	77,18%	74,40%
PP1	88,75%	93,25%	89,90%
PP2	96,03%	81,74%	86,22%
PP3	74,45%	81,60%	73,57%

Table 4.6: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 4

Period	Pre meal	Meal time	After meal
PP1	69,65%	S71,08%	81,93%
PP2	71,32%	71,16%	64,96%
PP3	70,68%	43,47%	62,23%
PP4	70,44%	64,51%	69,98%
PP1	32,37%	42,79%	75,02%
PP2	33,55%	44,59%	62,59%
PP3	66,40%	57,81%	71,55%
PP4	43,38%	47,52%	68,75%

Table 4.7: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 5

Period	Pre meal	Meal time	After meal
PP1	80,26%	94,70%	85,28%
PP2	88,69%	83,55%	82,42%
PP3	90,12%	84,31%	80,54%
PP4	70,40%	94,38%	88,71%
PP1	86,86%	91,54%	87,35%
PP2	79,74%	88,65%	84,34%
PP3	82,07%	83,08%	87,18%
PP4	86,45%	81,46%	89,01%

Table 4.8: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 7

Period	Pre meal	Meal time	After meal
PP1	50,81%	62,26%	41,68%
PP1	53,48%	46,07%	43,59%

Table 4.9: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 8

Period	Pre meal	Meal time	After meal
PP1	54,20%	74,4%	39,63%
PP2	45,16%	51,37%	50,16%
PP3	22,16%	16,42%	12,65%
PP1	5,83%	18,75%	26,20%
PP2	23,30%	30,07%	23,45%
PP3	17,46%	16,66%	14,12%

Table 4.10: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 13

Period	Pre meal	Meal time	After meal
PP1	100,0%	94,4%	100,00%
PP2	94,10%	92,4%	91,4%
PP1	98,1%	66,6%	66,6%
PP2	91,5%	91,76%	90,06%

Table 4.11: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 14

Period	Pre meal	Meal time	After meal
PP1	68,27%	88,54%	90,65%
PP2	61,78%	80,06%	90,15%
PP3	85,62%	88,88%	96,72%
PP1	46,11%	58,18%	85,57%
PP2	37,21%	56,99%	86,25%
PP3	42,50%	80,12%	85,98%

Table 4.12: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 15

Period	Pre meal	Meal time	After meal
PP1	25,61%	38,67%	36,08%
PP2	26,55%	34,89%	43,56%
PP3	21,34%	29,77%	31,60%
PP4	36,80%	47,86%	34,66%
PP1	32,78%	69,96%	65,75%
PP2	43,98%	59,65%	45,56%
PP3	21,20%	34,56%	38,04%
PP4	40,56%	46,90%	39,11%

Table 4.13: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 16

Period	Pre meal	Meal time	After meal
PP1	38,68%	51,99%	51,82%
PP1	66,08%	74,62%	60,44%

Table 4.14: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 17

Period	Pre meal	Meal time	After meal
PP1	91,74%	83,74%	77,13%
PP2	86,26%	84,45%	78,84%
PP3	89,47%	95,65%	70,33%
PP1	88,67%	86,96%	83,45%
PP2	84,50%	84,27%	85,18%
PP3	79,72%	93,64%	82,03%

Table 4.15: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 18

Period	Pre meal	Meal time	After meal
PP1	78,26%	83,23%	75,62%
PP2	81,00%	65,79%	64,57%
PP1	75,29%	84,29%	72,55%
PP2	74,26%	74,80%	65,42%

Table 4.16: Lunch and dinner TIRs computed for each of the three time segments of for each period of subject 20

Period	Pre meal	Meal time	After meal
PP1	38,57%	68,53%	63,46%
PP2	61,00%	63,52%	62,40%
PP3	54,82%	46,62%	57,84%
PP4	60,22%	58,73%	61,82%
PP5	41,35%	54,77%	51,31%
PP1	67,74%	61,30%	51,72%
PP2	74,09%	62,94%	55,44%
PP3	49,12%	46,86%	62,63%
PP4	55,18%	50,00%	28,95%
PP5	57,10%	48,23%	46,78%

4.4.3 Approach C

The results regarding TIRs calculated in three diverse time periods during the night, as explained in Subsection 3.3.2, are reported. The analysis focused primarily on understanding which parameters has the higher influence while working with the night settings.

Tables 4.17, 4.18,4.19,4.20,4.21,4.22,4.23,4.24,4.25,4.26,4.27 and 4.28 show the TIRs, computed for the three nocturnal time segments. Total stands for the overall night control from 00:00 to 06:30, First period is referred to 00:00-03:30 while second period is 03:30-06:30. The caption TIR(%) PP is used to denote the TIRs computed in the period n with specific Personal Profile settings while Hours (h) reports the hours spent in the hypoglycaemia, normoglycaemia and hyperglycaemia for each period and each time segment.

Table 4.17: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 3.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	54,02	14,59	31,38	48,7	9,48	41,77	59,9	20,29	19,8
Hour(h)	57	15	33	27	5	23	30	10	10
TIR(%) PP2	55,07	20,83	24,09	58,6	18,9	22,39	50,21	23,40	26,38
Hours(h)	25	10	11	15	5	6	10	5	5
TIR(%) PP3	39,02	14,5	46,37	33,10	10	56,7	46,1	20,0	33,84
Hours(h)	340	127	404	157	48	270	183	79	134

Table 4.18: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 4.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR(%)	32,7	10,3	56,96	20,47	6,37	73,14	47,45	15,12	37,42
Hours(h)	85	27	148	29	9	104	56	18	44
TIR(%) PP2	30,2	9,57	60,16	18,99	5,73	75,26	43,7	14,18	42,04
Hours(h)	64	20	128	22	7	87	42	14	40
TIR(%) PP3	22,8	9,46	67,7	16,62	6,6	76,76	30,18	12,86	56,95
Hours(h)	40	16	119	16	6	74	24	10	46
TIR(%) PP4	24,81	11,10	64	21,9	8,44	69,61	27,17	14,20	57,6
Hours(h)	57	25	145	26	10	85	29	15	60

Table 4.19: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 5.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	32,6	11,52	55,78	23,53	8,71	67,7	43,5	14,8	41,5
Hour(h)	132	47	226	52	19	149	80	27	77
TIR(%) PP2	38,7	12,4	48,8	33,29	8,16	58,5	45,24	17,51	37,24
Hours(h)	112	36	141	52	13	92	59	23	49
TIR(%) PP3	50,8	10,95	38,2	50,9	8,66	49,3	50,67	13,67	35,64
Hours(h)	172	37	130	94	16	74	78	21	56
TIR(%) PP4	223,4	10,95	65,58	17,11	8,44	74,4	30,97	13,91	55,11
Hours(h)	16	8	45	6	3	28	10	4	17

Table 4.20: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 7.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	47,14	8,95	43,50	35,9	7,69	56,31	60,21	10,43	29,35
Hour(h)	430	82	400	177	38	277	253	44	123

Table 4.21: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 8.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	15,31	7,06	77,6	20,98	5,71	73,29	8,64	8,64	82,70
Hour(h)	22	10	109	16	4	56	5	5	53
TIR(%) PP2	10,9	3,68	85,41	10,53	3,45	86,00	11,32	3,94	84,73
Hours(h)	55	18	429	28	9	232	27	9	197
TIR(%) PP3	9,11	2,08	88,10	6,74	1,16	92,08	11,93	3,11	84,89
Hours(h)	43	10	420	17	3	236	25	7	183

Table 4.22: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 13.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	0,00	3,4	96,5	0,0	5,60	94,39	0,0	0,93	99,0
Hour(h)	0	1	19	0	1	10	0	0	9
TIR(%) PP2	45,63	9,3	45,05	45,9	9,22	44,78	45,23	9,40	45,35
Hours(h)	352,58	79,5	449	189,2	43	241,4	163,3	37	207,4

Table 4.23: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 14.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	5,45	3,37	91,17	2,35	1,20	96,4	9,23	6,01	64,75
Hour(h)	14,41	9	241	3,41	2	141	11	7	101
TIR(%) PP2	4,96	2,42	82,61	4,82	1,48	93,68	5,11	3,45	91,43
Hours(h)	27	13	507	14	4	268	13	9	238
TIR(%) PP3	2,84	0,71	96,4	1,06	0	98,93	4,90	1,55	93,47
Hours(h)	2	0	56	0,33	0	31	1,30	0	25,08

Table 4.24: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 15.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	36,3	9,02	54,5	25,9	6,36	67,6	48,73	12,14	39,12
Hour(h)	39	10	59	15	4	40	24	6	19
TIR(%) PP2	37,10	8,46	54,4	25,9	7,27	66,7	49,64	9,8	40,54
Hours(h)	65	15	95	24	7	62	41	8	33
TIR(%) PP3	19	5,3	75,5	13,15	3,74	83,10	25,	7,09	67,02
Hours(h)	40	11	161	15	4	94	25	7	67
TIR(%) PP4	32,77	6	61,2	24,29	5,39	70,30	42,47	6,7	50,8
Hours(h)	146	27	273	58	13	167	88	14	106
TIR(%) PP5	29,8	9,6	60,5	21,38	11,32	67,29	39,16	7,69	53,14
Hours(h)	8	2	15	3	1,3	9	5	0,3	6

Table 4.25: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 16.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	43,34	9,75	46,89	41,85	7,97	50,17	45,07	11,81	43,10
Hour(h)	289	65	312	149	28	172	138	37	160
TIR(%) PP2	36,76	11,89	51,33	41,62	9,40	48,96	31,08	14,81	54,10
Hours(h)	138	45	193	84	19	99	54	26	94
TIR(%) PP3	53,43	12,32	34,24	56,11	8,70	35,18	50,22	16,6	33,11
Hours(h)	44	10	28	25	4	16	19	6	12

Table 4.26: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 17.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	25,57	9,35	65,06	21,3	7,03	71,6	30,67	12,14	57,17
Hour(h)	167	61	425	76	2[0.25ex]5	255	91	36	170

Table 4.27: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 18.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	25,55	10,90	63,54	21,37	7,87	70,74	30,52	14,49	54,98
Hour(h)	93,58	40,31	233	42,5	16	141	51	24,25	92
TIR(%) PP2	25,90	11,33	62,76	21,67	7,78	70,53	30,86	15,49	53,63
Hours(h)	191,2	84,00	463,5	42,50	31,08	281,5	105,0	52,58	182,0

Table 4.28: TIRs computation during the night and hours spent in each hypo-,normo- and hyperglycaemia for patient 20.

Periods and Hours	Total			First period			Second Period		
	hypo	normo	hyper	hypo	normo	hyper	hypo	normo	hyper
TIR (%) PP1	36,2	11,4	52,3	25,6	7,66	66,72	48,8	16,02	35,14
Hour(h)	162	52	235	62	19	163	100	33	72
TIR(%) PP2	32,22	14,51	53,25	28,30	8,37	63,32	36,91	21,8	41,2
Hours(h)	74	34	123	37	11	80	37	23	43
TIR(%) PP3	23,78	7,36	68,84	21,08	5,18	73,72	26,9	9,9	63,16
Hours(h)	43	13	125	21	5	72	23	8	53
TIR(%) PP4	24,3	14,23	61,3	19,8	9,6	70,4	29,70	19,9	50,67
Hours(h)	23	13	58	10	5	36	13	9	22
TIR(%) PP5	17,53	8,54	73,9	14,6	5,95	79,3	20,7	11,45	67,7
Hours(h)	26	13	110	12	4	63	14	8	47

Chapter 5

Discussion

This part discusses, in each of its sections, the results reported in Chapter 4, achieved with the different machine learning approaches described in Subsection 3.3.1 and consideration about the pump settings' analysis, as described in Subsection 3.3.2.

5.1 Machine Learning Approaches

Regarding Logistic Regression method, results are mediocre even though a slight improvement can be appreciated compared to the previous study. This is quite encouraging considering the extension of the time range to 180 days and the significant work made for the pre-processing steps, as described in Subsection 3.2.1. Normalising the data turned out to be useless and no enhancement in the results were visible.

The confusion matrices show how results were moderate at best: for example, Figure 4.1a, related to subject 1, shows 7104 cells were there was no injection (0)) were correctly predicted versus 915 were there was injection (1) were correctly predicted. This means that the approach does not efficiently recognise how and why the change in basal rate is chosen by the Control-IQ™ technology. This reflects on the same subject's $Prec$, Rec and $F1$ values reported in Table 4.1. An analogous analysis can be made on subjects' 13 and 18 results, visible at Figures 4.4a and 4.5b and at Table 4.1.

For subjects 2,3 and 13 the situation is even worst: in fact, the Logistic Regression fails to predict the injection label, meaning that the probability to predict a 1 is so low, that even if the algorithm only predicts 0, it is still accurate. This means that the Accuracy score, in this case, is not a reliable metric. The low value of this approach on this specific subject is especially notable for $Prec$, Rec and $F1$ values which are all equal to 0.00 or rather near.

For what concern subjects 4,5,8, 11,15 and 19 they show the inverse trend, in the sense that they have data mainly imbalanced on 1s: for example, subject 5 has 6020 values for the true positive square compared to the 3310 values for the true negative one. This is also demonstrated by the results visible in Table 4.1, where the metrics lean toward the injection label.

Instead, the remaining subjects show a discrete results visible on both confusion matrices (Figures 4.1a,4.2b, 4.2c, 4.3a,4.3b, 4.3d, 4.4b,4.4d, 4.5a, 4.5b and 4.5d) and in Table 4.1, underlying that, if the database is more balanced than the one that has been used, it is a quite reliable method to detect and understand the changes made by the sensor.

The ROC curves in Figure 4.6 are the best obtained, which means they have the largest area under the curve, only confirms the previous discussion.

The results obtained by logistic regression are quity satisfactory. The main problem may be traced back to the characteristics of the record: a very imbalanced dataset, that is also very uneven, due to the disproportion of non-null values in the glycaemic and basal columns, especially in the carbohydrates one.

Even though some of these patients can be grouped by similarity, generally speaking the whole analysis gave conflicting results.

The Random Forest approach was implemented in an attempt to improve the results of the unsatisfactory analysis of Control-IQ™ decision, about to whether change or not the basal rate, coming from the aforementioned Logistic Regression.

The first attempt to use this algorithm was not so satisfactory, leading to the improvement of the split of train and test data to overcome the problem of high imbalanced database, as explained in Subsection 3.3.1. In fact, the results obtained from the majority of the patients are more stable and acceptable compared to the ones achieved by them in the previous approach. This can also be seen in subjects' 5 and 8 confusion matrices (Figures 4.8a,4.8d) and values reported in Table 4.2, showing that balancing the data was a good choice for the improvement of the results and that the obtained results for each subject is in full accordance with this analysis. This also means that accuracy scores are generally a lot more valid and trustworthy and more homogeneous.

The same consideration can be made for all the subjects that were performing similarly to the just quoted, exception made for patients 2 and 13. Probably, their database ware so scarce, and thus heavily unbalanced on zeros, that none of this approach can lead to appreciable results. All this considerations are also verified by the results reported in Table 4.2, where the $Prec$, Rec and $F1$ are always around the zero for label 1 as already hinted for Table 4.1. Also in Table 4.3 this trend is clearly visible: subjects 2 and 13 are those who have the lower Acc_B, proving the elevated imbalanced dataset with respect the other patients where the Acc_B remains stable and similar to the Accuracy score.

Normalisation was also tested to verify if results could be improved but no enhancements have been obtained.

To sum up the results gained through the classification problem, the prevalence of the Random Forest with respect the Logistic Regression can be affirmed even though a greater generalization of the former approach is required, maybe adding other and more significant predictors.

About the Zero-inflated Regressor, it was implemented to further generalize the approach with unbalanced data and to aggregate the classification and regression problem in a single algorithm. Initially, as deeply explained in Subsection 3.3.1, no additional predictors were added, thus feeding it with the glycaemic values, carbohydraets and the 5,10,15,20,25 and 30 minutes time-shifted glycaemic values, but the outcomes were so discouraging that have not been reported here. For this reason, the rate of changes at 5,10,20 and 30 minutes were added, reaching 12 indipendent variables.

The metrics used for the evaluation of this model are MAE, MSE, $RMSE$ and R^2 score. The MAE represents the average of the absolute difference between the actual and predicted values in the dataset, the MSE is the average of the squared difference between the original and predicted values in the data set and measures the variance of the residuals while the $RMSE$ is the square root of MSE and how well a regression model can predict the value of a response variable in absolute terms. The R^2 represents the proportion of the variance in

the dependent variable which is explained by the linear regression model. It is a scale-free score i.e. irrespective of the values being small or large, the value of R square will be less than one.

In general, the lower value of MAE, MSE, and $RMSE$ implies higher accuracy of a regression model. However, a higher value of R^2 is considered desirable because tells how well the predictor variables can explain the variation in the response variable.

Going back to our results, firstly a general consideration about the four different combination should be made: all of them showed a similar trend in the results, decreasing the errors and significantly increasing the R^2 after the addition of the new predictors. The combination between Random Forest and Multivariate Linear Regression continues to be stable enough even after the increase in the time horizon and the new features. The Gradient Booster coupled with both Random Forest regressor and Multivariate Linear Regressor showed an appreciable improvements of all the metrics and demonstrated the validity of this classifier when working with glycaemic data. Surprisingly, also the ExtraTrees classifier and regressor have revealed a huge stability with this database and high speed of computation, despite the huge amount of data used.

Deeply on the results visible in Table 4.4, the outcomes are strongly discordant among all the subjects. Half of them (Sub 1,2,8,9,10,11,12, 13, 15, 17, 19 and 20) reports low values of R^2 associated with high error, demonstrating that to the connection between the change of insulin rate and glycaemia was not fully understand. This tendency is common to all the four combinations.

For the remaining subjects the results are more promising and encouraging. For example subject 5 has obtained the best performance, in terms of high R^2 and low errors, when the Gradient Boosting and Random Forest regressor have been used. The same consideration can be made for subjects 6, 7 and 14, On the other hand, for the same patiens and for Sub 3, Sub 4 and Sub 18 appreciable results are obtained with the ExtraTrees combination.

The general low values of R^2 don't mean that the model is bad or worthless of being interpreted: it is not possible to include all the relevant predictors to explain an outcome variables, like the endogenous ones related to some psychological factors, seasonality, changes in habits and so on. Thus, the future studies must consider some of these fundamental variables that can strongly influence the diabetes management and convert to a model where categorical predictors, together with the continuous ones obtained thanks to the sensor, can be added.

5.2 Pump settings' analysis

The results reported in Section 4.4 for all approaches will be commented here. Firstly, the outcomes coming obtained by Approach A will be discussed and then Approach B and C divided for each patient.

About the five subjects considered for the first approach, the following considerations can be made, looking at Figure 4.13:

1. Subject 3: there is a similar behaviour in all the four changes, keeping the TIR in the desirable range (>70%) in the first half of the day while in the second half a drop in the time in range is visible for all the profile except the third. In fact, an important increase in TIR is notable: in this period, only a change in I:C was performed in the second half of the day, proving that this patient is more influenced by the insulin-to-carbohydrate

ration than changes on the basal rate. This is confirmed by the fact that during period 4, another change in ICR was made for the afternoon leading to a sudden decrease of the TIR. Same consideration can be proposed for the TIRs compted during lunch and dinner time where the Personal Profile activated during the third time range was the one to keep the TIR constant and closer to the threshold.

2. Subject 5: in this case, all the Personal Profile set demonstrate to be valid in keeping the TIR in the so called "green" range. Considering that the ICR settings were changed only twice during the 180 days while the BR was constantly modified, it can be hypothesized that this patient is more influenced by the BR changes, even though they don't significantly affect the adherence to the targets. Similar is the behaviour during the meals.

3. Subject 15: here the BR was the parameters that changed the most compared to the I:C, underlying the this subject is strongly and positively influenced by the BR. In fact, the changes were mainly made in the second half of the day where a significant drop of the TIR can be seen. Period 5 counts only three days, thus the results are not statistically significant. The lunch TIRs slowly decreased through the periods while those computed during the dinner were gradually increasing, supporting what it was previously stated.

4. Subject 18: only two profiles were modified leading to a small decrease in the TIR value. The only change reported is the ICR, meaning that it is has a deep influence on the glycaemic control. Same observation can be made regarding the meal time.

5. Subject 20: in this case, all the changes made throughout the 180 days lead to a worsening of the glycaemic control in the second half of the day. This is also supported by the droop of TIR during dinner time. Since the main madification were made on the target BR, the decrease can be justified by it.

Regarding Approaches B and C, they will be evaluated both for each subject. In depth:

- Subject 4: for what concern the lunch analysis made in the three time segments, as visible in Table 4.5, TIR has always remained above the threshold. Only in the third period the percentage decrease a little bit but it can be due to some endogenous facts. Probably the reason is the modulation of the time segment at lunch time (from 13:00 to 12:30) that has also change the values of the ICR value. Regarding the postprandial spike, the TIR values are lower compared to previous two settings, meaning that maybe changing the setting at lunch time can influence the subsequent glycaemic control. This is stated also by the mean glucose value computed for the range 14:00-16:00 for each period(101,94 mg/dL vs 95,92 mg/dL vs 145,86mg/dL). Regarding the dinner time, a similar trend is visible with a clear reduction in the after dinner time in range. Since no modification in BR and I:C were reported, surely other external factors are influencing the evening control. Also the MGV is higher and the SD is greater (PP1=0,49, PP2=0,49, PP3=0,57) meaning that the targer BR values are not adeguate. For the night control, the normoglyceamia isn't the preponderant status for the patient but oscillates between hypo and hyper glycaemia, as can be seen in Table 4.17. What is interesting to be observed is that the patient spend more time in the hypoglycaemia situation in all the three periods then hyperglyceamia, thus not showing the "dawn phenomenon".

- Subject 4: despite some oscillations around the threshold for the lunch time, it is interesting to underlying that as we have previously stated in the approach A, this patient is strongly affected by the ICR: no changes in this parameters throughout the periods have been made in the slots 18:00-21:00, reaching lower values of TIR, far from the threshold (Table 4.6). This is visible also from the SD (SD PP1=0,73 vs SD PP4=0,87 for premeal and SD PP1=0,57 vs SD PP4=0.67), that becomes greater period by period. For approach C, a situation of hyperglycaemia is visible during all night while in the second half (03:30-06:30) it passes from a situation of hypo to hyperglycaemia during the 180 days (Table 4.18). Again, the reason is mainly due to the changes of ICR made for period 3.

- Subject 5: the control during lunch time is adequate keeping the glucose in the ranges. Noteworthy the dinner time: no time segments have been set before 21:00, maintaining the same BR target fixed at 15:00 and, during the four periods, the BR changed the most (Table 4.7), confirming what has been said before in Approach A. The curious aspect is that, despite the TIRs are above the 70% threshold, during the range 21:00-23:00 the MGV are high (PP1=134mg/dL, PP2=145mg/dL, PP3=153mg/dL, PP4= 151mg/dL) as well as the SD(PP1=0,71, PP2=0,74, PP3=0,84 and PP4=0,62). About the Approach C, this subject alternate phases of hypoglycaemia with phases of hyperglycaemia, not only during the same period but also among them even though the BR and ICR changes in the last period (Table 4.19).

- Subject 7 : this subject has no parameters changes for the 180-days span. Both lunch and dinner control weren't satisfactory especially in the post prandial phase in which a drastic reduction of TIR is visible (Table 4.8), associated with high MGV 200 mg/dL for both) and very high SD (1.15 for both in the phases 14:00-16:00 and 21:00-23:00). During the night, the subject spent the first half in hypoglycaemia and then in hyperglycaemia with a sensible predominance of hyperglycaemia (252.5 h vs 177 h). No further consideration about which parameters influences the most can be made due to the absence of changes (Table 4.20).

- Subject 8: the glycaemic control for this patient is very peculiar: despite three changes in the BR for the time segments, the TIRs are far from the suggested target values during the 6 time segments under analysis for the meal study (Table 4.9), suggesting that the BR values are not efficient. This behaviour is more evident during the night, where the patient spent almosto 90% of the time in hyperglycaemia (Table 4.21). Perhaps, external factors had influenced the treatment.

- Subject 13: the first period is not statistically significant since it is constituted by only three days, therefore it will not be take into consideration. For period 2, the lunch TIRs are always in the safe range keeping a MGV during the postprandial at 116 mg/dL and low values of SD (0.19), meaning that there are no much differences between the target values and the injected insulin. For the dinner time, an after meal time segment was added compared while the other parameters stayed the same, obtaining good results considering the large period of time (Table 4.10). During the night, instead, even if there is a balance between hypo and hyper situation (45,63% vs 45,08%) the hours spent in hyperglycemia are higher (353h vs 449h), as visible in Table 4.22. In this phase, a time segment at 04:00 was added but probably the chosen settings are not efficient to avoid hyperglycaemia.

- Subject 14: for both meal time, a significant improvement is visible especially in the post prandial regulation where the TIRs have reached satisfactory targets. Probably, rearranging the time segments was useful for this patient since they increased from 5 to 7 segments, mainly during the night and and meal time. Deeply, in period 3 the greater improvement are reported: this is due to the variation of ICR, meaning that these changes were efficient (Table 4.11). For the overnight period, the integration of one time segment in period 2 and 3 wasn't so successful since the patient still face the hyperglycaemia (Table 4.23).

- Subject 15: the fifth period is not so significant since it is about the last three days of our range, thus it will not be considered. For this patience a lot of parameters changes were done, making difficult to understand the reasons behind such a poor glycaemic control. In fact, during both lunch and dinner time the TIRs are far from the suggested threshold, reaching peaks of MGV of 262,79 mg/dL and 241,55 mg7dL for post lunch and post dinner during PP3, respectively. Moreover, the SD are very high (average value of SD for all the 180 days is 1.1) suggesting that the settings are so incorrect for this subject that the pump algorithm has to work far from the clinician recommendations or the endogenous factors have a great impact on the treatment. During the night, the hyperglycaemia trend is confirmed, even though a target is set for the middle of the night. So, the BR and ICR changes were not very efficient.

- Subject 16: in this case, period 1 shows the best management of glycaemic fluctuation in both lunch and dinner phases, as visible at Table 4.13. Also the MGV states this, keeping the glucose at 139 mg/dL during the phase 14:00-16:00 and 132,14 mg/dL for 21:00-23:00. But, even if in the other two time periods normoglycamia is maintained with TIRs far above the 70%, the MGV are quite high (for example, for period 3 during the post prandial phase values of 151,93 mg/dL and 143,5 mg/dL were registered) suggesting that this patient has great glucose excursion. Since the most intense changes were made for the BR values, we can hypothesize that this patient is strongly influenced by the BR setting. This is also visible in the SD: in fact, the excursion were smaller in the first period while for the other two they were more significant (PP1=0,47, PP2=0,70 and PP3=0,92 during 14:00-16:00 and PP1=0,53, PP2=0,71 and PP3=0,68 during 21:00-23:00). Some additional time segments were added in the third period but they seems to not influence the glycaemic control. About the overnight control, subject 16 wavers between the hypo- and hyperglycaemia.The major changes carried out were those relative to the BR, keeping fixed throughout the 18a days the same ICR values, corroborating our first thoughts about the BR influence.

- Subject 17: this subject has no parameters changes for the 180-days span. It is interesting to note that, compared to Subject 7, even though no changes have been registered, the TIRs during the meals and the night (Tables 4.14 and4.26) are stable and not so drastically low. Looking at the SD (during the lunch periods were 0.56, 0.44 and 0.48 while for the dinner periods 0.38,0.29 and 0.36), we can imagine that this patient is, for sure, dependent on the BR changes.

- Subject 18: only two periods have been define here, due to the ICR changes. Unfortunately, there was a single parameter change for a time segments not considered in none of these approaches, but some general consideration can be made. For example,

from period 1 to period 2 a slight decrease in TIRs can be noted, particularly in the post prandial segment Table (4.15), together with an increase in the MGV (145 mg/dL vs 157,4 mg/dL for lunch time and 146,06mg/dL vs 159,60 mg/dL for dinner time) and in the SD (0,57 vs 0,64 for lunche and 0,55 vs 0,62 fur dinner), underlying that, maybe, the BR has an impact on the glycaemic control more than ICR. During the night, the patient spent most of the time in a hyperglycaemia situation, mainly in the dawn phenomenon phase (53h vs 31h for hypoglycaemia), meaning that the settings were not so efficient.

- Subject 20: for this patient, the majority of the periods are defined by the BR changes, suggesting that it is the one to influence the most the overall control. In fact, when changes of BR were made, it lead to an increase of the TIRs during the first four period for lunch time, as visible at Table 4.16. What it has just hinted, it's confirmed by the results obtained during the dinner analysis: throughout all the periods BR changed, and probably, these changes are not adequate, primarily on the after-dinner phase were TIRs are smaller than the other two phases and the MGV are higher period-by-period (PP1=180,2mg/dL, PP2=172,53mg/dL, PP3=176,07mg/dL, PP4=209,9 mg/dL). During the night, the patient have faced more episodes of hyperglylycemia than hypoglycemia, mainly in the second half of the night and in the second half of the 180-days of span (Table 4.28). These fluctuations are also related to the BR changes made in the 00:00-06:30 time slot, thus validating our hypothesis.

To conclude, in average, all patients spent their time in the suggest glucose range with some oscillations that could be mainly related to other factors, such as the psyco-physical condition or particular domestic dynamics, and not only due to wrong settings.

This preliminary study demonstrates that there is a strong correlation between the changes made for the insulin pumps parameters and the glucose oscillations. This is more evident during the meal time and the night, opening the gates to a new field of investigation.

Moreover, it would be interesting to deeply investigate the night control since most of the patients are reporting low percentages of time spent in the normoglycaemia range suggested by the Control-IQ algorithm.

Chapter 6

Conclusion

Hybrid closed-loop systems such as Tandem™'s t:slim X2™ insulin pump can provide better glycaemic control than gold standard insulin self-injection therapy, but they still do not fully mimic glucose metabolism.

These systems have also been shown to reduce the burden of diabetes management and improve the overall quality of life for patients who use them. Although they have the power to significantly change the way T1D is managed, more research is needed to improve their performance.

In this particular work, the focus is on improving the performance of this hybrid closed-loop system, based on the Control-IQ™, and its user-personalized parameter settings, leading to an automatic decision. Several drawbacks should be underlined, such as the availability of data: it was scarce and, for many subjects, pieces of information were missing, both for the Machine Learning approaches and the pump settings (ISF). Additionally, the storage of said data is not adequate for satisfactory and easy analysis. That means that the results of this thesis only represent a preliminary step towards what could be a definitive and reliable algorithm to be used by the clinical team.

Despite this, some significant and precious information can be gather from this study such as which algorithm best perform with unbalanced dataset, the importance of an adequate and precise pre-processing, what parameters can be used for evaluate the glycaemic control and the meaning and differences of the pump's settings for each subject.

For future studies, it will be interesting to work with a greater time range covering an entire year as well as working with more patients would be an excellent way to gain a deeper insight into the topics of interest. In any case, subjects need to be educated about uploading data and ensuring that their efforts may lead to tighter and more precise glycaemic control and development in the diabetes treatments. Also changes in the storage of data are desirable, especially those of the pump settings.

It would also be helpful to create clusters of patients according to some specific characteristics or parameters such as gender, age or glycaemic management, to see if they mark off some differences in the results.

As it could be imagined, machine learning approaches showed how algorithms that are oriented to imbalanced data work better on this dataset. More predictors should be take into consideration in order to underlying any differences and gain precious information for the development of a reliable algorithm to be used by the clinical team. About that, more subject-specific information should be added like weight, time from the diagnosis, additional information about habits, illness and so on. Hence, it is highly recommended to patients

to keep a personal diary in order to annotate all these valuable information that can help clinicians to adequately modify the treatment.

Moreover, identify in advance which parameter can mostly influence the classification algorithms to obtain more accurate results could be an important step forward limiting the dispersion of results and computational time. Knowing which parameters directly impact on the basal rate allow us to develop a more sensitive algorithm that can positively affect the glycaemic control, even though such approaches cannot grasp synergistic influences of parameters on the dependent variable.

Regarding the pump settings' analysis, it is essential and crucial to work on more data belonging to more subjects. This study is quite limited to be able to make any general assumption on its outcome and even though the analysis of the relationship between the number of changes and TIRs values showed a strong connection, it cannot be generalised and further research is needed.

It would be interesting to use some other metrics to evaluate the glycaemic control, mainly to understand if the computed TIRs are reporting the reality or there are more fluctuations of the glycaemic curve, hidden by the time in range.

Despite the outstanding problems described above, this work represents the first attempt to create a complete algorithm that can be embedded in a single sensor capable of automatically modifying and adjusting pump settings based on blood glucose levels to deliver the correct insulin dose.

Further research should be carried out to achieve a fully closed system able to realistically simulate healthy glucose metabolism. The development of such a system will change the lives of all those affected by T1D, especially for children and adolescents.

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