DEVELOPMENT AND VALIDATION OF STRATEGIES TO MITIGATE THE RISK OF HYPOGLYCEMIC EVENTS IN TYPE 1 DIABETES MELLITUS

Arthur Hirata Bertachi

Universitat de Girona

DOCTORAL THESIS

Development and validation of strategies to mitigate the risk of hypoglycemic events in type 1 diabetes mellitus

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ARTHUR HIRATA BERTACHI

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DOCTORAL PROGRAMME IN TECHNOLOGY

Supervised by: Dr. Ningsu Luo Ren and Dr. Josep Vehí Casellas

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DOCTORAL THESIS

DEVELOPMENT AND VALIDATION OF STRATEGIES TO MITIGATE THE RISK OF HYPOGLYCEMIC EVENTS IN TYPE 1 DIABETES MELLITUS

A dissertation presented in partial fulfillment of the requirements for a doctoral degree from the University of Girona.

By:

Arthur Hirata Bertachi

Supervisors:

Prof. Dr. Ningsu Luo

Prof. Dr. Josep Vehí

To my wife Lyvia and our little girl Vivian, who put colors inside of my world.
To my parents, Antonio and Deusa.

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LIST OF PUBLICATIONS

During the research work leading to this thesis, journal and conference publications are listed below, sorted by publication date.

Journals

1. Lyvia Biagi, **Arthur H. Bertachi**, Ignacio Conget, Carmen Quirós, Marga Giménez, Javier F. Ampudia-Blasco, Paolo Rossetti, Jorge Bondia, and Josep Vehí, Extensive Assessment of Blood Glucose Monitoring During Postprandial Period and Its Impact on Closed-Loop Performance, *Journal of Diabetes Science and Technology*, 11(6):1089-1095, **2017**.

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3. Carmen Quirós, **Arthur Bertachi**, Marga Giménez, Lyvia Biagi, Judith Viaplana, Clara Viñals, Josep Vehí, Ignacio Conget, and Jorge Bondia, Control de la Glucemia Durante el Ejercicio Físico Aeróbico y Anaeróbico Mediante un Nuevo Sistema de Páncreas Artificial, *Endocrinología, Diabetes y Nutrición*, 65(6):342-347, **2018**.

4. Lyvia Biagi, **Arthur Bertachi**, Carmen Quirós, Marga Giménez, Ignacio Conget, Jorge Bondia, and Josep Vehí, Accuracy of Continuous Glucose Monitoring before, during, and after Aerobic and Anaerobic Exercise in Patients with Type 1 Diabetes Mellitus, *Biosensors*, 8(1):22, **2018**.

5. **Arthur Bertachi**, Aleix Beneyto, Charrise M. Ramkissoon, and Josep Vehí, Assessment of Mitigation Methods to Reduce the Risk of Hypoglycemia for Announced Exercise in a Uni-hormonal Artificial Pancreas, *Diabetes Technology & Therapeutics*, 20(4):285-295, **2018**.

6. Lyvia Biagi, **Arthur Bertachi**, Marga Giménez, Ignacio Conget, Jorge Bondia, Josep A. Martin-Fernandez, and Josep Vehí, Individual Categorisation of Glucose Profiles Using Compositional Data Analysis, *Statistical Methods in Medical Research*, 1(1):1-1, **2019**. (Published online ahead of print).

7. Aleix Beneyto, **Arthur Bertachi**, Jorge Bondia, and Josep Vehí, A New Blood Glucose Control Scheme for Unannounced Exercise in Type 1 Diabetic Subjects, *IEEE Transactions on Control Systems Technology*, 1(1):1, **2019**. (Published online ahead of print).

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9. Josep Vehí, Ivan Contreras, Silvia Oviedo, Lyvia Biagi, and **Arthur Bertachi**, Prediction and Prevention of Hypoglycaemic Events in Type-1 Diabetic Patients using Machine Learning, *Health Informatics Journal*, **2019**. (Accepted for publication).

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11. Silvia Oviedo, Ivan Contreras, **Arthur Bertachi**, Carmen Quirós, Marga Giménez, Ignacio Conget, and Josep Vehí, Minimizing Postprandial Hypoglycemia in Type 1 Diabetes Patients Using Multiple Insulin Injections and Capillary Blood Glucose Self-Monitoring with Machine Learning Techniques, *Computer Methods and Programs in Biomedicine*, **2019**. (Submitted).

12. Lyvia Biagi, **Arthur Bertachi**, Marga Giménez, Ignacio Conget, Jorge Bondia, Josep A. Martin-Fernandez, and Josep Vehí, Probabilistic Model of Transition Between Categories of Glucose Profiles in Patients with Type 1 Diabetes Using a Compositional Data Analysis Approach, *Journal of Biomedical and Health Informatics*, 1(1):1-1, **2019**. (Submitted).

Conferences

1. Lyvia Biagi, **Arthur H. Bertachi**, Ignacio Conget, Carmen Quirós, Marga Giménez, Francisco J. Ampudia-Blasco, Paolo Rossetti, Jorge Bondia, and Josep Vehí, Accuracy of Continuous Glucose Monitoring During Postprandial Period and its Influence on Closed-loop Performance, In *10th International Conference on Advanced Technologies & Treatments for Diabetes*, *Paris - France*, page A39, **2017**. (*abstract*).

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Book chapter

1. Lyvia Biagi, **Arthur Bertachi**, Josep Antoni Martín-Fernández, and Josep Vehí, Compositional Data Analysis of Daily Glucose Profiles of Type 1 Diabetes Patients, In *II Conference of Pre-doctoral Researchers Abstract Book* edited by Miquel Solà, pages 115-116, **2018**.

2. Ivan Contreras, **Arthur Bertachi**, Lyvia Biagi, Silvia Oviedo, Charrise Ramkissoon, and Josep Vehí, Artificial Intelligence for Decision Support Systems in Diabetes, In *Artificial Intelligence in Precision Health: From concept to applications* edited by Debmalya Barh, **2019**. (Accepted for publication).

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NOMENCLATURE

The following acronyms and abbreviations can be found in this thesis.

Acronyms and abbreviations

ANN	Artificial Neural Network
AOBN	Activity on board
AP	Artificial Pancreas
AUC	Area Under the Curve
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CL	Closed-Loop
COB	Carbohydrate on board
CSII	Continuous Subcutaneous Insulin Infusion
D7P	Dexcom SEVEN PLUS CGM system
DCCT	Diabetes Control and Complications Trial
DG4	Dexcom G4 PLATINUM CGM system
DG5	Dexcom G5 CGM system
DG6	Dexcom G6 CGM system
DIA	Duration of Insulin Action
DKA	Diabetes Ketoacidosis
DM	Diabetes Mellitus
DRB	Dynamic rule-based algorithm
FDA	Food and Drug Administration
FSL	FreeStyle Libre
FN	False Negative
FP	False Positive
HBGI	High Blood Glucose Index
IFB	Insulin Feedback
IOB	Insulin On Board
isCGM	Intermittently Scanned Continuous Glucose Monitoring
L1	Level 1
L2	Level 2
LBGI	Low Blood Glucose Index

LGS	Low Glucose Suspension
MARD	Mean Absolute Relative Difference
MDI	Multiple Daily Injections
MLP	Multilayer Perceptron
MS4EH	Mitigation Strategies for exercise-induced Hypoglycemia
MPC	Model Predictive Controller
PK	Pharmacokinetics
PLGS	Predictive Low Glucose Suspension
PREC	Precision
SAFE	Safety Auxiliary Feedback Element
SAP	Sensor-Augmented Pump
SMBG	Self-Monitoring Blood Glucose
SVM	Support Vector Machine
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TN	True Negative
TP	True Positive
UKPDS	United Kingdom Prospective Diabetes Study
$\mathbf{VO_{2max}}$	Maximal Oxygen Consumption Capacity

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Abstract

Type 1 diabetes mellitus (T1DM) is a chronic condition resulting from the destruction of insulin-producing pancreatic β-cells due to an autoimmune process that may occur at any age, but tends to develop in childhood and adolescence. The causes of this destructive process are not fully understood, and it results in an impairment of insulin secretion by the pancreas. Therefore, individuals afflicted with T1DM require an uninterrupted supply of exogenous insulin to survive. If insulin is not provided, blood glucose levels tends to rise to dangerous high levels (hyperglycemia) and subjects can face several complications associated with the damage and failure of various organ systems. In the 90's, the diabetes control and complications trial demonstrated that intensive insulin therapy is able to reduce the risk of these complications, but at the same time increase the risk associated with the occurrence of low blood glucose levels (hypoglycemia), which in severe cases may lead to seizures and even death.

Current intensive insulin therapy is based on the delivery of insulin through multiple daily injections (MDI) or through continuous subcutaneous insulin infusion by an insulin pump. Combining an insulin pump and blood glucose measurements provided by a continuous glucose monitoring (CGM) system arose the first automated devices to manage T1DM, by interrupting insulin infusion to reduce the risk of hypoglycemia. More recently, the so-called Artificial Pancreas emerged, which is a closed-loop system to regulate insulin infusion automatically based on a control algorithm. However, the great variability observed in glucose metabolism and big disturbances caused by meals and physical activity are major hurdles to achieve tight glycemic control.

The proposals of this work pay special attention to improve glycemic control in patients with T1DM under real-life conditions, focusing in hypoglycemia avoidance. Therefore, novel strategies are presented to improve the performance of the Artificial Pancreas device under development by the Spanish Consortium on Artificial Pancreas and Diabetes Technology, to cope with announced meals and aerobic exercise. Firstly, a novel methodology to adjust in real time a specific constraint of the control system, taking into account a previous approach validated in clinic, have been presented and tested in simulation. Secondly, mitigation strategies to reduce the risk of exercise-induced hypoglycemia have been proposed and extensively validated in silico and preliminary results of a clinical trial with real patients are also presented. Additionally, a new decision support system is proposed to predict the occurrence of nocturnal hypoglycemia in adult patients under MDI therapy. Data from ten adults have been collected in order to obtain predictive models using machine learning algorithms, considering CGM, insulin and physical activity data.

RESUM

La diabetis mellitus tipus 1 (T1DM) és una malaltia crònica resultant de la destrucció les cèl·lules pancreàtiques beta productores d'insulina degut a un procés autoimmunitari que pot ocórrer a qualsevol edat, però tendeix a aparèixer durant la infància i l'adolescència. Les causes d'aquest procés destructiu no són completament conegudes, però el resultat és una deficiència en la secreció d'insulina del pàncrees. Per tant, els individus amb T1DM requereixen un subministrament ininterromput d'insulina exògena per a sobreviure. Si no es proveeix insulina, els nivells de glucosa en sang tendeixen a augmentar cap a nivells perillosament alts (hiperglucèmia) i els individus poden patir vàries complicacions associades amb danys i fallades de diversos òrgans del seu sistema. Durant els anys 90, l'assaig de control i complicacions de la diabetis va demostrar que la teràpia intensiva d'insulina és capaç de reduir el risc d'aquestes complicacions, però al mateix temps incrementa el risc associat amb l'aparició de nivells baixos de glucosa en sang (hipoglucèmia), que en cas de ser greu pot provocar convulsions i inclús la mort.

La teràpia intensiva d'insulina actual es basa en l'administració d'insulina a través de múltiples injeccions diàries (MDI) o mitjançant la infusió continua d'insulina de forma subcutània (CSII) amb una bomba d'insulina. Combinant una bomba d'insulina i mesures de glucosa en sang subministrades per un sistema de monitorització continu de glucosa (CGM) va fer aparèixer els primers dispositius automàtics per a gestionar la T1DM, interrompent la infusió d'insulina per tal de reduir el risc d'hipoglucèmia. Més recentment, ha sorgit l'anomenat pàncrees artificial, que és un sistema en llaç tancat per a regular de forma automàtica la infusió d'insulina segons un algoritme de control. Tanmateix, la gran variabilitat observada en el metabolisme de la glucosa i les grans pertorbacions causades per menjars i activitat física són les principals barreres per aconseguir un control glucèmic acurat.

Les propostes d'aquest treball presten especial atenció a millorar el control glucèmic de pacients amb T1DM en condicions de vida real, centrant-se en evitar la hipoglucèmia. Per tant, es presenten noves estratègies per millorar el rendiment del dispositiu pàncrees artificial que està essent desenvolupat pel consorci espanyol per al pàncrees artificial i tecnologies per a la diabetis, per fer front menjars i activitat física aeròbica que ha sigut anunciada. En primer lloc, una metodologia nova d'ajust en temps real d'una restricció específica del sistema de control, tenint en compte un enfocament anterior ja validat clínicament, ha estat presentada i provada en simulació. En segon lloc, estratègies de mitigació per a reduir el risc d'hipoglucèmia degut a l'exercici físic han sigut presentades, extensament validades 'in silico' i es presenten els resultats previs d'un assaig clínic amb pacients reals. Addicionalment, un nou sistema de suport per a la presa de decisions és proposat per a predir l'ocurrència d'hipoglucèmies nocturnes en

pacients adults amb teràpia MDI. Les dades de deu adults van ser recollides per tal d'obtenir models predictius utilitzant algoritmes d'aprenentatge de màquina, considerant dades d'CGM, dades d'insulina i dades d'activitat física.

RESUMEN

La diabetes mellitus tipo 1 (T1DM) es una condición crónica como resultado de la destrucción de las células pancreáticas beta encargadas de producir la insulina debido a un proceso autoinmune que puede ocurrir a cualquier edad, pero que tiende a desarrollarse en la niñez y adolescencia. Las causas de este proceso destructivo no están comprendidas de forma completa, y éste resulta en la incapacidad del páncreas de secretar insulina. Por lo tanto, los pacientes afectados por la T1DM requieren un suministro ininterrumpido de insulina exógena para sobrevivir. Si la insulina no es suministrada, los niveles de glucosa tienden a subir hasta niveles peligrosos (hiperglicemia) y los sujetos pueden enfrentarse a muchas complicaciones asociadas con daños y fallas de varios sistemas de órganos. Durante los años 90, la prueba clínica de control de la diabetes y complicaciones demostró que la terapia intensiva con insulina es capaz de reducir el riesgo de estas complicaciones, pero al mismo tiempo incrementa el riesgo asociado con la ocurrencia de bajos niveles de glucosa en sangre (hipoglicemia), que en casos severos podría llevar a convulsiones o incluso a la muerte.

Actualmente, la terapia intensiva con insulina está basada en el suministro de insulina a través de múltiples inyecciones diarias (MDI) o a través de la infusión subcutánea continua usando una bomba de insulina. La combinación de una bomba de insulina con las medidas de glucosa en sangre proporcionadas por un medidor continuo de glucosa (CGM) hizo surgir los primeros sistemas automatizados para la gestión de la T1DM, que interrumpen la infusión de insulina para reducir el riesgo de hipoglicemia. Más recientemente, surgió el llamado Páncreas Artificial, que es un sistema de lazo cerrado para regular la infusión de insulina automáticamente con base en un algoritmo de control. Sin embargo, la gran variabilidad observada en el metabolismo de la glucosa y las grandes perturbaciones causadas por las comidas y la actividad física son grandes obstáculos para alcanzar un control riguroso de la glicemia.

Las propuestas de este trabajo ponen especial atención en la mejora del control glicémico en pacientes con T1DM bajo condiciones de vida cotidiana, enfocándose en evitar la hipoglicemia. Por lo tanto, se presentan nuevas estrategias para mejorar el desempeño de un dispositivo de Páncreas Artificial desarrollado por el consorcio español de Páncreas Artificial y tecnología en diabetes, con el fin de que éste pueda hacer frente a comidas anunciadas y ejercicio aeróbico. Primero, se ha presentado y validado en simulación una nueva metodología para ajustar en tiempo real una restricción específica del sistema de control, teniendo en cuenta una propuesta previa validada clínicamente. En segunda instancia, se han propuesto y validado extensivamente estrategias de mitigación para reducir el riesgo de hipoglicemia inducida por ejercicio usando datos in sillico y resultados parciales de un ensayo clínico. Adicionalmente, se propone un

nuevo sistema de apoyo a decisión para predecir la ocurrencia de hipoglicemia nocturna en pacientes adultos bajo la terapia MDI. Los datos de 10 adultos han sido recogidos con el fin de obtener modelos predictivos utilizando algoritmos de aprendizaje de máquina, considerando datos de CGM, datos de insulina y datos de actividad física.

CHAPTER 1

INTRODUCTION

This introductory chapter presents an overview of the diabetes mellitus, the motivation and challenges related with the research on type 1 diabetes mellitus and the objective of this work. The structure of the thesis is detailed.

1.1 Diabetes Mellitus: background and numbers

The World Health Organization (WHO) states that noncommunicable diseases, or chronic diseases, are the result of a combination of genetic, physiological, environmental and behaviour factors and tend to last for long periods, being the leading cause of mortality in most countries, except in African continent. These diseases have reached epidemic proportions, and the deaths caused by chronic diseases are projected to rise, with the greatest impact in low- and middle-income regions. In 2012, a total of 56 million deaths occurred worldwide due to chronic diseases, of these the four major diseases responsible for such deaths were: cardiovascular disease, cancers, respiratory disease and diabetes (WHO, 2015).

The term ‘diabetes’ was used firstly in the ancient Greek to describe the excessive passing of urine, meaning ‘go through’ (Zaccardi et al., 2016). The first clinical description of such condition stated that “diabetes is a wonderful affection not very frequent among men, being a melting down of flesh and limbs into urine” (Reed, 1954). In the 1600s, the term ‘mellitus’ was also included to describe this condition, because of the sweet taste of urine. In 1889, the researches Joseph von Mehring and Oskar Minkowski were the first to indicate that the pancreas contained regulators to control blood sugar, observing symptoms of diabetes in dogs

after pancreas removal. The link between diabetes, pancreas and insulin emerged only in 1910, when Edward Albert Sharpey-Schafer indicated that diabetes was caused due to a deficiency in a substance produced in the pancreas, and called this pancreatic substance as 'insulin' (Zaccardi et al., 2016).

Presently, diabetes mellitus (DM) is considered a chronic disease that occurs either when the pancreas stops to produce insulin in the normal way (Type 1 Diabetes Mellitus (T1DM)) or when the body cannot effectively use the insulin produced by the pancreas (Type 2 Diabetes Mellitus (T2DM)), characterized by the inability of the body to keep the concentration of glucose in blood into normal levels (normoglycemia). In healthy subjects, blood glucose levels in the bloodstream are maintained in a very narrow range due to the action of the pancreatic endocrine hormones. Insulin is a hormone produced by a group of cells in the pancreas called islet cells, and within the islet cells are the β-cells. These cells are responsible to produce and release insulin as needed, to maintain blood glucose levels within normal range (Scheiner, 2012). In subjects with DM, as the pancreas no longer produces insulin or the body cells do not uptake it properly, the concentration of glucose in the bloodstream tends to increase, reaching above normal levels (hyperglycemia). However subjects with either T1DM or T2DM, may also experience low levels of blood glucose concentration (hypoglycemia) when exogenous insulin or medications are used erroneously in the treatment.

According to the International Diabetes Federation (IDF), approximately 425 million people worldwide, between 20-79 years, are estimated to live with DM in 2017, i.e., approximately 8.8% of adults. The prevalence of diabetes for men is higher than among women (9.1% vs. 8.4%). Figure 1.1 shows that such disease affects countries in all continents. An even more aggravating fact is that such numbers are growing steadily. In 2000, the total number of people with diabetes was 151 million, and projections for 2045 also show a raise to 629 million people living with such condition. Table 1.1 shows the ten countries that most have people living with diabetes in 2017 and the projections of which will be the top ten countries in 2045. Such numbers show an alarming increasing burden of diabetes in the world.

Diabetes is a global health-care problem, leading to a great economic impact due to heathcare expenditure for both patients/families and to health public services. The main costs are due to loss of work due to diabetes-related complications and direct medical costs (WHO, 2016). Public policies related with DM prevention and management should pay attention especially on people of lower socio-economic conditions (Kim et al., 2015). Total healthcare expenditures for DM in 2017 was 727 billion US dollars, and it is expected a 7% growth for 2045 (IDF, 2017).

Approximately 50% of people who has DM are unaware of their disease. The sooner

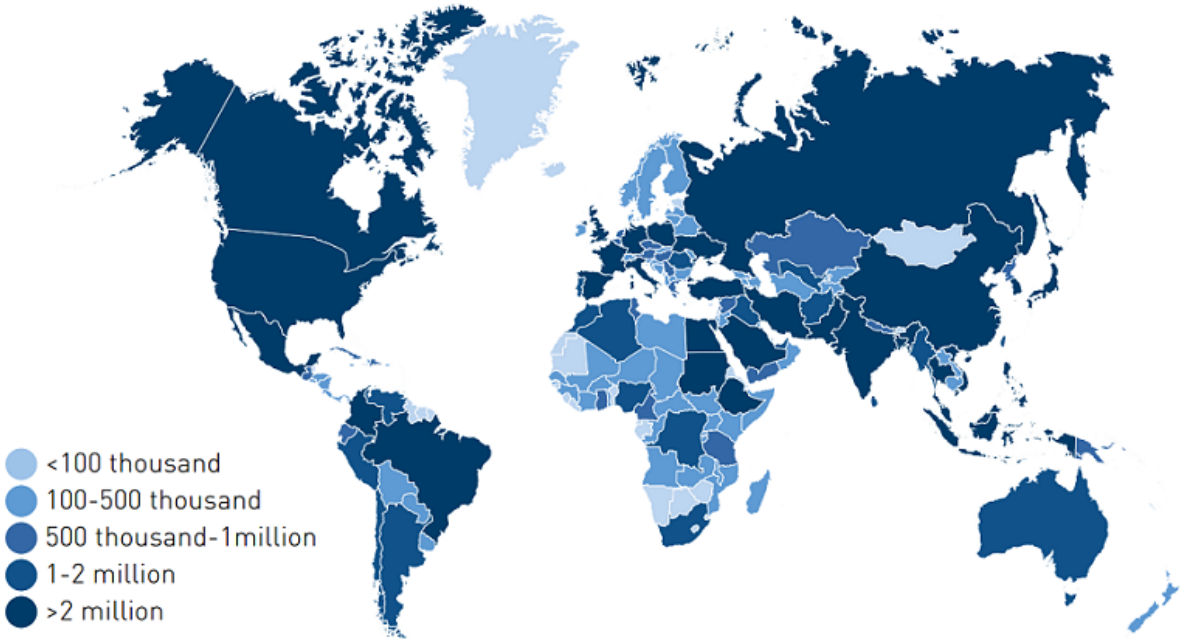

Figure 1.1: People living with diabetes worldwide. Estimated number for adults (20-79 years) in 2017. Taken from: International Diabetes Federation (2017).

subjects know about their conditions, the better are the chances to reduce the risk of future complications, since appropriate care may be provided. In low income countries, the proportion of undiagnosed cases achieves 76.5% for people aged 20-79 years (IDF, 2017). DM can be diagnosed based on tests using subjects' plasma glucose. If any of the following conditions is found, a subject should be considered to have diabetes according with the most recent recommendations provided by the American Diabetes Association (ADA) (2018a):

- Fasting plasma glucose[1] $\geq 126\ mg/dL$.
- 2-h plasma glucose $\geq 200\ mg/dL$ by an oral glucose tolerant test using 75-g of anhydrous glucose dissolved in water.
- HbA_{1c} test[2] $\geq 6.5\%$.
- Random plasma glucose $\geq 200\ mg/dL$ in patients with classic symptoms of hyperglycemia or hyperglycemic crisis.

The symptoms of T1DM and T2DM are similar, but tend to appear quicker in T1DM subjects. The most common symptoms are the following: unusual thirst, weight change, frequent

[1]Fasting plasma is define as no caloric intake for at least 8-h.

[2]The HbA_{1c} test, or glycosylated hemoglobin, is a clinical test performed to measure the amount of hemoglobin with attached glucose, and reflects the average blood glucose levels over the past 3 months.

Table 1.1: Top ten countries in number of people, between 20-79 years, living with diabetes in 2017 and in 2045 according to the International Diabetes Federation (IDF, 2017).

	2017		2045	
Rank	Country	Number of people (in million)	Country	Number of people (in million)
1	China	114.4	India	134.3
2	India	72.9	China	119.8
3	United States	30.2	United States	35.6
4	Brazil	12.5	Mexico	21.8
5	Mexico	12.0	Brazil	20.3
6	Indonesia	10.3	Egypt	16.7
7	Russia	8.5	Indonesia	16.7
8	Egypt	8.2	Pakistan	16.1
9	Germany	7.5	Bangladesh	13.7
10	Pakistan	7.5	Turkey	11.2

urination, increased fatigue, slow healing of cuts and bruises, blurred vision, and constant hunger. If not treated, DM leads to chronic complications with significant morbidity and mortality (Garcia et al., 1974; Lind et al., 2014). Since the first clinical description of the disease, performed by the Greek physician Aretaeus around 120 A.D., it is known that subjects affected by such disease would have shorter lives (Reed, 1954). Intensive treatment of diabetes reduces the risks of complications related with the disease, as showed by the Diabetes Control and Complications Trial (DCCT) Research Group (DCCT, 1993) and by the United Kingdom Prospective Diabetes Study (UKPDS) (King et al., 1999).

1.2 Type 1 Diabetes Mellitus

T1DM is characterized by extreme absence of insulin production by the pancreas. Formerly known as insulin-dependent diabetes or juvenile onset diabetes, T1DM represents around 5-10% of all patients with DM. T1DM is the result of the action of the autoimmune system, which destroy the pancreatic β-cells in the islets of Langerhans over a period of months or years (Scheiner, 2012). T1DM is typically diagnosed during childhood or adolescence, but it can occur in any age. Just before diagnosis, the subject affected by such disease will face very high concentration of glucose into bloodstream. After the diagnosis, exogenous infusion of insulin is required to compensate the lack of insulin production by the pancreas. Further explanations regarding T1DM treatments are discussed later, in Chapter 2.

1.3 Type 2 Diabetes Mellitus

T2DM is more common than T1DM and is caused by insulin resistance: the sugar-lowering effect of insulin is impaired and therefore prompts an increase in insulin production is required to keep blood glucose into normal levels, but over time an inadequate production of insulin can also be observed. This disease is a progressive illness, and its symptoms are minimal for several years before diagnosis. Because it is a disease that manifests itself slowly, the true time of onset is difficult to determine. About one-third to one-half of the T2DM population may be undiagnosed because the symptoms are not acute enough to promote a visit to a physician (IDF, 2017) and about 20% of subjects already have kidney disease by the time of diagnose (Walsh et al., 2003). T2DM is commonly diagnosed in older adults, but it is also seen in children and adolescents due to poor diet, physical inactivity and obesity.

Subjects with T2DM retains partial insulin production and may require only a healthier diet and the practice of physical activity, although some cases require drug treatment or even insulin when the others approaches are not effective to control blood sugars. But there are already studies considering closed-loop (CL) therapy to automate insulin delivery also for subjects with T2DM (Kumareswaran et al., 2014; Thabit et al., 2017).

1.4 Diabetes Mellitus in Brazil

Brazil is a country of continental proportions and comprises almost 50% of South American territory, with an estimated population of over 200 million people. Brazil is divided into five different regions (south, southeast, mid-west, north and northeast) with a disparity in population density, socioeconomic levels and cultural aspects between regions. Economic status plays an important role into education level in Brazil: people with a higher income presenting a higher education level (Cobas et al., 2013a). In addition to this, there are inter-regional disparities in per capita investment in diabetes care, with more investment in the southeast and mid-west regions, and less investment at north and northeast.

As showed in Table 1.1, Brazil is the fourth country in number of people with diabetes (20-79 years) worldwide in 2017 with 12.5 million people (prevalence of 8.7%), and of those, 5.7 million are undiagnosed (International Diabetes Federation, 2017). In the first study to estimate the costs of T1DM treatment in Brazil, researchers observed that the average annual medical expenditure per capita was a 1319 US dollars, with the major costs related with outpatient treatment, i.e. insulin and supplies for self-monitoring of blood glucose (Cobas et al., 2013b). Another study showed that the average T2DM-related costs was 1335 US dollars per patient

per year (Coutinho and Júnior, 2015).

The most commonly used therapy by Brazilians living with T1DM is the combination of intermediate- or long-acting insulin with short-acting insulin, and the great minority of patients uses an insulin pump. In de Souza et al. (2015), data from 3005 patients (56% females) showed that 80.8% of the patients were treated with insulin injection therapy and only 1.5% used an insulin pump. It may be a reflect of patients' economic class, as the majority of patients are from either low or very low income classes. Only 11.6% of patients with T1DM in Brazil are able to achieve the recommended glycemic targets (Coutinho and Júnior, 2015), evidencing the critical situation in T1DM management.

1.5 Complications

As previously mentioned, individuals with T1DM had their β-cells destroyed, requiring external infusion of insulin to reduce the concentration of glucose in the bloodstream. Early signs and symptoms of hyperglycemia are: frequent urination, blurred vision, fatigue, increased thirst, weakness, confusion. Acute hyperglycemia may also causes seizures and coma (Huang et al., 2008; Whiting et al., 1997). Prolonged hyperglycemia can lead to a condition known as diabetes ketoacidosis (DKA), which is caused by elevated levels of ketones in the blood. When there is no insulin available in the blood to facilitate glucose uptake, the body starts to use fat as energy source. However, the process to break down fat makes the blood acidic, and ketones are the byproduct of this process. Over the time, if T1DM is not properly treated, important organs in the body can be affected and such complications may be disabling or life-threatening for those living with this disease. The main T1DM complications due to chronic hyperglycemia are:

- Retinopathy: diabetic retinopathy is a highly specific micro-vascular complication of diabetes and is a progressive complication that destroys small blood vessels of the retina, affecting the eyes. It is estimated that diabetic retinopathy is the most frequent cause of new cases of blindness in the United States. Usually, retinopathy does not occur in subjects with T1DM during the first 3 to 5 years of the disease, but nearly all patients may develop it after 20 years living with diabetes. (Naslafkih and Sestier, 2003). Reported prevalence of moderate or worse retinopathy ranges from 23% to 59% on those with T1DM (Bjerg et al., 2018).

- Nephropathy: diabetic kidney disease is also a progressive complication due to poorly diabetes management. Due to damages caused in the small blood vessels of the kidney, the organ has its filtering ability impaired. This complication can lead to reduced renal

function, and patients may need dialysis or transplantation in end-stage renal failure (Thomas and Karalliedde, 2019).

- Cardiovascular disease: subjects with T1DM are more likely to have high cholesterol and hypertension, both damaging the cells lining the artery walls. DM increases the risk for stroke in people aged 20 to 65 years more than 5 times, when compared with subjects without DM. The majority of adults older than 65 years will die of some form of heart disease. (McCarthy et al., 2016).

- Neuropathy: diabetic neuropathy is a set of clinical syndromes that affects different regions of the nervous system and it is a very common complication of DM. Excess sugar can injure the walls of the tiny blood vessels (capillaries) that nourish your nerves, causing nerve damage. In the developed countries of the world, this complication accounts for more hospitalizations than all the other complications combined (Vinik et al., 2013).

- Foot damage: The complications caused by DM can include nerve damage and poor blood circulation. These problems make the feet vulnerable to skin sores (ulcers). The major morbidity associated with neuropathy is foot ulceration. A non-healing ulcer that causes severe damage to tissues and bone may require amputation of a toe, foot or part of a leg. Globally, there is an amputation every 30 seconds, and up to 75% are preventable (Vinik et al., 2013).

The devastating consequences of the long-term complications of T1DM led in part to the establishment of a clinical study to evaluate the hypothesis posited that achieving near-normal glucose would ameliorate the long-term complications of diabetes. In the 80's, the DCCT compared intensive insulin therapy with conventional therapy, on more than 1,400 T1DM subjects. Intensive insulin therapy was able to improve HbA_{1c} outcomes, and also showed to reduce the long-term complications of T1DM. However, the adverse effect of intensive insulin therapy was a threefold increased risk of hypoglycemia (DCCT, 1993; Nathan, 2014). Hypoglycemia is a major short-term complication of diabetes. The symptoms of hypoglycemia includes: weakness or shakiness, sweating, dizziness, hunger and confusion. Severe hypoglycemia can also lead to altered consciousness, seizures, coma, and even death. In older people, low blood glucose may lead to strokes or heart attacks (Snell-Bergeon and Wadwa, 2012) and may also have harmful effects on neuropsychological and intellectual function in children (Cato et al., 2014).

1.6 Motivation

Hypoglycemia is an acute metabolic complication of T1DM and is a life-threatening condition, that can lead to serious physical and psychological, which in extreme cases can lead to death (Tanenberg et al., 2010). However, keeping glucose at high levels, focusing only on avoiding hypoglycemia, is also dangerous and causes various complications, including reducing life expectancy. Results from the DCCT showed that tightening glucose control using intensive insulin therapy reduces the long-term complications of T1DM, but on the other hand the hypoglycemic-risk is also increased (DCCT, 1993). Lower HbA_{1c} values are associated with the increased hypoglycemic-risk, however, poor controlled individuals, with higher HbA_{1c}, also spent more time with low blood glucose levels (Gimenez et al., 2018). Repeated exposure to hypoglycemia leads to a change in the symptom complex that characterises hypoglycemia, leading to impaired awareness of hypoglycemia (hypoglycemia unawareness) (McNeilly and McCrimmon, 2018). Beyond the physiological complications caused by hypoglycemia, distressing experiences caused by hypoglycemia negatively impact the psychological of subjects with T1DM, and fear of hypoglycemia influences health behaviors used for T1DM management, impairing glycemic control (Martyn-Nemeth et al., 2017). Therefore, both physiological and psychological burdens of hypoglycemia are the basis for the continued development of strategies and tools to avoid it.

Thus, hypoglycemia is the limiting factor in the management of T1DM, for both physicians and patients. Some of the hypoglycemia-related problems in T1DM management are presented below:

- **Postprandial period:** postprandial glucose control is a challenging issue in everyday diabetes care. Indeed, postprandial excursions are the major contributors to glycemic variability in subjects with T1DM. Nevertheless, the ultimate goal is to track blood glucose levels back to near-normoglycemia without lead to hypoglycemia in the late postprandial period due to excessive insulin. A major problem of glycemic control during postprandial period is directly related with insulin dynamics. Although fast-acting insulin analogues represented an advancement on postprandial control (Heinemann et al., 2011; Luijf et al., 2010), the effects of insulin still takes to long to begin, and the desire to reduce glycemic peaks may lead to hypoglycemia few hours after the meal (Goodwin et al., 2015). Patients should estimate the amount of carbohydrates (CHO) from meals to calculate a insulin bolus to compensate the rising in blood glucose levels caused by CHO intake, however regular CHO-matched bolus is not able to guarantee optimal glycemic control, due to the different sources of uncertainty (macronutrient composition (Smart et al., 2013; Bell et al., 2015), misestimations in CHO counting (Deeb et al.,

2017), physical activity performed previous to the meal (Manohar et al., 2012; Ozaslan et al., 2017), patient-specific parameters and also due to the intra-individual variability. Therefore, postprandial glycemic control is essential to achieve the glycemic targets (Ketema and Kibret, 2015).

- **Exercise-induced hypoglycemia:** although regular physical activity is recommended for individuals with T1DM, fear of exercise-induced hypoglycemia is a major barrier for subjects engage physical activity regularly (Brazeau et al., 2008). Several factors influence blood glucose levels during exercise (type of exercise, duration, intensity, subjects' fitness, etc), and it is a great hurdle even for CL systems (Riddell et al., 2015; van Bon et al., 2011; Breton, 2008). Several CL systems were evaluated against aerobic exercise (Bertachi et al., 2018b), however, no gold standard methodology has been established so far. Dual-hormonal systems, with both insulin and glucagon recommendations, reduces the occurrence and severity of exercise-induced hypoglycemia (Taleb et al., 2016; Haidar et al., 2013a), but it adds more complexity for the system and innovative approaches are still required to overcome intrinsic limitations of CL performance during exercise (Bally and Thabit, 2018).

- **Nocturnal hypoglycemic events:** nocturnal hypoglycemia can lead to various adverse situations in T1DM patients, including consciousness, seizure, or even death (Tanenberg et al., 2010). Moreover, these adverse events have a negative impact on patients' life, affecting their sleep and their functioning and productivity the next day (Brod et al., 2013, 2011). Recently, CL systems have shown to be able to improve glycemic control during overnight period and have reduced the occurrences of hypoglycemic events when compared with traditional therapy (Brown et al., 2015; Nimri et al., 2013). However, at least for the next few years, the minority of T1DM patients will be able to use such system. T1DM patients under multiple daily injections (MDI) therapy do not have any kind of mechanism to assist them while they are sleeping. During the day, patients can take actions to correct their glycemic levels whether necessary. However, during overnight, patients can not take any actions while are sleeping, and such hazard is aggravated in patients suffering from hypoglycemia unawareness. At present, nocturnal hypoglycemia still remains a substantial clinical problem on T1DM management, and further research with innovative approaches are required to overcome it.

1.7 Research Objective

The main objective of this research is to design safe strategies to efficiently control blood glucose levels and improve life conditions for those who live with T1DM, focused on the prevention of hypoglycemia, but also avoiding excessive hyperglycemia. Firstly, the thesis is focused on the development of novel strategies to improve the performance of a CL prototype that is being developed by the Spanish Consortium on Artificial Pancreas and Diabetes Technology. Later, the thesis is focused on the development of a decision support system capable to predict nocturnal hypoglycemia for subjects with T1DM under MDI therapy combined with continuous glucose monitoring (CGM) system and physical activity monitor.

To achieve the main objective, the study addressed the following aims:

- To design and validate a new strategy to adjust a specific constraint of the insulin controller to cope with the intra-day variability existing in patients' daily life, intended to be used by an AP system operating 24 h per day.
- To develop and assess mitigation strategies to be incorporated in the CL system to reduce the risk of hypoglycemic episodes caused by aerobic exercise.
- To develop a personalized decision support system for T1DM patients under MDI therapy, using machine learning techniques to predict the occurrence of nocturnal hypoglycemic events.

1.8 Thesis Structure

This thesis is organized as follow:

- Chapter 2: **Blood glucose control on T1DM** presents an overview of the state-of-art therapies applied to blood glucose control in T1DM. It describes the devices employed in T1DM treatment, from insulin injections up to CL systems. The main challenges related with T1DM are also presented.
- Chapter 3: **Closed-loop control schemes** is directed to depict the CL system that have been developed over the last years by the Spanish Consortium on Artificial Pancreas and Diabetes Technology. This system is composed by a proportional-derivative (PD) controller and also by a safety layer that limits the recommendations provided by the PD-controller, avoiding excessive accumulation of insulin in the subcutaneous tissue.

The UVa/Padova T1DM simulator, employed to validate the experiments in silico, is also detailed in this Chapter.

- Chapter 4: **Novel strategies to improve closed-loop performance** describes the research performed on CL therapy. The strategies developed to improve the controller's performance under realistic and challenging conditions are described. It is presented in this Chapter a novel strategy to adjust a specific constraint of the controller which limits the amount of insulin accumulated in body. Moreover, mitigation strategies to reduce the risk exercise-induced hypoglycemia are presented.
- Chapter 5: **Prediction of nocturnal hypoglycemia using machine learning techniques** is dedicated to describe the application of machine learning techniques to predict the occurrence of nocturnal hypoglycemic events in patients under MDI therapy. Results encompassing real data collected from ten patients are presented.
- Chapter 6: **Conclusion** is dedicated to the conclusion and contributions of this work. Prospects of future research are also addressed.

CHAPTER 2

BLOOD GLUCOSE CONTROL ON T1DM

2.1 Introduction

Intensive insulin therapy is essential to maintain blood glucose into regular levels in all people with T1DM and those with T2DM in an advanced stage. In this chapter it is presented the state-of-art regarding the management of T1DM. Firstly, the glucose-insulin biological system is described to expose the function of the pancreas to control blood glucose levels in health subjects. In the sequence, the technological devices considered for T1DM management are depicted, including the Artificial Pancreas, which is a CL system intended to regulate insulin infusion automatically.

2.2 Blood glucose regulation

Glucose is the most important source of energy and it is essential for the human metabolism (Mergenthaler et al., 2013). After eating a meal, a series of chemical reactions transform the macronutrients obtained from food into components that can be used for the body's basic processes. Although all three macronutrients (fat, protein and CHO) are important for the survival and development of the human body, it is CHO that causes the greatest impact on blood glucose balance for those suffering from T1DM. During the digestion process after a meal, CHO is broken into its simpler form, and then is transported via the bloodstream to the peripheral tissues, increasing glucose concentration in the blood.

In healthy subjects, the insulin secreted by the pancreatic β-cells is necessary to get the

glucose out of the bloodstream to be used as fuel into the body's cells. Glucose is the major source of energy for most cells of the body, but the brain only uses glucose as source of energy (Scheiner, 2012). Therefore, it is always necessary to have a certain amount of insulin in the blood, to facilitate the transport of glucose into cells. Insulin is usually secreted by two different ways: basal and bolus insulin. Basal insulin (or background insulin) is a steady release of insulin intended to stabilize blood glucose levels during fasting and overnight periods. It can vary between days and also during the same day, depending on the subject's activities or stress levels. Bolus insulin is provided when eating occurs. At this moment, insulin needs to be released to cover the CHO content of a meal. In the first 15 minutes after the meal, the insulin stored in the β-cells is rapidly released, and it is followed by a gradual increase in insulin secretion over the next hour and a half to three hours, in response to the rising effects caused by the meal in blood glucose concentration (Walsh et al., 2003; Walsh and Roberts, 2006).

However, even healthy subjects can experience hypoglycemia, e.g. after long periods without food, during intense physical activities. In such situations, when blood sugar falls, the pancreas reduces insulin production and the counterregulatory hormones work to avoid that glucose levels achieves hypoglycemia. The major counterregulatory hormone is the glucagon, although epinephrine (also known as adrenaline), cortisol, and growth hormone also play an important role to avoid severe hypoglycemia. Glucagon is also produced in the islets of Langerhans of the pancreas, but by the α-cells. However, the counterregulatory functions have also been shown to be compromised in people with DM (Cryer, 2002). Once glucagon is released, it stimulates hepatic glucose production, in order to avert hypoglycemia. The glycogen stored in the liver is converted into glucose, increasing blood glucose levels (Kulina and Rayfield, 2016). Therefore, both insulin and glucagon compose a complex feedback system that keeps blood glucose within a narrow range, between 70 and 100 mg/dl for healthy people in fasting conditions. The basic mechanism of a healthy subject for blood glucose regulation, based on insulin and glucagon hormones, is illustrated in Figure 2.1.

2.3 Evolution of T1DM treatment and technological devices

In the 1920s, Frederick Banting led the research to produce pancreatic extracts from dogs' pancreas (Leeder, 2013). Banting and colleagues reported their first approach to use insulin to treat DM on a 14-year old boy (Banting et al., 1922), and their results guided to the beginning of the 'real' treatments, giving hope to those who suffered from DM in those days. In 1923, thanks to his work to "discover" insulin, Banting was awarded with the Nobel Prize in Medicine/Physiology.

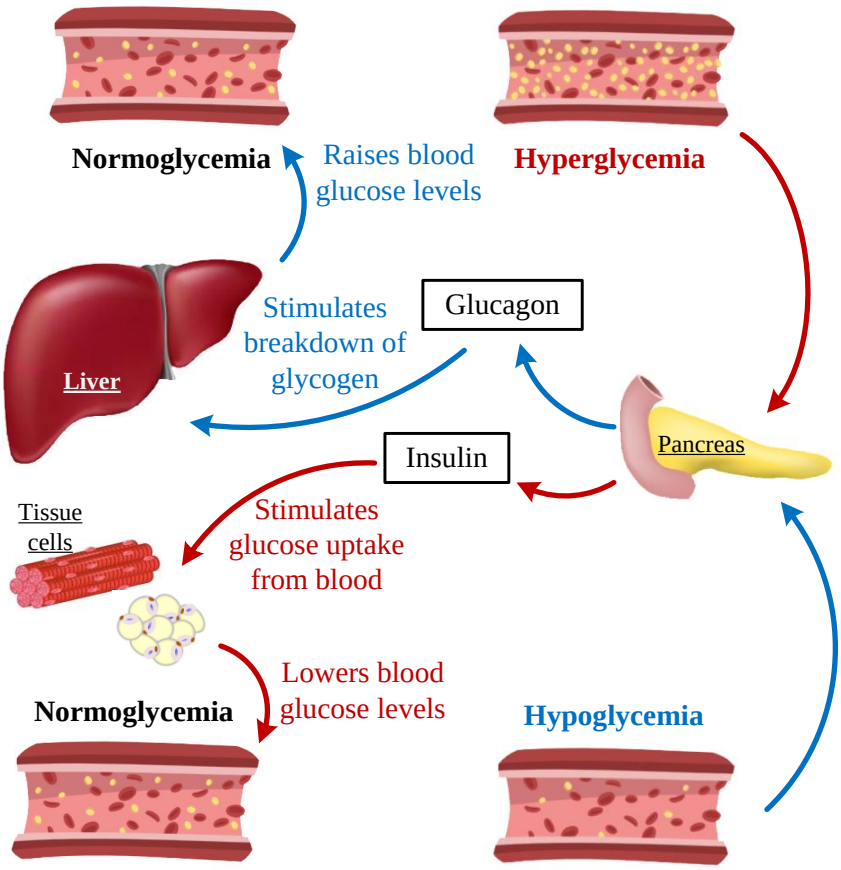

Figure 2.1: The secretion of insulin and glucagon by the pancreas in health subjects is responsible to keep blood glucose levels into normoglycemia.

Since Banting's discovery, much effort was devoted on insulin production and purification. Initially, insulin started to be produced from the pancreas of cattle and pigs. Nowadays, there are several formulations of insulin, which differ basically in three characteristics: onset of action, peak action and effective duration. The onset of action indicates when the effects of insulin are detected. The time that insulin takes to achieve its optimum performance is characterized as the time of peak action. The length of time during which insulin effects are exhibited is the effective duration. Usually, insulin is classified as: rapid-, short-, intermediate- and long-acting. The invention of rapid-acting insulin analogs was able to improve substantially postprandial glycemic control, but researches consider that an even more rapid insulin could reduce even more glycemic excursions caused by meals (Heinemann and Muchmore, 2012). In 2014, the Food and Drug Administration (FDA) agency approved an inhaled insulin for adults. Such insulin is considered ultra-fast-acting, because has a faster absorption when compared with subcutaneous rapid-acting insulin (Al-Tabakha, 2015). The action profiles of some insulins

are presented in Table 2.1 and the pharmacokinetic profiles of different types of insulin are illustrated in Figure 2.2.

Table 2.1: Characteristics of different types of insulin (Hirsch, 2005; Al-Tabakha, 2015).

Insulin Type	Name	Onset	Peak	Duration
Ultra-rapid-acting	Afrezza*	Shorter than lispro	50 min	2 – 3 h
Rapid-acting	Lispro	5 – 15 min	30 – 90 min	4 – 6 h
Rapid-acting	Aspart	5 – 15 min	30 – 90 min	4 – 6 h
Short-acting	Regular	30 – 60 min	2 – 3 h	8 – 10 h
Intermediate-acting	NPH	2 – 4 h	4 – 10 h	12 – 20 h
Long-acting	Extended zinc	6 – 10 h	10 – 16 h	18 – 24 h
Long-acting	Glargine	2 – 4 h	None	20 – 24 h

*Inhaled insulin

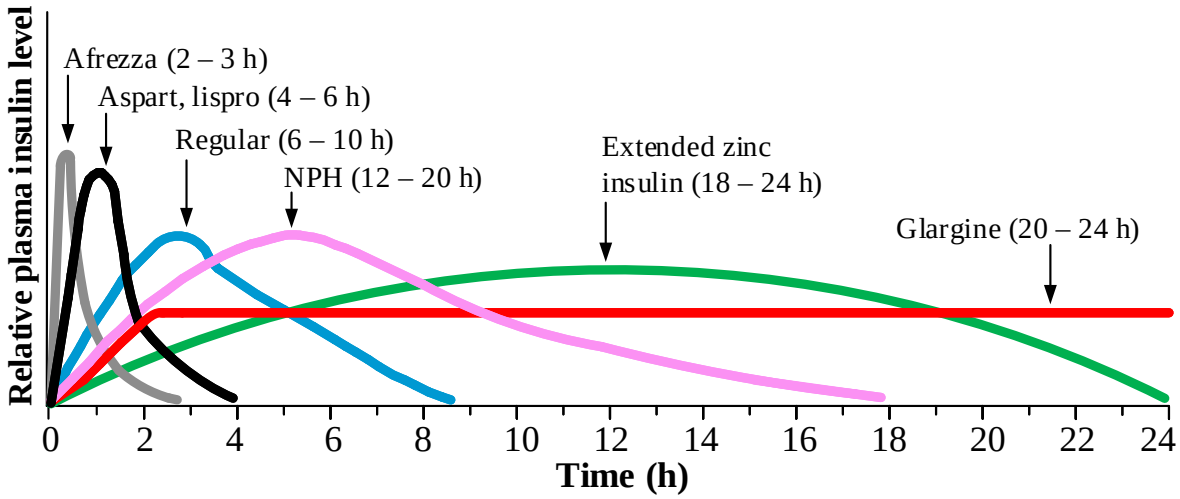

Figure 2.2: Pharmacokinetic profiles of human insulin and insulin analogues. Approximate duration of insulin action is presented between parentheses and have a widely variability. Adapted from: Hirsch (2005) and Al-Tabakha (2015).

In the early years of insulin use, subjects injected insulin using regular glass syringes and insulin dosage was based on the appearance of symptoms: decrease the dosage in case of hypoglycemia/seizures or increase dosage if urination increased. Estimation of blood glucose concentration were performed using urine tests at clinical facilities (Scheiner, 2012).

Over the next decades, remarkable clinical and technological advances have taken T1DM management to a superior level. In the past, patients had to follow a very restricted diet and fixed insulin doses. Currently, subjects with T1DM can vary insulin doses to fit CHO intake and physical activity and also eat when they wish. The results reported by the DCCT encouraged

tighter glycemic control through intensive insulin therapy. Thus, making use of the right tools is one of the keys to achieve success on T1DM management. In the following sections, it is presented the main devices that have emerged on intensive insulin therapy for glucose monitoring and insulin delivery.

2.3.1 Glucometer

The glucometer is a portable glucose meter device available for blood glucose monitoring both in point of care testing sites and in home monitoring. In order to perform a measurement, a small sample of blood (usually taken from the fingertip) is placed on the test pad and then this test strip is inserted into the device. After a short period of time, the measurement value is shown in a display. This procedure is known as Self Monitoring of Blood Glucose (SMBG) and can be performed quickly anywhere, due to its simplicity. Figure 2.3 illustrates this procedure.

Figure 2.3: Glucometer usage.

SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. It is an essential tool for patients to make daily management decisions related to food intake and insulin dosing, particularly prandial and correction insulin boluses. It enables patients to avoid acute complications of type 1 diabetes, such as hyper- and hypoglycemia. In addition, SMBG also reduces the long-term complications of T1DM. Miller et al. (2013) reported that the frequency of SMBG per day is strongly associated with lower HbA_{1c} values for a large population of T1DM subjects. Generally, patients are instructed to perform at least 4 SMBG tests per day, but patient's specific needs and goals should dictate SMBG frequency and timing.

Disadvantages of SMBG are the need for multiple finger-stick blood samples each day, the limited data available, since SMBG only provides a single snap shot of glucose levels, and the impact of user error on test accuracy (Patton and Clements, 2012).

2.3.2 Continuous Glucose Monitoring (CGM)

The standard CGM device commonly consists of an abdomen-worn, subcutaneous sensor that measures blood glucose levels and transmits this information to a base unit for processing and display. The monitor must be positioned in close proximity, usually on the belt or inside pants' pockets. The monitor generates an average value that is considered as the blood glucose reading. Commonly, CGM readings are available every five minutes, but this may vary according to the manufacturer. Each sensor has its own applicator device, which makes the insertion of the sensor to be performed quickly and almost painlessly.

The first commercial CGM was released in 1999 by Medtronic (Medtronic, Northridge, CA, USA). Such device just stored glucose readings values for up to 3 days, and data should be downloaded later for retrospective analysis. The following generations of CGM devices showed a continuous evolution of the glucose monitoring technology, both in usability and in accuracy of measurements. A major advantage of CGM technology is that it can provide a continuous measurements glucose concentration in real-time, which adequately reflects blood glucose concentration and can help to identify trends and patterns in glucose control with only a single needle stick to place the sensor. CGM offers the capability of expressing the frequency and severity of adverse glycemic episodes much more clearly than SMBG tests. It also has multiple ways of alerting the patient including audio or vibratory alarms with custom parameter thresholds that may be preset either by the patient or by the physician.

To expose the advancement of CGM technology, it is presented here the example of four different CGM system developed by Dexcom (Dexcom, San Diego, CA, USA) over the last years. The Dexcom SEVEN PLUS (D7P) system was released in 2009 and was the third-generation of CGM system developed by the company. The D7P system required that users calibrate the system every 12 hours at minimum using a SMBG test and the sensor lasted for up to 7 days. Three years later, in 2012, the Dexcom G4 PLATINUM (DG4) system has been released. The system also lasted for up to 7 days and patients had to calibrate it every 12 hours at minimum, but with improved accuracy in comparison with the DG7 (see Table 2.2). In 2015, the Dexcom G5 (DG5) system hit the market, also lasting for up to seven days and requiring calibration. But on December 2016, the FDA approved the non-adjunctive use of the DG5 system for insulin dosing recommendation (Shapiro, 2017). This approval meant that patients can use the CGM measurements instead of SMBG for diabetes treatment decisions, and DG5 has been the first CGM system to have this label. The most recent CGM system released is the Dexcom G6 (DG6) system. Users of this model do not need to prick their fingers for diabetes management, since the device is factory-calibrated and is also approved as a non-adjunctive device for diabetes management. In addition, the sensor lifetime has been extended to 10 days.

Table 2.2 shows some characteristics of the models mentioned above, including the mean absolute relative difference (MARD) reported in clinical studies to assess the accuracy of each system. Figure 2.4 illustrate the most recent CGM system provided by Dexcom.

Table 2.2: Characteristics of different CGM systems manufactured by Dexcom.

	Launch (month/year)	Sensor lifespan	Calibration frequency	Non-adjuntive use	MARD	Reference
D7P	Nov/2009	7 days	12 h	✗	16.0%	(Christiansen et al., 2013)
DG4	Oct/2012	7 days	12 h	✗	13.0%	(Christiansen et al., 2013)
DG5	Sep/2015	7 days	12 h	✓	9.0%	(Welsh et al., 2019)
DG6	Mar/2018	10 days	–	✓	9.9%	(Welsh et al., 2019)

Figure 2.4: Applicator, display and sensor/transmitter from the new generation of Dexcom CGM system (DG6). Taken from: http://www.dexcom.com.

In 2014, the company Abbott (Abbott Diabetes Care, Alameda, CA, USA) launched in Europe the FreeStyle Libre (FSL) flash glucose monitoring system. The FSL provides the same type of glucose data than real-time CGM, but introduced a new concept to monitor blood glucose: users must use a hand-held reader to scan the sensor to receive the instantaneous readings and also historic results with a 15-min frequency for up to 8 h. The reader has also a screen, in which trends of glucose are informed and patients can insert treatment-related information, such as insulin doses and meal intake. Therefore, the FSL is commonly known as Intermittently Scanned Continuous Glucose Monitoring (isCGM), because patients need to scan the sensor frequently to obtain sensor's measurements. The sensor should be inserted on the back of the upper arm and lasts for up to 14 days. The FSL has a factory-calibrated system which do not require calibration and also received the non-adjunctive use approval.

CGM technology also allowed the introduction of new clinically meaningful outcomes to evaluate the glycemic control on T1DM patients, going beyond the HbA_{1c} results. HbA_{1c} test fails to capture glycemic variability, not addressing the associated risk of hyper- and hypoglycemia in the results (McCall and Kovatchev, 2009). Individuals with the same HbA_{1c} can present very different incidence of adverse events (see Figure 1 from Kovatchev and Cobelli (2016)). Due to CGM technology, new approaches to evaluate glycemic control have emerged, and it is common to assess glycemic control based on the percentage of time spent into different glycemic ranges. The most used ranges are (American Diabetes Association, 2018b; Agiostratidou et al., 2017):

- Target range: blood glucose in the range 70-180 mg/dl;
- Hyperglycemia Level 1 (L1): blood glucose >180 mg/dl and blood glucose ≤250 mg/dl;
- Hyperglycemia Level 2 (L2): blood glucose >250 mg/dl;
- Hypoglycemia Level 1: blood glucose ≤70 mg/dl;
- Hypoglycemia Level 2: blood glucose <54 mg/dl;

For further information regarding CGM technology, readers are referred to Olczuk and Priefer (2018).

2.3.3 Insulin pen

Insulin-delivery pens have been developed to counter the problems and inconveniences caused by syringes and were introduced in 1985. Insulin pens are more flexible, convenient and accurate when compared with syringes. There are two basic types of pen: disposable and reusable. Disposable pens do not require the installation of an insulin reservoir, and are discarded when insulin is consumed. Differently, reusable pens need to be loaded with insulin cartridges, but can be used for several years (Pisano, 2014).

Very recently, manufacturers started to develop smart insulin pens. Smart pens deliver insulin in the same way that the “non-smart” models, but the device can record the amount and timing of each dose and such information can be used elsewhere for different purposes, e.g. suggest insulin boluses. The first FDA-approved smart insulin pen was launched on December 2017 (Klonoff and Kerr, 2018).

2.3.4 Insulin pump

The first manufactured insulin pump was introduced in the 1970s, but as it was about the size of a microwave oven, it was mainly used to treat DKA in hospitals. Modern pumps are the size of a cell phone and can be ported discreetly. Basically, an insulin pump consists of a reservoir, a small battery-operated pump, and a control mechanism. The infusion set (cannula and tubing system) is other important piece of insulin pumping and it is responsible to transfer the pumped insulin to the subcutaneous tissue, but it is one of the major causes of problems observed (Heinemann and Krinelke, 2012) and must be changed every few days.. Figure 2.5 shows an insulin pump and the infusion set.

Figure 2.5: Insulin pump and infusion set being used by a patient.

Insulin pumps provides a constant subcutaneous infusion of rapid-acting insulin and mimics normal pancreatic insulin delivery better than insulin injections. Subjects and physicians can set multiple basal profiles to adjust insulin infusion rate based on insulin requirements. Patients can have a basal profile to use during workdays and another basal profile to use on weekends. In addition to the basal delivery, the pump can also deliver a large amount of insulin in a short period of time, i.e., an insulin bolus. Premeal boluses are delivered at mealtime based on patient's estimation, and bolus can be delivery into different wave forms, according with the expected meal absorption rate in bloodstream. Intensive insulin therapy based on an insulin pump is also known as continuous subcutaneous insulin infusion (CSII) therapy. Some of the advantages of CSII therapy are listed below:

- Multiple basal rates;
- Improved safety and reliability;
- Wireless link with glucometer readings;

- Bolus calculator;
- Different options for bolus delivery;
- Historical of insulin delivered;
- Download of the stored data;
- Possibility of concomitant CGM;

2.4 Intensive insulin therapy

Intensive insulin therapy can be defined as a comprehensive system of diabetes management with the patient and management team as partners, because it requires a lot of commitment from patients and a good level of understanding of diabetes, that is provided by experts. The DCCT study showed that intensive insulin therapy is able to improve blood glucose control and also reduces the risk of developing long-term complications. Such approach is designed to control blood sugar levels and requires close monitoring of blood sugar levels and regular infusion of insulin, accordingly on patients' activities.

The current standard of care for patients with T1DM under intensive insulin therapy includes insulin delivery either by MDI or CSII, although MDI is the most common. Both methods consider the basal-bolus strategy to deliver the required amount of insulin, and are adjusted based on individual requirements and characteristics. In addition, subjects must be able to estimate the amount of CHO content in a meal based on CHO counting techniques (Brazeau et al., 2013).

In MDI therapy, the basal-bolus approach considers long- and rapid-acting insulin doses to keep blood glucose into normal ranges. In general, basal insulin is given once a day using long-acting insulin. The size of the basal dose depends on the total daily insulin dose (TDD) of each patient. The TDD is calculated based on individual's parameters, such as weight and physical activity level. On average, TDD for adults ranges from 0.5 to 0.7 IU/kg/day and from 0.2 to 0.5 IU/kg/day for pediatric subjects (Walsh and Roberts, 2006).

Typically, basal insulin doses are approximately 50% of the TDD, in units of IU. However, basal percentage will be higher than 50% for someone who consumes a low CHO diet and lower for someone on a high CHO diet. Insulin boluses are given into two different ways using rapid-acting doses: as meal bolus or as a correction bolus. The regular meal bolus is calculated as:

$$Bolus = \frac{M_{CHO}}{CR} + \frac{mBG - tBG}{CF} \tag{2.1}$$

where M_{CHO} is the estimation of CHO content of a meal in grams, CR is a subject-specific parameter which indicates how many grams of CHO one unit of insulin covers in units of grams/IU, mBG is the measured preprandial blood glucose concentration in units of mg/dl, obtained by a SMBG test. tBG is the desired target of blood glucose in units of mg/dl, CF is a subject-specific parameter which indicates how many mg/dl the blood glucose concentration will be reduced by one unit of insulin, in mg/dl/IU. The subject-specific parameters CR and CF are initially selected by the physician. More information regarding how these parameters are tuned can be founded elsewhere (Walsh et al., 2003; Walsh and Roberts, 2006; Walsh et al., 2011).

A correction bolus is computed similarly to the meal bolus to correct unexpected hyperglycemia, but the meal-related portion from Eq. (2.1) is not included. Therefore, MDI is associated with the performance of complex calculations before eating or correcting hyperglycemia, and patients usually makes use of bolus calculators incorporated into glucometers or smartphone applications (Vallejo-Mora et al., 2017).

In CSII therapy, basal-bolus approach is similar with the MDI therapy in terms of insulin delivery. An important difference is that in CSII only fast-acting insulin is injected by the pump. Therefore, basal insulin is characterized by flux of insulin along the day, with the possibility of programming different rates according with patients' needs. For meal bolus delivery, patients must inform the amount of CHO content of the meal and must insert a blood glucose reading obtained by a SMBG test.

In addition to the delivery of basal and bolus doses, blood glucose self-monitoring is indispensable for those who are treated with intensive insulin regimens. The ADA recommends that patients on intensive insulin regimens should check blood glucose prior to meals and snacks, occasionally following meals, at bedtime, prior to exercise, when low glucose is suspected, after treating low glucose and prior to critical tasks such as driving (ADA, 2018b). The following sections present some comparisons between different devices for insulin delivery and blood glucose monitoring combined in the treatment of T1DM.

2.4.1 MDI+SMBG versus CSII+SMBG

Although MDI regimen that includes frequent self-monitoring of blood glucose levels and structured diabetes education can achieve good glycemic control in many individuals with T1DM, several studies have shown that CSII is associated with improved glycemic control and reduction on hypoglycemic events. However, subjects poorly controlled on MDI benefit more from switching to CSII than patients well controlled (Pickup and Sutton, 2008). A clinical study conducted by Bolli and colleagues (Bolli et al., 2009) randomized two groups of T1DM

patients naive to CSII and MDI therapy with similar HbA_{1c} at baseline, and after 24 weeks of intervention, observed that both MDI and CSII therapies achieved similar results. In this study, it was also observed that CSII is considerable more expensive than MDI (including devices and consumables), and may influence the decision of which therapy to adopt.

2.4.2 MDI+SMBG versus MDI+CGM

CGM allows patients to follow in real-time blood glucose levels, being able to observe glucose trends to take insulin-related decisions and also being warned by alarms or alerts when a glucose threshold is violated. However, there are several barriers that limit the adherence of CGM technology, including financial, physiological and technical factors (Anhalt, 2016; Shivers et al., 2013; Bartelme and Bridger, 2009). Even with these barriers, studies have shown that the addition of CGM on MDI therapy improves glycemic control on T1DM patients. The Type 1 Diabetes Exchange registry database was used to assess the impact of CGM on HbA_{1c} in insulin injection users, and the results have shown a lower mean HbA1c in patients with CGM when compared with patients without CGM, 7.6% vs 8.8% (Foster et al., 2016).

2.4.3 CSII+SMBG versus CSII+CGM

CSII therapy is recommended to those who may have special needs, such as long duration of disease with low insulin requirements or hypoglycemia unawareness with frequent, severe hypoglycemia on MDI. Furthermore CSII is better than MDI considering the positive effects on quality of life and the possibility to adjust easily basal insulin rates according to patients' lifestyle and needs (Bruttomesso et al., 2009). CSII therapy under SMBG self-monitoring relieve patients from insulin injection, but self-monitoring of blood glucose levels is still required. The addition of a CGM system adds another device to be worn by patients, and very few models of CGM systems release patients from finger-pricks. In 2009, Rodbard and colleagues reported that the utilization of CGM on CSII therapy improved significantly 18 different clinical criteria analyzed, but observed that the magnitude of improvement was generally greater in subjects with a higher HbA_{1c} (Rodbard et al., 2009).

2.5 The beginning of automation in T1DM treatment

As presented previously, the technological advancements were able to provide improvements in the glycemic control of the patients, but at the cost of demanding greater commitment from patients and also a higher level of education in diabetes management. T1DM treatment was still

totally dependent on the actions taken by patients, either to apply an injection as a correction bolus or to change the basal profile of an insulin pump.

The beginning of the first home-use automated devices for T1DM was with the introduction of the Sensor-Augmented Pump (SAP) therapy. SAP integrates CGM and CSII technology into one sophisticated system. These two devices, in conjunction with an algorithm, are able to act automatically, suspending insulin infusion to avoid hypoglycemia or to reduce its severity. Among SAP devices, stand out the Medtronic MiniMed 530G and the Medtronic MiniMed 640G, launched in 2013 and 2015, respectively. The MiniMed 530G introduced the Low Glucose Suspend (LGS) feature, that automatically suspends insulin delivery for up to 2 h when the CGM value reaches or falls below a set threshold. Later, the MiniMed 640G introduced a more refined feature known as Predictive Low Glucose Suspend (PLGS). Such feature is able to suspend insulin infusion in case of blood glucose predictions below a set threshold, and then resume insulin when glucose levels rise to safe levels. In several studies SAP therapy achieved better glycemic control when compared with MDI and CSII therapy, especially by reducing the occurrence of nocturnal hypoglycemic events (Biester et al., 2017; Bergenstal et al., 2013; Garg et al., 2012; Choudhary et al., 2011). Moreover, SAP therapy with insulin suspension feature tends to be more cost-effective in patients with poor glycemic control when compared with CSII+SMBG (Jendle et al., 2017; Roze et al., 2015).

2.6 Artificial Pancreas Research

The artificial pancreas (AP) is a big step forward automatic control of blood glucose. An ordinary AP system is composed of three components: a CGM, an insulin pump, and a control algorithm. Historically, the first CL system designed to treat humans with T1DM dates back to the 1960's (Cobelli et al., 2011). The Biostator was the first commercial device to achieve tight BG control. However, it was too bulky, invasive, and complex to be used outside of a clinical environment. Now, current technology used in T1DM care are minimally invasive, lightweight, and portable. These advancements along with multiple agencies advocating for the device (Kowalski and Lum, 2009) have accelerated the rate of development. An illustration of a general CL system is presented in Figure 2.6.

Several technological advancements in AP technology have taken place since the publication of Steil et al. (2006), which showed the feasibility of automated insulin delivery to treat T1DM. Formerly, systems were tested on patients in a controlled clinical environment (Atlas et al., 2010), only during the night (Hovorka et al., 2010), tested in non-human subjects (El-Khatib et al., 2009). The number of outpatient studies performed each year increased

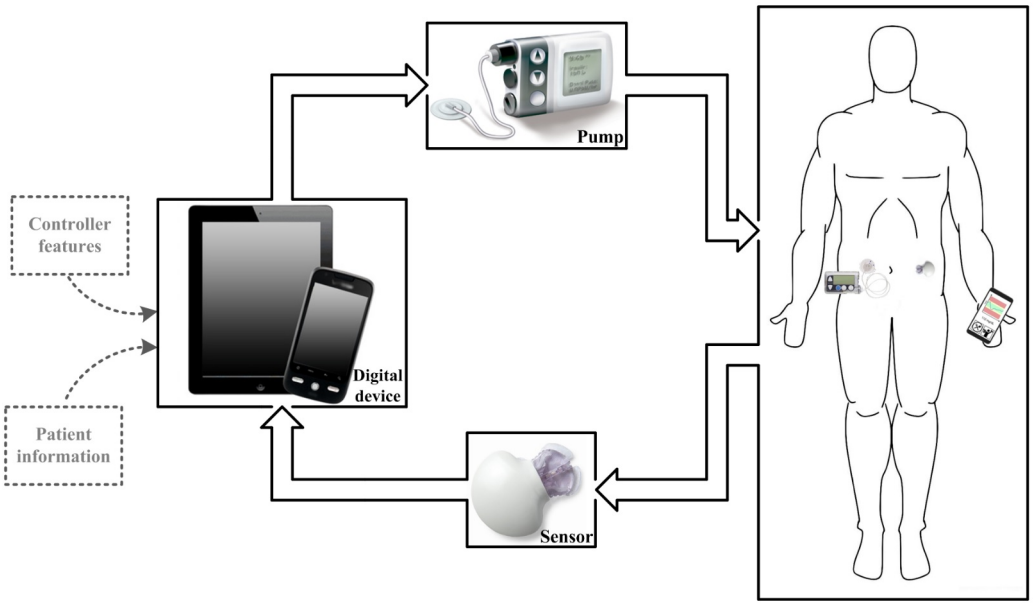

Figure 2.6: Main components of an insulin-only AP system: control algorithm embedded into a digital device, insulin pump and glucose sensor.

consistently over the past decade, and such studies were essential to push researches to obtain remarkable achievements (Bertachi et al., 2018b). The rate of development of the AP is increasing rapidly and there is a fast turnover of newly published research. A meta-analysis of outpatient randomized controlled trials showed that AP systems improved glucose control in outpatient settings when compared with CSII or SAP therapy, increasing in approximately 12% the time spent in target range and reducing in 2.45% the time spent below 70 mg/dl (Weisman et al., 2017).Very recently, FDA approved the Medtronic MiniMed 670G, the world's first CL system to hit the market.

AP systems can be classified into two different categories according with its level of automation: hybrid or fully automated. Hybrid systems require that users inform manually the CHO estimation from every meal, and therefore the AP can deliver an insulin bolus. Differently, fully automated systems do not need any further action from users, eliminating the need of CHO counting and provide the appropriate insulin automatically, reducing partially the burden of T1DM management.

In addition, AP system can be divided as uni-hormonal or bi-hormonal. An uni-hormonal (or insulin-only) AP just considers insulin as control action. On the other hand, bi-hormonal (or dual-hormone) AP considers glucagon as additional hormone, to rise blood glucose levels. Bi-hormonal systems have been tested extensively over the last five years, however it is often reported that due to the instability of glucagon, cartridges must be frequently replaced. Currently,

there is no stable glucagon solution commercially available so far, although research has been conducted to overcome this (Pohl et al., 2015), nor are there dual-chamber pumps, studies presently use two pumps which can be bulky and lead to patient dissatisfaction (Barnard et al., 2015). It is expected that when dual-hormone systems reach the market, dual-chamber pumps will be already developed.

Most of the AP systems are based on two control algorithms: Model Predictive Controller (MPC) or Proportional–Integral–Derivative (PID), although other algorithms were also tested (Lunze et al., 2013). The commercial approved Medtronic Minimed 670G system employs a PID algorithm to suggest insulin dosage, but also has several safety layers incorporated.

2.6.1 Challenges for the AP

2.6.1.1 Meals

Meals can be considered the major cause of glucose variability in T1DM (Kudva et al., 2014). The two main drawbacks to CL control during the postprandial period are attributed to the delayed CGM readings due to the interstitial-plasma time lag and the delay in insulin action. A significant challenge to the AP, inherent to the CGM is the time required for glucose to diffuse from the blood into the interstitial space, where the CGM probe is inserted. Current CGM technology inherently under- or overestimate BG levels because the BG concentration found in the interstitial fluid is not a perfect reflection of the BG concentration in the plasma (Del Favero et al., 2014).

The delay experienced due to both for pharmacokinetic and pharmacodynamic behavior of insulin also attributes to the difficulty experienced during the postprandial period. Currently "fast-acting" is not fast enough to achieve optimal postprandial control (Gingras et al., 2018). In other words, the effects of the meal appears first in the bloodstream than the effects of the insulin bolus, due to the delayed effects of subcutaneously administered insulin. Ultra-fast or ultra-rapid insulin produces a faster onset of insulin action, which better mimics the first-phase insulin response in healthy subjects (Danne and Bolinder, 2014). However, such insulin analogue is not available so far.

The use of pramlintide and exenatide have also been investigated to improve postprandial glycemia together with CL therapy. The use of these adjunctive therapies suggest a reduction in postprandial peaks and thereafter in insulin overdosing. In Weinzimer et al. (2012) patients received pramlintide subcutaneously at meal time and no insulin boluses were delivered to cover meals. Authors noticed that pramlintide delayed the time from meal peak approximately by 1 hour and also decreased glucose excursions by an average of 25 mg/dl, when compared

with insulin alone. Similar results were obtained by Sherr et al. (2016), where they observed an average reduction of 37 mg/dl in glucose excursions after meals, and also a significant delay in glucose meal peak due to pramlintide. Although the results have shown better results than insulin only therapy, in both studies the hormones were injected manually and further research is required before these hormones can be used in CL systems.

2.6.1.2 Exercise

It is well established that regular exercise is beneficial in healthy subjects. Meanwhile, for individuals with T1DM, exercise creates a paradox by increasing overall health, like blood pressure reduction, improvement of cardiovascular fitness and lipoprotein profile, (Brazeau et al., 2012) but poses greater challenges for glycemic control. One of the strongest barriers for subjects with T1DM to engage physical activities is the fear of exercise-induced hypoglycemia (Brazeau et al., 2008).

During exercise, the availability of glucose transporter-4 (GLUT-4) is increased. Therefore, the rate of glucose uptake increases, especially due to the regulatory response in blood flow to the skeletal muscles, and insulin sensitivity is also altered (Thorell et al., 1999; Goodyear and Kahn, 1998). Exercise is generally classified as aerobic or anaerobic. Aerobic exercise involves repeated and continuous movement of large muscle groups (walking, cycling, swimming). Anaerobic exercise involves quick bursts of energy and are performed at maximum effort for a short time (weight lifting and high-intensity interval training). Aerobic exercise causes a drop in blood glucose concentration in most subjects with T1DM, and trained individuals may have greater falls than untrained individuals (Khalifah et al., 2016). On the other hand, a slight increase in blood glucose levels is observed during aerobic exercise(Yardley et al., 2013). However, the effects of exercise is not fully understood nor quantified, which is evidenced by the scarce availability of mathematical models that describe the impact of physical activities on the glucose regulation system.

Recently, Riddell and colleagues provided a consensus report to guide patients to take the best actions to make feasible and safe the practice of physical activities by subjects with T1DM. This publication recommend different actions to be taken within conventional insulin therapy to properly manage blood glucose before, during and after exercise, with different recommendations for aerobic and anaerobic sessions (Riddell et al., 2017). However, it is still not clear how CL systems should be configured to deal with exercise, and thus, this challenge is one greatest hurdles on AP development (Riddell et al., 2015; van Bon et al., 2011; Breton, 2008).

Indeed, different approaches to prevent exercise-induced hypoglycemia have been tested

recently in CL therapy. In Ly et al. (2017), the target glucose was set at 120 mg/dl, but when exercise was announced, the target glucose increased to 160 mg/dl. This study was able to decrease the percentage of time spent in hypoglycemia from 7.6% in the SAP arm to 2.0% in the CL arm. In Blauw et al. (2016a), heart rate signal was used to indicate physical activity, which reduced insulin administration during that period. This study showed a non-significant decrease in the percentage of time spent below 70 mg/dl from 2.4% in the conventional therapy to 1.3% in CL therapy. In Jacobs et al. (2016), a dual-hormone controller reduced insulin and increased glucagon delivery for 90 minutes after the start of exercise. This study also obtained non-significant results with a decrease in the percentage of time spent below 70 mg/dl from 0.8% in the SAP to 0.3% in the CL period. The FDA-approved Medtronic 670G requires that patients set a temporary glucose target from 120 mg/dl to 150 mg/dl when practicing exercise. However, this recommendation has been found insufficient in preventing hypoglycemia due to aerobic exercise (Weaver and Hirsch, 2018).

Physical activity detection in real time has been investigated (Turksoy et al., 2015) and can be a useful tool that will minimize the error attributed to patient inputs. Various studies have incorporated physical signals (e.g. Heart Rate, Energy Expenditure, Galvanic Skin Response) into the controller during exercise (Turksoy et al., 2013; Breton et al., 2014; Turksoy et al., 2014; Blauw et al., 2016a), and although this approach may increase controller performance and reduces patients' burden, it also increases the overall complexity and cost of the system.

2.6.1.3 Hardware Reliability

As with all electromechanical systems, the AP is susceptible to malfunctions. The AP is intended to be a fully integrated system, i.e. with automated data transfer from the CGM to the controller and from the controller to the insulin pump. Therefore, it is essential that those designing the system be aware of the kinds of failures that can occur, to ensure the safety of the users at all times.

Bequette (2014) presents an evaluation of failures that can occur in an AP and indicates that CGM anomalies (fouling of sensors, loss of signal, signal degradation) and the insulin infusion set failures are the two most frequent hardware-based failures. Heinemann and Krinelke (2012) have said that the insulin infusion set is the main culprit of CSII malfunctions and often cause users to abandon pump therapy. Blauw et al. (2016b) features an extended review of design requirements to improve safety in the AP, not only considering hardware failures, but also other situations such as cyber-security and issues related with the control algorithm.

Although the use of CGM is associated with a reduction in HbA_{1c}, the reliability of CGM is still a problem for CL strategies. Data flow between the transmitter and the receiver of a

CGM is wireless and data can be intermittently missed. Schmidt et al. (2013) reported that 5.5% of CGM data during their clinical trial were missed (196 of 3564 values). Therefore, because of this known lack of data the control algorithm must be designed to utilize past CGM measures or predict future CGM values for insulin administration decisions. Furthermore, a high incidence of problems related to pump connectivity were reported as being responsible for more than 50% of CL interruption in some cases (Thabit et al., 2014).

2.6.1.4 User Error

Current CGM and CSII pumps require frequent intervention by the patient or a caregiver. Some CGM sensors must be calibrated often and the sensors must be replaced every 7-14 days; and the insulin cartridge and infusion set must be replaced frequently. These replacements, if not done correctly can lead to infection and further complications. Sensor miscalibrations can lead to erroneous CGM readings, causing incorrect insulin dosing.In many of the outpatient studies conducted, the research team provided beforehand technical training on device operation to the participants. This training is beneficial and reduces the risk associated with patient error, but does not eliminate it. Further studies investigating the impact of hazardous situations on the AP are needed to test the safety limits of the device.

Different levels of automation can be observed in the systems tested. Hybrid CL systems that utilize feed-forward actions require the patient to report known external events, such as meal and exercise information, which improve the system's performance. This kind of AP system is susceptible to human error, which can ultimately compromise its performance. Alternatively, fully CL systems that utilize feedback action require no intervention from the patient and are able to perform necessary modifications to overcome external disturbances. However, due to the slow response of insulin after delivery and the interstitial-plasma time lag experienced by CGM, feedback systems perform poorly in the postprandial period.

2.7 Alternative approaches

Alternative approaches exist for patients who have extreme difficulties to manage their disease based on insulin therapy. The whole pancreas transplantation is considered as the most effective treatment for T1DM. This transplant is considered a large surgical procedure, and consists of the removal of the pancreas from a donor that will be implanted in an adult with T1DM, but it may bring life-threatening complications for the recipient (Júnior et al., 2015). An alternative approach to pancreas transplantation is the so-called islet allotransplantation. This procedure has been studied by the Clinical Islet Transplantation Consortium, and is based on

the transplantation health islet cells with β-cells from the pancreas of a deceased organ donor. Although the islet transplantation is less invasive than the pancreas transplantation procedure, FDA is still evaluating the feasibility, safety and effectiveness of such approach (Bottino et al., 2018).

2.8 Summary

In this Chapter, a brief introduction of the glucose regulatory system in healthy subjects has been presented. Individuals with T1DM suffers from extreme absence of insulin production from the pancreatic β-cells and need to administer insulin exogenously to survive. In case of poor glycemic control, subjects can exhibit several long-term complications. Current intensive insulin therapy has also been described, which relies on basal-bolus approach, and requires constant engagement from patients to achieve recommended values of HbA_{1c}. The main existing technological devices consider T1DM treatment were also presented: insulin pens, insulin pump, glucose meter and CGM. Finally, the AP, the ultimate goal of automatic blood glucose regulation has been introduced, and the main challenges that such system must cope were depicted.

CHAPTER 3

CLOSED-LOOP CONTROL SCHEMES

3.1 Introduction

This Chapter presents the control algorithm developed by the Spanish Consortium on Artificial Pancreas and Diabetes Technology over the last decade. The principal controller is composed by a proportional-derivative (PD) algorithm and also by the so-called safety auxiliary feedback element (SAFE) layer, which is intended to avoid insulin overdosing, by a feedback loop based on insulin on board (IOB). An additional control loop based on a predictive PD algorithm, which has been incorporated to the principal controller to provide CHO recommendations to avoid hypoglycemia, is also detailed. Finally, the computational model used to validate the CL strategies in silico is also depicted, based on a simulator developed by the University of Virginia and University of Padova, the UVa/Padova T1DM simulator.

3.2 Principal Controller

Initially, the control algorithm was designed especially for postprandial period, to avoid the over-correction of insulin caused by the natural rise in blood glucose after a meal. Excessive insulin aiming to reduce glycemic excursions after a meal could lead to hypoglycemia in the late postprandial period, and therefore, a new control-loop scheme was developed. This controller has been evaluated both in silico and in real patients in a clinical facility (Rossetti et al., 2017). In a second clinical trial, the controller has been tested against announced aerobic and anaerobic exercise (Quirós et al., 2018). Later, a CHO recommender system has been

developed and incorporated into the control scheme, aiming to work coordinately with the insulin controller to reduce the risk of hypoglycemia (Beneyto et al., 2018). In the sequence, both structures are presented, the insulin-only system and the insulin-CHO system.

3.2.1 Insulin controller

The insulin control algorithm consists of two loops. The inner loop is composed by a proportional derivative (PD) controller with an insulin feedback (IFB) compensation. The outer loop contains the SAFE layer (Revert et al., 2013). This layer is based on the sliding mode reference conditioning technique (Garelli et al., 2011) and acts on the glucose reference signal when a specific constraint, related with the maximum IOB allowed ($\overline{IOB}$), is violated. Figure 3.1 shows the block diagram of the insulin control loop.

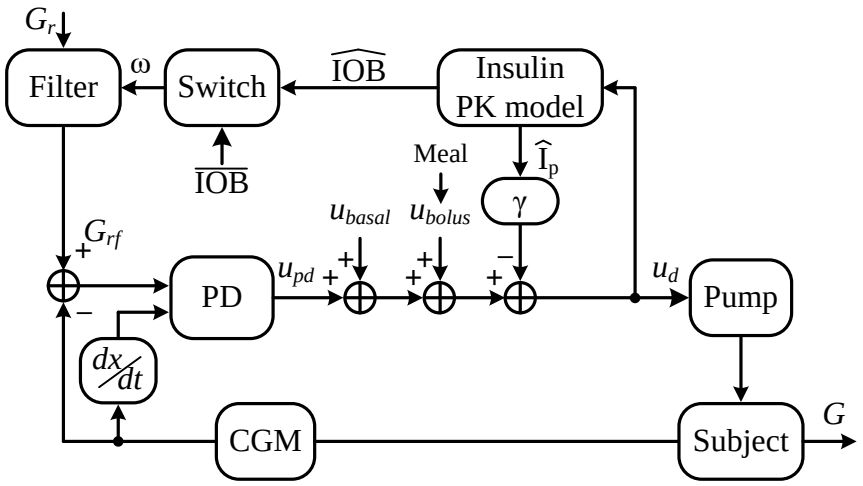

Figure 3.1: Control scheme based on a PD controller with IFB and with the SAFE layer.

The control action produced by the PD controller is presented in Equation (3.1).

$$u_{pd}(t) = K_p\left(\left(G_{rf}(t) - G(t)\right) + T_d\dot{G}(t)\right) \tag{3.1}$$

where K_p is the proportional gain, T_d is the derivative time, G_{rf} is the glucose reference filtered after the action of the SAFE layer, and G is blood glucose concentration provided by the CGM.

Then, the control action computed by the PD is augmented by two feed-forward signals: u_{bolus} and u_{basal}. The signal u_{basal} is the insulin obtained from patients' daily basal profile. The term u_{bolus} is an impulse signal in case of the announcement of meals to compensate CHO intake.

The IFB algorithm (Steil et al., 2011) emulates the beta-cells physiology in healthy subjects, suppressing insulin secretion as plasma insulin concentration increases. The combination of

the PD algorithm with both SAFE layer and IFB algorithm has already been investigated and shown to be more effective than when they are used separately (Sala-Mira et al., 2017). The final control action signal provided to the insulin pump is shown in Equation (3.2).

$$u_d(t) = u_{pd}(t) + u_{basal}(t) + u_{bolus} - \gamma \hat{I}_p(t) \tag{3.2}$$

where γ is gain parameter and $\hat{I}_p$ is the is the estimated deviation of plasma insulin from steady state conditions (basal levels).

The term G_{rf} in Equation (3.1) is the conditioned reference due to the action of the SAFE layer to maintain IOB below $\overline{IOB}$. Since IOB is inaccessible, an insulin absorption model is considered to estimate IOB (Wilinska et al., 2005), through Equation (3.3).

$$\begin{aligned} \dot{C}_1(t) &= u_d(t) - K_{DIA} C_1(t); \quad & C_1(0) &= 0 \\ \dot{C}_2(t) &= K_{DIA}\,(C_1(t) - C_2(t)); \quad & C_2(0) &= 0 \\ \widehat{IOB}(t) &= C_1(t) + C_2(t) \end{aligned} \tag{3.3}$$

where $C_1(t)$ and $C_2(t)$ are two compartments, K_{DIA} is a constant related with the duration of insulin action (DIA) and $\widehat{IOB}$ is the estimation of IOB. Figure 3.2 shows the IOB curves obtained from the model presented in Equation (3.3) for DIA values of 2 h, 4 h, 6 h and 8h.

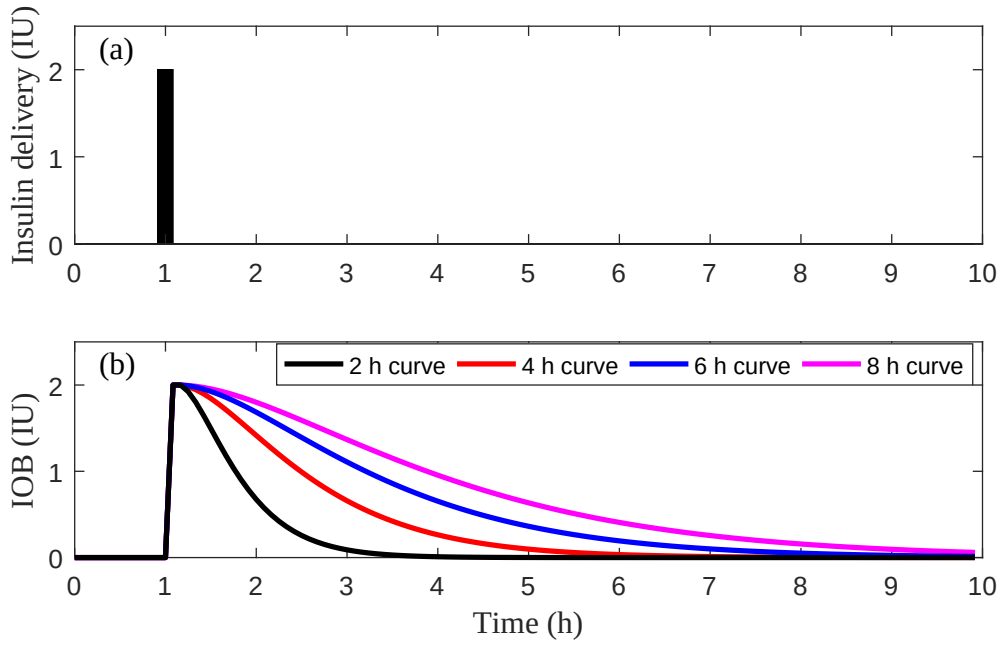

Figure 3.2: Estimated IOB due to a single insulin dosis. (a) Insulin delivery; (b) Estimated IOB levels for different values of K_{DIA}. Adapted from León-Vargas et al. (2013b)

The SAFE layer has a software-based nature and consist on two main elements: a switching block responsible to generate a discontinuous signal to maintain $\widehat{IOB}$ into the desired range and a first-order filter to smooth the discontinuous signal before being applied to the PD controller.

Consider the sliding function $\sigma(t)$ definded by Equation (3.4), the switching logic is define in Equation (3.5).

$$\sigma(t) = \widehat{IOB}(t) - \overline{IOB}(t) + \tau\left(\dot{\widehat{IOB}}(t) - \dot{\overline{IOB}}(t)\right) \tag{3.4}$$

$$\omega(t) = \begin{cases} W & \text{if } \sigma(t) > 0 \\ 0 & \text{otherwise} \end{cases} \tag{3.5}$$

with $W > 0$ mg/dl.

Finally, the discontinuous signal is filtered by Equation (3.6) and generates smooth changes in the glucose reference signal applied in the PD controller.

$$\dot{G}_{rf}(t) = -\lambda\left(G_{rf}(t) - G_r(t) + \omega(t)\right) \tag{3.6}$$

Note that when $\sigma(t) > 0$, $\widehat{IOB}$ is greater than $\overline{IOB}$. In order to drive $\widehat{IOB}$ to the desired range, i.e., below $\overline{IOB}$, u_{final} must be decreased. The addition of W in Equation (3.6) generates G_{rf} greater than G_r, diminishing the insulin suggestion provided by the main controller, and thus, reducing $\widehat{IOB}$. When $\widehat{IOB}$ is below $\overline{IOB}$, no further action is provided by the outer loop, letting the controller work freely. Therefore, the selection of the constraint $\overline{IOB}$ is critical in the design of the CL system. This parameter regulates insulin infusion based on an estimation of the IOB. As higher $\overline{IOB}$, more insulin the controller will be allowed to suggest.

The values of the parameters applied in the insulin loop are presented in Table 3.1.

Table 3.1: Tuning of the parameters for the insulin loop

Symbol	Description	Value	Units
T_d	Derivative time	90	min
I_{TDD}	Total daily insulin	patient specific	IU/day
K_p	Proportional gain	$\frac{60 \cdot I_{TDD}}{\tau_d \cdot 1500}$	IU/min
G_r	Glucose target	100	mg/dl
W	Switching gain	350	mg/dl
K_{DIA}	Constant related with the DIA	0.013	min^{-1}
γ	IFB gain	25.2	L/h
τ	Constant gain	10	min
λ	Filter cut-off frequency	0.1	min

3.2.2 Selection of $\overline{IOB}$

The selection of the constraint $\overline{IOB}$ is a critical point in the design of the control system. Previously, $\overline{IOB}$ has been adjusted to improve glycemic control during postprandial period and has been tested in an inpatient trial with real patients. This was a randomized study performed in two clinical centers with 20 subjects with T1DM. Each subject underwent a 8-h standardized mixed meal test on four occasions: two occasions with CL control and two occasions with conventional CSII therapy[1].

In this first clinical trial to evaluate the performance of the PD controller with the SAFE layer, an individualized constraint $\overline{IOB}$ was designed to control postprandial blood glucose levels after the consumption of a meal with 60 grams of CHO along with an augmented bolus (Super Bolus), which included the amount of basal insulin that would be delivered in the next 60 minutes in the case of conventional CSII therapy (Rossetti et al., 2017):

$$\text{Super Bolus} = \frac{M}{CR} + \int_{t}^{t+60} u_{basal(t)} \tag{3.7}$$

After the meal intake, manual adjustments of basal insulin were performed based on the CL recommendations. In this trial, $\overline{IOB}$ has been selected based on the estimation of IOB 90 minutes after the Super Bolus delivery (considering basal conditions prior the meal). Therefore, each patient had an specific $\overline{IOB}$ adjustment, but the same for every meal.

In the aforementioned clinical trial, the CL system achieved better postprandial outcomes, reducing significantly the time spent in hyperglycemia without increase the risk of hypoglycemia, when compared with the conventional CSII therapy. However, a limitation of this study is that $\overline{IOB}$ was tuned for this specific meal, restricting its applications for 24-h operation, and novel techniques to adjust $\overline{IOB}$, including during physical activity and also regardless the size of meals.

3.2.3 CHO recommender loop

The CHO recommender system uses feedback signals to compute current control actions, inhibition signals to coordinate both loops, and past and predicted control actions to determine whether to recommend fixed amounts of 15 grams of fast-acting CHO. The complete control scheme with both insulin and CHO loops is illustrated in Figure 3.3.

Note the second feedback loop for the CHO controller that has been added to the previous insulin-only controller is highlighted in purple. This feedback loop added: 1) a new PD

[1]More information regarding this clinical protocol can be obtained at clinicaltrials.gov (NCT02100488).

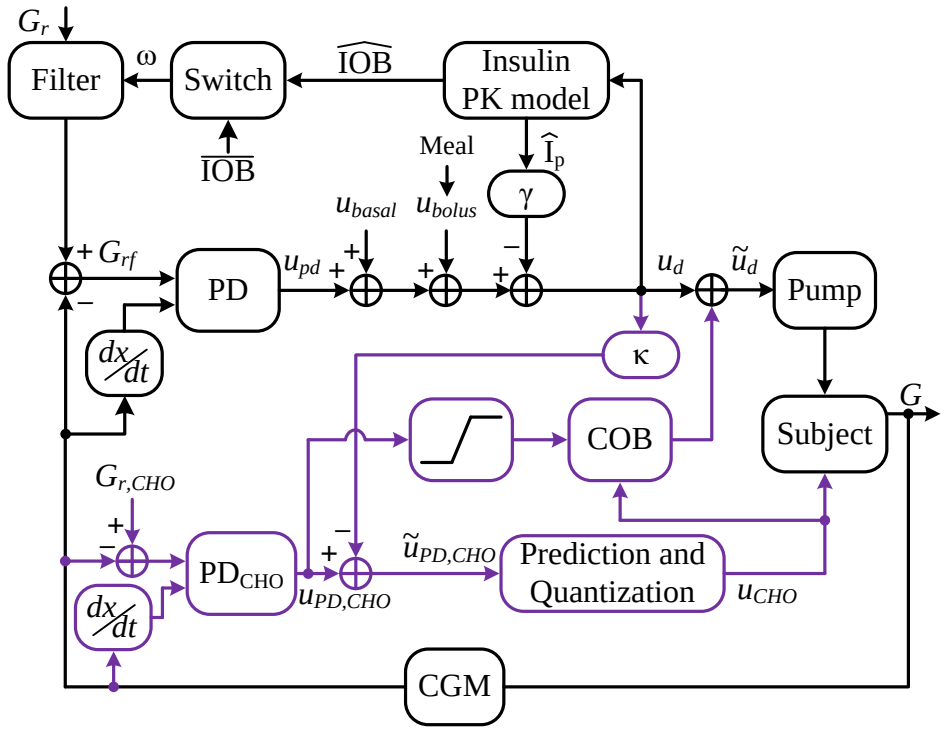

Figure 3.3: Control scheme based on a PD controller with IFB, the SAFE layer and also with the CHO recommender loop in purple. Adapted from Beneyto et al. (2018).

controller; 2) an online recursive estimation in CL for BG prediction; 3) a quantification of the CHO controller action; and 4) inhibition signals between both loops in both directions.

The PD_{CHO} controller has a different reference signal than the PD controller employed in the insulin loop. It computes control actions that would require insulin extraction from the body, i.e., negative control actions. Later, these actions are transformed to the equivalent effect caused by the consumption of CHO, increasing blood glucose levels. An autoregressive model of fourth order is considered to provide predictions up to 20 minutes ahead of time. The system uses predicted CHO actions together with past and current CHO control actions. Additionally, the coordination between both control loops (insulin and CHO) are performed through the inhibition signals κ and COB (Carbohydrate on board). The gain κ inhibits the CHO control action when insulin is recommended by the insulin controller.

The COB is a concept similar to IOB, and represents the amount of CHO that has been consumed but that still has not appeared in plasma. Based on the COB, the insulin controller do not counteract the increase on blood glucose caused by the CHO recommended by the system. The COB is computed based on Equation (3.8), representing the percentage of remaining CHO

(Hovorka et al., 2004):

$$COB(t) = 1 - \frac{\int_{t^*}^{t} \frac{D(t^*) \cdot f \cdot t \cdot e^{-\frac{t}{\tau_{\max}}}}{\tau_{\max}^2} dt}{f \cdot D(t^*)} \tag{3.8}$$

where t^* corresponds to the time instant when CHO is consumed, D is the amount of CHO consumed, f is the CHO bioavailability and $\tau_{\max}$ is the time-to-maximum of CHO absorption. As the CHO controller suggests CHO with fast-absorption rate, $\tau_{\max}$ is set to 20 min. Figure 3.4 illustrates the COB for a meal intake with 20 g of CHO.

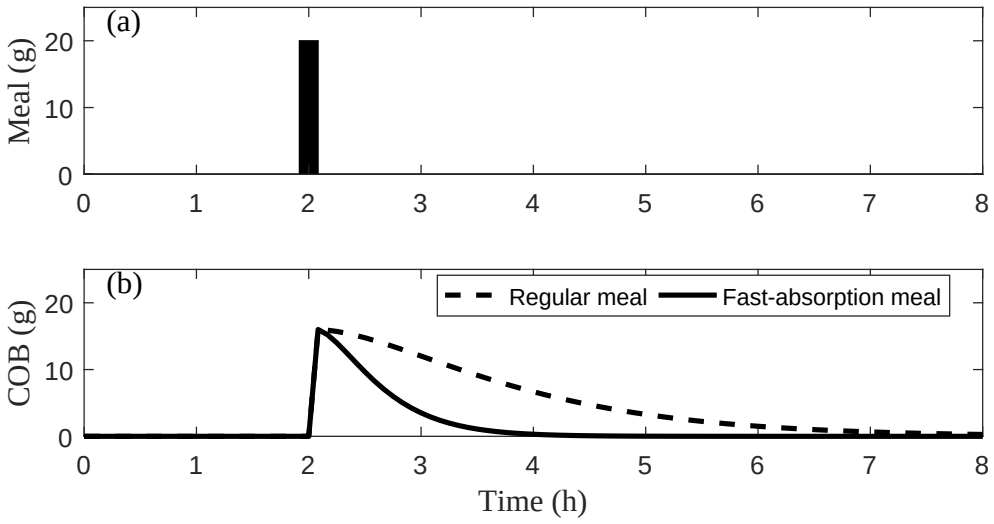

Figure 3.4: Estimated COB after a meal consumption. (a) Meal with 20 g of CHo consumed; (b) COB profiles for a regular meal and for a fast-absorption meal, used to treat hypoglycemia, such as gels and tablets.

Further information regarding the CHO control loop and the parameters' tuning can be obtained in Beneyto et al. (2018).

3.3 T1DM Simulator

The development of more accurate mathematical models on blood glucose regulation (Dalla Man et al., 2007; Hovorka et al., 2004; Bergman et al., 1979) have been essential to accelerate the development of AP designs. Among T1DM simulators, stands out the work done by the University of Virginia and University of Padova, to develop the notorious UVa/Padova Simulator. In 2008, the FDA accepted this computational model as a substitute for preclinical trials to test CL algorithms for T1DM management (Kovatchev et al., 2009). In this work, the version S2013 of

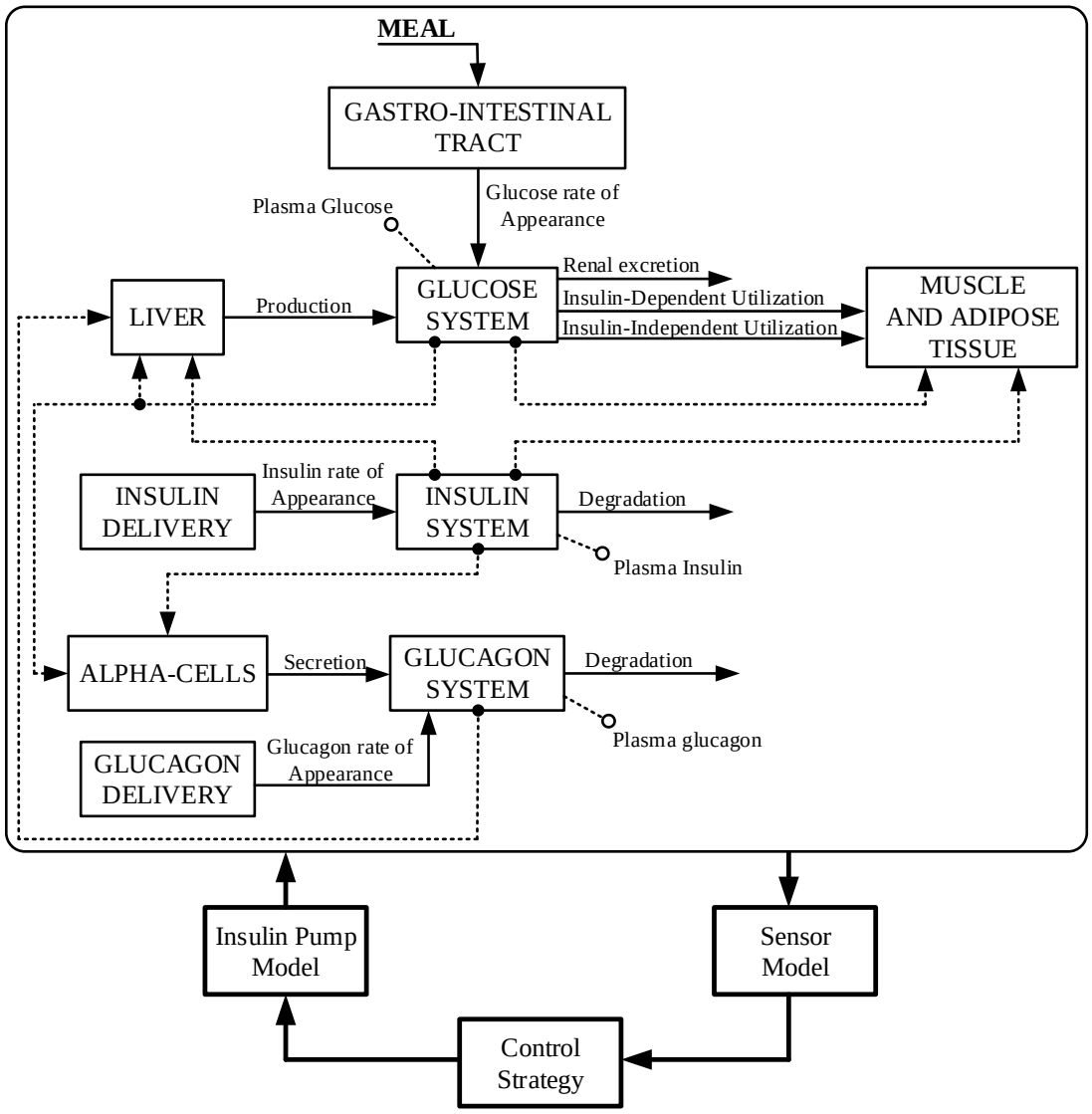

Figure 3.5: Scheme of the glucose regulatory system considered in the UVa/Padova S2013 T1DM simulator. Solid lines represent glucose, insulin and glucagon fluxes. Dashed line represent control signals. Adapted from Dalla Man et al. (2014).

the UVa/Padova simulator (Dalla Man et al., 2014) has been slightly modified to incorporate intra-patient variability and also physical activity disturbance in the simulations.

3.3.1 UVa/Padova Simulator

The scheme of the UVa/Padova S2013 simulator is illustrated in Figure 3.5.

3.3.1.1 Glucose rate of Appearance

When a meal is consumed, it causes an increase in plasma glucose. The glucose transit through the stomach and intestine is described as:

$$\begin{aligned}
&Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t); && Q_{sto}(0) = 0 \\
&\dot{Q}_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t) + D \cdot \delta(t); && Q_{sto1}(0) = 0 \\
&\dot{Q}_{sto2}(t) = -k_{empt}(t, Q_{sto}) \cdot Q_{sto2}(t) + k_{gri} \cdot Q_{sto1}(t); && Q_{sto2}(0) = 0 \\
&\dot{Q}_{gut}(t) = -k_{abs} \cdot Q_{gut}(t) + k_{empt}(t, Q_{sto}) \cdot Q_{sto2}(t); && Q_{gut}(0) = 0 \\
&Ra(t) = \tfrac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW}; && R_a(0) = 0
\end{aligned} \tag{3.9}$$

where Q_{sto}(mg) is the amount of glucose in the stomach, with Q_{sto1} (mg) representing the solid phase and Q_{sto2} (mg) representing the liquid phase. Q_{gut} (mg) is the amount of glucose in the intestine. k_{gri} (mg^{-1}) is the rate of grinding , k_{abs} (mg^{-1}) is the rate constant of instestinal absorption, BW (kg) is the subject's body weight, R_a (mg/kg/min) is the rate of appearance of glucose in plasma, f is is the fraction of intestinal absorption which actually appears in plasma (bio-availability), D (mg) is the amount of ingested glucose and k_{empt} (mg^{-1}) is the rate of constant of gastric emptying, which is a nonlinear function of Q_{sto}, computed as:

$$k_{empt}(t, Q_{sto}) = k_{\min} + \frac{k_{\max} - k_{\min}}{2} \left\{ \tanh\left(\alpha \left(Q_{sto}(t) - b \cdot D\right)\right) - \tanh\left(\beta \left(Q_{sto}(t) - c \cdot D\right)\right) + 2 \right\} \tag{3.10}$$

with $k_{\min}$ $k_{\max}$ are the maximum and minimum rate of gastric emptying, α and β regulates the rate of gastric emptying and are computed as:

$$\alpha = \frac{5}{2 \cdot D \left(1 - b\right)} \tag{3.11}$$

$$\beta = \frac{5}{2 \cdot D \cdot c} \tag{3.12}$$

where b is the percentage of the dose D for which the rate of gastric emptying decreases and c is the is the percentage of the dose D for which the rate of gastric emptying increases.

3.3.1.2 Glucose subsystem

The glucose subsystem consists of a two compartment model that describes glucose kinetics. Insulin-independent utilization occurs in the first compartment, while insulin-dependent utilization occurs in the second compartment. The Equations that describe this subsystem are presented below, with the suffix b denoting basal state:

$$\begin{aligned}
&\dot{G}_p(t) = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 \cdot G_p(t) + k_2 \cdot G_t(t); && G_p(0) = G_{pb} \\
&\dot{G}_t(t) = -U_{id}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t); && G_t(0) = G_{bp} \cdot \tfrac{k_1}{k_2} \\
&G(t) = \tfrac{G_p}{V_g}; && G(0) = G_b
\end{aligned} \tag{3.13}$$

where G_p and G_t (mg/kg) are the amount of glucose in plasma and in rapidly-equilibrating tissues, G (mg/dL) is plasma glucose concentration, EGP (mg/kg/min) is the endogenous glucose production, k_1 and k_2 (min^{-1}) are rate parameters, U_{ii} (mg/kg/min) is the insulin-independent utilization and is constant, U_{id} (mg/kg/min) is the insulin-dependent glucose utilization. E (mg/kg/min) is the renal excretion and is computed as:

$$E(t) = \begin{cases} k_{e1}\left(G_p(t) - k_{e2}\right) & \text{if} \quad Gp(t) > k_{e2} \\ 0 & \text{if} \quad Gp(t) \leq k_{e2} \end{cases} \tag{3.14}$$

with k_{e1} and k_{e2} (min^{-1}) are the glumerular filtration rate and the renal threshold of glucose, respectively.

3.3.1.3 Glucose utilization subsystem

The glucose utilization by the body is modeled by two components: insulin-independent (U_{ii}) and insulin-dependent (U_{id}). Insulin-independent utilization encompasses glucose uptake by the brain and erythrocytes. The insulin-dependent utilization depends non-linearly from glucose in the tissues:

$$U(t) = U_{ii}(t) + U_{id}(t) \tag{3.15}$$

$$U_{ii}(t) = F_{cns} \tag{3.16}$$

$$U_{id}(t) = \frac{\left[V_{m0} + V_{mx} \cdot X(t)\,(1 + r_1 \cdot risk)\right] G_t(t)}{K_{m0} + G_t(t)} \tag{3.17}$$

with

$$\dot{X}(t) = -p_{2u} \cdot X(t) + p_{2u}\,(I(t) - I_b) \quad X(0) = 0 \tag{3.18}$$

where U is glucose utilization, F_{cns} is a constant, V_{mx} (mg/kg/min per pmol/l) is the disposal of insulin sensitivity, V_{m0} (mg/kg/min) and K_{m0} (mg/kg) are the Michaelis-Menten parameter of glucose utilization at zero insulin action, r_1 is a constant parameter. X (pmol/l) represents the remote insulin, p_{2u} (min^{-1}) is the rate constant of insulin action on peripheral glucose utilization, I (pmol/l) is plasma insulin concentration. U_{id} increases when glucose decreases below a certain threshold:

$$risk = \begin{cases} 0 & \text{if} \quad G \geq G_b \\ 10\left[f(G)\right]^2 & \text{if} \quad G_{th} \leq G < G_b \\ 10\left[f(G_{th})\right]^2 & \text{if} \quad G < G_{th} \end{cases} \tag{3.19}$$

$$f(G) = \log\left(\frac{G}{G_b}\right)^{r2} \tag{3.20}$$

where G_{th} (mg/dl) is the hypoglycemic threshold and r_2 is a model parameter.

3.3.1.4 Subcutaneous glucose kinetics

The subcutaneous glucose kinetics is described by a first-order linear system:

$$\dot{G}_s(t) = -\frac{1}{k_{sc}} \cdot G_s(t) + \frac{1}{k_{sc}} \cdot G(t); \quad G_s(0) = G_b \tag{3.21}$$

where G_s (mg/dl) is the subcutaneous glucose and k_{sc} is a transfer rate constant.

3.3.1.5 Insulin subsystem

The insulin subsystem is described by a two compartment model, in which the insulin flow from the subcutaneous compartments, enters the bloodstream and is degraded in the liver and in the periphery. The Equations for this subsystem are:

$$\begin{aligned} \dot{I}_l(t) &= -(m_1 + m_3)\, I_l(t) + m_2 I_p(t); & I_l(0) &= I_{lb} \\ \dot{I}_p(t) &= -(m_2 + m_4)\, I_p(t) + m_1 \cdot I_l(t) \cdot Ra_i(t); & I_p(0) &= I_{pb} \\ I(t) &= \frac{I_p(t)}{V_I} \end{aligned} \tag{3.22}$$

where I_l and I_p (pmol/kg) are insulin masses in liver and in plasma, respectively, I (pmol/l) is plasma insulin concentration, Ra_i (pmol/kg/min) is the rate of appearance of insulin from the subcutaneous tissue, V_I (l/kg) is the insulin distribution volume, and m_1, m_2, m_3 and m_4 are rate parameters.

3.3.1.6 Subcutaneous insulin kinetics

The subcutaneous insulin absorption is represented by a two compartment model:

$$\begin{aligned} \dot{I}_{sc1}(t) &= IIR(t) - (k_{a1} + k_d)\, I_{sc1}(t); & I_{sc1}(0) &= I_{sc1ss} \\ \dot{I}_{sc2}(t) &= k_d \cdot I_{sc1}(t) - k_{a2} \cdot I_{sc2}(t); & I_{sc2}(0) &= I_{sc2ss} \\ Ra_i(t) &= k_{a1} \cdot I_{sc1}(t) + k_{a2} \cdot I_{sc2}(t) \end{aligned} \tag{3.23}$$

where I_{sc1} and I_{sc2} (pmol/kg) are the first and second subcutaneous compartments, IIR (pmol/kg/min) is the insulin infusion rate, k_{a1} and k_{a2} (min^{-1}) are absorption constants, k_d (min^{-1}) is the degradation constant, and the suffix ss stands for steady state conditions.

3.3.1.7 Endogenous glucose production subsystem

The endogenous glucose production is described by:

$$\begin{aligned}
&\dot{X}^L(t) = -k_i\left(X^L(t) - I^{'}(t)\right); && X^L(0) = I_b\\
&\dot{I}^{'}(t) = -k_i\left(I^{'}(t) - I(t)\right); && I^{'}(t) = I_b\\
&\dot{X}^H(t) = -k_H \cdot X^H(t) + k_H \cdot \max\left[(H(t) - H_b), 0\right]; && X^H(0) = 0\\
&EGP(t) = k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot X^L(t) + \xi \cdot X^H(t)
\end{aligned} \tag{3.24}$$

where X^L is the delayed insulin action in the liver, H is plasma glucagon concentration, X^H is the delayed glucagon action on EGP, $1/k_h$ is the delay between glucagon concentration and action, ξ is the liver responsivity to glucagon. Finally, k_{p1}, k_{p2}, k_{p3}, k_i are rate parameters.

3.3.1.8 Glucagon subsystem

The glucagon kinetics is described as:

$$\dot{H}(t) = -n \cdot H(t) + SR_H(t) + Ra_H(t); \quad H(0) = H_b \tag{3.25}$$

where H is the glucagon concentration, n is the clearence rate, and SR_H and Ra_H are the glucagon secretion and the glucagon appearance in the subcutaneous tissue, respectively. Glucagon secretion is described as the sum of two components:

$$SR_H(t) = SR_H^s(t) + SR_H^d(t) \tag{3.26}$$

The dynamic component appears only when glucose levels are decreasing and is computed as:

$$SR_H^d(t) = \delta \cdot \max\left(-\frac{dG(t)}{dt}, 0\right) \tag{3.27}$$

where δ is the α-cell responsivity to the glucose rate of change. The static component is computed as:

$$\dot{SR}_H^s(t) = \begin{cases} -\rho\left[SR_H^s(t) - \max\left(\sigma_2 \cdot [G_{th} - G(t)] + SR_H^b, 0\right)\right] & \text{if} \quad G(t) \geq G_b \\ -\rho\left[SR_H^s(t) - \max\left(\frac{\sigma \cdot [G_{th} - G(t)]}{I(t)+1} + SR_H^b, 0\right)\right] & \text{if} \quad G(t) < G_b \end{cases} \tag{3.28}$$

where σ_2 is the α-cell responsivity to glucose levels, $1/\rho$ is the delay between static glucagon secretion and plasma response. Note that static secretion is stimulated when $G < G_b$ and inhibited otherwise.

3.3.1.9 Subcutaneous glucagon kinetics

The subcutaneous glucagon kinetics is described by a two compartment model:

$$\begin{aligned} \dot{H}_{sc1}(t) &= -(k_{h1} + k_{h2})\, H_{sc1}(t) + HIR(t); \quad & H_{sc1}(0) &= H_{sc1b} \\ \dot{H}_{sc2}(t) &= k_{h1} \cdot H_{sc1}(t) - k_{h3} \cdot H_{sc2}(t); & H_{sc2}(0) &= H_{sc2b} \\ Ra_H(t) &= k_{h3} \cdot H_{sc2}(t) \end{aligned} \tag{3.29}$$

where H_{sc1} and H_{sc2} are glucagon concentration in the subcutaneous space, HIR is the glucagon infusion rate, Ra_H is glucagon rate of appereance, k_{h1}, k_{h2} and k_{h3} are rate parameters describing subcutaneous glucagon kinetics.

3.3.2 Exercise Model

The exercise model used in this work has also been developed by University of Padova (Dalla Man et al., 2014) (Model C) and acts like a disturbance that increases the glucose-uptake by increasing the insulin sensitivity. This disturbance acts during and also after exercise, mimicking the effect of exercise, which exhibits lasting effects after the cessation of exercise. The model is presented by the following Equations:

$$\dot{Y}(t) = -\frac{1}{T_{HR}}\left[Y(t) - (HR(t) - HR_b)\right] \quad Y(0) = 0 \tag{3.30}$$

$$\dot{Z}(t) = -\left[\frac{f(Y(t))}{T_{in}} + \frac{1}{T_{ex}}\right] \cdot Z(t) + f(Y(t)) \quad Z(0) = 0 \tag{3.31}$$

$$f(Y) = \frac{\left(\frac{Y}{a \cdot HR_b}\right)^n}{1 + \left(\frac{Y}{a \cdot HR_b}\right)^n} \tag{3.32}$$

$$W(t) = \begin{cases} \int_0^t (HR(t) - HR_b); & t < t_z \\ 0; & t \geq t_z \end{cases} \tag{3.33}$$

where HR_b is the basal heart rate and HR is the heart rate which regulates different levels of exercise. Y is the delayed version of the over-basal signal, Z is a signal used to raise the insulin-dependent glucose clearance after an onset of exercise, W is the area under the curve of $(HR(t)–HR_b)$. More details related with the model can be obtained in Dalla Man et al. (2014).

Moreover, the model has been fitted to real data collected from an exploratory clinical trial carried out by our research group (Quirós et al., 2018). In this trial, each subject completed six exercise studies in the hospital setting, spaced at least 1 week apart. In three of the studies, the patient performed aerobic exercise sessions, with resistance exercise in the remaining three studies. Clinical data from aerobic exercise sessions performed by five subjects was used to fit

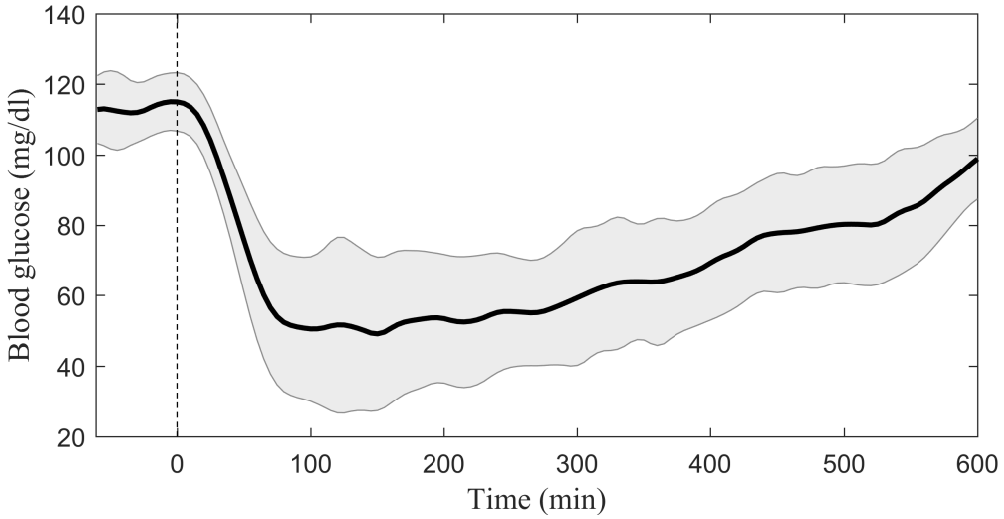

Figure 3.6: Glucose drop due to 50 min of physical activity considering the modified model. Results are presented as mean ± SD for 10 adults. The vertical dashed line indicates the start of exercise.

the model: four males, with a mean age of 37 ± 10.9 years, 21.2 ± 12.2 years since T1DM onset, body mass index of 24.9 ± 1.0 kg/m^2, and HbA_{1c} 7.8 ± 0.5%. Aerobic exercise comprised three series of 15 minutes of a stationary bicycle with 5 minutes of rest between them in a cicloergometer at 60% of VO_{2max}. Further information regarding the fitted model is presented in Bertachi et al. (2018a). Figure 3.6 shows the effects caused by the modified-model in the adult cohort from the UVa/Padova simulator, considering 50 minutes of unannounced exercise and only standard basal delivery without any meal disturbance before or after the exercise session.

3.3.3 Intra-patient variability

To allow evaluation of CL strategies in realistic and challenging virtual scenarios, it is necessary to incorporate in the simulator intra-patient variability. In this way, in silico scenarios may be able to mimic variability observed in real patients (Scheiner and Boyer, 2005; Haidar et al., 2013b).

Circadian variability has been included to simulate different requirements of insulin during the day, and follows a sinusoidal variation. The parameters V_{mx} and k_{p3}, which are related with the insulin sensitivity are modified accordingly:

$$q(t) = q_0 + 0.3 \cdot q_0 \cdot \sin\left(\frac{2\pi}{24 \cdot 60}\right) t + 2\pi \cdot rand \tag{3.34}$$

where $q(t)$ is the corresponding time varying parameter; q_0 is the default individual parameter value (V_{mx} or k_{p3}), and $rand$ is a uniformly distributed random number between 0 and 1.

Additionally, meal absorption rate, meal bio-availability, and insulin absorption parameters assume different values after every single meal consumption, according with the following Equations:

$$\begin{aligned} p(t) &= p_0 + P \cdot p_0 \cdot \big(2 \cdot f(M) - 1\big) \\ f(M) &= rand(k_{meal}) \qquad\qquad k_{meal} = 1, 2, 3 \ldots n_{meals} \end{aligned} \tag{3.35}$$

where $p(t)$ is the corresponding time varying parameter; p_0 is the default individual parameter value (k_{abs}, f, k_d, k_{a1} or k_{a2}), P is a gain set to 0.1 for f and 0.3 for the others parameters, k_{meal} is a meal counter based on the total amount of meals (n_{meals}) consumed in the simulation period. In other words, the aforementioned parameters are modified randomly around the standard value every time a meal is consumed to increase the variability observed in blood glucose between meals.

3.4 Summary

In this Chapter, the CL controller has been depicted. A major problem of such controller is the adjustment of the constraint $\overline{IOB}$, which limits the control action computed by the PD controller. In Chapter 4, a new method to adjust $\overline{IOB}$ is presented, aiming to improve the performance of the controller in front of meals and aerobic exercise. The T1DM simulator presented in this Chapter is considered to evaluate in silico the modifications proposed in the control scheme.

CHAPTER 4

NOVEL STRATEGIES TO IMPROVE CLOSED-LOOP PERFORMANCE

4.1 Introduction

In this chapter novel strategies to improve the performance of the CL system described in Chapter 3 are presented. Firstly, it is introduced a new approach to adjust the limits of IOB considering two distinct periods: fasting and postprandial periods. This new approach is evaluated in silico in different scenarios. Secondly, it is presented mitigation strategies to reduce the risk of exercise-induced hypoglycemia caused by aerobic exercise. These strategies are evaluated in silico considering an exercise model fitted with clinical data. In addition, preliminary results of an ongoing clinical trail are also presented.

4.2 Adjustments of $\overline{IOB}$ for 24 hours operation

In this work a new tuning approach for $\overline{IOB}$ is presented. In patients with T1DM, insulin requirements varies during the day and also between days (intra- and inter-day variability). This means that it is very unlikely to observe in similar situations, e.g. postprandial excursions caused by foods with the same amount of CHO and accompanied by a ordinary insulin bolus, the same postprandial response. This fact makes difficult to achieve good results the standard basal/bolus therapy. Moreover, postprandial glucose is strongly associated with HBA_{1c} and therefore plays an important contributions to achieve the glycemic targets (Ketema and Kibret,

2015).

The AP under development by our research group has been evaluated clinically in front of meals Rossetti et al. (2017), and an individualized $\overline{IOB}$ tune was considered in order the improve postprandial glycemic control. Considering that patients were in basal levels of IOB, $\overline{IOB}$ was computed as the estimation of IOB 90 minutes after the administration of an augmented bolus. This augmented bolus was computed by adding to the standard bolus the amount of basal insulin that would have been delivered in the next hour in the case of being in open-loop therapy.

Due to the huge amount of insulin in meal boluses, $\widehat{IOB}$ violates $\overline{IOB}$ and a high frequency discontinuous signal is generated by the SAFE layer in order to return $\widehat{IOB}$ back to $\overline{IOB}$ limit. This action forces insulin delivery to zero for approximately 90 minutes, minimizing the effects of controller overcorrection. When $\widehat{IOB} < \overline{IOB}$, insulin infusion may be restored if the controller deem necessary.

However, a single value of $\overline{IOB}$ may not be sufficient for 24 hours operation, especially due to the large intra-patient variability in T1DM and to the different activities performed by subjects in their daily-life. The major problem observed in the strategy presented previously is that too high values of $\overline{IOB}$ may cause that the SAFE layer be ineffective, because it will act in very few conditions, e.g., only after a meal bolus. It is comprehensible having higher $\overline{IOB}$ tuning during postprandial periods, especially because subjects tends to underestimate CHO content in meals Brazeau et al. (2013). However, during late postprandial period, where the effects of meals have been covered either by the bolus or by the controller suggestions, such high values of $\overline{IOB}$ may lead to excess of insulin in the body, increasing the risk of hypoglycemia.

In this work a new method to tune $\overline{IOB}$ to overcome the limitations presented by the former strategy is proposed. The new approach is called “dynamic rule-based” (DRB) algorithm and it is intended to be used on hybrid artificial pancreas systems for 24 h operation. The proposed approach combines two different strategies to set $\overline{IOB}$ for different situations: 1) fasting periods: where no big disturbance is expected and the controller must deal mainly with intra-day variability and 2) postprandial periods: where a substantial raise in blood glucose levels is expected due to the consumption of a meal, and more insulin might be required. Figure 4.1 shows the incorporation of the DRB algorithm into the insulin-only control scheme.

4.2.1 Fasting periods

In stationary period (sleeping hours or daytime fasting periods), the absence of external disturbances makes the intra-day variability the major challenge for the controller. The basal

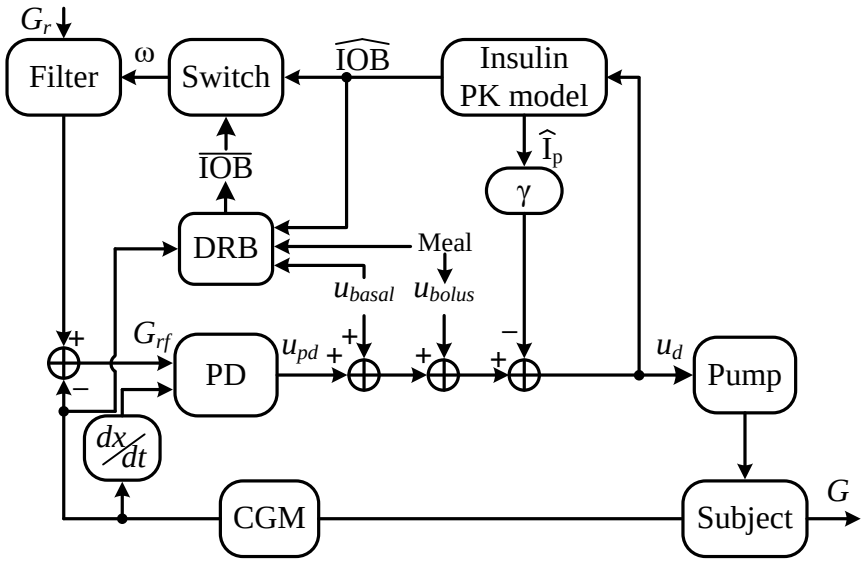

Figure 4.1: The incorporation of the DRB algorithm in the control scheme allows a dynamic time-varying $\overline{IOB}$.

insulin profile from patients' open-loop therapy is considered to create a baseline for $\overline{IOB}$, as shown in Equation (4.1).

$$\overline{IOB}_{bl}(t) = K_{IOB}\left(\frac{2 \cdot u_{basal}(t)}{60 \cdot K_{DIA}}\right) \tag{4.1}$$

where $\overline{IOB}_{bl}$ is the baseline for $\overline{IOB}$ and K_{IOB} is a gain that regulates the amplitude of $\overline{IOB}_{bl}$, with $K_{IOB} > 0$. In case of $K_{IOB} < 1$, $\widehat{IOB}$ will not be allowed to be greater than it would have been during open-loop therapy. On the other hand, with a $K_{IOB} > 1$, the insulin controller can suggest more insulin than what is programmed by the open-loop therapy. Thus, K_{IOB} should be selected in order to protect patients from hypoglycemia but also allowing the control algorithm to suggest insulin above open-loop regimen when necessary. Thus, during fasting periods, $\overline{IOB}$ is set to be equal to $\overline{IOB}_{bl}$. In this work the parameter K_{IOB} is set to 1.3 for daytime period (06:00−23:00) and to 1.1 for nighttime period (23:00−06:00). However, such parameter can be easily adjusted by physicians. It can be increased in case of hyperglycemia or decreased in case of hypoglycemia, during fasting periods.

Although this approach may be able to provide good glycemic control in front of intra-day variability, patients in free-living conditions take CHO on several occasions during the day, requiring a greater amount of insulin for these periods. Therefore, the strategy of $\overline{IOB}$ during fasting periods is combined with another one, intended for postprandial periods.

4.2.2 Postprandial periods

The tuning of $\overline{IOB}$ during postprandial period is an extension to the method already validated clinically by Rossetti and colleaguesRossetti et al. (2017). Here the method is generalized for meals with different amount of CHO and also includes a set of rules based on blood glucose readings to modify $\overline{IOB}$. This set of rules has been designed to determine if it is necessary to increase $\overline{IOB}$, for cases which the bolus was not enough to reduce blood glucose to normal levels.

The method works as follows: in case of the announcement of a meal, an insulin bolus is delivered as a feed-forward action. This bolus is an augmented version of the standard bolus computation, by adding a portion of the future basal delivery according with the size of the meal, as shown in Equation (4.2).

$$u_{bolus} = \frac{M_{CHO}}{CR} + \frac{mBG - tBG}{CF} + \left(\int_{t}^{t+60} u_{basal}(t) \right) \cdot \frac{M_{CHO}}{60} \tag{4.2}$$

where u_{basal} is the basal profile obtained from patients' pump in IU/h. Therefore, the standard bolus is augmented proportionally to the estimated CHO content of the meal.

After the bolus, $\widehat{IOB}$ automatically surpass $\overline{IOB}$, and then u_d is forced to zero while $\widehat{IOB}$ is greater than $\overline{IOB}$, due to the action of the SAFE layer. The parameter T_{IOB} (in minutes, Equation (4.3)) is introduced to regulate the starting time after the meal from when $\overline{IOB}$ may be increased. After T_{IOB} minutes, blood glucose readings start to be evaluated in order to check whether $\overline{IOB}$ needs to be increased, aiming to drive blood glucose below a selected target ($\underline{G}$ in mg/dl). If in this moment, blood glucose is greater than a threshold ($\overline{G}$ in mg/dl), a new IOB limit is computed to control postprandial blood glucose. Finally, when blood glucose returns to values below $\underline{G}$, $\overline{IOB}$ returns to follow $\overline{IOB}_{bl}$. Note that the parameters $\underline{G}$ and $\overline{G}$ can be adjusted intuitively by physicians, with $\overline{G} \geq \underline{G}$. For a more aggressive postprandial control, these parameters should be decreased.

$$T_{IOB} = 1.5 \cdot M_{CHO} \tag{4.3}$$

$$\overline{IOB}_{PP} = \max\left(\widehat{IOB}(k-1), \overline{IOB}_{bl}(k) \right) \tag{4.4}$$

where k is the current sampling time of the system.

The final tuning for $\overline{IOB}$ is determined during a real-time procedure, based on the dynamic behavior of patients basal profile and also in the rule-based strategy to increase $\overline{IOB}$ during postprandial periods. Figure 4.2 depicts a flowchart of the proposed method to facilitate the understanding and Figure 4.3 depicts the application of the method in one representative virtual patient during a simulation. Notice in Figure 4.3 (d) the behaviour of the constraint $\overline{IOB}$ due to

the dynamic rule-based algorithm. Indeed, the increase of $\overline{IOB}$ for a short period allowed the controller to suggest insulin, driving glucose levels back to normoglycemia sooner.

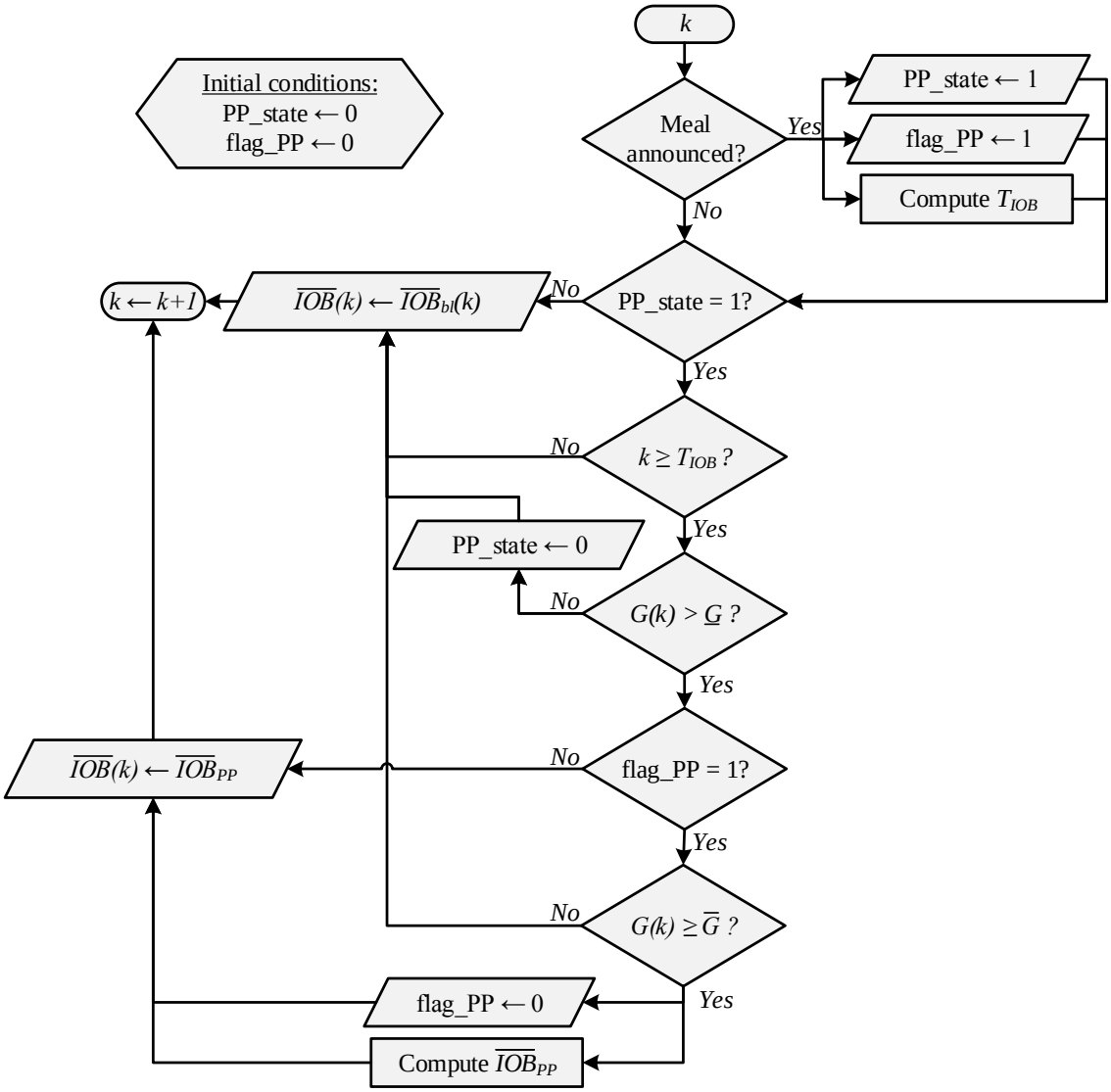

Figure 4.2: Flowchart describing how the proposed dynamic rule-based algorithm works. While there is no meal announcement (fasting condition), $\overline{IOB}$ follows IOB_{bl}. When a meal is announced, T_{IOB} is computed. Within T_{IOB} minutes, the feedback signal G is evaluated to assess whether there is a need to increase the $\overline{IOB}$ to drive glucose levels back to the desired bounds.

In summary, the dynamic rule-based strategy has been designed to make use of patients' basal profile, which is an indicative of insulin requirements along the day, jointly with the approach already tested clinically with real patients, which achieved good results during postprandial control. In addition, a feedback signal has been incorporated to adjust $\overline{IOB}$ in

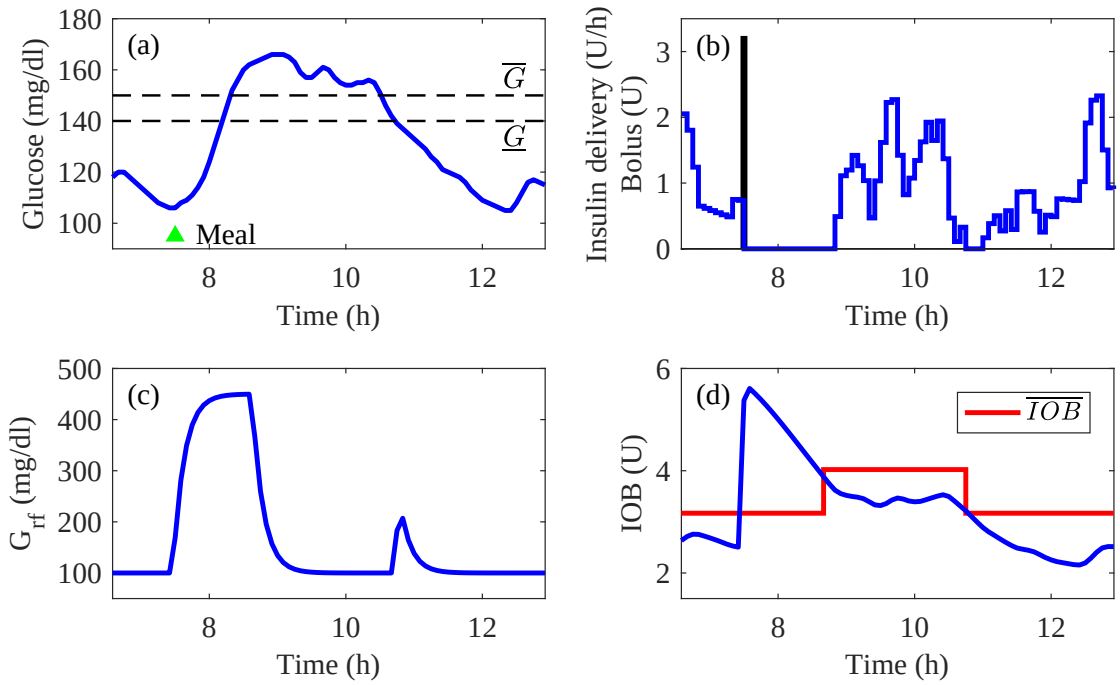

Figure 4.3: Operation of the dynamic rule-based algorithm during a postprandial period. Note that after the meal, the algorithm deemed necessary to increase $\overline{IOB}$ because blood glucose levels were above $\overline{G}$. (a) Glucose measurements; (b) Insulin delivery; (c) The reference signal G_{rf}; (d) Estimation of IOB and $\overline{IOB}$ generated by the DRB algorithm.

real-time, aiming to track glucose back to near-normoglycemia safely. In the following sections, the adult cohort from the simulator is consider to evaluate the efficacy of the method in different scenarios under challenging conditions. Table 4.1 summarizes some of the characteristics of the three scenarios considered to evaluate the DRB algorithm. Further details regarding each one of the scenarios are presented in the following sections.

Table 4.1: Description of the scenarios considered to evaluate the performance of the DRB algorithm.

Scenario	Simulation duration	Meals per day	Meal size	Outcomes analysis
A	12 days	1	60 g	Postprandial
B	45 days	1	40-120 g	Postprandial
C	14 days	3	50-90 g	24 h

All the outcomes presented in the following sections and so on are computed based on CGM measurements. Individual metrics are computed and then the results are presented as the median (25^{th} - 75^{th} percentiles) among the cohort, except for the total number of hypoglycemic

events, which is calculated as the sum of every hypoglycemic events for the whole cohort. A hypoglycemia event is defined as blood glucose below a defined glucose threshold for at least 15 minutes and to consider a new event, blood glucose has to return above the glucose threshold for at least 15 minutes. Hypothesis testing was done using Wilcoxon two-sided signrank test, considering a significance level of 0.05.

4.2.3 Description of Scenario A

This scenario is considered to compare the performance of the dynamic rule-based algorithm ($\overline{IOB}_{DRB}$) against the method already validated clinically, with a fixed value for $\overline{IOB}$ ($\overline{IOB}_F$). In a 12-day scenario, the adult cohort consumed a single meal containing 60 grams of CHO per day, between 08:00 and 19:00, in order to assess the postprandial control under different conditions of insulin sensitivity incorporated in the simulator. The size of the meal has been selected to conduct a fairly comparison, since the former strategy was clinically validated for this specific meal size. Meal boluses match perfectly CHO content from meals, and are calculated identically for both arms.

4.2.4 Results - Scenario A

Table 4.2 shows the metrics for Scenario A. These metrics assess the performance of $\overline{IOB}_{DRB}$ and $\overline{IOB}_F$ during postprandial period (i.e. 4-h following the meal), once the last has been designed for such purpose. The metrics used for this evaluation are: average blood glucose levels, percentage of time spent in different glycemic ranges, blood glucose level 3 h after the meal, and the total insulin delivered by the controller after the meal bolus.

Table 4.2: Population metrics for postprandial glycemic control in Scenario A.

	Mean CGM	Percentage of time spent in				CGM 3h	Total
	(mg/dl)	70–140	70–180	>180	<70	(mg/dl)	Basal (IU)
$\overline{IOB}_{DRB}$	146.44 (137.9 - 153.8)	38.69 (35.4 - 48.5)	94.20 (76.8 - 100.0)	5.80 (0.0 - 23.2)	0.00 (0.0 - 0.0)	148.36 (130.4 - 168.3)	3.47† (2.9 - 4.0)
$\overline{IOB}_F$	145.78 (136.2 - 152.1)	38.54 (36.6 - 56.3)	93.60 (77.1 - 100.0)	6.40 (0.0 - 22.9)	0.00 (0.0 - 0.0)	148.71 (130.4 - 164.0)	3.58 (3.1 - 4.2)

† p-value<0.05 between $\overline{IOB}_{DRB}$ and $\overline{IOB}_F$.

Note that both strategies achieved similar results for postprandial control. Although $\overline{IOB}_{DRB}$ obtained numerical results slightly superior than $\overline{IOB}_F$ in the time spent in glycemic ranges, no significant difference was observed in any these metrics. Such similitude can also be observed in Figure 4.4, through the aggregated traces of blood glucose levels for all the 120 meals

consumed by the cohort in Scenario A. The new strategy ($\overline{IOB}_{DRB}$), besides being applicable for meals of any size, achieved equivalent outcomes when compared with the former strategy, which has been designed for meals with 60 grams of CHO and have already been tested in real patients.

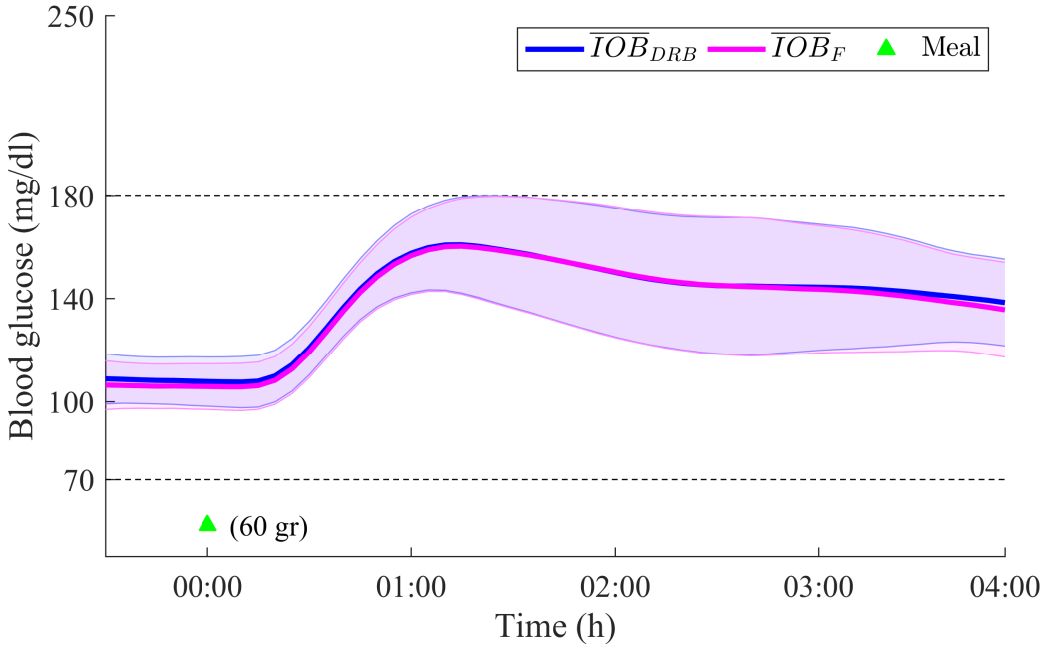

Figure 4.4: Aggregate population CGM readings during the 4 h after meals consumption in Scenario A for a total of 120 meals. Blue lines are mean ± SD for $\overline{IOB}_{DRB}$ and pink lines are mean ± SD for $\overline{IOB}_{F}$. Dashed black lines represent glucose thresholds of 70 mg/dl and 180 mg/dl.

Considering the whole period of simulation (and not just the 4 hours following the meal), a total of 5 L1 hypoglycemic events occurred in the $\overline{IOB}_{F}$ arm, while no events occurred in $\overline{IOB}_{DRB}$ arm. This indicates that a single value of $\overline{IOB}$ may not be sufficient to reduce the risk of hypoglycemia along the day.

4.2.5 Description of Scenario B

This scenario is considered to compare the performance of the dynamic rule-based algorithm ($\overline{IOB}_{DRB}$) in front of meals with CHO content varying between 40 and 120 grams. In a 45-day scenario, the adult cohort consumed a single meal per day, between 08:00 and 19:00. It is considered just a single meal in order to avoid the accumulated effects of meals in the results. Postprandial outcomes are compared against the same controller, but without the rules

considered for postprandial period, i.e., $\overline{IOB}$ follows $\overline{IOB}_{bl}$ ($\overline{IOB}_{bl}$ arm) and also against $\overline{IOB}_{F}$.

4.2.6 Results - Scenario B

Table 4.3 shows the metrics during postprandial period in Scenario B for the three methods applied in this scenario.

Table 4.3: Population metrics for postprandial glycemic control in Scenario B.

	Mean CGM	Percentage of time spent in				CGM 3h	Total
	(mg/dl)	70–140	70–180	>180	<70	(mg/dl)	Basal (IU)
$\overline{IOB}_{DRB}$	146.79†,‡ (144.7 - 154.7)	41.52 (35.4 - 48.5)	85.86‡ (77.7 - 90.2)	14.14 ‡ (9.8 - 20.8)	0.00 (0.0 - 0.0)	150.07† (140.3 - 157.9)	3.19†,‡ (2.1 - 3.6)
$\overline{IOB}_{F}$	148.96 (147.0 - 156.2)	38.10 (25.3 - 47.3)	84.38 (77.1 - 86.3)	15.63 (13.7 - 22.9)	0.00 (0.0 - 0.0)	153.14 (141.4 - 164.0)	3.43 (2.6 - 4.1)
$\overline{IOB}_{bl}$	147.91 (144.5 - 155.4)	40.63 (35.4 - 48.8)	83.33 (77.7 - 88.1)	16.67 (11.9 - 20.8)	0.00 (0.0 - 0.0)	151.43 (140.3 - 158.9)	2.79 (1.8 - 3.3)

† p-value<0.05 between $\overline{IOB}_{DRB}$ and $\overline{IOB}_{F}$.
‡ p-value<0.05 between $\overline{IOB}_{DRB}$ and $\overline{IOB}_{bl}$.

Differently from Scenario A, in Scenario B meals from different sizes were considered to evaluated the postprandial performance of the controller, which is more realistic. Results showed a slight superiority of the $\overline{IOB}_{DRB}$ against the other two methods in all the glycemic metrics analyzed, with statistical significance some of them. Comparing $\overline{IOB}_{DRB}$ and $\overline{IOB}_{bl}$ arms, it is possible to notice that the rules implemented to increase IOB during postprandial period could reduce significantly the mean glucose (146.79 mg/dl vs 147.91 mg/dl) and also the time spent in hyperglycemic range (14.14% vs 16.67%). Considering the whole period of simulation (45 days), a total of 8 L1 hypoglycemic events and 2 L2 hypoglycemic events occurred for both $\overline{IOB}_{DRB}$ and $\overline{IOB}_{bl}$, while the arm with the fixed $\overline{IOB}$ had a total of 20 L1 hypoglycemic events and 4 L2 hypoglycemic events in total.

4.2.7 Description of Scenario C

A 14-day scenario, mimicking typical day scenario from real patients, is considered to assess the performance of the proposed method under realistic conditions. In this scenario, a total of three meals are consumed per day. Breakfast is consumed at 7:30 (50 grams), lunch is consumed at 13:00 (90 grams) and dinner is consumed at 19:00 (70 grams), with a coefficient of variation for the meal size of ±10%. An error of ±15% on CHO counting has also been

included to challenge the system. A total of four different strategies are applied in this scenario: 1) $\overline{IOB}_{DRB}$, 2) $\overline{IOB}_F$, 3) $\overline{IOB}_{bl}$, and 4) the same insulin controller, but without $\overline{IOB}$, and with standard meal boluses.

4.2.8 Results - Scenario C

Table 4.4 shows the results considering the whole duration of Scenario C.

Table 4.4: Population metrics for 14-day period in Scenario C for three strategies to adjust $\overline{IOB}$: $\overline{IOB}_{DRB}$, $\overline{IOB}_F$ and $\overline{IOB}_{bl}$. Additionally, the CL system without $\overline{IOB}$ has been tested.

	$\overline{IOB}_{DRB}$	$\overline{IOB}_F$	$\overline{IOB}_{bl}$	Without $\overline{IOB}$
Mean CGM (mg/dl)	134.41 (129.9-138.0)	130.19† (128.3-134.6)	135.82‡ (132.5-141.7)	113.22人 (109.3-115.8)
Insulin/day (IU)	40.97 (36.3-49.2)	40.96 (37.0-50.2)	40.99 (35.9-46.4)	44.56人 (39.0-54.8)
Percentage of time spent				
70-140	66.56 (58.4-72.0)	68.13† (62.7-70.0)	65.17‡ (52.5-70.0)	78.26人 (75.3-84.4)
70-180	92.45 (91.8-97.7)	92.81 (90.6-96.7)	91.36‡ (89.7-97.2)	94.25 (86.6-95.5)
>180	7.40 (2.3-8.1)	7.18 (2.9-9.4)	8.30‡ (2.8-10.3)	2.69人 (2.3-5.3)
<70	0.00 (0.0-0.0)	0.00 (0.0-0.4)	0.00 (0.0-0.0)	3.37人 (1.4-6.2)
Hypoglycemic events				
L1	4	7	4	124
L2	2	2	2	58

† p-value<0.05 between $\overline{IOB}_{DRB}$ and $\overline{IOB}_F$.
‡ p-value<0.05 between $\overline{IOB}_{DRB}$ and $\overline{IOB}_{bl}$.
人 p-value<0.05 between $\overline{IOB}_{DRB}$ and Without $\overline{IOB}$.

The results display the solid performance of the strategies using the SAFE layer when compared with the insulin controller without IOB limitation, mainly to avoid hypoglycemia. The $\overline{IOB}_F$ strategy is the one with the lowest mean glucose values and spent more time in tight range (70-140 mg/dl), but the fixed value of $\overline{IOB}$ has led to more hypoglycemic events. On the other hand, the $\overline{IOB}_{DRB}$ achieved slightly better outcomes than $\overline{IOB}_{bl}$, due to the strategy to increase $\overline{IOB}$ during postprandial periods. Moreover, both strategies had the same number of hypoglycemic events.

4.2.9 Discussion

The results in Table 4.4 confirm clearly that the action of the SAFE layer avoids the overreaction of the insulin controller due to the rise of glucose, caused by the meals. This safety layer has been considered by others in silico studies (Revert et al., 2013; León-Vargas et al., 2013a; Hu and Li, 2015) with different control algorithms. In all of these studies the controller with the SAFE layer reduced substantially the time spent in hypoglycemic range when compared with the same controller without the SAFE layer. However, only a single value of $\overline{IOB}$ has been used in these works, and the tuning of such parameter is still a hurdle in the design of the system.

The method proposed to adjust $\overline{IOB}$ uses a time-variant baseline for $\overline{IOB}$ and after the announcement of a meal, a set of rules are considered to increase the limit of IOB in case of high blood glucose levels. The method take into account patients' basal profile, which is an indicative of the variations in insulin requirements along the day. With the announcement of the meal, an augmented bolus is calculated based on the size of the meal, and after T_{IOB} minutes, $\overline{IOB}$ may be increased based on a feedback signal to drive glucose back to the desired range. The selection of the parameters $\overline{G}$ and $\underline{G}$ has been based on the recommended guidelines for management of postmeal glucose provided by IDF, however both of them can be adjusted in case of recurrent hyper- or hypoglycemia. Both the augmented bolus and T_{IOB} are an extension of the strategy already validated clinically. Therefore, the method proposed adjust $\overline{IOB}$ in an online fashion, according with the size of the meal, patients' basal profile and feedback signal.

Although the results obtained by proposed method are only slightly better when compared with the other strategies which included the SAFE layer, it was observed a reduction on the occurrence of hypoglycemic events without leading to excessive hyperglycemia. Moreover, the starting point of the proposed method was another strategy which has already been extensively tested both in silico and clinically, making the task of achieving significantly better results even more difficult. Nevertheless, it has been possible to improve the performance of the AP system. In addition, it also allows modification on the parameters of the proposed algorithm to be performed intuitively by physicians, if they deem necessary further improvements on glycemic control.

4.3 Mitigation strategies to reduce the risk of exercise-induced hypoglycemia

According the ADA, all individuals with T1DM should practice exercise or physical activity to improve their overall health, which includes glycemic control (Colberg et al., 2016). However,

the effects of physical activity on glucose levels depends on the type, duration and intensity of the activity. All of these factors make the correct management of insulin delivery during and after exercise difficult, since the prediction of the real effects of exercise on glucose control is not a trivial task. While aerobic exercise (e.g., swimming, jogging, cycling, or walking) tends to decrease blood glucose levels, anaerobic exercise (e.g., resistance exercise/weight lifting, sprints, and high-intensity intervals) leads to an increase on it. But physio-pathological basis of these assumptions have not been fully established. In adults with T1DM, the main concern of physical activity is the fear of hypoglycemia and it may discourage T1D subjects to exercise regularly (Pinsker et al., 2016; Yardley and Sigal, 2015; Brazeau et al., 2008). The use of present and future diabetes supportive technologies may help patients with T1D to have a healthier and more active lifestyle by increasing patients' willingness to practice physical activity (Colberg et al., 2015).

Researchers have long been concerned about how to handle exercise and T1DM. Recently, a consensus statement (Riddell et al., 2017) has been published containing different strategies that can be used within conventional insulin therapy to regulate blood glucose levels before, during and after exercise. One obstacle of exercise management is the variability in BG response to different types of exercise. Moreover, different algorithms have been tested to help patients to reduce the risks of exercise-induced hypoglycemia by suggesting supplemental CHO intake (Francescato et al., 2015; Stella et al., 2017).

Although the AP has demonstrated in several clinical trials that it can achieve improved glycemic outcomes when compared to SAP therapy, it is not clear how these CL systems can deal with exercise in free-living conditions, especially in insulin-only systems. In some situations, depending on blood glucose levels and IOB, suspending insulin infusion may not be sufficient to avoid hypoglycemia for aerobic exercise. Taleb and colleagues (Taleb et al., 2016) compared the efficacy of insulin-only and dual-hormone systems in front of announced exercise. For both, continuous and interval exercise, no CHO has been consumed prior to exercise start and the only feed-forward action taken was to increase the glucose target during exercise. Their results showed that the insulin-only system spent more time in the hypoglycemic range and more hypoglycemic events occurred when compared with the dual-hormone system, due to the counterregulatory action provided by glucagon suggestions. Moreover, different AP systems were challenged by unannounced exercise, and albeit the automatic system outperformed conventional pump therapy, exercise-related hypoglycemic episodes still occurred (Dovc et al., 2017; Huyett et al., 2017).

The AP under development by the Spanish Consortium on Artificial Pancreas and Diabetes Technology has been tested in front of announced aerobic and anaerobic exercise sessions

on a pilot clinical trial (Quirós et al., 2018). Five subjects with T1DM aged 37 ± 10.9 years, insulin pump users, and with a mean HbA1c level of 7.8 ± 0.5%. Every subject performed three aerobic and three anaerobic sessions. The aerobic exercise studies comprised three series of 15 minutes of stationary bicycle at 60% of maximum heart rate with 5 min of rest between them. In the anaerobic exercise studies, patients performed five series of eight repetitions of four weight exercises involving different muscle groups, with a weight equivalent to 70% of maximum capacity, with periods of 90 seconds of rest between repetitions. For both types of exercise, three feed-forward actions were conducted in order to reduce the risk of exercise-induced hypoglycemia: 1) patients consumed 23 grams of fast-acting CHO at the beginning of exercise; 2) the target glucose level increases from 100 mg/dl to 150 mg/dl from the start of exercise during a 45 minutes and then gradually falls over two hours to reach 100 mg/dl again; and 3) during the same period, the signal u_{basal} (see Equation (3.2)) was reduced to zero. However, in this pivotal clinical trial CL operation started at 10:45 and exercise sessions started at 11:00. After the arrival of the patients to the hospital, blood glucose levels were regulated via intravenous glucose/insulin infusion, aiming to secure a plasma glucose level about 150 mg/dl before CL operation.

Although the CL system performed well for both types of exercise, in everyday life patients may engage exercise under different conditions, and therefore, new strategies are necessary to manage deal with the expected variability on patients' conditions. In other words, patients can commence exercise as soon as he/she wake up or soon after breakfast. These situations requires different actions to deal with exercise, due to different levels of IOB and blood glucose. Thus, it has been developed new strategies to deal with daily life operation of the AP in front of aerobic exercise, so-called mitigation strategies for exercise-induced hypoglycemia (MS4EH).

Firstly, it is considered the actions that can be taken if the patient announces exercise Δt_1 minutes before the actual onset of the physical activity. At this moment, there are mainly two different actions to reduce the risk of exercise-induced hypoglycemia in insulin-only systems: suggest exogenous CHO intake and adjust insulin delivery.

The system may suggest CHO intake based on two different rules that are evaluated at the moment of the exercise announcement: 1) based on CGM measurements; and 2) considering the IOB at the moment of announcement. Following the recommendations presented by Riddell et al. (2017) the system suggests 20 grams of CHO if CGM readings are below 90 mg/dl or 10 grams if glucose levels are between 90-124 mg/dl at the announcement. Besides that, more CHO may be suggested taking into account insulin concentrations in the body. The system computes the excessive IOB and converts this excess in CHO. In other words, the system informs the patient the amount of CHO they should consume to compensate for the excess of

insulin that is accumulated in the body. Then, the final CHO suggestion is:

$$CHO_G = \begin{cases} 20; & \text{if} \quad G(k) \leq 90 \\ 10; & \text{if} \quad 90 < G(k) \leq 124 \\ 0; & \text{otherwise} \end{cases} \tag{4.5}$$

$$CHO_{IOB} = \left(\widehat{IOB}(k) - 0.5 \cdot IOB_{basal}(k)\right) \cdot CR \tag{4.6}$$

$$CHO_{FF} = \min\left((CHO_G + CHO_{IOB}), \max\left(\frac{\left(\overline{G_{ex}} - G(k)\right)}{K_{CHO}}, 0\right)\right) \tag{4.7}$$

where k is the sample time of the system, $\overline{G_{ex}}$ is the maximum desired blood glucose during exercise caused by CHO intake, and K_{CHO} is a population gain related with the increase on blood glucose caused by fast-acting CHO, set to 2.7 (Beneyto et al., 2018). The final CHO suggestion is rounded to the nearest multiple of five, to replicate the size of commercial products.

As it is expected blood glucose fall due to an increase in insulin sensitivity and glucose utilization incorporated by the aerobic exercise model and these effects lasts for several hours after exercise (Campbell et al., 2015; McMahon et al., 2007). Thus, further actions are taken in order to reduce the insulin suggestions provided by the controller, aiming to reduce insulin concentration in the blood. These modifications happens in two different stages, as illustrated in Figure 4.5.

- **Exercise configuration – stage 1**

This stage starts when the patient announces exercise. From this moment on, several parameters of the insulin controller are modified, and these modifications lasts for up to Δt_2 minutes after the ending of exercise or if any of the following conditions ("escape conditions") are observed after the ending of exercise:

i) $G(k_1) > 140$ mg/dl $\wedge$ $\dot{G}(k_1) > 0$ mg/dl/min, $\forall k_1 \in (k-2, ..., k)$

ii) $\dot{G}(k_1) > 1$ mg/dl/min $\wedge$ $\tilde{u}_d(k_1) = 0$ IU/h, $\forall k_1 \in (k-2, ..., k)$

iii) $\dot{G}(k_2) > 1.5$ mg/dl/min $\wedge$ $\tilde{u}_d(k_2 j) = 0$ IU/h, $\forall k_2 \in (k-1, k)$

where k stands for the current sample time, and k_1 and k_2 represents different time intervals related with k. Taking the first condition as example, it is necessary that $G(k-2)$, $G(k-1)$ and $G(k)$ must be greater than 140 mg/dl and also $\dot{G}(k-2)$, $\dot{G}(k-1)$ and $\dot{G}(k)$ must be greater than 0 mg/dl/min, since k_1 is defined as the samples at instants $k-2$, $k-1$ and k.

- **Exercise configuration – stage 2**

This stage starts as soon as the stage 1 is concluded. During this mode, the controller begins to return to its default configuration in a smoothly way, i.e., all the parameters that had been altered during stage 1 return to their original values in a linear fashion during the following Δt_3 minutes.

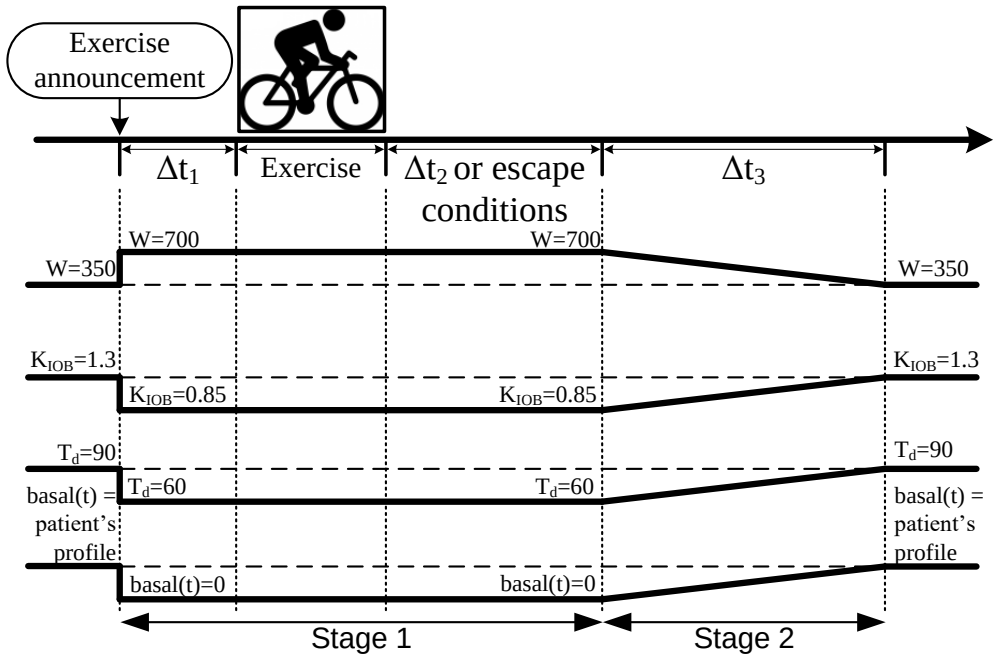

Figure 4.5: Illustration of the modifications applied in the controller's parameters to reduce exercise-induced hypoglycemia due to aerobic exercise. During the time interval Δt_3, all the parameters that have been modified at the exercise announcement return linearly to their original values over this interval.

It has been considered Δt_1 equals 20 min. Although is likely that increasing the value of Δt_1 would lead to less hypoglycemic events, and consequently less time in hypoglycemia, it was limited to 20 min because longer periods might not be realistic in real life. For the insulin only AP, Δt_2 and Δt_3 have been set to 120 minutes and 240 minutes, respectively. In addition, the next meal bolus after an exercise session is reduced by 50% and omit any correction bolus for this specific meal.

4.3.1 Description of Scenarios D and E

The adult cohort from the simulator has been tested during 15-day scenario under realistic conditions to evaluate efficacy of the proposed method. Patients consumed three meals per day,

at 08:30, 13:00 and 19:00, containing 35 grams, 65 grams and 50 grams of CHO, respectively. An error of ± 15% on CHO estimation from meals has also been incorporated in the simulations. Every other day (starting on Day 1), the CL system was challenged by continuous aerobic exercise sessions for 50 minutes at 60% VO_{2max}. In the first scenario (Scenario D), each patient engaged in 8 exercise sessions during the 15-day simulation period. The first four exercise sessions were distributed at different times (07:00, 10:00, 15:00 or 21:00), and the last four sessions repeated the time schedule of the first four. The second scenario (Scenario E) is identical to Scenario D, including exercise intensity and duration. The only difference is the time schedule in which the exercise sessions occurred. In Scenario E the sessions occurred at 07:00, 12:00, 18:00 and 23:00. Each scenario mimics different schedules of physical activities. In Scenario D, most of exercise sessions happen during postprandial conditions. while in Scenario E physical activity begins farther away from meals.

4.3.2 Results

In order to evaluate the beneficial impact of the proposed actions in the glycemic control, the CL system with mitigation strategies for exercise-induced hypoglycemia (CL+MS4EH arm) is compared against the CL system without any action (CL arm), i.e. the CL system faced unannounced exercise sessions.

The outcomes for the 15-day simulation are: average glucose level, percentage of time spent into different glycemic ranges and the number of L1 and L2 hypoglycemic events per day. The exercise-related outcomes are: the value of CGM reading when exercise begins, the amount of suggested CHO at the exercise announcement, the minimum value of glucose in the first two hours after the start of the exercise, the number of L1 and L2 hypoglycemic events per exercise session, the total number of L1 and L2 hypoglycemic events for the entire cohort and percentage of time spent below 70 mg/dl and 54 mg/dl, divided in two periods: during the first two hours after the beginning of exercise and from 2 hours after the start of exercise to 6 hours after the start of exercise. These outcomes have been selected to allow the assessment of the effects of the proposed actions to reject the disturbance caused by aerobic exercise.

Results for Scenario D and E are presented in Table 4.5 and in Table 4.6, respectively. In addition, Figures 4.6 and 4.7 illustrate the comparison between the glycemic control and insulin delivery in both CL+MS4EH and CL arms, for all the exercise sessions in both scenarios for the entire cohort.

In summary, each scenario had a total of 450 meals and 4000 minutes of physical activity, for the entire adult cohort. In both scenarios, the CL system with the proposed mitigation strategies to reduce exercise-induced hypoglycemia (CL+MS4EH) is able to outperform the

Table 4.5: Population outcomes of Scenario D. Overall outcomes encompass the whole period of simulation (15 days). Exercise-related outcomes encompass all the 80 sessions performed by the entire cohort.

	CL+MS4EH	CL
Overall outcomes (15 days)		
Mean glucose (mg/dl)	127.83 (126.3-130.3)†	119.43 (116.7-122.1)
% of time spent in glucose levels		
70-180 mg/dl	96.97 (95.9-98.0)†	94.31 (93.1-96.0)
>180 mg/dl	2.53 (1.4-4.0)†	0.82 (0.4-2.3)
<70 mg/dl	0.49 (0.2-0.7)†	4.27 (3.2-6.4)
<54 mg/dl	0.05 (0.0-0.2)†	1.84 (0.8-2.1)
Hypoglycemic events		
L1 events per day	0.13 (0.1-0.2)†	0.83 (0.7-0.9)
L2 events per day	0.03 (0.0-0.1)†	0.47 (0.3-0.5)
Exercise-related outcomes (8 sessions per patient)		
Glucose at exercise start (mg/dl)	158.63 (155.4-162.3)†	134.44 (127.6-139.6)
CHO at announcement (g/session)	35.31 (33.1-38.8)†	0.00 (0.0-0.0)
From exercise start + 2 h		
Minimum glucose (mg/dl)	79.94 (73.6-85.4)†	44.56 (42.6-49.5)
% of time <70 mg/dl	4.50 (1.0-9.0)†	46.25 (43.0-55.5)
% of time <54 mg/dl	1.00 (0.0-3.0)†	26.25 (16.5-34.0)
Hypoglycemic events		
L1 events per session	0.19 (0.0-0.4)†	1.00 (1.0-1.0)
L2 events per session	0.06 (0.0-0.1)†	0.69 (0.5-0.9)
Total L1	16	78
Total L2	6	56
From 2 h after exercise start + 4 h		
% of time <70 mg/dl	2.30 (0.0-3.1)†	19.77 (15.1-29.8)
% of time <54 mg/dl	0.13 (0.0-0.8)†	4.72 (0.0-13.0)
Hypoglycemic events		
L1 events per session	0.00 (0.0-0.0)†	0.50 (0.4-0.6)
L2 events per session	0.00 (0.0-0.0)	0.06 (0.0-0.1)
Total L1	1	39
Total L2	0	13

† p-value<0.05 between CL+MS4EH and CL.

Table 4.6: Population outcomes of Scenario E. Overall outcomes encompass the whole period of simulation (15 days). Exercise-related outcomes encompass all the 80 sessions performed by the entire cohort.

	CL+MS4EH	CL
Overall outcomes (15 days)		
Mean glucose (mg/dl)	127.45 (125.1-129.9)†	119.59 (117.2-122.5)
% of time spent in glucose levels		
70-180 mg/dl	98.18 (96.2-98.8)†	93.66 (92.9-94.9)
>180 mg/dl	1.59 (0.9-3.4)†	0.91 (0.4-2.5)
<70 mg/dl	0.31 (0.2-0.5)†	5.21 (4.4-6.3)
<54 mg/dl	0.00 (0.0-0.1)†	2.00 (1.7-2.3)
Hypoglycemic events		
L1 events per day	0.13 (0.1-0.1)†	0.73 (0.7-0.9)
L2 events per day	0.00 (0.0-0.0)†	0.53 (0.5-0.6)
Exercise-related outcomes (8 sessions per patient)		
Glucose at exercise start (mg/dl)	145.56 (143.6-159.1)†	128.19 (123.0-132.8)
CHO at announcement (g/session)	35.31 (32.5-38.1)†	0.00 (0.0-0.0)
From exercise start + 2 h		
Minimum glucose (mg/dl)	81.94 (77.6-87.0)†	39.88 (37.9-44.6)
% of time <70 mg/dl	2.25 (0.5-3.5)†	52.25 (50.5-54.5)
% of time <54 mg/dl	0.00 (0.0-0.0)†	31.50 (26.0-36.5)
Hypoglycemic events		
L1 events per session	0.13 (0.1-0.3)†	1.00 (1.0-1.0)
L2 events per session	0.00 (0.0-0.0)†	0.88 (0.9-0.9)
Total L1	12	79
Total L2	1	65
From 2 h after exercise start + 4 h		
% of time <70 mg/dl	1.66 (0.0-2.6)†	30.44 (21.8-44.0)
% of time <54 mg/dl	0.00 (0.0-0.0)†	5.91 (3.8-11.5)
Hypoglycemic events		
L1 events per session	0.00 (0.0-0.0)†	0.38 (0.3-0.8)
L2 events per session	0.00 (0.0-0.0)†	0.13 (0.1-0.3)
Total L1	2	48
Total L2	0	17

† p-value<0.05 between CL+MS4EH and CL.

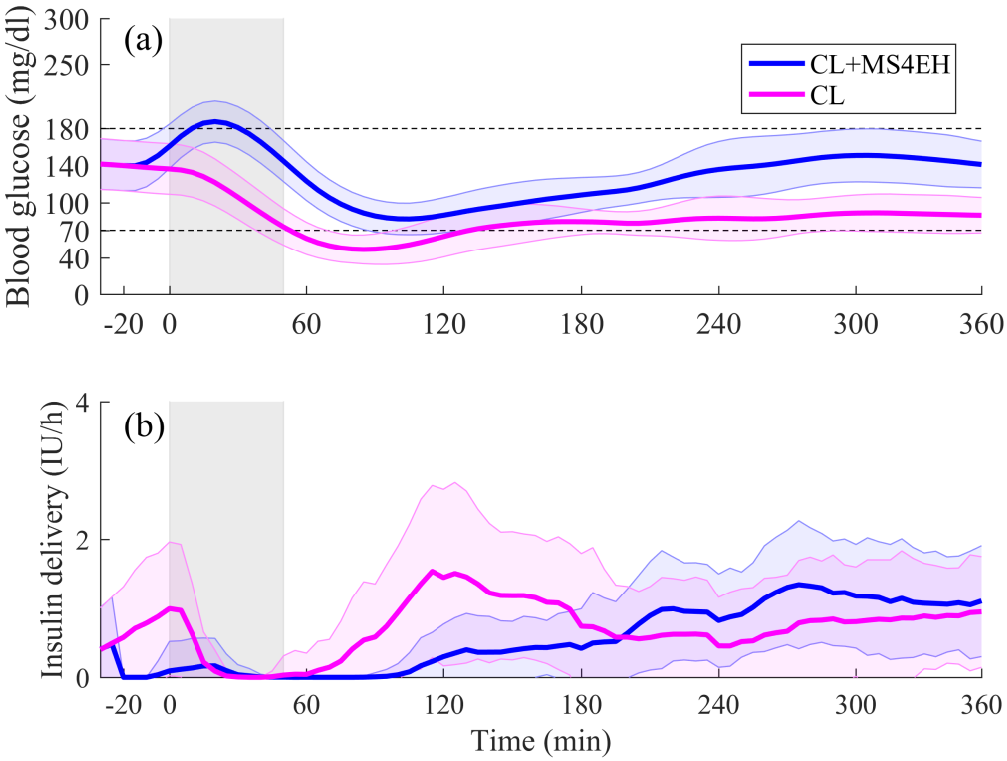

Figure 4.6: Aggregated population for all the exercise sessions in Scenario D. (a) CGM readings in mg/dl; (b) Insulin delivery in IU/h. Blue lines are mean ± SD for CL+MS4EH and pink lines are mean ± SD for CL. Gray shaded area represents the exercise period. Dashed black lines represent glucose thresholds of 70 mg/dl and 180 mg/dl in graph (a).

original CL system stand-alone (CL), this is primarily shown by the statistically significant reduction in the time spent below 70 mg/dl for the 15-day period (0.49% vs 4.27% in Scenario D, and 0.31% vs 5.21% in Scenario E) and also by the reduction on hypoglycemic episodes per day in both Scenarios. Additionally, the mitigation strategies combined with the CL algorithm nearly eliminated completely the occurrence of severe hypoglycemia, characterized by L2 events per day (0.03 events/day in Scenario D, and 0.00 vs events/day in Scenario E).

The exercise-related outcomes, in Tables 4.5 and 4.6, show that the proposed actions have been able to minimize the number of L1 and L2 hypoglycemic events in both scenarios. In Scenario D, the total amount of L1 and L2 hypoglycemic events in the 6 h postexercise period for the entire cohort were reduced from 117 to 17 and from 69 to 6, respectively. Besides that, the minimum glucose measured during the first two hours after the beginning of exercise shows that the actions are able to reduce significantly the risk of exercise-induced hypoglycemia (79.94 mg/dl vs 44.56 mg/dl, $p<0.05$), although a few events still occurred.

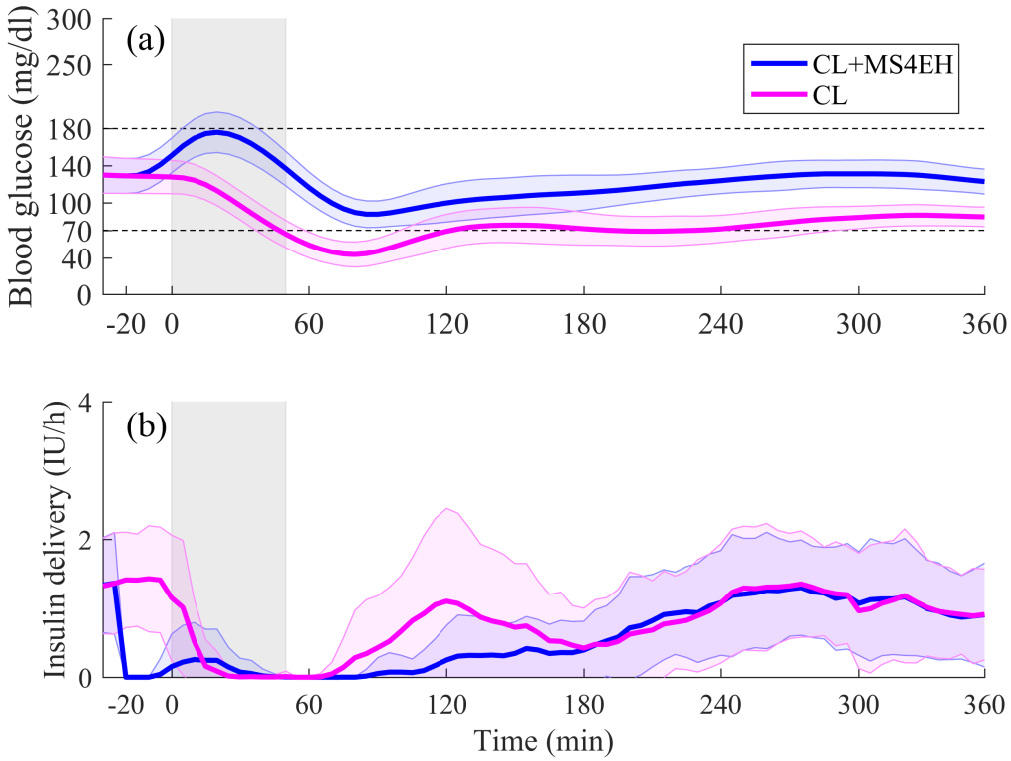

Figure 4.7: Aggregated population for all the exercise sessions in Scenario E. (a) CGM readings in mg/dl; (b) Insulin delivery in IU/h. Blue lines are mean ± SD for CL+MS4EH and pink lines are mean ± SD for CL. Gray shaded area represents the exercise period. Dashed black lines represent glucose thresholds of 70 mg/dl and 180 mg/dl in graph (a).

Similar improvement can be observed in Scenario E. The total number of L1 hypoglycemic events in the 6 h postexercise period was reduced from 127 to 14, and the total number of L2 hypoglycemic events was reduced from 82 to 1. In this scenario, an impressive reduction in the percentage of time spent below 70 mg/dl in the first two hours after the onset of exercise has been achieved (2.25% vs 52.25%, $p<0.05$). Likewise, the time spent in the severe hypoglycemia has also been reduced from 31.5% to 0.00%.

In both Figures 4.6 and 4.7 can be noted that the when exercise is announced, blood glucose tends to increase due CHO recommendations computed by Equation (4.7). In both Scenarios, the median CHO recommendation have been the same, 35.31 grams per exercise session. Note that after the announcement of exercise, the control action provided by the insulin controller is reduced, even with the increase in blood glucose caused by the CHO intake. This happens due to the modifications applied in the controller's tuning, especially on T_d and K_{IOB}. On the other hand, in the CL arm the control actions are reduced only when the effects of

exercise are reflected on blood glucose levels, and it lead to higher IOB levels during exercise. Moreover, after blood glucose's nadir, insulin controller counteracts delivering more insulin due to the positive slope observed in blood glucose. This fact can be observed in both Figures, at approximately 120 minutes after the beginning of exercise. Notice that even with blood glucose levels below the glucose target, the CL arm keeps delivering insulin in both Scenarios constantly. Therefore, patients spent excessive time in both hypoglycemic ranges.

To evaluate the robustness of the proposed method in front of exercise sessions with different intensity, Scenarios D and E have the intensity of exercise sessions decreased and increased by 20% from the original intensity. Tables 4.7 and 4.8 show solely the exercise-related outcomes considering only the CL system with the MS4EH actions.

Table 4.7: Population outcomes for the CL+MS4EH control system in Scenario D with exercise intensity increased and decreased by 20%. Exercise-related outcomes encompass all the 80 sessions performed by the entire cohort.

	Intensity -20%	Intensity +20%
Exercise-related outcomes (8 sessions per patient)		
Glucose at exercise start (mg/dl)	158.81 (155.1-162.3)	158.75 (155.3-162.3)
CHO at announcement (g/session)	35.31 (33.1-38.8)	35.31 (33.1-38.8)
From exercise start + 2 h		
Minimum glucose (mg/dl)	92.94 (86.1-101.6)	68.94 (67.1-74.9)
% of time <70 mg/dl	1.25 (0.0-3.5)	10.25 (5.0-13.0)
% of time <54 mg/dl	0.00 (0.0-0.0)	3.25 (0.0-4.0)
Hypoglycemic events		
L1 events per session	0.06 (0.0-0.1)	0.50 (0.3-0.6)
L2 events per session	0.00 (0.0-0.0)	0.13 (0.0-0.1)
Total L1	6	35
Total L2	2	7
From 2 h after exercise start + 4 h		
% of time <70 mg/dl	0.26 (0.0-2.8)	3.06 (0.0-4.1)
% of time <54 mg/dl	0.00 (0.0-0.0)	0.77 (0.0-1.3)
Hypoglycemic events		
L1 events per session	0.00 (0.0-0.0)	0.00 (0.0-0.0)
L2 events per session	0.00 (0.0-0.0)	0.00 (0.0-0.0)
Total L1	0	0
Total L2	0	0

As expected, decreasing the intensity of exercise on 20% reduced the occurrence of hypoglycemic events in both Scenarios, and the opposite effects are observed in when exercise intensity is increased. However, even with more intense exercise, the performance of the

Table 4.8: Population outcomes for the CL+MS4EH control system in Scenario E with exercise intensity increased and decreased by 20%. Exercise-related outcomes encompass all the 80 sessions performed by the entire cohort.

	Intensity -20%	Intensity +20%
Exercise-related outcomes (8 sessions per patient)		
Glucose at exercise start (mg/dl)	145.25 (143.5-159.1)	145.44 (143.5-159.1)
CHO at announcement (g/session)	35.00 (32.5-38.1)	35.31 (31.3-37.5)
From exercise start + 2 h		
Minimum glucose (mg/dl)	94.75 (92.5-101.4)	75.19 (68.1-76.0)
% of time <70 mg/dl	0.00 (0.0-2.0)	7.25 (3.5-10.5)
% of time <54 mg/dl	0.00 (0.0-0.0)	0.00 (0.0-2.0)
Hypoglycemic events		
L1 events per session	0.00 (0.0-0.1)	0.25 (0.1-0.5)
L2 events per session	0.00 (0.0-0.0)	0.00 (0.0-0.1)
Total L1	4	24
Total L2	0	4
From 2 h after exercise start + 4 h		
% of time <70 mg/dl	0.00 (0.0-1.3)	2.45 (0.3-3.1)
% of time <54 mg/dl	0.00 (0.0-0.0)	0.38 (0.0-0.8)
Hypoglycemic events		
L1 events per session	0.00 (0.0-0.1)	0.00 (0.0-0.1)
L2 events per session	0.00 (0.0-0.0)	0.00 (0.0-0.1)
Total L1	3	3
Total L2	0	5

CL+MS4EH arm is superior when compared with the CL stand-alone strategy with the original exercise intensity.

4.3.3 Discussion

The actions taken before the onset of exercise are the ones that can prevent hypoglycemia during brief aerobic exercise. If a larger period for Δt_1 could be considered, more actions could be taken, such as a reduction of the prior meal bolus before an exercise session. In the study conducted by Schiavon et al. (2013) their goal was to optimize open-loop therapy to improve the time spent in target range during and after exercise in virtual subjects. Their results also indicated that exercise announcement is required to reduce exercise-induced hypoglycemic occurrences. In contrast to the strategy presented in this work, their study did not suggest CHO at the moment of exercise announcement and the anticipatory actions were taken by adjusting basal infusion. Their results indicated that reducing basal delivery 90 minutes before exercise

and also during exercise was safe and effective. However, in some situations, announcing exercise with 90 minutes in advanced may be not practicable, and for these situations, CHO consumption may be necessary. In the strategy presented here, if possible, informing the algorithm with 90 minutes in advanced would lead to less IOB, and consequently to a reduction in the amount of suggested CHO. However, the system is able to deal with later announcements of exercise due to the proposed CHO action, once patients have announced exercise to the system, they will be asked to eat easily consumable food such as tablets, gels or liquids already available in the market. Moreover, the amount of CHO suggested in the Scenarios evaluated are consistent with those recommended by Riddell et al. (2017).

In general, it is well-known that the effects of exercise last for a longer period after its cessation (Riddell et al., 2017; Campbell et al., 2015). However, the exact duration and magnitude of these effects is not known and may depend on several factors. The heuristic actions proposed in this work improved glycemic control. In real life, exercise sessions will not be as uniform as the ones considered through simulations. However, due to the simplicity of the actions, it is feasible to create a mechanism to adapt the intervals Δt_2 and Δt_3 individually, using a Case Base Reasoning algorithm for instance. Finally, in real-life operation, the system could learn from the patient's behavior and adapt the actions accordingly, improving glycemic control even more during post-exercise periods.

In both scenarios evaluated with the CL+MS4EH configuration, the amount of CHO delivered was similar. However, blood glucose levels at the beginning of exercise were significantly higher in Scenario D than in Scenario E. As the final CHO suggestion depends on CGM readings and IOB estimation, it is assumed that in Scenario D the contribution of CHO_{IOB} was higher than CHO_G in the final CHO suggestion (see Equation (4.7)). This was expected due to the fact that most of exercise sessions in Scenario D were during the postprandial period.

Both Scenarios D and E considered different schedules of physical activities. In Scenario D, most of exercise sessions happen during postprandial conditions. Generally, it is expected that exercise starts with elevated blood glucose and IOB levels. Although, elevated blood glucose concentrations may be helpful in avoiding hypoglycemia during exercise, elevated IOB plays the opposite role. In Scenario E physical activity begins farther away from meals, the CL system face the reverse scenario, where the subject will have lower blood glucose and IOB levels before exercise sessions. This trade-off between BG concentration and IOB levels represented different challenges to exercise management on T1DM.

Through the robustness analysis performed by modifying exercise intensity in Scenarios D and E, the CL combined with the MS4EH is able to reduce the risk of exercise-induced hypoglycemia. Even with the strategies developed for aerobic exercise with 60% of VO_{2max},

the mitigation strategies could reduce the occurrence of hypoglycemic events. However, if exercise intensity is too or even if subjects give up from exercising after the announcement, hyperglycemia may occur due to the consumption of CHO without any bolus. However, the escape conditions will act in such situation, reducing hyperglycemia severity.

This work has some limitations, as in all in silico studies. Firstly, it is considered the same mathematical model for all the exercise sessions, which may reproduce the same effects and resulted in the same outcomes for the controller. However, exercise sessions occurred on different times during the days, making use of the intra-patient variability in insulin sensitivity also added in the simulations, once the effects of exercise are also applied to insulin sensitivity. These modifications diminish the repeatability between exercise sessions, resulting in a more realistic scenario.

Another limitation is that the proposed strategy requires two announcements: the first one to announce the beginning of exercise and the second one to announce the ending. This could be avoided through the inclusion of a detection mechanism to feed into the control algorithm. However, as the only input considered in this work is glucose measurements, any detection mechanism would generate a delay between the start of exercise and its detection.

4.4 MS4EH combined with the CHO recommender system

In the previous Sections, the mitigation strategies have been tested in an insulin-only CL configuration. Thus, the controller system is only able to act by reducing blood glucose levels through insulin dosing suggestions.

The CHO recommender system, described in Section 3.2.3, is an additional control loop incorporated in the control scheme, which uses CGM readings as feedback signal to compute control actions to determine whether to recommend fixed doses of CHO intakes to minimize hypoglycemia exposition, and also computes inhibition signals to coordinate both insulin and CHO control loops, in order to avoid oscillatory behaviors after the consumption of CHO recommendations. Therefore, such control scheme can face unannounced exercise sessions and has been evaluated against the insulin-only controller, being able to reduce significantly the time spent in hypoglycemia and also the occurrence of hypoglycemic events (Beneyto et al., 2018).

However, a limitation of the aforementioned approach is that patients should consume CHO when the controller triggers a recommendation, and if patients do not follow these recommendations, the CL performance is harmed in terms of hypoglycemia avoidance. Such situation is likely to occur during a physical activity, e.g., a subject during a competitive activity

may not be willing to be interrupted to consume CHO several times. Alternatively, subject could consume CHO while preparing for exercising and this action would likely reduce CHO intake during physical activity.

Therefore, the arrangement of the MS4EG with the CHO recommender system may reduce the need of CHO consumption after the beginning of exercise. In this scheme, exercise announcement is still required, but the MS4EG have been slightly modified, and the Equations (4.6) and (4.7) are refined by Equations (4.8) and (4.9), respectively.

$$CHO_{IOB} = \left(\widehat{IOB}(k) - 0.7 \cdot IOB_{basal}(k)\right) \cdot CR \tag{4.8}$$

$$CHO_{FF} = \min\left((CHO_G + CHO_{IOB} - COB), \max\left(\frac{\left(\overline{G_{ex}} - G(k)\right)}{K_{CHO}}, 0\right)\right) \tag{4.9}$$

where CHO_G is computed by Equation (4.5) and COB is the amount the CHO on board due to previous CHO recommendations. Furthermore, the variables Δt_2 and Δt_3 have its duration reduced to 30 minutes and 60 minutes, respectively.

The modifications performed in the MS4EH actions take into account the inclusion of the CHO recommender system in the control loop. Previously, the actions performed due to exercise announcement suppressed the insulin suggestions more acutely to avoid hypoglycemia after exercise, because it was the only possible action to be taken. Now, such modifications are slightly relaxed because the CHO recommender system can act in case of a predicted hypoglycemic risk after the ending of exercise, due to the predictive nature of the CHO loop.

4.4.1 Description of Scenario F

The adult cohort from the simulator has been tested during 15-day scenario under realistic conditions to evaluate efficacy of the proposed method. Patients consumed three meals per day, at 08:30, 13:00 and 19:00, containing 35 grams, 65 grams and 50 grams of CHO, respectively. An error of ± 15% on CHO estimation from meals has also been incorporated in the simulations.

Continuous aerobic exercise sessions for 50 minutes at 60% of VO_{2max} have been schedule every other day at 10:00 (day 1), 21:00 (day 3), 07:00 (day 5), 18:00 (day 7), 23:00 (day 9), 12:00 (day 11), 07:00 (day 13) and 15:00 (day 15). Therefore, such scenario mixes the characteristics of Scenarios D and E, encompassing exercise sessions in postprandial period and farther away from meals.

4.4.2 Results

The performance of three different strategies are assessed in this scenario: 1) the CL controller with the original MS4EH actions (CL+MS4EH) as used in Section 4.3, 2) the CL controller

aided by the CHO recommender system (CL+CHO), and 3) the CL controller with the modified MS4EH actions aided by the CHO recommender system (CL+MS4EH+CHO).

Results are presented in Table 4.9. Numerical outcomes show that the CL+MS4EH+CHO arm is able to achieve the lowest percentage of time spent below 70 mg/dl during the 15 days of simulation and also reduced the occurrence of L1 hypoglycemic events per day, with statistical significance when compared with the other two arms. However, it is in the CL+MS4EH+CHO arm where patients consumed the higher amount of CHO per day (excluding ordinary meals), with 26.17 g/day as median. In the CL+MS4EH arm subjects consumed CHO only at the announcement of exercise (19.17 g/day), and in the others strategies, the CHO recommender system might have recommended CHO in other occasions.

The exercise-related outcomes confirm the superiority of the CL+MS4EH+CHO against the other strategies. In all 80 exercise sessions, only 5 L1 hypoglycemic events occurred in the 6 h period after the beginning of exercise. Moreover, the percentage of spent below 70 mg/dl have been reduced significantly both for early and late postexercise periods, when compared with the other two strategies, with the CL+MS4EH+CHO achieving 0.00% as median.

The unexpected amount of L1 hypoglycemic events during late postprandial period observed in the CL+CHO arm occurred mainly in two patients, which contributed with 13 of the total 18 events. More investigation should be performed to better understand the reason why the CHO controller could not avoid such events.

The CL+MS4EH+CHO suggested to patients less CHO at the announcement of exercise when compared with the CL+MS4EH arm (28.75 vs 35.94 g/session, $p<0.05$), while in the CL+CHO patients faced unannounced exercise. However, in the first two hours after the beginning of exercise, the CL+CHO arm recommended 30 grams of CHO per exercise sessions, and in the following 4 hours recommended an additional 9.38 grams of CHO per session. The CL+MS4EH+CHO arm suggested only 10.34 grams of CHO in the first two hours after the commencement of exercise, with additional 2.81 grams in the following four hours.

Figure 4.8 shows the aggregated plot of CGM readings, insulin delivery and recommended CHO for all the 80 exercise sessions. It is possible to note that the CL+MS4EH+CHO arm usually recommended CHO rescues in the final period of exercise, which allows patients to complete the 50 minutes of activity before ingesting CHO. On the other hand, the CL+CHO arm recommended CHO intake in the middle of exercise sessions. Finally, the CL+MS4EH arm just suggest CHO intake 20 minutes before the commencement of exercise, totaling 35.94 grams per session.

Table 4.9: Population outcomes of Scenario F. Overall outcomes encompass the whole period of simulation (15 days). Exercise-related outcomes encompass all the 80 sessions performed by the entire cohort.

	CL+MS4EH	CL+CHO	CL+MS4EH+CHO
Overall outcomes (15 days)			
Mean glucose (mg/dl)	126.42 (123.8-127.3)	123.78 (119.7-128.6)‡	126.39 (123.6-127.7)
% of time spent in glucose levels			
70-180 mg/dl	97.72 (96.3-98.2)†	97.93 (95.9-99.4)	98.14 (97.3-99.4)
>180 mg/dl	1.78 (0.9-3.1)	1.26 (0.3-2.4)	1.74 (0.6-2.7)
<70 mg/dl	0.72 (0.3-1.0)†	0.42 (0.0-1.5)‡	0.06 (0.0-0.1)
<54 mg/dl	0.14 (0.0-0.4)†	0.00 (0.0-0.0)	0.00 (0.0-0.0)
Hypoglycemic events			
L1 events per day	0.20 (0.1-0.3)†	0.20 (0.1-0.5)‡	0.07 (0.0-0.1)
L2 events per day	0.07 (0.0-0.1)†	0.00 (0.0-0.0)	0.00 (0.0-0.0)
CHO consumed (g/day)	19.17 (16.7-21.0)†	25.50 (20.0-31.0)	26.17 (23.7-31.7)
Exercise-related outcomes (8 sessions per patient)			
Glucose at exercise start (mg/dl)	155.25 (153.8-162.4)†	137.06 (131.6-138.0)‡	153.56 (151.6-161.6)
CHO at announcement (g/session)	35.94 (31.3-39.4)†	0.00 (0.0-0.0)‡	28.75 (25.6-33.1)
From exercise start + 2 h			
CHO recommended (g/session)	0.00 (0.0-0.0)†	30.00 (30.0-30.0)‡	10.31 (5.6-11.3)
Minimum glucose (mg/dl)	81.38 (74.8-87.5)†	78.06 (68.3-84.4)‡	88.69 (81.0-90.6)
% of time <70 mg/dl	5.00 (2.5-8.0)†	4.00 (0.0-16.0)‡	0.00 (0.0-2.0)
% of time <54 mg/dl	0.00 (0.0-0.0)	0.00 (0.0-0.0)	0.00 (0.0-0.0)
Hypoglycemic events			
L1 events per session	0.25 (0.1-0.3)†	0.25 (0.0-0.6)	0.00 (0.0-0.1)
L2 events per session	0.00 (0.0-0.0)	0.00 (0.0-0.0)	0.00 (0.0-0.0)
Total L1	17	25	5
Total L2	2	2	0
From 2 h after exercise start + 4 h			
CHO recommended (g/session)	0.00 (0.0-0.0)†	9.38 (5.6-16.9)‡	2.81 (1.9-9.4)
% of time <70 mg/dl	1.40 (0.0-2.3)†	1.15 (0.5-7.9)‡	0.00 (0.0-0.0)
% of time <54 mg/dl	0.00 (0.0-1.0)	0.00 (0.0-0.0)	0.00 (0.0-0.0)
Hypoglycemic events			
L1 events per session	0.00 (0.0-0.0)	0.13 (0.0-0.3)	0.00 (0.0-0.0)
L2 events per session	0.00 (0.0-0.0)	0.00 (0.0-0.0)	0.00 (0.0-0.0)
Total L1	2	18	0
Total L2	1	1	0

† p-value<0.05 between CL+MS4EH and CL+MS4EH+CHO.

‡ p-value<0.05 between CL+CHO and CL+MS4EH+CHO.

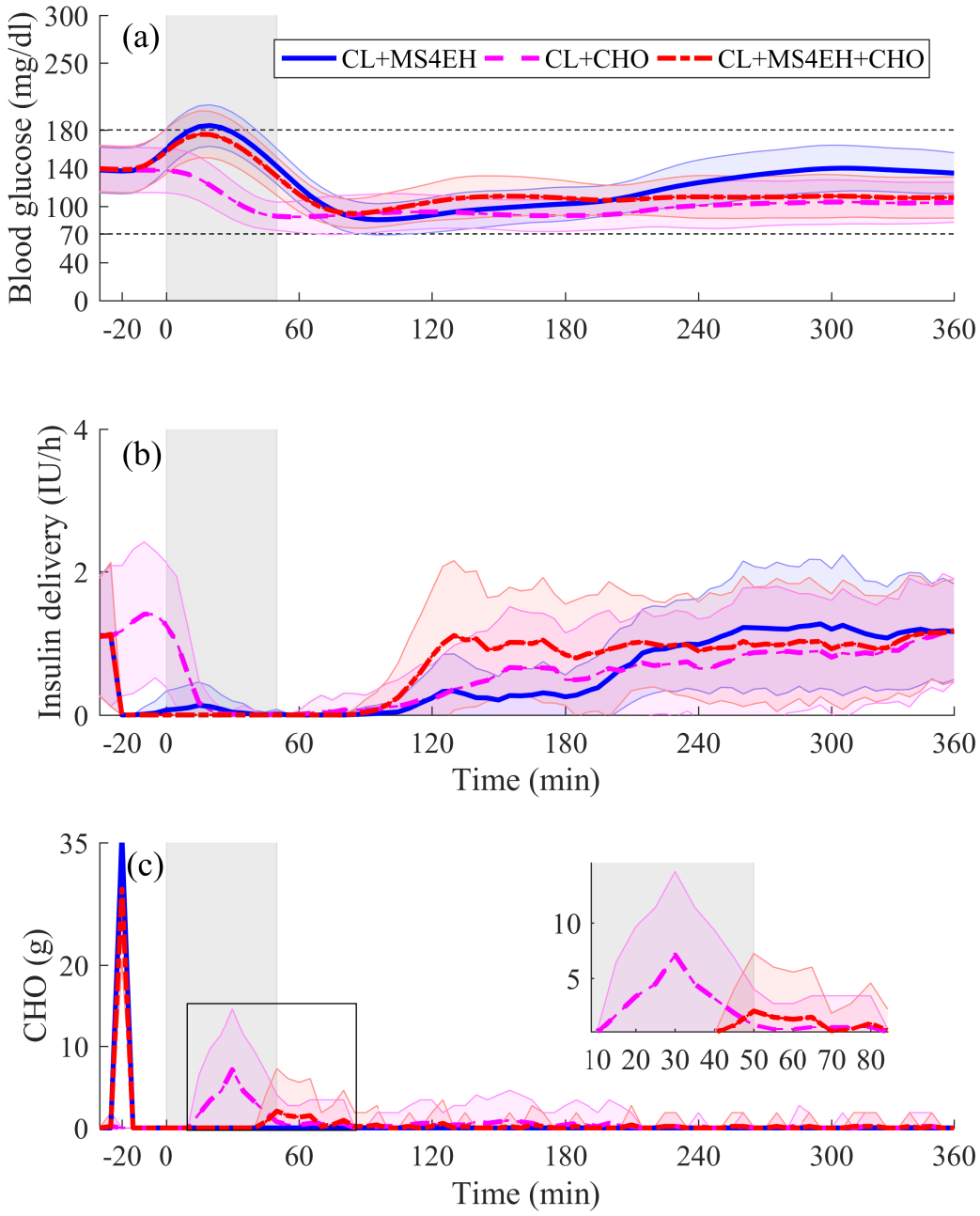

Figure 4.8: Aggregated population for all the exercise sessions in Scenario F. (a) CGM readings in mg/dl; (b) Insulin delivery in IU/h; (c) CHO consumed by patients in grams. Blue lines are mean ± SD for CL+MS4EH, pink lines are mean ± SD for CL+CHO and red lines are mean ± SD for CL+MS4EH+CHO. Gray shaded area represents the exercise period. Dashed black lines represent glucose thresholds of 70 mg/dl and 180 mg/dl in graph (a).

4.4.3 Preliminary results from a clinical trial with real subjects

The Spanish Consortium on Artificial Pancreas and Diabetes Technology is currently performing a clinical trial with 10 adult subjects with T1DM to evaluated the efficacy of the AP system challenged by aerobic exercise[1].

Each subject undergoes three exercise tests, each one at 1-2 week intervals, thus completing the 3 experiments in about 6 weeks. In each of the trials, participants uses a different insulin therapy: 1) conventional CSII therapy, 2) CL control without exercise announcement (CL+CHO) presented by Beneyto et al. (2018), and 3) CL control with exercise announcement, with the MS4EH actions combined with the CHO recommender loop (CL+MS4EH+CHO) presented in Section 4.4. In the day of the experiment, the participant engages 3 sets of 15 minutes of cycloergometer at 70% of VO_{2max} with 5 minutes of rest between each set.

Patients were admitted in the clinical facility around 08:00, after consuming breakfast at home (without restrictions regarding size or composition). In the arms with automatic control, the CL were started around 8:45 with patients in postprandial period, considering the DRB strategy presented in Section 4.2 (slight modified since patients received a standard meal bolus at home), intended to drive blood glucose levels to the target before the commencement of exercise, planned for 12:00. In the arms that required announcement, exercise was informed for the system 20 minutes in advance. Venous blood samples will be collected for glucose determination trough reference method (YSI 2300 STAT Plus, YSI Inc. Life Sciences, Yellow Springs, OH) every 15 minutes before/after exercise, and every 10 minutes during the exercise. If any venous blood readings falls below 70 mg/dl, 15 grams of glucose should be provided as a hypoglycemia rescue.

The clinical trial is still being conducted to date. Figure 4.9 presents the results obtained for five patients and Table 4.10 depict some numerical outcomes for those patients, only for the CL+MS4EH+CHO arm.

Most of the patients achieved fair outcomes. Three subjects spent 100% of the time in target range, while subject 'PAT6' spent 6.12% of the time below 70 mg/dl. For this patient, the controller recommended the ingestion of 15 grams of CHO during the physical activity (see the triangle in Figure 4.9 (a)). Although the hypoglycemic event occurred, it was not a severe event, since the lowest CGM value was 66 mg/dl. On the other hand, Patient 'PAT7' reached hyperglycemic levels after the ending of exercise. As can be noted in Figure 4.9 (a), aerobic exercise did not caused the expected drop in blood glucose levels for this patient. However, the same patient also suffered from hyperglycemia on the other two arms of the clinical trial as well. Considering the time instant where t=180 min (the last CGM sample of the clinical trial),

[1]More information regarding this clinical protocol can be obtained at clinicaltrials.gov (NCT03577158).

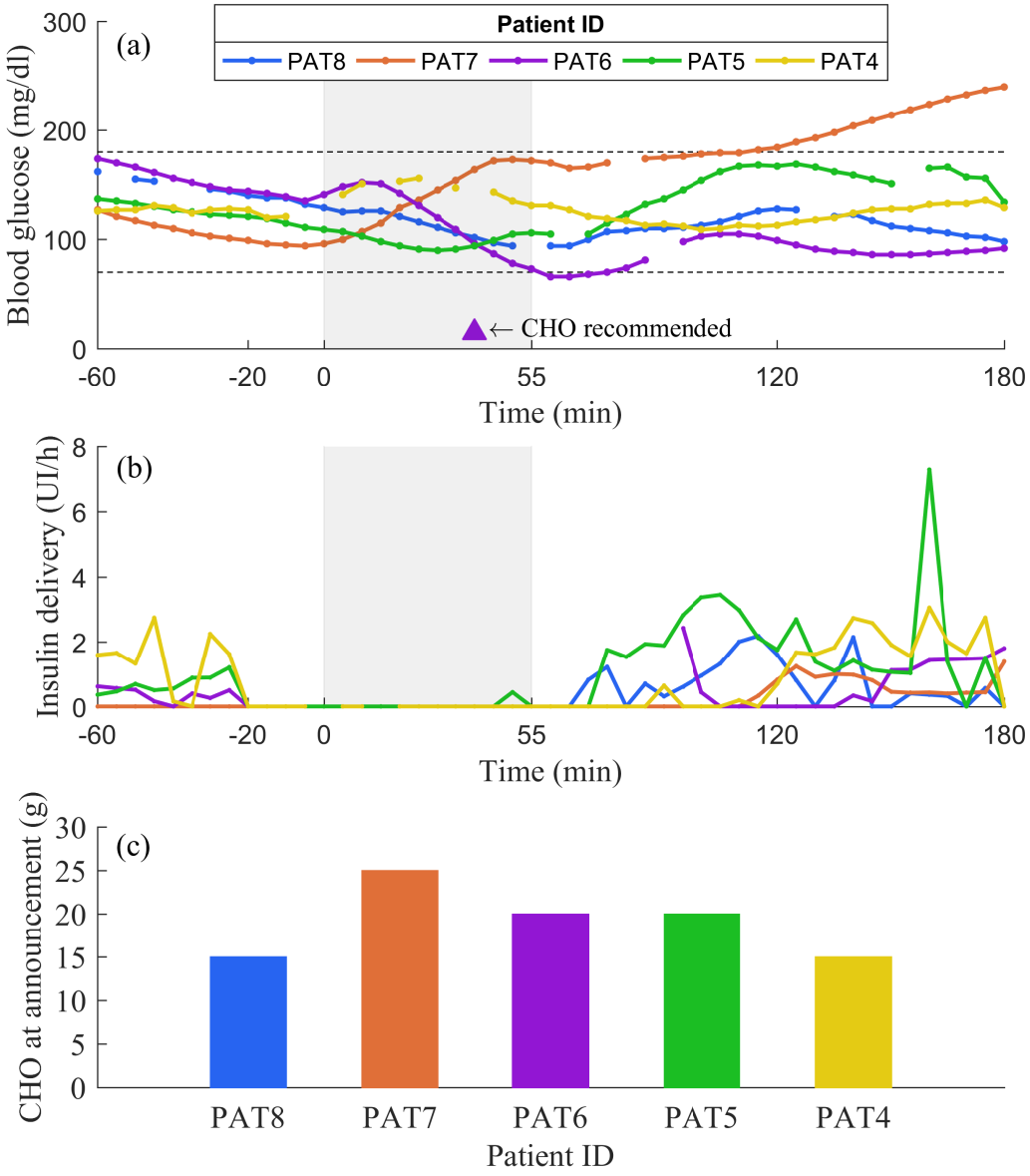

Figure 4.9: Preliminary results from the ongoing clinical trial in the exercise announcement arm for five subjects. (a) CGM readings in mg/dl; (b) Insulin delivery in IU/h; (c) CHO consumed by patients in grams at the announcement, which occurred 20 minutes before exercise. Gray shaded area represents the exercise period. Dashed black lines represent glucose thresholds of 70 mg/dl and 180 mg/dl in graph (a).

CGM readings were: 244 mg/dl, 229 mg/dl and 240 mg/dl for the conventional CSII therapy, CL with unannounced exercise and CL with announced exercise, respectively. Therefore, it is supposed that the basal insulin profile for this patient is not adequate. Additionally, the amount

of CHO consumed at the announcement ranged from 15 to 25 grams per sessions, in accordance with the guidelines found in the literature (Riddell et al., 2017).

Table 4.10: Individual outcomes obtained for five subjects during the ongoing clinical trial. Results are computed based on the last four hours of the study, which are represented in Figure 4.9.

Patiend ID	CHO at announcement (g)	CHO recommended (g)	Percentage of time spent in		
			<70 mg/dl	70-180 mg/dl	>180 mg/dl
PAT8	15	0	0.00	100.00	0.00
PAT7	25	0	0.00	71.43	28.57
PAT6	20	15	6.12	93.88	0.00
PAT5	20	0	0.00	100.00	0.00
PAT4	15	0	0.00	100.00	0.00

4.4.4 Discussion

This Section presented the junction of the MS4EH with the CHO recommender system in order to reduce even more the risks of hypoglycemia associated with aerobic exercise. As observed in Section 4.3, the inclusion of the MS4EH action in the standard CL system is able to reduce significantly the occurrence of exercise-induced hypoglycemia, but some events still occurred. Therefore, it was hypothesized that the arrangement of the MS4EH actions with the CHO recommender system would be able the outperform the previous method.

The results depicted in both Table 4.9 and in Figure 4.8 show clearly that the CL system with both CHO recommender and MS4EH actions is able to achieve the best exercise-related outcomes in the scenario analyzed. In none of the exercise sessions patients experienced L2 hypoglycemic events, and only five L1 episodes occurred due to physical activity, out of 80 sessions.

The partial results obtained from a clinical trial conducted with real T1DM patients indicate that the MS4EH strategy combined with the CHO recommender system is able to avoid severe hypoglycemia all the patients evaluated so far, replicating the in silico results. Furthermore, only one patient spent few minutes in L1 hypoglycemic range, with minimum CGM of 66 mg/dl.

The greatest advantage of unannounced strategy (CL+CHO arm) is that patients do not need to announce exercise, releasing them from consuming CHO before exercise. However, as depicted in Figure 4.8 (c), it is likely that subjects will need to consume CHO anyway during the physical activity. Besides that, this strategy achieved the highest amount of hypoglycemic events when compared with the others.

Therefore, consuming CHO before exercise might be necessary for insulin-only AP systems, just as it is for CSII therapy. Moreover, as the first generation of AP devices tends to be hybrid systems, the announcement of exercise might not be an additional burden for subjects. The forthcoming generation of dual-hormone AP system, with stable glucagon formulation, are more likely to not require any exercise announcement from patients.

4.5 Summary

In this Chapter, it has been presented different approaches to deal with the two most important challenges of the AP for domiciliary use: meals and exercise. A limitation of the AP under development by the Spanish Consortium on Artificial Pancreas and Diabetes Technology is that the CL algorithm relies on the SAFE layer to avoid insulin overdosing. However, the operation of the SAFE layer depends on the adjustment of the constraint $\overline{IOB}$, which was previously adjusted for foods with 60 grams of CHO. Therefore, it has been presented a novel methodology to adjust $\overline{IOB}$ in a real time fashion considering the operation of the AP during 24 hours per day, where patients will consume more than a single meal per day. Initially, the basal profile from patients' CSII therapy is used to create a baseline for $\overline{IOB}$, and this baseline is augmented by a gain for both day and overnight periods. Additionally, a set of rules are considered after the announcement of a meal, followed by an augmented meal bolus. These rules evaluated the need to increase $\overline{IOB}$ temporarily if high glucose values are observed during postprandial period. Results showed that the method can be applied in the AP for domiciliary use.

Regarding exercise management, it has been presented in this work mitigation strategies to reduce the risk of hypoglycemia caused by aerobic exercise, so-called MS4EH. Firstly, the MS4EH have been developed to deal with announced exercise sessions, considering a recent published consensus statement for exercise management on T1DM. At the announcement of exercise, patients are asked to consume a certain amount of CHO, determined based on blood glucose and IOB levels. Moreover, several parameters of the controller are modified in order to reduce the suggestions provided by the insulin controller during and after exercise. Secondly, the MS4EH actions have been slightly refined to be incorporated in the control scheme which considers an additional control loop, that suggests CHO intake to avoid hypoglycemia. This approach have been tested in a clinical trial with real subjects with T1DM, and preliminary results are also presented here.

CHAPTER 5

PREDICTION OF NOCTURNAL HYPOGLYCEMIA USING MACHINE LEARNING TECHNIQUES

5.1 Introduction

Nocturnal hypoglycemia is one of the most feared and dangerous situations that T1DM patients are exposed due to intensive insulin therapy. This Chapter is intended to present a new decision support system based on machine learning techniques to predict the occurrence of nocturnal hypoglycemia. Firstly, it is presented a general overview about nocturnal hypoglycemia, presenting the risks and causes associates with the occurrence of this acute complication, as well as the approaches already evaluated to deal with this problem. Later, the data set containing data from 10 adult patients under MDI therapy is presented as well as the entire data processing employed. Then, individualized prediction models have been developed and results are presented in terms of sensitivity and specificity.

5.2 Nocturnal hypoglycemia

Nocturnal hypoglycemia lacks a consensus definition, but in clinical practice it is referred to episodes that occur while subjects are sleeping. Such acute complication can affect both T1DM and T2DM, and it is a dangerous situation for patients. The DCCT trial showed that tightening glycemic control increases the risk of hypoglycemia, and data analyzed in this study showed that more than 50% of the episodes of severe hypoglycemia occurred while patients were

sleeping (The DCCT Research Group, 1991). When nocturnal hypoglycemia occurs, abnormal heart rhythms are observed (cardiac arrhythmia) when compared with nocturnal periods in normoglycemic range, and in extreme cases, sudden death during sleep can happen, so-called as 'dead in bed syndrome' (Graveling and Frier, 2017).

Although the occurrence of sudden death during sleep is rare, nocturnal hypoglycemia may have adverse consequences other than the death, causing confusion, sweating, seizures, and affects quality of life and work performance on the following day. Moreover, fear of nocturnal hypoglycemia is associated in adults with T1DM with poor sleep quality and greater sleep interruption to check blood glucose levels during the night (Martyn-Nemeth et al., 2018; Frier et al., 2016; Brod et al., 2013).

One of the most important defence against severe hypoglycemia is the capability to recognize falling glucose levels. This recognition is based on a complex hormonal system, which alerts patients to the falling levels (Matyka et al., 1999), and subjects with T1DM are less likely to be awakened by hypoglycemic events than healthy individuals (Banarer and Cryer, 2003). Repeated exposure to hypoglycemia leads to impairment of this complex system that characterises hypoglycemia, leading to impaired awareness of hypoglycemia (hypoglycemia unawareness) (McNeilly and McCrimmon, 2018). Nevertheless, subjects that suffer from impaired awareness of hypoglycemia are unable to detect falling glucose levels and suitably take a correction action to initiate self-treatment, increasing the risk of aggravating the severity of hypoglycemia (Ly et al., 2009).

There are several possible causes and risk factors for the occurrence of nocturnal hypoglycemic events while patients are sleeping. Risk factors that predispose an individual to nocturnal hypoglycemia include previous exposure to severe hypoglycemia, low HbA_{1C}, impaired awareness of hypoglycemia and increasing duration of diabetes. Potential causes that can contribute with nocturnal hypoglycemia include excessive insulin doses close to bedtime, long periods without meals (since overnight is typically the longest interprandial interval), alcohol consumption and physical activity during the day (Graveling and Frier, 2017).

Daytime physical activity is one of the most recognized causes of nocturnal hypoglycemia, especially due to the delayed effects in glucose utilization during recovery phase (Petruzelkova et al., 2017; McMahon et al., 2007; MacDonald, 1987). In a study conducted with children by Bachmann et al. (2016), nocturnal hypoglycemia was associated with two factors: bedtime glucose levels and daytime physical activity. Authors monitored physical activity with accelerometry, and one hour of vigorous exercise increased the risk of nocturnal hypoglycemia by 82%. Similar conclusions were obtained by (Metcalf et al., 2014), finding a 31% of increased risk of hypoglycemia during overnight when young adults performed moderate to vigorous

exercise in the previous day. Another possible cause of nocturnal hypoglycemia is alcohol consumption. In general, alcohol is a risk factor for hypoglycemia in T1DM patients. Due to the delayed effect associated with reduced nocturnal growth hormone secretion after alcohol consumption, hypoglycemia may occur in the late overnight period, before breakfast (Plougmann et al., 2003; Turner et al., 2001). Additionally, heavy alcohol consumption contributes to disease complications and may temporarily reduce patient competence with respect to performing critical tasks related to self-treatment, such as, bolus dosing, CHO counting and SMBG (Walter et al., 2016), and is more likely that patients may face more difficulties to properly counteract a hypoglycemic event.

Therapeutic approaches for T1DM management plays an important role on nocturnal hypoglycemic episodes. A study conducted by the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group (2010) patients with low HbA_{1C} levels have an increased risk to experience low blood glucose levels during night. This study also showed that hypoglycemia frequency was not associated with insulin infusion strategy, but only 7% of the subjects were MDI users. Wentholt et al. (2007) assessed the occurrence of nocturnal hypoglycemia in T1DM patients treated either by MDI or conventional CSII, and for both groups, hypoglycemia occurred in 33% of the nights. In this study, a small majority of subjects used MDI therapy (33 of 57), however subjects were monitored for a short period of 48 h. In the meta-analyses conducted by Fatourechi and colleagues (Fatourechi et al., 2009), no significant difference in nocturnal hypoglycemia was observed between randomized trials comparing conventional CSII and MDI.

Focused on MDI therapy, Kristensen et al. (2017) analyzed the difference caused by insulin analogues versus human insulin during overnight period in patients under MDI therapy. Their results indicated a reduction in the occurrence of hypoglycemia when patients were treated with insulin analogue (19 hypoglycemic events in 117 nights) instead of human insulin (41 hypoglycemic events in 101 nights). In the same study, authors observed that the number of doses of basal insulin was not associate with nocturnal hypoglycemia. Heller et al. (1999) have also shown that using insulin analogue as premeal bolus is able to reduce significantly the occurrence of nocturnal hypoglycemic events when compared with human regular insulin as premeal bolus.

The addition of CGM into CSII therapy created the first devices which allowed automated suspension of basal insulin delivery, the so-called SAP. Several trials comparing SAP with either LGS or PLGS showed that these features are able to reduce the occurrence of hypoglycemia or the time spent in hypoglycemia against conventional CSII therapy or MDI therapy, being an important tool to assist patients in front of hypoglycemia while they are sleeping (Steineck

et al., 2017). Petruzelkova et al. (2017) conducted a 1-week study at a pediatric diabetes camp to compare the efficacy of the SAP therapy, either with PLGS feature or without it, to prevent nocturnal hypoglycemia after prolonged physical activity. The PLGS system interrupt insulin in 78% of the nights (median of 1 activation per night per patient) with a median duration of 55 minutes. Although nocturnal hypoglycemic events were observed in both groups, the group without PLGS consumed significantly more CHO to prevent and treat hypoglycemia than those in the other group. In a home setting study for 42 nights, Buckingham et al. (2015) concluded that PLGS system is able to reduce significantly overnight hypoglycemia in a pediatric population without increase the time spent in hyperglycemia. In another home-setting study with adults subjects, Buckingham et al. (2013) noticed that insulin delivery was suspended in 53% of the nights by the PLGS algorithm, reducing in almost 50% the occurrence of hypoglycemic episodes when compared with the system without PLGS. Bergenstal et al. (2013) also reported that nocturnal hypoglycemic events occurred less frequently due the LGS feature.

In summary, SAP therapy with either LGS or PLGS feature is able to reduce the occurrence of nocturnal hypoglycemic episodes, but patients must use two devices simultaneously: CGM and insulin pump, increasing the cost associated with T1DM treatment. On the other hand, T1DM patients under MDI therapy do not have any kind of mechanism to assist them to reduce insulin levels while are sleeping. During the day, patients can take actions to correct their glycemic levels whether necessary. However, during overnight, patients can not take any actions while are sleeping, and insulin levels are in accordance with previous injections. Additionally, determining whether a hypoglycemic event will occur during sleep is not a trivial task for patients. As mentioned before, several factors influence overnight glycemic variability, and patients on their own are not able to understand the complex relationship between all of these factors to take the proper decision if they will or will not have a hypoglycemic event in the next hours. Therefore, mechanisms based on artificial intelligence to predict future hypoglycemic events may be very useful to help patients to manage their blood glucose levels while are preparing to sleep.

5.3 Machine Learning in DM research

Machine learning is a field of artificial intelligence used in data-analysis to create computational models based on retrospective data, through algorithms which provide a powerful conceptual and analytic framework capable of integrating multiple data types and sources. Over the last couple of decades, the evolution and of machine learning methods accompanied the progress

obtained by computer in both processing speed and storage capacity, broadly benefiting society in several fields of knowledge. Short-term prospects indicate they are likely to have considerable success in clinical practice. The main reasons for this growth include the explosive increase in the amount of available information, along with the improved performance of intelligent methodologies capable of handling and processing this information, both of which have led to the development of tools and applications which can enhance the effective management of complicated diseases.

Machine learning algorithms have been applied widely in biomedical engineering, including diagnostic and prediction of different types of cancer (Lynch et al., 2017; Asri et al., 2016; Kourou et al., 2015), identification of laryngeal pathologies (Fonseca et al., 2007), prediction of Alzheimer's disease through images of the brain (Ding et al., 2019), prediction of mortality and complications for patients admitted in intensive care units (Awad et al., 2017; Meyer et al., 2018), diagnosis of Parkison's disease based on vocal impairment (Lahmiri et al., 2017), and many other applications. For further details of machine learning techniques in healthcare and clinical applications, readers are refereed to another literature reviews (Miller and Brown, 2018; Hamet and Tremblay, 2017; Yoo et al., 2012; Wernick et al., 2010).

Due to the great socio-economic impact caused by DM worldwide, a large volume of diabetes-related data are available either for physicians tailor patients' therapy or for researchers to apply machine learning and data mining techniques to develop novel intelligent systems to aid both physicians and patients. In a recent literature review performed by Contreras and Vehi (2018), an impressive growth of articles including the terms 'diabetes' and 'artificial intelligence' has been observed over the last decade. The aim of machine learning utilization have a wide range in the context of diabetes management. In the aforementioned review, authors classified 141 papers into seven groups according to its application: prediction of blood glucose levels, detection of adverse glycemic events, advisory systems and meal bolus calculators, strategies for automatic control, risk and patient personalization, detection of meals/exercise/faults and daily-life support in diabetes management (Contreras and Vehi, 2018).

One of the most notorious application of machine learning methods in diabetes-related data is focused on the prediction of blood glucose levels, especially after the introduction of CGM devices. From a clinical perspective, having a continuous predictor would guide patients' decisions regarding the actions required to avoid undesirable hypo- or hyperglycemia. Numerous publications aimed this objective, using several machine learning techniques: grammatical evolution (Contreras et al., 2017), random forest (Georga et al., 2012), artificial neural networks (Zecchin et al., 2012), support vector machine (Bunescu et al., 2013) and others. Further information regarding prediction strategy for blood glucose levels can be obtained

elsewhere (Oviedo et al., 2017). When compared with continuous prediction of blood glucose levels, very few publications focusing on the prediction of adverse episodes can be found in the literature. In the review of blood glucose prediction strategies conducted by Oviedo et al. (2017), 87% of the publications focused on the continuous prediction of blood glucose levels, and the remaining 13% were intended to predict the occurrence of adverse glycemic events.

Sudharsan et al. (2015) applied different machine learning algorithms to predict hypoglycemia in T2DM. In their study, two different prediction windows have been used in a bi-class classification problem: a prediction window of 24 h when they considered only the last 11 SMBG readings as inputs for the models (value and timestamp) and another prediction window of 4 h including medication information as inputs altogether with SMBG. However, authors failed to inform the procedure used to label instances. For both approaches a higher degree of sensitivity and specificity were achieved, indicating that the models could be used to avoid hypoglycemia in T2DM.

Reddy et al. (2019) also applied machine learning techniques to predict the occurrence of a hypoglycemic episode while adults with T1DM are performing aerobic exercise. Data collected under different inpatient clinical trials have been used, with the duration of exercise between 30 and 45 minutes. Instances were labeled as any capillary blood glucose reading below than 70 mg/dl during or immediately after exercise. Features used as inputs for a random forest algorithm included anthropometric data, physical activity, glucose data, and hormone data (for data obtained during dual-hormone therapy). The random forest algorithm was able to achieve an accuracy of 86.7%, with sensitivity and specificity of 86.21% and 86.89%, respectively.

The prediction of postprandial hypoglycemia has been approached by Oviedo et al. (2019) through support vector machines. Retrospective data from 10 adults with T1DM under SAP therapy was used to generate personalized prediction models. For every meal intake available in the data, a prediction window of 4 h after the meal has been used to label the data, and data labeling considered different thresholds of glucose and pump suspension duration. In addition to the CHO content of the meal, several features obtained from glucose and insulin retrospective data were used to feed the models. Results achieved a median of 71% for sensitivity and 79% for specificity considering the entire cohort.

With respect to nocturnal hypoglycemia, some studies are directed to the detection of nocturnal hypoglycemia instead of its prediction (Snogdal et al., 2012; Ling and Nguyen, 2011; Skladnev et al., 2010). However, very few studies reported results of the prediction nocturnal hypoglycemia events as a bi-class classification problem. Takahashi et al. (2017) considered fasting glucose levels or post breakfast glucose excursions to predict nocturnal hypoglycemia in the following night on T1DM adults patients. Their conclusions indicated that fasting glucose

levels were significantly lower when hypoglycemia occurred in the next night, with 80% in sensitivity and 75% in specificity. Tkachenko et al. (2016) also approached the prediction of nocturnal hypoglycemia using a linear combination to aggregate several heuristic classifiers to determine if a nocturnal hypoglycemia would have occur. Authors evaluated their methodology into a selected number of instances obtained from two different data sets in patients with T1DM under MDI therapy, with either CGM or SMBG records. Only retrospective data from blood glucose levels were used as input features for their predictors. Finally, the aggregated predictor resulted in satisfactory metrics in terms of sensibility and specificity. The two studies mentioned above created predictions models based on population data. Moreover, both of them just considered blood glucose readings to create features to be used as predictor variables, while it is well established that other variables influence glycemic levels during overnight.

5.4 Decision Support System for prediction of nocturnal hypoglycemia on T1DM patients under MDI therapy

Considering that patients under MDI therapy are more exposed to nocturnal hypoglycemia than SAP users, and also complications and consequences of such adverse event in patients' lives, it is proposed in this work the development of an decision support system to aid patients with T1DM under MDI therapy to anticipate to occurrence of nocturnal hypoglycemic episodes based on predictions based on machine learning technique. Although a few number of published works have already addressed this problem, more effort is still required due to the significance of this problem in T1DM management.

Additionally, it is well established that physical activity performed during daytime have influence in the blood glucose during overnight. However, the heretofore works intended to predict nocturnal hypoglycemia did not included such information as input feature. Such omission is possibly due to the difficulty to quantify the accumulated effects of physical activities.

Therefore, it has been necessary to carry out a clinical trial to collect the necessary data from real patients, since clinical data from MDI users was not available to evaluate the feasibility of such approach.

5.4.1 Research design and clinical protocol

This was a longitudinal, prospective, interventional and open label study conducted at the Hospital Clinic of Barcelona and was approved by the ethical committee (Appendix A). Major

eligibility criteria included adults subjects (>18 years) with T1DM for at least five years, on MDI therapy using a rapid acting insulin analogue as prandial insulin, with an HbA_{1c} between 6.5% and 8.5%, able to perform CHO counting and without using a CGM over the last three months[1].

The study was designed to monitor patients during 12 weeks at home under free-living conditions, intended to collect data on daily activities performed by patients. During this period, every patient used an isCGM sensor and also a physical activity tracker. The FSL system (Abbott Diabetes Care, Alameda, CA, USA) has been used in this study as isCGM and the Fitbit Alta HR wristband (Fitbit, Inc., San Francisco, CA, USA) has been considered to obtain the data related with physical activity from patients.

In the initiation visit, patients received FSL sensors, the Reader device with its specific test strips for SMBG, and the Fitbit Alta HR wristband. Participants were trained on how to use the devices and on how to upload the data to the respective web servers of each manufacturer, allowing the research team to download the data during the study. Each patient received a total of 6 FSL sensors, with sensors' lifespan of two weeks.

Participants were instructed to use the Reader to scan the sensor with a maximum interval of 8 h between each scan, and also as they got ready for bed and as soon as they woke up. The FSL is an isCGM system whereby users must scan the sensor to obtain the instantaneous value of blood glucose concentration and also to get the historical data from the last 8 h of blood glucose levels. This information is shown in the Reader screen which also stores the data in its memory. If subjects take more than 8 h to perform the scan, the historical of data that exceeds this limit is lost.

In addition to sensor scans, patients were instruct to insert manually in the Reader every insulin dose (rapid-acting and long-acting), as well as the estimation of CHO content for every meal consumed during the study. Furthermore, the Reader has a built-in glucose meter for SMBG, and participants were instruct to perform their measurements using this tool. Regarding the Fitbit wristband, participants were informed to wear to device as much time as possible during the study (including sleeping), removing it just for showering, charging or water sports. The Fitbit was synchronized with the patient's mobile, through a Bluetooth connection.

A total of ten subjects were enrolled to participate in the study: 8 females, age 31.8 ± 16.8 years, HbA_{1c} 7.3 ± 0.5 %, body mass index 24.6 ± 3.6 kg/m^2, and duration of diabetes 20.0 ± 8.9 years. After the end of the 12-week monitoring period, some patients were asked if they would like to continue the study for a few more weeks using spare sensors. The study

[1] A complete list of inclusion and exclusion criteria as well as further information regarding this clinical protocol can be obtained at clinicaltrials.gov (NCT03711656).

began in October 2018 and ended in March 2019. All subjects completed the study and written informed consent was obtained from each patient. More detailed information regarding the clinical protocol can be found in Appendix B.

5.4.2 Methods

The development of individualized models have been carried out through several stages. Figure 5.1 illustrate the methodology considering in the initial phase, whereby raw data must be prepared to be applied in machine learning algorithms.

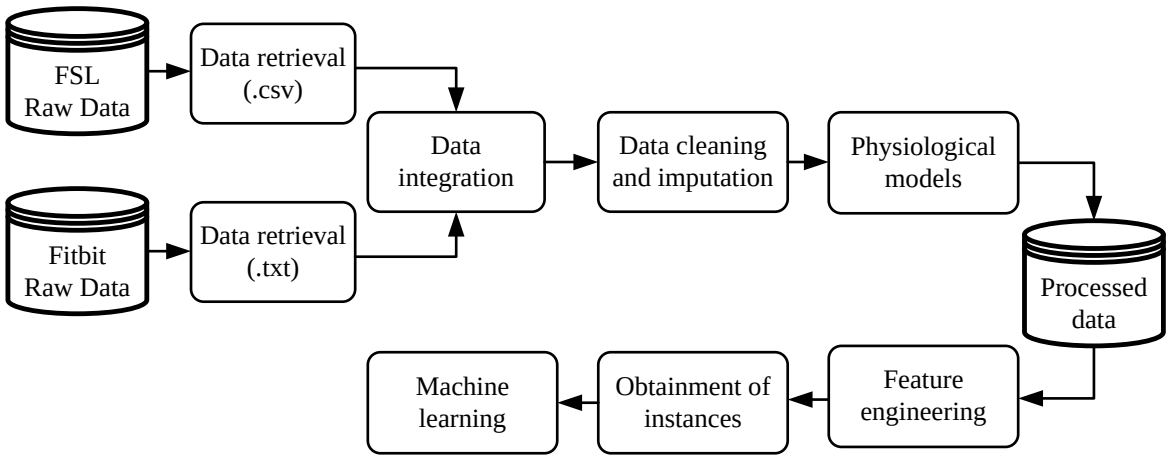

Figure 5.1: Methodology used to prepare the data from FSL and Fitbit before being applied to machine learning algorithms.

5.4.2.1 Data retrieval

The data from the devices used by the patients during the study have been downloaded directly from the web servers maintained by both manufacturers. For the FSL, subjects had to upload the data manually by connecting the Reader into a computer, and uploading the data through a web page. Later the data could be downloaded by the research team in a csv file. In this file, the following variables were available with their date and time stamps: historical data of blood glucose levels (sampled every 15 minutes), blood glucose level when a scan was performed, SMBG readings, fast-acting insulin doses, long-acting insulin doses, and CHO content of meals. Regarding the Fitbit wristband, the following variables were downloaded in a *txt* file with a 1 minute resolution: heart rate, estimation of calories burned, activity level for that time period, and the number of steps performed in that time period. Additionally, information related with the period when the patient was sleeping was also obtained.

5.4.2.2 Data integration

After the obtainment of the data, both files were merged within a single file. The variables were separated into different columns, all aligned based on their respective time stamps. Each day has a total amount of 1440 samples for each variable. For samples where there are no values for some variable, it has been assigned a *NaN*. Figure 5.2 illustrates one day with some of the variables acquired.

5.4.2.3 Data cleaning and imputation

With the data gathered, the next stage was performed to clean the data. This was necessary due to the fact that some patients made a small mistake to insert doses of fast-acting insulin. In such situations the insulin dose values were repeated, requiring the exclusion of one of them.

As mentioned before, the FSL system requires that patients to scan the sensor to obtain and save historical data of blood glucose levels. If patients took more than 8 hours to perform a scan, historical data is missed. To deal with this problem, the imputation of missing data was performed in a straightforward way: any gap in blood glucose levels data lower or equal than 120 minutes was imputed through linear interpolation. In cases of gaps larger than 120 minutes, no imputation was performed. Finally, a sampling period of 5 minutes was considered for all the data, reducing the number of samples of a single day to 288.

5.4.2.4 Physiological models

In addition to the previously mentioned IOB and COB models, it is also been considered in this work the activity on board (AOB) model, introduced by Ozaslan et al. (2017), that demonstrated a significant impact of AOB on postprandial glycemia. The AOB represents the accumulated effects of physical activity in the body. This information is obtained through the steps that patients perform during the day, and are stored thanks to the use of the Fitbit wristband. The total number of steps performed over each sampling time is weighted by an exponential decay curve:

$$AOB(t) = \text{steps}(t)e^{(-k_s t)} \tag{5.1}$$

$\text{steps}(t)$ is the total number of steps and $k_s = 0.0115$ is a constant related to the duration of the effects of physical activity on blood glucose control, set to 0.015. One AOB curve is obtained for each time instant, and the final value of the AOB represents the superposition of all the curves. Figure 5.3 represents illustrate the AOB computed for a short period of time.

The COB model has been applied in all the meals stored on the data, based on the model presented in Section 3.2.3. The IOB model has been applied only in the fast-acting insulin doses

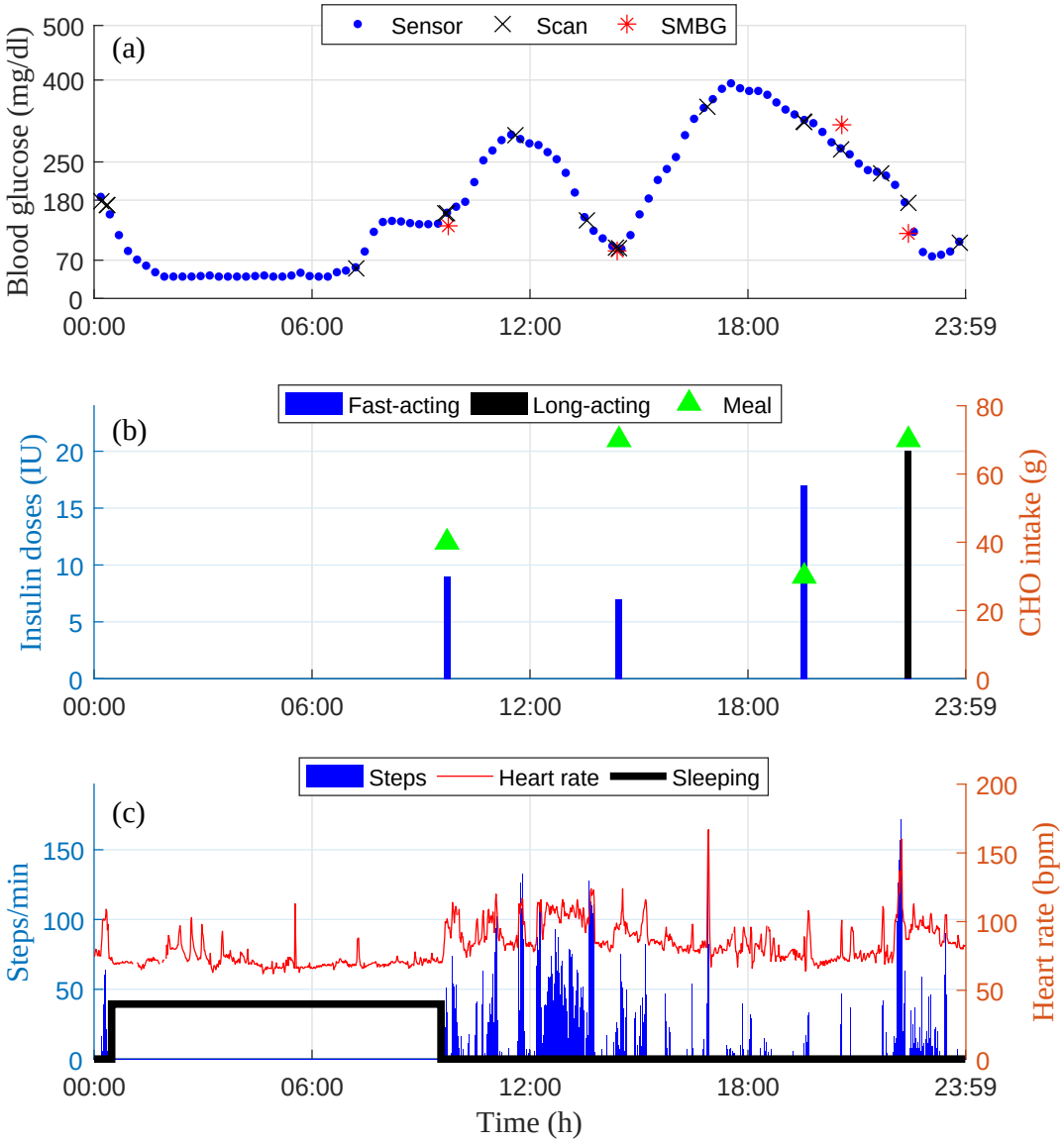

Figure 5.2: Illustration of the data gathered. (a) blood glucose levels: blue circles represent the historical data obtained from the sensor, black crosses represent scan measurements performed by the patient, red asterisks represent SMBG; (b) blue bars represent fast-acting insulin doses in the left y-axis, black bars represent slow-acting insulin doses in the left y-axis, and green triangles represent the amount of CHO from meals in the right y-axis; (c) blue bars represent the steps performed by the patient in the left y-axis, red line represents the heart rate in the right y-axis and solid black line indicates the sleeping period.

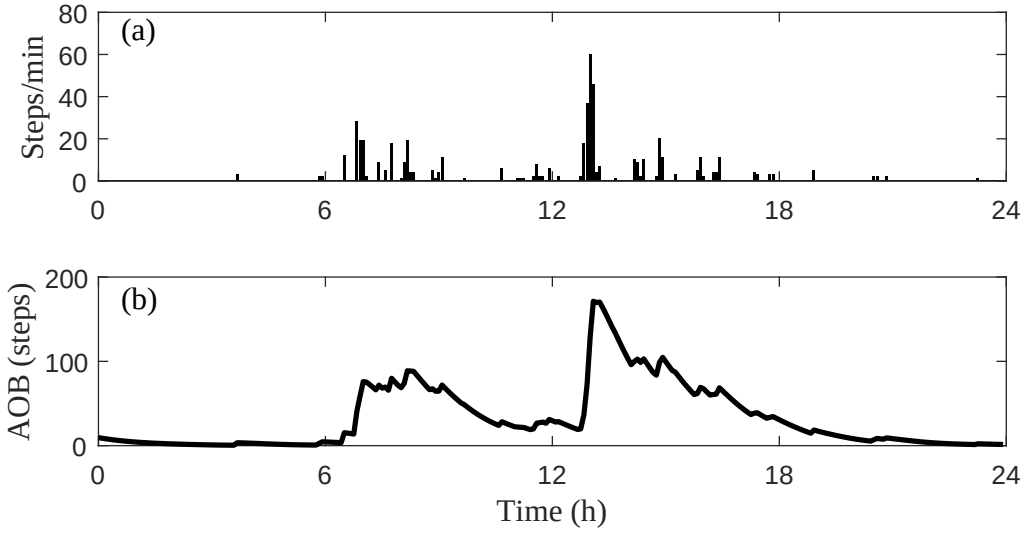

Figure 5.3: Illustration of the AOB model used quantify the effects of physical activity. (a) Steps performed by a patient along the day; (b) Estimated AOB.

due to two reasons: 1) generally subjects inject a single dose of long-acting insulin everyday. But it was observed on the data several days without any information regarding long-acting insulin, and 2) it has been observed a very few variability between the size of long-acting insulin and the timing of these doses. Indeed, in real-life treatment, subjects take such doses always either during the night or during the morning, based on physicians' recommendations.

5.4.2.5 Feature engineering and obtainment of instances

The nocturnal hypoglycemia prediction has been treated as a bi-class classification task, and therefore, supervised learning is considered in this work. On the data properly treated, several time-domain features were extracted to create different attributes used as inputs for the algorithm. In addition, blood glucose data during sleep period was considered for class labeling.

Considering k_0 as the sample when the subject started to sleep, the following features were generated, considering up to the last 6 hours of data before the patient goes to sleep:

BG_sleep: blood glucose level at k_0;

IOB_sleep: IOB at k_0, computed using only fast-acting insulin doses;

COB_sleep: COB at k_0;

AOB_sleep: AOB at k_0;

Mean_BG_0h1h: averaged blood glucose levels during the last hour before sleeping period, i.e., $mean(BG(k_0-1), BG(k_0-2)..., BG(k_0-12))$;

Mean_BG_1h2h: $mean(BG(k_0-13), BG(k_0-14), ..., BG(k_0-24))$;

Mean_BG_2h3h: $mean(BG(k_0-25), BG(k_0-26), ..., BG(k_0-36))$;
Mean_BG_3h4h: $mean(BG(k_0-37), BG(k_0-38), ..., BG(k_0-48))$;
Mean_BG_4h5h: $mean(BG(k_0-49), BG(k_0-50), ..., BG(k_0-60))$;
Mean_BG_5h6h: $mean(BG(k_0-61), BG(k_0-62), ..., BG(k_0-72))$;
AUC_{70}_0h1h: Area Under the Curve (AUC) for a blood glucose threshold of 70 mg/dl and blood glucose measurements over the last hour before sleeping period;
AUC_{70}_1h2h: AUC for a blood glucose threshold of 70 mg/dl and blood glucose measurements between 1 h and 2 h before sleeping period;
AUC_{70}_2h3h: AUC for a blood glucose threshold of 70 mg/dl and blood glucose measurements between 2 h and 3 h before sleeping period;
AUC_{70}_3h4h: AUC for a blood glucose threshold of 70 mg/dl and blood glucose measurements between 3 h and 4 h before sleeping period;
AUC_{70}_4h5h: AUC for a blood glucose threshold of 70 mg/dl and blood glucose measurements between 4 h and 5 h before sleeping period;
AUC_{70}_5h6h: AUC for a blood glucose threshold of 70 mg/dl and blood glucose measurements between 5 h and 6 h before sleeping period;
Rate_of_change_0m5m: the rate of change of blood glucose between k_0 and k_0-1, i.e., $(BG(k_0)-BG(k_0-1))/5$;
Rate_of_change_5m10m: the rate of change of blood glucose between k_0-1 and k_0-2;
Rate_of_change_10m15m: the rate of change of blood glucose between k_0-2 and k_0-3;
Rate_of_change_15m20m: the rate of change of blood glucose between k_0-3 and k_0-4;
Rate_of_change_20m25m: the rate of change of blood glucose between k_0-4 and k_0-5;
Rate_of_change_25m30m: the rate of change of blood glucose between k_0-5 and k_0-6;
LBGI_0h4h: Low blood glucose index (LBGI) computed with the last 4 h of blood glucose data before sleeping period;
LBGI_0h6h: LBGI computed with the last 6 h of blood glucose data before sleeping period;
HBGI_0h4h: High blood glucose index (HBGI) computed with the last 4 h of blood glucose data before sleeping period;;
HBGI_0h6h: HBGI computed with the last 6 h of blood glucose data before sleeping period;;
ΔBG_30min: difference between blood glucose at the beginning of sleep and blood glucose 30 minutes before sleeping, i.e., $\Delta BG\_30min = BG(k_0-6) - BG(k_0)$;
ΔBG_60min: difference between blood glucose at the beginning of sleep and blood glucose 60 minutes before sleeping, i.e., $\Delta BG\_60min = BG(k_0-12) - BG(k_0)$;
Calories_0h6h: Estimation of calories burned over the last 6 h;

In summary, a total of 29 different features were hand-crafted from the data. BG-related features considered the data imputed from the FSL sensor. The LBGI and HBGI are non negative numbers which indicate the extension/frequency of hypoglycemia and hyperglycemia, respectively (Kovatchev et al., 2000). Class labeling was performed considering the following 6 h after the beginning of sleep at k_0. If any blood glucose levels reading was lower or equal than 70 mg/dl, such instance was labeled as Class 1 (night with hypoglycemia). Otherwise, Class 0 (night without hypoglycemia) was assigned.

However, as the procedure for acquiring the data depended on the patients' commitment to insert information related with insulin dosing and CHO intake (necessary to compute IOB_sleep and COB_sleep), wearing the Fitbit wristband (necessary to calculate Calories_0h6h and AOB_sleep), and perform sensor scans regularly (necessary to compute the remaining features). So, to avoid instances with missing information, the following constraints must be fulfilled to in order to include only instances with reliable data in the final data set that will be presented for the machine learning algorithm.

- More than 75% of blood glucose data available in the previous 6 h before k_0;
- More than 50% of blood glucose data available in the following 6 h after k_0;
- At least one sample of blood glucose data available in the last 30 minutes before k_0;
- AOB(k_0), IOB(k_0) and COB(k_0) should be greater than 0.001;

The first three conditions are related with the availability of blood glucose data, used to either during the feature engineering process and also for class labeling. The acquisition of this variable depended on the scans performed by the patients. The last one is related with the features generated by the physiological models. Such condition has been included to remove the instances that patients did not followed the protocol to insert the data related with CHO intake and fast-acting insulin doses or did not used the Fitbit wristband properly. Moreover, some devices malfunctioned during the study, and did not saved steps and sleep-related data. The value 0.001 has been select because values smaller than this indicates that any of the aforementioned variables were not properly saved, indicating that such instance may not be reliable.

The total number of instances generated after the data processing procedure is presented in Table 5.1, as well as the distribution between instances labeled as Class 0 (night without hypoglycemia) and Class 1 (night with hypoglycemia).

The greatest amount of instances were obtained by Patients 12 and 62, because both of them received two extra sensors after the end of the 12-week period. On the other hand, only 14 instances were generated for Patient 51 due to the very poor data quality for this patient,

Table 5.1: Total number of instances for ten patients enrolled in the study. Class 0 is defined as a sleep period without hypoglycemia and Class 1 is defined as a sleep period with hypoglycemia.

Patient ID	Total instances	Class 1	Class 0
P12	104	24 (23%)	80 (77%)
P18	61	11 (18%)	50 (82%)
P23	78	15 (19%)	63 (81%)
P29	78	34 (44%)	44 (56%)
P34	73	13 (18%)	60 (82%)
P40	34	7 (21%)	27 (79%)
P45	34	21 (62%)	13 (38%)
P51	14	3 (21%)	11 (79%)
P56	55	20 (36%)	35 (64%)
P62	91	51 (56%)	40 (44%)

consequence of his/her lack of commitment to follow the clinical protocol, even with repetitive requests to improve his/her engagement along the study.

5.4.3 Performance metrics

For bi-class (or binary) classification problems, predictive models produce two types of outputs. The confusion matrix is a simple and convenient way to represent the results obtained by a classifier, based on the true labels and predicted outputs of a given set of instances. Consider the general classification problem formulated in Section 5.4.4, Figure 5.4 illustrates the confusion matrix for this classification problem.

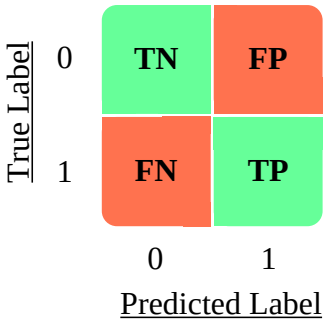

Figure 5.4: Confusion matrix for a binary classification problem. TN: True negative; FP: False positive; FN: False negative; TP: True positive.

The elements in green represent the number of points for which the predicted label is equal to the true label, while the elements in red are those that are mislabeled by the classifier. True

positive (TP) cases refer for positive cases classified correctly and true negative (TN) cases refer for negative cases classified correctly. False positive (FP) classifications refer to negative cases that are incorrectly labeled as positive, and false negative (FN) refer to positive cases that are incorrectly labeled as negative. In the present context, TP and TN mean the cases when nocturnal hypoglycemia appearance or absence, respectively, is correctly predicted. FP means that nocturnal hypoglycemia is predicted, but do not occur and FN means the opposite scenario. These elements of the confusion matrix are used to computed other metrics to evaluate the performance of the classifier.

The sensibility (SENS), or true positive rate, measures the proportion of actual positives that are correctly identified as such, and the specificity (SPEC), or true negative rate, measures the proportion of actual negatives that are correctly identified as such. Equations (5.2) and (5.3) depict how to compute SENS and SPEC, respectively. The precision (PREC), or predictive positive value, measures the proportion of all cases classified as positive in relation with the correct classified as positive, as is computed by Equation (5.4). The accuracy of a classifier represents the proportion of correct classifications among all the examples, and is computed according Equation 5.5.

$$SENS = \frac{TP}{TP + FN} \tag{5.2}$$

$$SPEC = \frac{TN}{TN + FP} \tag{5.3}$$

$$PREC = \frac{TP}{TP + FP} \tag{5.4}$$

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \tag{5.5}$$

However the analysis of a single metric among those presented above may fail to evaluate the performance of a classifier. For example, in the present context, a sensitivity of 100% indicates that every night with hypoglycemia has been correctly predict, but it does not show how many nights without hypoglycemia has been wrongly classified, i.e., it does not take into account FP. An alternative way to evaluate the efficacy of a classifier is to combine some of the previous metrics into a single measure. Equation 5.6 defines the G_{mean}, which considers both SENS and SPEC, giving them the same relevance for classification purposes. Another metric widely applied is the F_{score} (also known as $F1_{score}$), which is an harmonic mean of SENS and PREC, as is defined by Equation (5.7).

$$G_{mean} = \sqrt{SENS \cdot SPEC} \tag{5.6}$$

$$F_{score} = \frac{2 \cdot SENS \cdot PREC}{SENS + PREC} \tag{5.7}$$

5.4.4 Predictive models

As aforementioned, supervised learning has been select to deal with this bi-class classification problem, where data classification is performed by a two step process, consisting of a learning step and a classification step. Consider a given data set S defined as: $S = \{(x_i, y_i)\}$, $i = 1, ..., T$, where $x_i \in X$ is a sample in the q-dimensional feature space $X = \{f_1, f_2, ..., f_q\}$, and $y_i \in Y = \{0, 1\}$ is the class identity label associated with the instance x_i, with $y = 0$ the negative class and $y = 1$ the positive class, and T is the total instances in the data set. The objective of a classifier is to discover how the values of a vector containing different features are related with its associated label. Therefore, for given a set with T examples of the form $\{(x_1, y_1), ..., (x_T, y_T)\}$, machine learning techniques seek to map the unknown relation between x_i and y_i by function $f(x)$, where $f : X \rightarrow Y$, with X the feature space and Y the output space.

Personalized predictive models were generated by training Artificial Neural Networks (ANN) and Support Vector Machines (SVM). ANN is widely applied in supervised machine learning solutions, for both classification and regression problems. ANNs are computational models inspired by the way that the brain performs determined tasks. ANN simulate the brain by acquiring and maintaining knowledge based on information, through an extensive parallel distributed process created by single processing units, referred to as neurons. The acquisition of knowledge is performed through a learning process, and the maintenance of knowledge is possible through the connection strengths between neurons, known as synaptic weights. The learning algorithm, responsible for the learning process, works through the modification of the synaptic weights of the network attempting to obtain the desired objective (Haykin, 2009; Chris Bishop et al., 1995). Multilayer perceptron (MLP) network is one of the most widely used ANN for supervised learning and contain at least one layer that are hidden from both input and output layers. Each layer is composed of a finite number of neurons and each neuron is connected to every neuron in the next and previous layer. The output signal of a neuron is the weighted sum of the inputs, applied to a nonlinear activation function.

SVM have been introduced in the 90's by the mathematician Vladimir Vapnik and colleagues (Vapnik, 1995), and have been employed in several real world problems (Nayak et al., 2015; Hung and Chiu, 2017; Sapankevych and Sankar, 2009; Widodo and Yang, 2007). SVMs are widely used supervised machine learning algorithms applied in bi-class classification problems, that model a separating hyperplane in a multidimensional space aiming to separate the classes into distinct regions. The perpendicular distance from each training observation x_i is computed. The smallest perpendicular distance to a training observation from the hyperplane is known as the margin. The algorithm maximizes the margin between data samples that lie closest to the hyperplane, known as support vectors. An important characteristic of SVM, is the possibility to

transform the data data are not linearly separable into a new higher dimensional space, where the data can be linearly separable (Scholkopf and Smola, 2001). For this purpose, a kernel function is defined in terms of the scalar product in the original space.

Considering the instances obtained after the pre-processing stage (Figure 5.1), predictive models were obtained for each patient using either MLPs or SVMs. As several different factors influence blood glucose during the night, a total of 29 different attributes/features were hand-crafted from retrospective data, aiming to provide the necessary information to predict the nocturnal hypoglycemia. However, it is not known whether some of these features are favorable for this prediction problem, because some of them were generated based on its clinical significance (e.g., LBGI and HBGI), while some of them have already been related with the occurrence of nocturnal hypoglycemia (e.g., blood glucose at bedtime). Therefore, an exhaustive feature selector method have been applied and 2048 feature vectors have been selected in order to evaluated which set of features can provide the best predictions using the same MLP architecture. In all of these vectors, the features BG_sleep, IOB_sleep, COB_sleep and AOB_sleep are considered, and the remaining features were combined, resulting in 2048 possible combinations of features.

Each one of the feature vectors have been considered to create individualized prediction models. Due to the limited number of instances obtained for some patients, k-fold cross validation has been applied in the entire data set. This process should be repeated/iterated a number of times for problems with small sample size (Beleites et al., 2013). Figure 5.5 illustrate the procedure performed for each of the 2048 feature vectors. For each combination of features, stratified random sampling is performed, and thus maintaining the balance between classes. Later, k-fold cross validation ($k = 5$) is conducted, and the results for that iteration is obtained. This procedure is repeated 100 times for each feature vector, and the final result is obtained by averaging the results from the 100 repetitions.

As can be noted in Table 5.1, there is an intrinsic imbalance in the instances obtained. Such imbalance may deteriorate the performance of classifiers, which tends to prioritize the majority class. To deal with such problem, the adaptive synthetic sampling (ADASYN) algorithm (He and Garcia, 2009; He et al., 2008) has been considered during the training process, where synthetic instances from the minority class are created. The ADASYN can handle with the imbalanced data set and also generates synthetic examples from those who are more difficult to learn. The synthetic examples generated by the ADASYN have been used only during training, and no synthetic data have been used for evaluate the efficacy of any predictive model, during the testing phase.

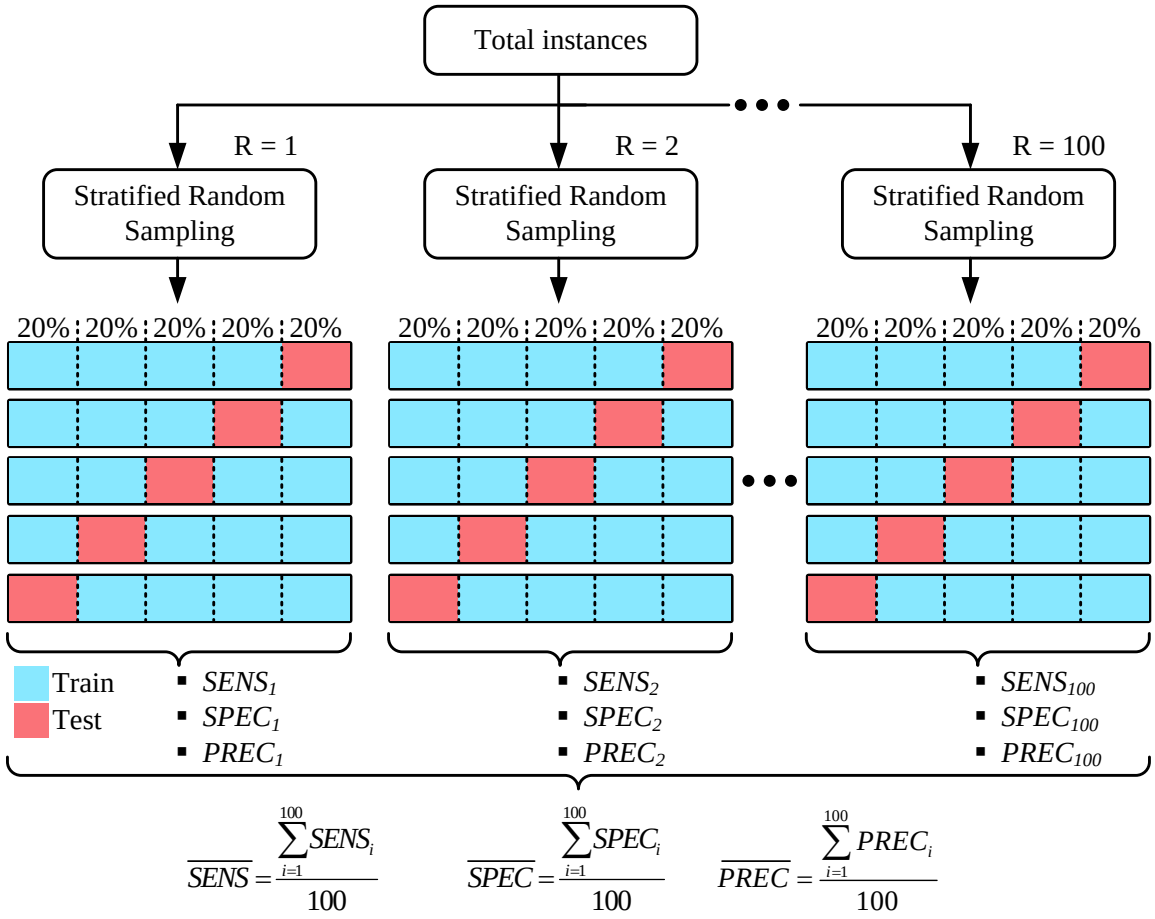

Figure 5.5: Repeated k-fold cross validation procedure. This process is performed for every feature vector in order to maximize the performance of the prediction models.

The software MATLAB has been used in this work. The ANN training and testing were performed using the Neural Network Toolbox. The details of the MLP architecture used in this work is presented in Table 5.2. The Statistics and Machine Learning Toolbox has been considered during the training and testing of the SVM models. For all the patients, the *linear* kernel has been considered, with the regularization parameter C set to 1.

5.4.5 Results

Table 5.3 present the results for the ten patients, considering the feature vector that obtained the maximum G_{mean} (Equation (5.6)) among all the features evaluated, for both MPL and SVM techniques. The averaged value over the 100 runs were considered for this purpose, i.e., $\overline{SENS}$ and $\overline{SPEC}$.

Analyzing the outcomes achieved by the MLP for the entire cohort, the median sensitivity

Table 5.2: Details of the ANN architecture.

Number of layers	2
Neurons in the hidden layer	12
Activation function hidden layer	Hyperbolic tangent
Neurons in the output layer	1
Activation function output layer	Logistic sigmoid
Learning algorithm	Scaled conjugate gradient
Early stopping (maximum failures)	10

Table 5.3: Averaged SENS, SPEC, accuracy and G_{mean} for the best feature vector of each patient over the 100 repetitions performed for both MLP and SVM. Results are presented in percentage.

Patient ID	Sensitivity		Specificity		Accuracy		G_{mean}	
	MLP	SVM	MLP	SVM	MLP	SVM	MLP	SVM
P12	64.08	67.63	63.19	61.30	63.39	62.76	63.28	64.31
P18	65.45	76.91	79.10	71.98	76.64	72.87	71.73	74.34
P23	66.47	74.93	78.86	81.75	76.47	80.44	72.11	78.18
P29	65.71	78.35	72.98	82.20	69.81	80.53	69.00	80.20
P34	63.08	69.00	86.57	84.50	82.38	81.74	73.70	76.14
P40	74.43	80.57	88.22	88.74	85.38	87.06	80.69	84.37
P45	77.81	81.43	78.62	86.54	78.12	83.38	77.95	83.86
P51	100.00	100.00	99.73	100.00	99.79	100.00	99.86	100.00
P56	79.90	79.15	91.37	82.09	87.20	81.02	85.44	80.54
P62	72.57	79.53	70.15	75.97	71.51	77.97	71.19	77.70
Median	69.52	78.75	78.98	82.15	77.38	80.77	72.90	79.19

indicates that almost 70% of the nocturnal hypoglycemic events could be avoided and in only 21% of the cases patients would have taken an unnecessarily action due to a FP prediction. P12 achieved the worst outcomes with a G_{mean} of 63.28%, but even so the results are acceptable since more than half of the hypoglycemia could be avoided.

The SVM achieved even better outcomes for almost all the patients when compared with the MLP, mainly in the sensitivity metric. Considering the median outcomes for the entire cohort, almost 80% of the nights with hypoglycemia would be avoided by this algorithm, and at the same time achieving more than 80% of specificity. P51 achieved 100% of accuracy. However, the very reduced number of instances obtained by this patient make necessary to be skeptical to take further conclusions about his/her results. Similarly with the MLP predictions, the worst outcomes were also obtained for P12, with a G_{mean} of 64.31%.

Additionally, Tables 5.4 and 5.5 depict the features employed in each one of the prediction models considered to obtain the results presented above. At the bottom of each Table it is possible to notice the amount of features used by the best prediction models obtained. The last column on the right indicates in how many patients a specific feature was considered in the prediction models.

Table 5.4: Feature vectors used by each individualized model produced by the MLP to obtain the results presented in Table 5.3. The last column on the right indicates how many patients used the respective feature. The last row indicate how many features have been used by each patient.

Features \ **Patient ID**	P12	P18	P23	P29	P34	P40	P45	P51	P56	P62	∑ →
BG_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
IOB_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
COB_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
AOB_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Mean_BG_5h6h	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
Mean_BG_4h5h	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
Mean_BG_3h4h	✗	✓	✗	✗	✓	✗	✗	✓	✗	✗	3
Mean_BG_2h3h	✗	✓	✗	✗	✓	✗	✗	✓	✗	✗	3
Mean_BG_1h2h	✗	✓	✗	✗	✓	✗	✗	✓	✓	✓	5
Mean_BG_0h1h	✗	✓	✗	✗	✓	✗	✗	✓	✓	✓	5
AUC_{70}_0h1h	✓	✗	✗	✓	✗	✗	✗	✗	✓	✗	3
AUC_{70}_1h2h	✓	✗	✗	✓	✗	✗	✗	✗	✓	✗	3
AUC_{70}_2h3h	✓	✗	✗	✓	✗	✗	✗	✗	✓	✗	3
AUC_{70}_3h4h	✓	✗	✗	✓	✗	✗	✗	✗	✓	✗	3
AUC_{70}_4h5h	✓	✗	✗	✓	✗	✗	✗	✗	✓	✗	3
AUC_{70}_5h6h	✓	✗	✗	✓	✗	✗	✗	✗	✓	✗	3
Rate_of_change_0m5m	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
Rate_of_change_5m10m	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
Rate_of_change_10m15m	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
Rate_of_change_15m20m	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
Rate_of_change_20m25m	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
Rate_of_change_25m30m	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	1
ΔBG_30min	✓	✓	✗	✓	✗	✗	✗	✓	✓	✓	6
ΔBG_60min	✗	✗	✓	✓	✗	✗	✓	✗	✗	✓	4
LBGI_0h6h	✗	✗	✓	✗	✓	✓	✗	✗	✗	✓	4
LBGI_0h4h	✗	✗	✗	✗	✓	✗	✗	✗	✓	✓	3
HBGI_0h6h	✗	✓	✗	✗	✗	✗	✗	✗	✗	✓	2
HBGI_0h4h	✗	✓	✓	✗	✓	✗	✗	✗	✓	✓	5
Calories_0h6h	✓	✓	✗	✗	✗	✗	✗	✓	✗	✓	4
∑ ↓	12	12	7	12	19	5	5	10	15	13	

Table 5.5: Feature vectors used by each individualized model produced by the SVM to obtain the results presented in Table 5.3. The last column on the right indicates how many patients used the respective feature. The last row indicate how many features have been used by each patient.

Features \ **Patient ID**	P12	P18	P23	P29	P34	P40	P45	P51	P56	P62	∑ →
BG_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
IOB_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
COB_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
AOB_sleep	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Mean_BG_5h6h	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	1
Mean_BG_4h5h	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	1
Mean_BG_3h4h	✗	✗	✗	✓	✓	✗	✗	✗	✗	✗	2
Mean_BG_2h3h	✗	✗	✗	✓	✓	✗	✗	✗	✗	✗	2
Mean_BG_1h2h	✗	✗	✗	✓	✓	✗	✗	✓	✗	✓	4
Mean_BG_0h1h	✗	✗	✗	✓	✓	✗	✗	✓	✗	✓	4
AUC_{70}_0h1h	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	0
AUC_{70}_1h2h	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	0
AUC_{70}_2h3h	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	0
AUC_{70}_3h4h	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	0
AUC_{70}_4h5h	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	0
AUC_{70}_5h6h	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	0
Rate_of_change_0m5m	✗	✗	✗	✓	✓	✗	✗	✓	✗	✗	3
Rate_of_change_5m10m	✗	✗	✗	✓	✓	✗	✗	✓	✗	✗	3
Rate_of_change_10m15m	✗	✗	✗	✓	✓	✗	✗	✓	✗	✗	3
Rate_of_change_15m20m	✗	✗	✗	✓	✓	✗	✗	✓	✗	✗	3
Rate_of_change_20m25m	✗	✗	✗	✓	✓	✗	✗	✓	✗	✗	3
Rate_of_change_25m30m	✗	✗	✗	✓	✓	✗	✗	✓	✗	✗	3
ΔBG_30min	✓	✗	✓	✓	✓	✗	✓	✗	✗	✓	6
ΔBG_60min	✗	✗	✗	✓	✗	✗	✗	✓	✓	✗	3
LBGI_0h6h	✓	✗	✗	✗	✗	✓	✗	✓	✓	✓	5
LBGI_0h4h	✓	✗	✗	✓	✗	✗	✗	✓	✓	✓	5
HBGI_0h6h	✗	✗	✓	✓	✗	✗	✗	✓	✗	✗	3
HBGI_0h4h	✗	✗	✗	✓	✗	✗	✗	✓	✗	✗	2
Calories_0h6h	✗	✓	✗	✗	✗	✗	✓	✓	✗	✓	4
∑ ↓	7	5	6	21	15	5	6	18	7	10	

For the models obtained by the MLP (Table 5.4), notice that P34 was the patient which required the largest amount of feature between all the cohort, totaling 19. On the other hand, the prediction models produced for P40 and P45 used only five attributes. Regardless the four first attributes, which have been included for all patients, the feature ΔBG_30min was the most employed feature, being employed for six patients. Curiously, features related with rate of change of blood glucose levels over the last 30 minutes before k_0 were employed only for a single patient (P34). Here it is important to mention that during the exhaustive feature selection procedure, features related with rate of change of blood glucose levels (6 features) were either all included in the feature vector or none of them were included.

In the SVM models, P29 required the largest amount of features between all the cohort, totaling 21. P18 and P40 employed only five features in the models. The feature ΔBG_30min was the most employed as well, but not with the same patients as employed by the MLP models. Only P12, P29 and P62 employed such feature for both techniques. On the other hand, the features related with the area under the curve below 70 mg/dl was not considered in any of the SVM models.

5.5 Discussion

In this Chapter a personalized decision support system has been proposed focused on T1DM patients under MDI therapy. The following 6 h after the commencement of sleep have been considered to label instances, which were applied to MLP networks and SVM classifiers for the obtainment of predictive models. The results indicate that the method could be able to assist patients to avoid hypoglycemia during sleep, with the SVM achieving best outcomes when compared with the MLP.

The effects of this approach are measurable. For instance, P56 had a total of 55 instances obtained, with 20 nights with hypoglycemia. Considering the results obtained by the MLP, in 16 of these nights the system would be able to predict the adverse event and in the remaining 4 nights hypoglycemia would still occur. In case of the prediction of hypoglycemia, a possible action that patients could take is the consumption of bedtime snacks (Kalergis et al., 2003). On the other hand, on the 35 nights without hypoglycemia observed in his/her instances set, in only 3 nights the decision system would alert the patient wrongly, and unnecessary CHO would consumed.

In this work the metric G_{mean} has been adopted to select the best prediction model. This choice was motivated because it apply the same weight on both SENS and SPEC metrics. Although the main objective is hypoglycemia avoidance, benefits should be balanced against

side effects. The occurrence of excessive false positives may lead patients to hyperglycemia during the night and patients may gain weight due to excessive CHO consumption at bedtime. Furthermore, better customization of the models could be achieved depending on the physiological response of patients during overnight period.

The repetitive k-fold cross validation process employed in this work reinforces the reliability of the predictions models, since each models have been evaluated 100 times with stratified random sampling. In this way, it was possible to reduce the of sample selection bias from the conclusions regarding the performance of the models.

A downside of the approach considered to predict nocturnal hypoglycemia in this work is the exhaustive feature selection methodology applied. A major limitation of this method is the computational cost required to evaluate all the feature vectors generated. Indeed, in the present study it took on average 27 hours to conclude the entire training/testing procedure of all the 2048 feature vectors analyzed for each patient for the MLP technique. For the SVM models, the procedure was completed within 3 hours on average[2]. For future applications considering online training of predictive models, other feature selection techniques should be considered or even some dimensionality reduction technique, like principal component analysis (Wang et al., 2014; Chandrashekar and Sahin, 2014).

Due to the exploratory nature of this study, only two machine learning algorithms were evaluated: MLP and SVM. However, other methods could be applied, such as random forest and naive bayes which have been widely applied in classification problems (Fernández-Delgado et al., 2014), or even an ensemble of different algorithms. The obtainment of instances illustrated in Figure 5.1 was developed in order to allow the application of any of these algorithms. Moreover, the selection of the random forest technique could reduce burden caused by the evaluation of different feature vectors, since the algorithm is based on random input variable selection and bootstrapping (Han et al., 2012).

Unfortunately, some patients presented a reduced number of instances. One of the causes was due to missing values of fast-acting insulin injections, that should have been saved by the patients manually. Thus, in the forthcoming clinical trials intended to collects data from MDI patients, smart insulin pens are recommended to reduce the influence of patients' engagement on the quality of the data. The use of the FSL also influenced the quality of the data, since it was required manual scans from patients to avoid data loss. A conventional CGM device would be more convenient to avoid this problem.

Future utilization of this decision support system could be implemented in patients' cell

[2]Considering a computer with the following specifications: Windows 10 Pro, Intel Core i7-4790 3.60 GHz, 16 GB RAM.

phone, based on a dedicated application. Therefore, patients would inform the system that he/she is preparing to sleep, and the decision system would advise the subject whether the consumption of a bedtime snack is indeed necessary.

5.6 Summary

In this Chapter, a novel decision support system intended to predict the occurrence of nocturnal hypoglycemic events has been presented. While such adverse situation is a major concern in T1DM management, and physical activity is directly related with its incidence, very few work has been performed in this field. Moreover, it is considered a group of patients under MDI therapy, whose do not have any kind of aid system to avoid hypoglycemia while sleeping. A clinical trial has been conducted in order to provide the necessary data to train machine learning models. In this work, MLP and SVM have been used considering different hand-crafted features obtained from retrospective data. The results obtained are encouraging, and randomized clinical trials are being planned to evaluated the efficacy of this decision support system operating in real time.

CHAPTER 6

CONCLUSION

Along the advancement of this thesis, work was focused on the development of strategies to improve glycemic control on patients with T1DM, while ensuring their safety by reducing the risk of hypoglycemia. Hypoglycemia is a life-threatening condition, that can lead to serious complications. At the same time, fear of hypoglycemia influences health behaviors used for T1DM management, impairing glycemic control. Therefore, strategies to reduce the risk of such condition are extremely important for T1DM management. This thesis concludes by pointing out the contributions presented in the previous chapters. Moreover, some directions for future research are also discussed to continue the research presented in this work.

6.1 Contributions

The major contributions of this thesis can be summarized in the following aspects:

- A DRB algorithm has been presented in order to adjust in real time the parameter $\overline{IOB}$. This constraint plays a key role in the insulin controller, which is the core of the AP system being developed by the Spanish Consortium on Artificial Pancreas and Diabetes Technology. This algorithm is intended to be employed in free living conditions, and thus must deal with multiple meals along the day and also with the intra-patient variability. The DRB algorithm generates a time-varying $\overline{IOB}$ based on fasting and postprandial periods. During fasting periods, $\overline{IOB}$ is adjusted based on a preset basal insulin profile, allowing the controller to regulate the amount of insulin injected in the body in accordance with patients' circadian variation. When a meal is announced, an augmented bolus is followed

by a set of rules to evaluate in real time whether $\overline{IOB}$ should be increased to drive glucose back to near-normoglycemia. This approach achieved fair results in silico, by reducing the time spent in hypoglycemia while hyperglycemia was not excessive.

- To reduce the risk of exercise-induced hypoglycemia, the MS4EH have been proposed. These strategies take into account ordinary recommendations for conventional insulin therapy and also employ a set of modifications in the controller's tuning during and after the announcement of aerobic exercise. The MS4EH have been evaluated over different in silico scenarios considering an insulin-only controller and also combined with a CHO recommender control loop. It has been shown that the MS4EH may be an adequate approach to reduce the risk of exercise-induced hypoglycemia for insulin-only AP systems. Although such strategy has been evaluated in the context of the AP system under development by the Spanish Consortium on Artificial Pancreas and Diabetes Technology, it could be reproduced by other AP systems with minor modifications. Clinical results obtained so far are promising, indicating that this strategy can be applied in real life.

- A decision support system has been proposed to predict the occurrence of nocturnal hypoglycemia in patients under MDI therapy, allowing them to take some anticipatory action to avoid hypoglycemia. Prediction models created by ANN obtained encouraging results, indicating the feasibility of this approach to be implemented soon.

- A data set of 10 adult patients under MDI therapy have been collected, and thus is available for future research. This data set contains information of insulin doses, CHO intake, blood glucose level measurements and SMBG readings, and also data collected by a physical activity monitor.

6.2 Future work

Besides the contributions presented, several improvements may be considered as continuity of this work:

- To incorporate meal detection strategies into the DRB algorithm. This would remove the necessity of the announcement of meals, reducing patients burden. With the detection of medium and large meals, the limits of IOB could be designed in order to follow a preset profile, allowing the controller to quickly respond to blood glucose rising without leading to hypoglycemia in the late postprandial period.

- To investigate new methodologies to explore the lower limit of IOB, which is the opposite of $\overline{IOB}$. This may reduce the risk of hyperglycemia due to the interruption of insulin over an extended period. This could be implemented by using an additional sensor to measure blood ketones levels.

- To create a supervisory scheme that could optimize controller's tuning considering long-term operation. For example, the MS4EH strategies could be adapted for patients who do not go through the expected drop in blood glucose caused by exercise. Possible candidates to address this problem would be the Run-to-Run and Case-Based Reasoning techniques.

- To evaluate different machine learning algorithms to improve the prediction capabilities of the decision support system. Likewise, several algorithms could work in parallel to improve the reliability of classifications. Moreover, feature selection techniques should be investigated to reduce the computational cost caused by the exhaustive feature selection considered in this work.

- To investigate the generation of population prediction models instead of personalized models. This could reduce the work load and financial cost associated with the data acquisition process. Moreover, population prediction models would accelerate the dissemination of the system, because products "ready-to-use" would be available for patients.

- To develop a mobile application to incorporate the decision support system to predict hypoglycemia. This application should allow patients to inform life events that could also be used as attributes for intelligent systems, i.e., consumption of alcoholic beverages or illness. Additionally, all the data processing stage was performed in an offline fashion in this work. Going forward into real life operation, this stage should be implemented in real-time in this application.

APPENDIX A

ETHICS COMMITTEE APPROVAL

This appendix presents the approval by the ethics committee of the Hospital Clinic of Barcelona.

CLÍNIC BARCELONA Hospital Universitari

DICTAMEN DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

NEUS RIBA GARCIA, Secretario del **Comité Ético de Investigación Clínica del Hospital Clínic de Barcelona**

Certifica:
Que este Comité ha evaluado la propuesta del promotor, para que se realice el estudio:

DOCUMENTOS CON VERSIONES:

Tipo	Versión
Protocolo	V8 de 02/07/2018
Hoja Información de Paciente	V4 de 10/07/2018

TÍTULO: Prediction and prevention of nocturnal hypoglycemia in persons with type 1 diabetes with multiple doses of insulin using machine learning techniques
PROMOTOR: UNIVERSITAT DE GIRONA
INVESTIGADOR PRINCIPAL: IGNACIO CONGET DONLO; MARGA GIMÉNEZ ÁLVAREZ

CIF – G-08431173

y considera que, teniendo en cuenta la respuesta a las aclaraciones solicitadas (si las hubiera), y que:

- El estudio se plantea siguiendo los requisitos de la legislación vigente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto, teniendo en cuenta los beneficios esperados.
- Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el ensayo (si procede).
- Que se han evaluado las compensaciones económicas previstas (cuando las haya) y su posible interferencia con el respeto a los postulados éticos y se consideran adecuadas.
- La capacidad del investigador y sus colaboradores, y las instalaciones y medios disponibles, tal y como ha sido informado, son apropiados para llevar a cabo el estudio.
- Que dicho estudio se incluye en una de las líneas de investigación biomédica acreditadas en este centro, cumpliendo los requisitos necesarios, y que es viable en todos sus términos.

Este CEIC acepta que dicho estudio sea realizado, debiendo ser debiendo ser comunicado a dicho Comité Ético todo cambio en el protocolo o acontecimiento adverso grave.

y hace constar que:
1º En la reunión celebrada el día 28/06/2018, acta 13/2018 se decidió emitir el informe correspondiente al estudio de referencia.
2º El CEIC del Hospital Clínic i Provincial, tanto en su composición como en sus PNTs, cumple con las normas de BPC (CPMP/ICH/135/95)
3º Listado de miembros:

Reg. HCB/2018/0649

HOSPITAL CLÍNIC DE BARCELONA
Villarroel, 170 - 08036 Barcelona (España)
Tel. 93 227 54 00 Fax 93 227 54 54
www.hospitalclinic.org

Presidente:
- BEGOÑA GÓMEZ PÉREZ (Farmacéutica Hospitalaria, HCB)

Vicepresidente:
- JOAQUIM FORÉS I VIÑETA (Médico Traumatólogo, HCB)

Secretario:
- NEUS RIBA GARCIA (Médico Farmacólogo Clínico, HCB)

Vocales:
- ITZIAR DE LECUONA (Jurista, Observatorio de Bioética y Derecho, UB)
- MONTSERRAT GONZALEZ CREUS (Trabajadora Social, Servicio de Atención al Usuario, HCB)
- JOSE RIOS GUILLERMO (Estadístico. Plataforma de Estadística Médica. IDIBAPS)
- OCTAVI SANCHEZ LOPEZ (Representante de los pacientes)
- MARIA JESÚS BERTRAN LUENGO (Médico Epidemiólogo, HCB)
- JOAQUÍN SÁEZ PEÑATARO (Médico Farmacólogo Clínico, HCB)
- SERGIO AMARO DELGADO (Médico Neurólogo, HCB)
- JULIO DELGADO GONZÁLEZ (Médico Hematólogo, HCB)
- EDUARD GUASCH I CASANY (Médico Cardiólogo, HCB)
- VIRGINIA HERNANDEZ GEA (Médico Hepatólogo, HCB)
- NURIA SOLER BLANCO (Farmacéutica Hospitalaria, HCB)
- MARINA ROVIRA ILLAMOLA (Farmacéutico Atención Primaria, CAP Eixample)
- JOSE LUIS BLANCO ARÉVALO (Médico Medicina Interna, HCB)
- MIRIAM MÉNDEZ GARCÍA (Abogada, HCB)
- MERCÈ VIDAL FLOR (Enfermera, HCB)

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, este se ausentará de la reunión durante la discusión del proyecto.

Para que conste donde proceda, y a petición del promotor,

Barcelona, a 19 de julio de 2018

Reg. HCB/2018/0649

HOSPITAL CLÍNIC DE BARCELONA
Villarroel, 170 - 08036 Barcelona (España)
Tel. 93 227 54 00 Fax 93 227 54 54
www.hospitalclinic.org

APPENDIX B

CLINICAL PROTOCOL

This appendix presents the clinical protocol approved by the ethical committee of the Hospital Clinic of Barcelona .

HOSPITAL CLÍNIC DE BARCELONA – UNIVERSITAT DE GIRONA

PREDICTION AND PREVENTION OF NOCTURNAL HYPOGLYCEMIA IN PERSONS WITH TYPE 1 DIABETES WITH MULTIPLE DOSES OF INSULIN USING MACHINE LEARNING TECHNIQUES

V8.02/07/2018

1. STUDY OUTLINE

Title: Prediction and Prevention of Nocturnal Hypoglycemia in Persons with Type 1 Diabetes with Multiple Doses of Insulin Using Machine Learning Techniques.

Investigators, study sites:

From Unidad de Diabetes. Hospital Clínic i Universitari de Barcelona. Diabetes Unit. Endocrinology and Nutrition. IDIBAPS, CIBERDEM. Telf: 932279846.

- Ignacio Conget, MD
- Marga Giménez, MD
- Clara Viñals, MD

From Univesitat de Girona. Institut d'informàtica i aplicacions. Modelling Identification and Control Engineering Lab.

- Josep Vehí, PhD
- Arthur Bertachi, Msc

Phase

IV

Objective

The main objective is to develop a novel system to predict and prevent nocturnal hypoglycemia in T1D patients, focused in patients under multiple daily injections therapy.

Indication

Diabetes management

Design

Longitudinal, prospective, interventional study, usual clinical practice.

Population

Eligible subjects will be patients with type 1 diabetes mellitus for more than five years, aged at least 18 years or older; on multiple doses of insulin (MDI), glycated haemoglobin between

7.5% and 9.5%; able to use an intermittently scanned continuous glucose monitoring (isCGM) and using carbohydrate counting.

Sample size

Due to the exploratory nature of the study, sample size calculation was not formally performed. Ten subjects with type 1 diabetes will be included in the study.

Study outcomes

- Primary outcomes:

Primary outcome will be sensitivity (SE) and specificity (SP) to predict Level 1 hypoglycemia[1].

Level 1: a hypoglycemia alert glucose value between 54-70 mg/dL (3.0–3.9 mmol/L) with or without symptoms.

A hypoglycemic event should be defined as follows. Beginning of a CGM event: readings below the threshold for at least 15 min are considered an event. For example, at least 15min, <70 mg/dL (3.9 mmol/L) to define a significant hypoglycemic event. End of a CGM event: readings for 15 min at >70 mg/dL (3.9 mmol/L).

SE and SP are calculated as:

$$SE=\frac{TP}{TP+FN}$$	(1)
$$SP=\frac{TN}{TN+FP}$$	(2)

where, TP are the true positive predictions, TN are the true negative predictions, FP are the false positive predictions and FN are the false negative predictions.

- Secondary outcomes

Secondary outcome will be sensitivity (SE) and specificity (SP) to predict Level 2 hypoglycemia[1].

Level 2: a glucose level of <54mg/dL (3.0 mmol/L) with or without symptoms.

A hypoglycemic event should be defined as follows. Beginning of a CGM event: readings below the threshold for at least 15 min are considered an event. For example, at least 15min, <54 mg/dL (3.0 mmol/L) to define a clinically significant hypoglycemic event. End of a CGM event: readings for 15 min at >70 mg/dL (3.9 mmol/L).

A second hypoglycemic event outcome of prolonged hypoglycemia is considered when CGM levels are < 54 mg/dL (3.0 mmol/L) for consecutive 120 min or more.

- Other secondary outcomes:

Mean glucose, SD and CV. Predicted HbA1c (sensor data).
Number of Severe hypoglycemia Clinical diagnosis: event requiring assistance (level 3)
Percentage of time in hypoglycemic ranges, mg/dL (mmol/L), %:

- Clinically significant/very low/immediate action required <54 (<3.0) (level 2)
- Alert/low/monitor 70–54 (3.9–3.0) (level 1)

Percentage of time in target range, mg/dL (mmol/L), %:

- Default 70–180 (3.9–10.0)
- Secondary 70–140 (3.9–7.8)

Percentage of time in hyperglycemic ranges, mg/dL (mmol/L), %
Alert/elevated/monitor > 180 (>10)
Clinically significant/very elevated > 250 (>13.9)
LBGI and HBGI.
Number of Level 3: severe hypoglycemia. This denotes cognitive impairment requiring external assistance for recovery but is not defined by a specific glucose value.

Outpatient data:
Total insulin dose per day, total basal insulin, total bolus insulin, ratio basal/bolus insulin, total CHO per day, capillary blood glucose values.
Activity tracker data: heart rate, steps, activity level, sleep quality.

2. BACKGROUND AND OBJECTIVES

Type 1 diabetes (T1D) accounts for 10–15% of the worldwide diabetes prevalence and its incidence is increasing worldwide by 3–5% percent annually[2]. Achieving optimal glucose control, as measured by HbA1c, reduces the risk of micro- and macrovascular complications, but can be challenging for people living with Type 1 diabetes due to hypoglycemia[3–5].

Hypoglycemia is a metabolic complication of T1D and is one of the major barriers to optimize glucose self-management. People with Type 1 diabetes on average have 1.8 self-treated incidences of hypoglycemia per week, and 0.2–3.2 episodes of severe hypoglycemia,

defined as hypoglycemia requiring the assistance of a third party, annually[6,7]. Recurrent hypoglycemia erodes hypoglycemia awareness and impaired awareness is seen in around a quarter of people with Type 1 diabetes[7].

Nocturnal hypoglycemia can lead to various adverse situations in T1D patients, including consciousness, seizure, or even death. Recently, closed-loop systems have improved glycemic control during overnight period and have reduced the occurrences of hypoglycemic events when compared with traditional therapy[8,9]. However, at least for the next few years, the minority of T1D patients will be able to use such system.

Sensor-augmented pump therapy allows insulin reduction in case of prediction or detection of low blood glucose levels. These hypo-management systems are able to reduce the occurrence of hypoglycemic episodes, especially the severe episodes[10,11]. However, patients must use two devices simultaneously: continuous glucose monitoring (CGM) and insulin pump.

T1D patients under multiple daily injections (MDI) therapy, i.e. without an insulin pump, don't have any kind of mechanism to assist them to adjust insulin injections in real-time. During the day, patients can take actions to correct their glycemic levels whether necessary. However, during overnight, patients can't take any actions while are sleeping.

Mechanisms to detect a future hypoglycemic event may be useful to help patients to manage their blood glucose levels whether any hypoglycemic event is predicted. In a study conducted with children with T1D[12], nocturnal hypoglycemia was associated with two factors: bedtime glucose and daytime physical activity. Another study also associated overnight hypoglycemia with previous-day physical activity in adolescents[13]. These studies indicate a strong relationship between the risk of nocturnal hypoglycemia with previous-day activities.

Machine learning is a field of artificial intelligence used in data-analysis to create computational models based on retrospective data. Supervised machine learning algorithms "learn" from past labeled data, and make use of this knowledge to perform important tasks by generalizing from the examples used in the "learning phase". In other words, the model aims to represent the complex relationship between inputs and outputs. The model is gradually improved by testing its predictions and correcting when wrong, using different kinds of algorithms[14]. Over the last decade, machine learning algorithms have been widely used in several fields, including applications in medicine[15,16] and diabetes research[17].

Machine learning algorithms will be used to "learn" the overnight glycemic behavior of each patient from past data. One great advantage of using this approach during overnight

period is that no big disturbance is expected to occur. Besides that, in open-loop therapy, the overnight basal insulin delivery is known in advance, i.e., at the moment that patients inform the system that they will sleep, the system already knows the total amount of insulin that will be delivered in the following hours, because patient's basal profile is already defined.

Nevertheless, machine learning methods need datasets to properly find patterns in the given data. Currently diabetes technology (i.e. continuous glucose monitoring (CGM)) allows to acquire and store patient's data along several days. The use of the aforementioned device in addition to an exercise tracker should provide relevant data that would allow the development of the proposed methodology. Besides that, the use of the exercise monitor is not expected to cause any clinical impact in patients' lives. Patients would just be asked to wear the exercise tracker and keep their habitual routines.

3. STUDY AIM

The objective is to develop a novel system to predict and prevent nocturnal hypoglycemia in T1D patients, focused in patients with MDI therapy. The general idea is to make use of previous-day information in the moment when patients go to sleep, and then predict if in the next following hours any hypoglycemic event will occur. If the system will have predicted any hypoglycemic event in that moment, it is expected that it will be able to warn the patient to take some action: such as reduce basal insulin dose or to consume a snack before sleep.

4. INVESTIGATIONAL PLAN

4.1. STUDY DESIGN

Longitudinal, prospective, interventional study. Every patient will use isCGM sensors and a physical activity tracker during 12-weeks. Moreover, during this period, patients will store in a mobile application (Freestyle LibreLink) or in a reader information regarding their diabetes management activities, such as insulin delivery doses and meal consumption. The study will consist in 4 visits:

Visit 1: recognition visit. After patients will sign the informed consent the following examinations and tests will be carried out within a period of two weeks before the visit 2:

• Medical History

• Physical examination including vital signs and anthropometric parameters.

• A1c "in situ finger-prick" (Alere Afinion™ AS100, Abbot) + Clinical Laboratory Tests, only if there is not a previous one within 6 months:

- ✓ Hematologic status: haemoglobin, hematocrit, red blood cells, mean corpuscular haemoglobin, white blood cell and differential count, platelet count.
- ✓ Clinical Chemistry: AST, ALT, glucose, sodium, potassium, creatinine.
- ✓ Glycated haemoglobin.

.

• Detection of asymptomatic hypoglycemia using a Clarke questionnaire validated in Spanish and Catalan (only if there is not a previous one within 6 months).

During the visit 1, the investigator will ensure that patient have the skills in managing isCGM, App and activity tracker.

Visit 2: initiation visit. If the recognition visit is positive, each patient will receive during the inception visit the necessary material to perform the data acquisition at home for the next 4 weeks (3 sensors and the activity tracker), the remaining of the sensors will be provided in Visit 3. In addition, during Visit 2, the research team will train the participants on how to use properly all the devices and mobile applications/reader related with the data acquisition.

Visit 3: follow-up visit. 4 weeks (+/- 7 days) after visit 2. Between Visit 2 and Visit 3, participants' engagement will be evaluated and an individual evaluation will be provided by the research team. If necessary, participants will be trained again regarding the study devices' usability. In this visit, the remaining of the isCGM sensors will be given for each participant (4 sensors).

Visit 4: follow-up and final visit. This visit will occur at least 12 weeks after Visit 2. Participants will have to return to the hospital facility to download devices and get the information acquired at the recognition visit.

4.2. STUDY SUBJECTS

10 subjects with type 1 diabetes mellitus for more than five years will be recruited among those attending in the Diabetes Unit of Hospital Clínic i Universitari de Barcelona. They must be in multiple daily insulin injections therapy.

4.2.1. Inclusion Criteria

- Patients ≥ 18 years with Type 1 Diabetes:
    - > 4 hipoglycemias / week (< 70 mg/dl, including day and night), last 2 weeks and / or
    - One severe hypoglycemia during the last year and / or
    - Hypoglycemia unawareness (Clarke Test ≥3)
- Disease duration > 5 years
- On multiple doses of insulin (MDI) therapy using a rapid acting insulin analogue as prandial insulin (lispro, aspart or glulisine) and any basal analogue as basal insulin.
- A1c 6.5 – 9.5 %
- Able to use an intermittently scanned continuous glucose monitoring (isCGM) system.
- Performing ≥4 self-monitoring blood glucose (SMBG) per day
- Using carb-counting
- Providing an informed consent
- No CGM user previously (during the last 3 months).

4.2.2. Exclusion Criteria

- Patients with a previous Diabetic Ketoacidosis (DKA) episode in the previous 6 months.
- Patients with a severe hypoglycemia in the previous 6 months.
- Severe diabetic complications or comorbidities: eye, renal, cardiovascular...from the clinicians point of view.
- Pregnancy and breastfeeding.
- History of drug or alcohol abuse.
- Scheduled surgery during the study period.

- Mental conditions that prevent the subject to understand the nature, purpose and possible consequences of the study.
- Subjects those are unlikely to meet the clinical study protocol, eg uncooperative attitude, inability to return for follow-up visits, or poor probability of completing the study.
- Using an experimental drug or device during the past 30 days.

4.2.3. Diseases and Treatments Prior and Concomitant

Additional diseases present at the time of giving informed consent shall be considered as comorbidities. Illnesses occurring for the first time or detected during the study, and concomitant disease worsen during the study will be considered as an adverse event and should be documented as such in the form of case reports. All additional treatments different from insulin, which are taken by the subjects at baseline or at any other time during the study, will be considered as concomitant therapy and should be documented before in the form of case reports.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the health of the subject and are unlikely to interfere with the study will be administered according to the investigator.

4.3. STUDY PROCEDURES AND SCHEDULE

4.3.1. Description of the study days

Visit 1: recognition visit. After patients will sign the informed consent the following examinations and tests will be carried out within a period of two weeks before the visit 2:

• Medical History

• Physical examination including vital signs and anthropometric parameters.

• A1c “in situ finger-prick” (Alere Afinion™ AS100, Abbot) + Clinical Laboratory Tests, only if there is not a previous one within 6 months:

- ✓ Hematologic status: haemoglobin, haematocrit, red blood cells, mean corpuscular haemoglobin, white blood cell and differential count, platelet count.
- ✓ Clinical Chemistry: AST, ALT, glucose, sodium, potassium, creatinine.

- ✓ Glycated haemoglobin.

• Detection of asymptomatic hypoglycemia using a Clarke questionnaire validated in Spanish and Catalan (only if there is not a previous one within 6 months).
During the visit 1, the investigator will ensure that patient have the skills in managing isCGM, App and activity tracker.

Visit 2: initiation visit. If the recognition visit is positive, each patient will receive during the inception visit the necessary material to perform the data acquisition at home for the next 4 weeks (2 sensors and the activity tracker), the remaining of the sensors will be provided in Visit 3. In addition, during Visit 2, the research team will train the participants on how to use properly all the devices and mobile applications/reader related with the data acquisition.

Visit 3: follow-up visit. 4 weeks (+/- 7 days) after visit 2. Between Visit 2 and Visit 3, participants' engagement will be evaluated and an individual evaluation will be provided by the research team. If necessary, participants will be trained again regarding the study devices' usability. In this visit, the remaining of the isCGM sensors will be given for each participant (4 sensors).

Visit 4: follow-up and final visit. This visit will occur at least 12 weeks after Visit 2. Participants will have to return to the hospital facility to download devices and get the information acquired at the recognition visit.

4.3.2. Patients schedule

The schedule for each patient will be as follows:
Day -2 weeks: Recognition visit **(Visit 1)**, no more than two weeks before the start of isCGM and physical activity monitoring.
Day 1: Initiation visit **(Visit 2)**, start of the study.
Day 28 – Day 35: Follow-up visit **(Visit 3)**, 4 weeks (+/- 7 days) after visit 2.
Day 84 – Day 98: Follow-up visit **(Visit 4)**, at least 12 weeks and no more than 14 weeks after Visit 1.

4.3.3. Study duration

The expected duration of this study will be 12 weeks, with subject recruitment planned to start in 18/06/2018 and ending of experiments projected until December 1st.

4.4. STUDY TREATMENTS AND PRODUCTS

Importantly, no experimental drugs will be used during the study. During the study period, patients will continue to perform their usual treatment at home and the data acquired by the devices will be obtained by the research team remotely.

4.4.1. Details of study products

The devices that will be used during the study are listed below:

- FreeStyle Libre System
- Fitbit Alta HR
- Cell phone compatible with the following apps: 1) FreeStyle Librelink, 2) Fitbit App.
- FreeStyle Libre reader

Participants will make use of their personal cell phones during the study. All the mobile apps will be installed and set up in patients' mobiles by the research team.

The participants will be trained by the research team to learn how to use properly all the devices. In addition, the participants may contact a member of the research team to help them to solve any technical issue during the study.

4.5. METHODS OF DATA COLLECTION

CGM will be performed during 12 weeks using a isCGM (intermittently scanned Continuous Glucose Monitoring), Freestyle Libre, (Abbott Diabetes Care, Witney, Oxon, UK). Insulin dose (rapid-acting and long acting), carbohydrates and SMBG per day will be recorded by the patient in the reader or in the App (LibreLink, Abbott Diabetes Care, Witney, Oxon, UK). Moreover, participants will be instructed to collect data about moderate or high intensity exercise, illness and other disturbances occurring during the study period at home.

Patients will wear a Fitbit Alta HR wristband (Fitbit, Inc., San Francisco, CA, USA) to track physiological variables such as heart rate, steps, activity level and sleep quality.

4.5.1. Blood collection and sampling schedule

Visit 1 recognition: If necessary Glycated haemoglobin (A1c), hematology and clinical chemistry: 15 ml of blood will be collected.
Visit 4. If necessary Glycated haemoglobin (A1c), hematology and clinical chemistry: 15 ml of blood will be collected.

4.5.2. Urine collection and sampling schedule

This type of analysis is not necessary in this study.

4.6. SAFETY

After the patients will have given the informed consent, while fasting, subjects will be examined as detailed above. Violation of the study criteria will exclude from participation in the study.

At visits other than recognition, the subjects will be asked to confirm that there have been no relevant changes in their medical condition since Visit 1. Body weight and vital signs will be recorded. If a violation of the protocol is recognized, subjects will be dropped out and replaced.

After the completion of all studies, subjects will have to return for a follow-up examination: while fasting, they will undergo a physical examination, vital signs registration, and laboratory safety variables determination.

5. ETHICAL AND LEGAL ASPECTS

Good clinical practice

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator (in this case the same person) abide by the principle of the good clinical practice (GPC) guidelines and the Declaration of Helsinki in the conduct, evaluation and documentation of this study. The study will also be carried out in keeping with local legal requirements.

Subjects information and informed consent

An informed consent document that includes both information about the study and the consent form will be prepared and given to the subjects. The documents will be in a language understandable to the subject and will specify who will inform the subject.

Before being admitted to the clinical study, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in an understandable form to him or her.

6. TREATMENT OF THE DATA AND RECORD OF THE REGISTERS. CONFIDENTIALITY OF THE DATA.

The treatment, communication and transfer of personal data of all participants will be adjusted to compliance with Regulation EU 2016/679 of the European Parliament and the Council of April 27th 2016 on the protection of natural persons as to the processing of personal data and the free circulation of data, being mandatory as of May 25th, 2018. The legal basis that justifies the processing of your data is the consent given in this act, in accordance with the provisions of the Article 9 of the EU Regulation 2016/679.

The data collected for these studies will be collected only identified by a code, so that no information will be included to identify the participants. Only the principal investigator and his collaborators with the right to access the source data (clinical history), will be able to relate the data collected in the study with the patient's clinical history.

The identity of the participants will not be available to any other person except for a medical emergency or legal requirement.

Health authorities, the Research Ethics Committee and authorized personnel may have access to the identified personal information, when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation.

Only encrypted data will be transferred to third parties and to other countries, which in no case will contain information that can identify the participant directly (such as name and surnames, initials, address, social security number, etc.). If this assignment occurred, it would be for the same purpose of the study described and guaranteeing confidentiality.

If a transfer of encrypted data is carried out outside the EU, either in entities related to the hospital where the patient participates, to service providers or to researchers who collaborate with us, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

As promoters of the project we commit ourselves to carry out the data processing according to EU Regulation 2016/679 and, therefore, to keep a record of the treatment

activities that we carry out and to make a risk assessment of the treatments that we perform to know what measures we will have to apply and how to do it.

In addition to the rights already covered by the previous legislation (access, modification, opposition and cancellation of data, deletion in the new Regulation) now the participants can also limit the processing of data collected for the project that are incorrect, request a copy or that move to a third party (portability). To exercise these rights should be directed to the principal investigator of the study or the Data Protection Delegate of Hospital Clinic of Barcelona through protecciodades@clinic.cat. They also have the right to contact the Data Protection Agency if are not satisfied.

The data can not be deleted even if a patient leaves the study, to guarantee the validity of the investigation and comply with the legal duties and the medication authorization requirements.

The Investigator and the Promoter must keep the data collected for the study at least up to 5 years after its completion. Subsequently, personal information will only be kept by the center for the care of your health and by the promoter for other scientific research purposes if the patient has given their consent to do so, and if it is allowed by the law and ethical requirements.

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