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TÍTULO: Implementation of MPC and PID Control Algorithms to the Artificial Pancreas for Diabetes Mellitus Type 1: Diabetes diary calculator (DDC) web application.

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DEDICATION

To God, for standing always by my side.

To Sandra and Tomas, for being my greatest support.

To Tanya, for being unconditional.

To my brother and sister, for making the stress to go away.

To my teachers, for sharing their knowledge.

To myself.

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RESUMEN

La diabetes es una enfermedad crónica que se produce cuando el cuerpo no produce suficiente insulina o no puede utilizar la insulina efizcamente. La Diabetes mellitus tipo 1 (DMT1) se considera una enfermedad autoinmune que ocurre cuando las células beta pancreáticas se destruyen y no se produce suficiente insulina para mantener la homeostasis glucémica, por lo que, el paciente vive con la necesidad de reemplazo de insulina de por vida.

Las terapias disponibles para pacientes de DMT1 se pueden dividir en terapias de lazo abierto y de lazo cerrado. En una terapia de lazo abierto, los pacientes deben autoadministrarse insulina exógena según las mediciones de la concentración de glucosa en sangre y la estimación del contenido de carbohidratos en sus comidas. Las terapias de control de lazo cerrado o páncreas artificial (PA) comprenden una bomba de infusión de insulina subcutánea continua y un sensor de monitorización continua de glucosa con un algoritmo que ajusta automáticamente la infusión de insulina en tiempo real, funcionando como un páncreas sano con poca o ninguna intervención del usuario. Los algoritmos ampliamente utilizados para el desarrollo de PA son el Control Predictivo por Modelo (MPC por sus siglas en inglés) y el control proporcional-integral-derivado (PID por sus siglas en inglés) que se han modificado para ayudar a los pacientes con DMT1 a regular sus niveles de glucosa en sangre.

El desarrollo de PA debe considerar otros parámetros como la ingesta de alimentos y la actividad física. Estos parámetros son alteraciones que pueden ocurrir sin previo aviso, lo que puede reducir los niveles de glucosa en sangre y causar hipoglucemia. Por lo tanto, en este trabajo se comparan dos algoritmos de control (MPC y PID) ingresando parámetros como la glucosa, insulina, ingesta y ejercicio para comprender principalmente como se puede compensar los efectos del ejercicio y la comida para evitar la hipoglucemia. Además, se realiza una aplicación móvil con el propósito de integrar este análisis y ayudar a llevar un mejor control de los pacientes con DMT1.

Palabras claves: Páncreas Artificial, Diabetes Mellitus Tipo 1, Ejercicio, Algoritmos de control.

ABSTRACT

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot use insulin effectively. Type 1 Diabetes Mellitus (T1DM) is considered a chronic autoimmune disease that occurs when pancreatic beta cells are destroyed and the body does not produce enough insulin to maintain glycemic homeostasis, so the person lives with the need for insulin replacement for life.

The therapies available for T1DM patients can be divided into open loop and closed loop therapies. In an open-loop therapy, patients need to self-administer exogenous insulin based on blood glucose concentration measurements and estimation of the carbohydrate content in their meals. Closed-loop control (CLC) therapies or Artificial Pancreas (AP) comprise a continuous subcutaneous insulin infusion pump, a continuous glucose monitor (CGM) sensor and a CLC algorithm that automatically adjusts insulin infusion in real time, functioning as a healthy pancreas would regulate glucose levels through the administration of hormones with little or no user input. The CLC algorithms widely used for AP development are Model Predictive Control (MPC) and Proportional-Integral-Derivative (PID) control have been modified in order to help TD1M patients to regulate their blood glucose levels (BGLs).

The development of APs has to consider disturbances such as meal intake and physical activity. These disturbances can be unannounced which can bring blood glucose levels down and cause hypoglycemia. Therefore, in this work, two control algorithms are compared facing meal intake and exercise in order to compensate the effects of exercise and food and avoid hypoglycemia. In addition, a mobile application is developed with the purpose of integrating this analysis and help Type 1 Diabetes Mellitus patients carry a better control of blood glucose levels.

Keywords: Artificial Pancreas, Type 1 Diabetes Mellitus, Exercise, Control algorithms.

TABLE OF CONTENTS

Dedication IV
Acknowledgements V
Resumen VI
Abstract VII
Table of Contents VIII
List of Illustrations XI
List of Tables XIII
Nomenclature XIV
Acronyms XV
Chapter I: Introduction 1
1.1 Problem Statement 2
1.2 Objectives 2
1.2.1 General 2
1.2.2 Specific 2
1.3 Hypothesis 3
1.4 Structure 3
Chapter II: Background 4
2.1 Diabetes Mellitus Type I 4
2.2 Complications 6
2.3 Laboratory tests 7
2.4 Treatment 8
2.4.1 Open Loop Insulin Delivery 9
2.4.2 Closed Loop Insulin Delivery 9
2.5 Exercise and T1DM 10
2.6 Summary 13
Chapter III: State of the Art 15
3.1 Systems of glucose-insulin dynamics 16
3.1.1 Bergman Minimal Model 17
3.1.2 Hovorka et al. Model 18
3.1.3 Sorensen's Physiological Model 20
3.1.4 Comparison of Bergman, Hovorka and Sorensen physiological model 22
3.2 Meal Intake models 22
3.2.1 Dalla et al. Model 23

3.2.2 Fisher Model . . . 23
3.2.3 Lehmann and Deutsch Meal Model . . . 23
3.3 Exercise Models . . . 24
3.3.1 Roy and Parker Model . . . 25
3.4 Control Algorithms . . . 26
3.4.1 Model Predictive Control Algorithm . . . 26
3.4.2 Proportional-Integer-Derivative Control Algorithm . . . 30
3.5 Applications for self-monitoring of blood glucose levels . . . 32
3.6 Summary . . . 33
Chapter IV: Materials and Methods . . . 35
4.1 Pancreas Artificial simulation components . . . 35
4.2 Extension of the Bergman Minimal Model . . . 36
4.2.1 Extended Bergman Minimal Model with Meal Disturbance . 37
4.2.2 Extended Bergman Minimal Model with effects of Exercise disturbance . . . 39
4.3 Closed Loop Insulin Delivery with MPC controller . . . 40
4.3.1 Closed Loop Insulin Delivery with MPC controller against meal disturbance . . . 41
4.4 Closed Loop Insulin Delivery with PID controller . . . 42
4.4.1 Closed Loop Insulin Delivery with PID controller against meal disturbance . . . 43
4.4.2 PID Controlled Insulin therapy with extended Bergman Minimal Model with effects of Exercise disturbance and meals . 45
4.5 Mobile Application for Self-Monitoring of BGL . . . 47
Chapter V: Results . . . 50
5.1 Extension of the Bergman Minimal Model . . . 50
5.1.1 Extended Bergman Minimal Model with Meal Disturbance . 50
5.1.2 Extended Bergman Minimal Model with effects of Exercise disturbance . . . 51
5.2 Closed Loop Insulin Delivery with MPC controller against meal disturbance . . . 52
5.3 Closed Loop Insulin Delivery with PID controller . . . 53
5.3.1 Closed Loop Insulin Delivery with PID controller against meal disturbance . . . 53
5.3.2 Closed Loop Insulin Delivery with PID controller against meals and Exercise disturbance . . . 54

5.4 Diabetes Diary Web Application 56
Chapter VI: Discussion 59
Chapter VII: Conclusions 66
7.1 Conclusions 66
7.2 Future Works 67
7.3 Scientific disclosure 67
Bibliography 68
Appendix A: S-function for Diabetic Patient with meal intake 78
Appendix B: S-function for Diabetic Patient with meal intake and exercise . . 85
Appendix C: APMonitor model of a MPC controller for blood glucose levels with meal intake as a disturbance 92
Appendix D: Code for the insulin prediction of the DDC Application 93

LIST OF ILLUSTRATIONS

2.1 Chronic complications of type 1 diabetes mellitus (T1DM). Own elaboration from Saberzadeh-Ardestani et al.(2018). 7
3.1 Graphical representation of physiological models or glucose-insulin/glucagon systems integrated with Artificial pancreas system. Own elaboration from Cobelli et al.(2011). 15
3.2 General Hardware design of a Closed Loop Artificial Pancreas. Own elaboration from Cobelli et al.,(2011). 16
3.3 Schematic flow diagram for glucose kinetics of Bergman Minimal Model (Richard N Bergman, 2021). 17
3.4 Schematic flow diagram for glucose and insulin subsystems of Hovorka et al. (2002). 19
3.5 Schematic flow diagram for compartments of Sorensen (1985). Own elaboration from Sorensen (1985) 21
3.6 Modular architecture for Del Favero et al. (2019) Artificial Pancreas study. Taken from S. D. Patek et al., 2012 (2012). 28
3.7 Block diagram representation of the simulation done by Huyett et al. (2015). Taken from Huyett et al. (2015). 31
4.1 Representation of the components of a closed-loop or Artificial Pancreas therapy. Own elaboration from Cobelli et al.(2011). 36
4.2 Schematic flow diagram for extended Bergmann Model with meal disturbance and Snacks (Hedengren et al., 2014). 38
4.3 Schematic of Simulink of the Extended Physiological Bergmann Model with exercise and meals. Own elaboration from Hedengren et al. (2014) 39
4.4 Schematic representation of the extended Bergmann Model with meal disturbances. Own elaboration from Cobelli et al. (2011) 41
4.5 Schematic flow diagram for AP with meal disturbance and Snacks. From Hedengren et al. (2014). 42
4.6 Schematic representation of closed-loop insulin delivery with PID controller with meal disturbance and Snacks. Own elaboration from Rhee et al. (2017). 43
4.7 Schematic flow diagram for AP with meal disturbance and Exercise. Own elaboration from Rhee et al.,(2017). 43

4.8 Schematic flow diagram for AP with meal disturbance and Snacks (Hedengren et al., 2014). 45
4.9 Schematic of Closed Loop Insulin Therapy PID Controlled and the Extended Physiological Bergman Model with exercise and meals during 24 hours 46
4.10 Schematic of Closed Loop Insulin Therapy PID Controlled and the Extended Physiological Bergman Model with exercise, meals and unannounced snacks during 24 hours 47
4.11 Web Application Diary Entries with Django python framework . . . 49
5.1 Simulation of Extended Physiological Bergmann Model with meals and snacks during 24 hours 51
5.2 Simulation of exercise during 1 hour 51
5.3 Simulation of exercise during 1 hour and three meals 52
5.4 MPC therapy performance with meal disturbance and Snacks during 24 hours (Hedengren et al., 2014). 52
5.5 AP performance with meal disturbance and Snacks during 24 hours (Hedengren et al., 2014). 54
5.6 Closed Loop Insulin Therapy for exercise during 1 hour and meals . . 55
5.7 Closed Loop Insulin Therapy for exercise during 1 hour, meals and 10gr of snacks 56
5.8 Prediction result after user entries 57
5.9 Web Application Database of Entries with Django python framework 57

LIST OF TABLES

2.1 Blood sugar levels reference in fasting and after eating (American Diabetes Association, 2021). 6
2.2 Exercise Intensities according to PVO_2^{max} (Rai and Sen, 2016) . . . 13
3.1 Description of parameters of Bergman Minimal Model (Welch et al., 1990; Richard N Bergman, 2021). 18
3.2 Description of parameters of Hovorka model (Hovorka, Shojaee-Moradie, et al., 2002; Hovorka, Canonico, et al., 2004). 20
3.3 Comparison of mathematical complexities of physiologic models of glucose metabolism 22
3.4 AP with MPC and exercise studies reviewed. 29
3.5 PID AP and exercise studies reviewed. 32
3.6 Summary of revision of the state of the art 34
4.1 Parameters used to model exercise and meal ingestion in a diabetic type 1 patient from Roy and Robert S. Parker (2007). 40
4.2 MPC controller Modeling with APmonitor 42
5.1 Overall outcomes of MPC Control Strategy 53
5.2 Overall outcomes of PID Control Strategy 54
5.3 Overall outcomes of PID Control Strategy against meals and exercise 55
5.4 Overall outcomes of PID Control Strategy against meals, exercise and snacks 56
6.1 Performance Comparisons.
* Same Physiological Model used 62
6.2 Commercially available mobile medical apps for T1DM management 65

NOMENCLATURE

VO_2^{max}**.** Maximal oxygen uptake refers to the oxygen consumption of a subject when exercising as hard as possible for that subject(A. B. Lumb, 2017).

PVO_2^{max}**.** Percentage of maximal oxygen consumption.

Blood Ketone Test. A ketone blood test measures the amount of ketones in the blood.Ketones are substances produced in the liver when fat cells break down in the blood. This test is used to diagnose ketoacidosis (Bektas et al., 2004).

Cytotoxyc T Lymphocite. CTLs are generated by immune activation of cytotoxic T cells (Tc cells). They are generally CD8+, which makes them MHC class I restricted. CTLs are able to eliminate most cells in the body since most nucleated cells express class I MHC molecules.

Dysglycemia. General definition for any abnormalities in blood glucose levels such as hyperglycemia, hypoglycemia, impaired glucose tolerance test, impaired fasting glucose.

Fasting. Defined as no caloric intake for at least 8h (American Diabetes Association, 2021) .

GAD65. Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). GAD65 antibody is the major pancreatic islet antibody and an important serological marker of predisposition to type 1 diabetes.

GLUT4. GLUT4 is the insulin-regulated glucose transporter found primarily in adipose tissues and striated muscle (skeletal and cardiac).

Glycogenolysis. Process that breaks down the glycogen into glucose.

Glycolysis. process of breaking down a glucose molecule into pyruvate, ATP and NADH.

Glyconeogenesis. Process that synthesizes glucose from gluconeogenic precursors (lactate, alanine, glycerol and pyruvate) circulating in the bloodstream.

IA-2. Receptor-type tyrosine-protein phosphatase-like N, also called "IA-2", is an enzyme that in humans is encoded by the PTPRN gene. This PTP represents a receptor-type PTP. It was found to be an autoantigen that is reactive with insulin-dependent DM patient sera.

Polyuria. Excessive or an abnormally large production or passage of urine.

ACRONYMS

A-mMPC Adaptative modular Model Predictive Control

ADA American Diabetes Association

AP Artificial Pancreas

APCs Antigen presenting cells

BG blood glucose

BGLs blood glucose levels

BW bodyweight

CGM continuous glucose monitor

CLC Closed-loop control

CR carbohydrate-to-insulin ratio

CRF cardiorespiratory fitness

DDC Diabetes Diary-Calculator

DM Diabetes Mellitus

EGP endogenous glucose production

EHRA exercise-induced hypoglycemia reduction algorithm

FFC feedforward compensator

FLC fuzzy logic controller

GAD Glutamic acid decarboxylase

GLUT4 glucose transporter type 4

HLA human leukocyte antigen

IFB insulin feedback

ILC iterative learning control

IMC internal model control

INEC Instituto Nacional de Estadísticas y Censos

IVGTT intravenous glucose tolerance test

L-MPC Learning Model Predictive Control

MET Metabolic Equivalent Values

mMPC modular Model Predictive Control

MPC Model Predictive Control

OLC Open-loop Control

PID Proportional- Integer-Derivative

R-EMPC dynamic R-parameter economic model predictive control

R2R Run-to-Run

SAP sensor-augmented insulin pump

SMRC slinding mode reference conditioning

SSM safety supervision module

T1DM Type 1 Diabetes Mellitus

UVa University of Virginia

Chapter 1

INTRODUCTION

Diabetes Mellitus (DM) is a complex metabolic disorder associated with an increased risk of micro-vascular and macro-vascular disease (Zaccardi et al., 2016) that happens because of pancreas cannot produce enough insulin or when the organism cannot utilize the insulin in an effective way. Insulin is a hormone that regulates and distributes the glucose within the body's tissues.

According to statistics from National Institute of Statistics and Censuses (INEC by its acronym in Spanish), in 2019, DM was the second cause of death in Ecuador, with a total of 4,890 deaths per year (Dirección de Estadísticas Sociodemográficas, 2019). This disease is behind ischemic heart diseases, which are the main cause of death for Ecuadorians (Núñez-González, Delgado-Ron, and Simancas-Racines, 2020).

The treatment for this illness consist in the subcutaneous or intravenous injection of insulin based on calculations taking into account previous or actual blood glucose levels (F. Doyle, Jovanovič, and Seborg, 2007). Nevertheless, this practice can carry mistakes and result in very low or very high levels of blood glucose in the patients which end up causing dizziness or serious organ damage.

The major changes in blood glucose levels are determined by the patient's meal intake and physical activity, also called disturbances. Both of these disturbances are studied in this work as well as its effects on the glucose levels.

Technological breakthroughs have enable the continuous measurement of subcutaneous glucose concentration with CGM, and the subcutaneous insulin delivery with insulin pumps. Furthermore, the use of these breakthroughs and a controller algorithm closed a loop between the CGM, the insulin pump and the user to allow an automatic regulation of the glucose profile (Kovács et al., 2013).

To test and design an appropriate closed loop insulin delivery, an adequate model representing the glucose and insulin dynamics is necessary. The Bergman minimal model (Richard N Bergman, Finegood, and Ader, 1985) proved to be the simplest mathematical model followed by the higher complexity of the Hovorka model (Hovorka, Shojaee-Moradie, et al., 2002) and the Sorensen model (Sorensen,

1985). These models aim to quantify the glucose and insulin levels as a function of carbohydrates intake, external and internal insulin dynamics, basal glucose and insulin level, and other parameters. These models allow a better understanding of an automated insulin delivery system as it models the responses of a virtual patients to different scenarios.

An example of scenario is exercise. Exercise and physical activity have been strongly recommended by the American Diabetes Association because regular physical activity in people with diabetes is associated with increased cardiorespiratory fitness which leads to an improved blood lipid profile, the reduction in long-term cardiovascular disease risk (Reddy et al., 2019), improved psychological well-being, and possible benefits in bone health (Garcia-Tirado et al., 2019). On the other hand, physical activity is also associated with an imbalance between hepatic glucose production and glucose disposal into muscle, where glucose levels can fall rapidly.

1.1 Problem Statement

Type 1 Diabetes Mellitus patients have a great risk for both hypoglycemia and hyperglycemia. Closed-loop insulin delivery are challenged by exercise and meals. Since glucose levels can change rapidly because of exercise or meals.

1.2 Objectives

1.2.1 General

- Study and compare control strategies that could compensate the effect of exercise and meals on glucose level, preventing a hypo- or hyperglycemic event.

1.2.2 Specific

- Implement a mathematical model of the effects of exercise and meals on blood glucose levels of a Type 1 Diabetes Mellitus patient.
- Review of studies around exercise effects and closed-loop insulin delivery systems that aim to compensate the exercise effects.
- Compare the Model Predictive Control and Proportional-Integer-Derivative controller compensation of the effects of exercise and meal disturbances on blood glucose levels.

- Use the output blood glucose modelled to develop a companion Web Application using a K-nearest neighbor predictor of insulin bolus after meal intake and physical activity.

1.3 Hypothesis

Prolonged exercise causes serious problems to the patient's safety when it is not regulated. A control strategy could impede glucose level changes caused by exercise. Controlling glucose levels caused by different perturbations can help improving people's quality of life.

1.4 Structure

Chapter 1 describes the problem statement, hypothesis and objectives of the thesis project. Chapter 2 explains Type 1 Diabetes Mellitus per se to set the framework and context of this thesis. It lists the disease-related complications and challenges in current treatment modalities and their limitations. The second part of this chapter reviews the concept of closed-loop insulin delivery, clinical evaluations in various settings.

Chapter 3 explains the "state of the art" of the study of exercise effects in blood glucose levels in patients with type 1 diabetes mellitus. Also, it describes the trials done with closed-loop therapies and exercise.

Chapters 4 describes the experimental implementation of models of closed-loop insulin delivery systems with a controller of type PID and MPC. It includes aerobic exercise and meal disturbances, using the extended Bergman Minimal Model on Matlab-Simulink. In addition, it proposes a prediction model using K-nearest neighbor to predict insulin dosage using data obtained from simulations.

Chapter 5 shows the results of the simulations made and the different closed-loop systems responses, and the predictions of insulin bolus made using the data obtained from simulations. Then, chapter 6 discusses the results obtained and compares them to other investigations. Finally, chapter 7 shows concluding remarks and future work.

Chapter 2

BACKGROUND

This chapter describes the pathophysiology of diabetes (section 2.1). Then, it describes complications in the different disease stages, in section 2.2. There are laboratory tests used to diagnose the onset of diabetes and progression, these are describe in section 2.3. The different treatments available for patients are explained in section 2.4. The impacts of physical activity in diabetic patients are described in section 2.5. Furthermore, another approach for the control of T1DM is the use self-monitoring of blood glucose levels applications (apps) described in section 2.6. Finally, a summary of the chapter is provided at the end (section 2.7).

2.1 Diabetes Mellitus Type I

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease that destroys beta cells from pancreatic islets, and the body does not produce sufficient insulin to maintain glycemic homeostasis. And the patient lives with a life-long need for insulin replacement. Although it may occur at any age, T1DM most typically presents in adolescence with a peak onset around puberty (Saberzadeh-Ardestani et al., 2018).

As well as the majority of autoimmune disorders, the primary cause of T1DM is still unknown. As stated before, T1DM characterizes by selective, specific involvement of β-cells and there are no apparent pathological alterations of the other Langerhans cells, like α- (secreting glucagon), γ- (somatostatin), and PP- (pancreatic polypeptide) cells (Zaccardi et al., 2016).

However, there is one hypothesis that states that the CD8+ Cytotoxic T lymphocytes, recognizing β cell-specific peptides presented by HLA class I molecules, have a crucial role in selective β cell death (Skowera et al., 2008; Liblau et al., 2002; Velthuis et al., 2010).

Therefore, the HLA locus links to TD1M, and it proposes that the polymorphism in HLA class I genes contributes to the later stages of β-cell destruction. The findings that proves that an HLA class I risk variant can bind to T1DM autoantigens, including proinsulin epitopes, support that statement (Saberzadeh-Ardestani et al., 2018).

T1DM pathology is characterized as

- Immune System is elicited against β-cells antigens and the proinflammatory responses start
- Antigen presenting cells (APCs) present β-cell antigens
- Chronic immunological responses start due to inefficient regulation of this responses.
- Destruction of β-cells

This β-cell induces the release of antigens and initiation of immune responses against other β-cells. Generally, dendritic cells present the antigens to T cells. If the autoreactive T cells escape thymic-negative selection, an autoimmune response could stimulate autoreactive cytotoxic T and B cells. Finally, the effector mechanism of β-cell destruction requires the cooperation of dendritic cells, macrophages, T, B, and natural killer cells (Saberzadeh-Ardestani et al., 2018; Wållberg and Cooke, 2013). Nevertheless, the complete identification of the immunological mechanisms causing the β-cell destruction is not available, because of many cell subsets that may participate in the pathogenesis of the disease (Wållberg and Cooke, 2013).

Furthermore, after the destruction and loss of pancreatic β-cell function, the disease progress into a presymptomatic stage. Then, it is possible to identify the presence of autoantibodies like GAD65, and the glucose intolerance starts or dysglycemia. Finally, the clinical symptoms and diabetes signs show (symptomatic stage) such as hyperglycemia, polyuria, weight loss, among others (Insel et al., 2015).

Studies showed that the patients younger than five years of age develop the first autoantibody between 6 and 24 months of age (Ilonen et al., 2013; Krischer et al., 2015). The progression from one to more autoantibodies occurs most commonly within 2-4 years of the first autoantibody detection.

For T1DM patients is important to maintain blood glucose levels in the normoglycemic range (70 - 110 mg/dl). However, this becomes hard at different times of the day because of traditional activities such as eating or moderate physical exercise such as running. Table 2.1 shows the BGLs of different kinds of patients at three times of day (American Diabetes Association, 2021).

Table 2.1: Blood sugar levels reference in fasting and after eating (American Diabetes Association, 2021).

Blood Sugar (mg/dl)	Normal	Pre diabetes or Impaired Glucose	Diabetic
Fasting	80-100	101-230	$\geqslant$120
After eating	170-200	190-230	230-300
2-3h after eating	120-140	140-160	$\geqslant$ 200

The low BGLs (less than 60 mg/dl) often may induce an acute medical condition such as consciousness' loss or even a comma. On the other hand, high BGLs associate with long-term effects such as diabetic nephropathy, neuropathy, and retinopathy (Lunze et al., 2013).

2.2 Complications

Katsarou et al.,(2017) divide the progression of the disease into three stages. It depends on the appearance of the β-cell autoantibodies, the loss of β-cells, and the dysglycaemia (Tuomilehto and Rydén, 2018):

- The first stage is where the β-cell autoimmunity starts (auto-antibodies are present), there is loss of β-cells and no dysglycemia nor symptoms.
- Stage 2, there are signs of hyperglycemia (polyuria, thirst, hunger, weight loss) but no more symptoms.
- The symptomatic stage or stage three presents clinical symptoms, and the long-term complications start.

The complications divide into microvascular and macrovascular (Katsarou et al., 2017). The microvascular complications imply nephropathy, neuropathy, and retinopathy (Garcia-Tirado et al., 2019; Hajizadeh et al., 2019a; Hackney and Constantini, 2013). Macrovascular complications manifest predominantly as coronary heart disease, cerebrovascular disease, and peripheral artery disease. These conditions are not specific to diabetes but are risks for T1DM patients (Papatheodorou et al., 2018). Figure 2.1 shows more complications according to Saberzadeh-Ardestaniet al., (Saberzadeh-Ardestani et al., 2018).

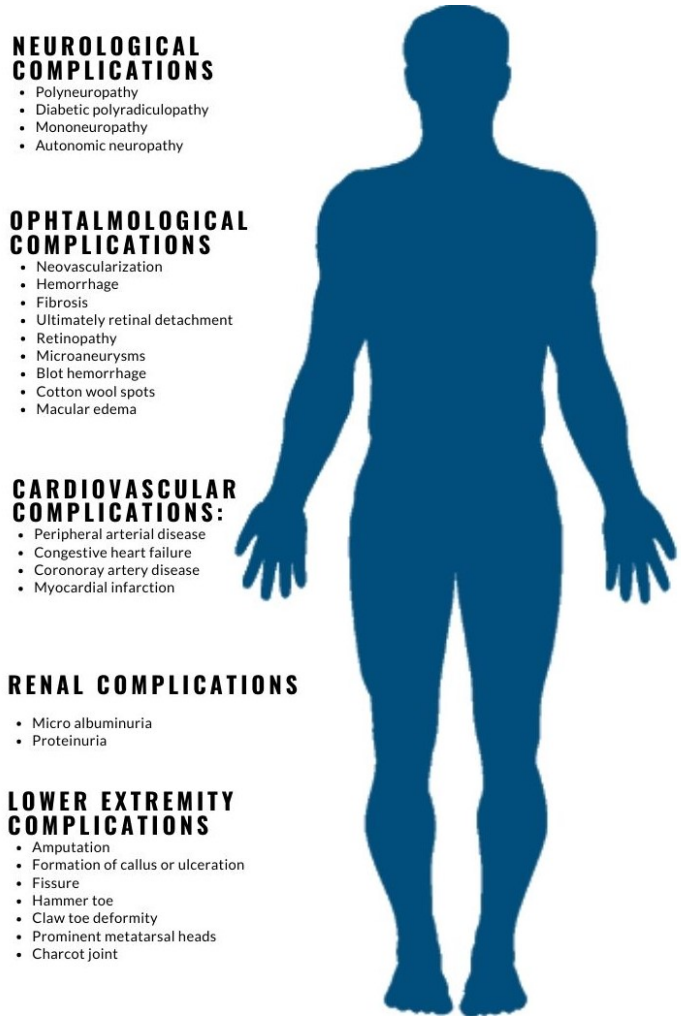

Figure 2.1: Chronic complications of type 1 diabetes mellitus (T1DM). Own elaboration from Saberzadeh-Ardestani et al.(2018).

2.3 Laboratory tests

Type 1 Diabetes Mellitus is very common in children younger than 15 years of age (Katsarou et al., 2017). Therefore, adults are often misdiagnosed with Diabetes Mellitus Type 2 because the presence of the β-cell-targeting autoantibodies is not detected. In consequence, the classification of diagnosis in DM in adults remains a challenge (Katsarou et al., 2017). In 2021, the ADA's diagnostic criteria for DM is based on signs of abnormal glucose metabolism (American Diabetes Association, 2021). As for T1DM, the recommendation for its screening is the presence of Glutamic acid decarboxylase (GAD) autoantibody.

Diabetes autoantibodies: This test distinguishes between type 1 and type 2 diabetes when the diagnostic is unclear. Since the islet cell autoantibodies strongly associate

with the development of type 1 diabetes. The appearance of autoantibodies (GAD65, IA-2, or insulin) indicates autoimmune pathogenesis of β-cell killing and suggests T1DM (Pihoker et al., 2005; Katsarou et al., 2017). The appearance of GAD65 or IA-2 is associated with age and genetic differences (Ilonen et al., 2013; Krischer et al., 2015).

Insulin: To monitor insulin production, urine and/or blood ketone tests monitor people present at the emergency room with symptoms suggesting acute hyperglycemia. It also monitors those who have ketoacidosis. A build-up of ketones occurs whenever there is a decrease in the amount or effectiveness of insulin in the body (Bektas et al., 2004).

2.4 Treatment

Patients need to maintain strict metabolic control to prevent the complications of this disease. This control is a big problem for patients and their families since the risk of low blood glucose levels is high. Nowadays, insulin-dependent diabetic patients manually control their blood glucose levels (Lunze et al., 2013). Nevertheless, the breakthroughs in the treatment of T1DM include the devices for blood glucose monitoring and HbA_{1c} at home. Analogs of insulin and CGM sensors help delay or prevent hypoglycemic or hypoglycemic events (Atkinson and Eisenbarth, 2001).

The insulin treatment aims to mimic the physiological insulin secretion to optimize glycaemic control and prevent complications (Robinson et al., 2003). There are two types of insulin administered subcutaneously: soluble human insulin or regular and rapid-acting insulin analog. While the regular insulin is slowly absorbed, the rapid-acting insulin (Humalogue and Aspart insulin) was modified to be absorbed more quickly (Atkinson and Eisenbarth, 2001; Robinson et al., 2003; Mortensen et al., 2000; Garg et al., 1999). The rapid-acting insulin allows injections even after a meal but before a meal is better (Atkinson and Eisenbarth, 2001). After the measurement of the BGLs e.g. with a test strip, the patient determines the size of the insulin bolus and injects it subcutaneously with an insulin pump or with an insulin pen (Lunze et al., 2013).

The insulin pumps could be expensive but allow users to program multiple basal rates of administration and bolus administration with a meal intake (Atkinson and Eisenbarth, 2001).

However, external disturbances such as stress, illnesses, or infections have to be taken into account since these can alter the insulin bolus size needed. Nevertheless,

for a patient is difficult to take all effects into the calculation and might face a hyper- or hypoglycemic event.

Therapies available divide into two categories, open-loop, and closed-loop therapies. An Open-loop Control (OLC) therapy has a system where people with T1DM need to self-administer exogenous insulin based on measurements of their BG concentration and an estimation of carbohydrate (CHO) content in their meals (Reddy et al., 2019).

2.4.1 Open Loop Insulin Delivery

Current OLC therapies can be divided into two approaches: multiple daily injections of insulin or insulin pump therapy. Multiple daily injections start by measuring BG levels using a glucose meter and administer the insulin dose subcutaneously. The insulin pump therapy uses an insulin basal profile programmed into the pump to continuously administer insulin subcutaneously 24/7 with bolus doses to compensate meals (Beneyto et al., 2018).

In addition, a sensor-augmented insulin pump (SAP) therapy combines the technology of an insulin pump with a CGM sensor that transmits glucose readings to the person wearing the device. Unlike a closed-loop insulin delivery system, the device still requires some manual adjustment and input from the wearer (Del Favero, Toffanin, et al., 2019).

To avoid the likelihood of a hyper- or hypoglycemic event to happen because of human errors in determining the insulin dose manually, and limit the dramatic variation in BGLs, closed-loop insulin delivery systems are developed (Lunze et al., 2013).

2.4.2 Closed Loop Insulin Delivery

CLC consist on a controlling algorithm, various level of signal verification, fault detection, safety checks, hardware components that are reliable, and an interface that allow the user to monitor the system performance and respond to alarm.

In this case, CLC systems, or AP, have hardware components such as subcutaneous insulin infusion pump and a continuous glucose monitor, the CLC algorithm that automatically adjusts insulin infusion in real time, such as Model Predictive Control or Proportional- Integer-Derivative Control. This control system can work as a healthy pancreas in the regulation of glucose levels via hormone delivery with few input from the user (Beneyto et al., 2018; M. D. Breton et al., 2014).

One of the most popular CLC algorithm is the Model Predictive Control. The

MPC is not a single algorithm but a strategy that consist on modeling a process to predict future behaviours of the process. This strategy can be optimized by adding constraints on inputs,states and outputs in order to satisfy an objective (Agachi et al., 2016; Bequette, 2013). Furthermore, this approach is able to compute the sequence of control actions that is predicted to be the most effective, at each control step, according to a predetermined cost function. This system adds a compensation for delays by means of feed-forward action and constraint handling (Huyett et al., 2015; Del Favero, Toffanin, et al., 2019; Magni et al., 2007).

In addition, a PID algorithm can also be designed, tuned and implemented in different ways (Bequette, 2013). However, the most common representation of the PID algorithm is:

$$u\big(t\big) = u_0 + Pe\big(t\big) + I\int_0^t e\big(t\big)dt + D\frac{de}{dt}$$

And the tuning parameter are given by:

$$P = k_c, I = \frac{k_c}{\tau_I}, D = k_c\tau_D,$$

The PID controller is a control loop mechanism that calculates an error value $e(t)$, or the difference between the desired set-point and a measured process variable. Then, it applies a correction based on proportional, integral, and derivative terms (Araki, 2009).

Common AP technology can be classified in two categories: fully closed-loop systems, where the subject is not a part of the control and hybrid systems, where it allows the subject to perform feed-forward actions to compensate for known disturbances(Beneyto et al., 2018).

2.5 Exercise and T1DM

ADA strongly recommends exercise and physical activity. Regular physical activity in people with T1DM is associated with increased CRF leading to improved blood lipid profiles and reduction in long-term cardiovascular disease risk (Reddy et al., 2019), improved psychological well-being, and possible benefits in bone health (Garcia-Tirado et al., 2019). Nevertheless, physical activity in T1DM causes glucose levels to fall rapidly, because of an imbalance between hepatic glucose production and glucose disposal into muscle.

Aerobic exercise is a type of exercise that produces an increased rate of glucose disposal in the bloodstream caused by increased glucose uptake in muscles. The

rapid uptake of glucose in muscles attributable to insulin-independent translocation of GLUT4 and increased muscle blood flow during exercise (Reddy et al., 2019; Beneyto et al., 2018; M. D. Breton et al., 2014; Huyett et al., 2015; Jacobs et al., 2016; Hobbs et al., 2019).

The onset of exercise produces a redistribution of the blood flow per organ (Hernández-Ordoñez and Campos-Delgado, 2008): an increment in the blood flow of heart/lungs and peripheral tissue, a decrease in the flow of kidneys and splanchnic organs. Since the involved tissue requires more energy to meet the required load, the peripheral glucose and insulin uptake rates rise (Hernández-Ordoñez and Campos-Delgado, 2008).

Blood glucose concentrations fall unless the patient ingests carbohydrates. Insulin concentrations do not decrease rapidly enough at the onset of the activity and rise in the systemic circulation (Quirós et al., 2018; Riddell et al., 2017; Mallad et al., 2015; Reddy et al., 2019; Hobbs et al., 2019). The recommendations for patients with T1DM for physical activity include:

- To decrease basal insulin or reducing insulin delivery 90 minutes before the start of exercise to attenuate hypoglycemia
- To ingest carbohydrates before and during exercise to avoid hypoglycemia (Reddy et al., 2019; Beneyto et al., 2018; Ramkissoon et al., 2019).

The lasting effect of increased insulin sensitivity also increases the risk of post-exercise hypoglycemia for at least 12h (Beneyto et al., 2018). Also, there is a risk of hypoglycemia after 45 minutes of aerobic exercise (Riddell et al., 2017).

Exercise also increases heart rate and oxygen consumption. Oxygen consumption is necessary because of the metabolic breakdown of the energy sources in the muscle and work associated with exercise. This workload can express as PVO_2^{max}, and it allows to monitor than altered glucose uptake of muscles (Lenart and Robert S Parker, 2002). The oxygen consumption during exercise at a constant workload increases at the start of exercise, it reaches the point at which oxygen supply matches oxygen demand, and then it plateaus(Glynn and Fiddler, 2009). Now, the maximal oxygen uptake (VO_2^{max}) is the maximum that the body can uptake and use and is the gold standard measure of exercise capacity measured in $ml/kg/min$. The VO_2^{max} depends on the patients' weight, age, gender, height, lung function, and fitness level,

the activity it is performing. It is exercise-specific, and it increases for activities involving large muscle groups (Glynn and Fiddler, 2009).

Furthermore, PVO_2^{max} average for a person in the basal state is 8% (Roy and Robert S. Parker, 2007). This percentage increases rapidly at the onset of exercise, then reaches the ultimate value within 5-6 min, and reaches a plateau (Ahlborg, Felig, et al., 1982). It reaches this threshold, and the anaerobic metabolism supplements the aerobic system because of the energy demand that exceeds the aerobic system's capacity (Rai and Sen, 2016).

As the physical activity starts, the glycogen of muscle is broken down to produce glucose, then goes under glycolysis producing pyruvate and reacts with oxygen to produce CO_2, water, and energy. As for exercise duration increases, the rate of hepatic glycogenolysis diminishes because of the limited supply of liver glycogen stores (Ahlborg, Felig, et al., 1982). The rate of glucose produced via liver gluconeogenesis does not compensate for the decrease in glucose release by liver glycogenolysis, thereby resulting in a net decrease in hepatic glucose release during prolonged exercise (Horton and Terjung, 1988). Hence, the plasma glucose concentration declines and hypoglycemia occurs (Ahlborg, Felig, et al., 1982; Ahlborg, Wahren, Felig, et al., 1986). Also, liver glycogen content declines more rapidly with increasing exercise intensity (Ahlborg, Wahren, Felig, et al., 1986). As the intensity increases, the rate with which the cardiovascular system can no longer supply the muscle with oxygen and results in the accumulation of lactate and makes impossible the continuity of the exercise (Rai and Sen, 2016).

During the recovery period, the substantial depletion of liver glycogen stores during prolonged exercise, suppresses the rate of glycogenolysis significantly, leading to a net decrease in the hepatic glucose release rate (Roy and Robert S. Parker, 2007; Horton and Terjung, 1988). However, the already suppressed net hepatic glucose release rate is elevated significantly as a consequence of an increase in hepatic gluconeogenesis (Horton and Terjung, 1988).

The PVO_2^{max} is an indicator of cardiovascular fitness. Cardiorespiratory fitness (CRF) is a direct measure of VO_2^{max} during progressive increasing of exercise intensity, and it value expresses relative to body weight (mL/kg/min). A good CRF in patients with T1DM relates to better overall glucose control and a reduction of serum lipids (Faulkner, 2010). A diminished CRF links to the presence of cardiovascular autonomic neuropathy in long-term diabetes (Röhling et al., 2017).

Current guidelines suggest that people with T1D should perform at least 150 minutes of moderate-intensity or 90 minutes of vigorous-intensity physical activity (see Table 2.2) per week with no more than two consecutive sedentary days (Hackney and Constantini, 2013). Therefore, it is essential to describe the effects of exercise quantitatively by adding them to glucose-insulin models to have realistic simulations (Hernández-Ordoñez and Campos-Delgado, 2008).

Table 2.2: Exercise Intensities according to PVO_2^{max} (Rai and Sen, 2016)

Exercise Intensity	PVO_2^{max}	Note
Basal Level	8%	No exercise
Prolonged moderate level aerobic exercise	65%	the heart rate of 150 bpm for a 30-year-old patient
Vigorous exercise	>75%	160 bpm

2.6 Summary

T1DM is a chronic autoimmune disease that starts with the progressive loss and destruction of beta cells (Saberzadeh-Ardestani et al., 2018). Then the dysglycaemia unfolds long-term macrovascular and microvascular complications (Tuomilehto and Rydén, 2018). Diagnosis of diabetes consists of the detection of autoantibodies such as GAD65 or IA-2 and insulin production monitoring (Ilonen et al., 2013). Furthermore, T1DM is treated conventionally by the administration of insulin through pens or insulin pumps (Lunze et al., 2013). The insulin delivery is calculated based on carbohydrate intake, physical activity, and blood glucose concentration, known as open-loop therapy (Reddy et al., 2019). Miscalculations of insulin bolus could cause hyperglycaemic and hypoglycaemic events (Lunze et al., 2013). Closed-loop insulin delivery therapy is in development and could potentially avoid adverse events by automatically adjusting the insulin bolus based on blood glucose concentration from a CGM, an insulin pump, and a control algorithm (M. D. Breton et al., 2014).

This closed-loop insulin delivery or Artificial Pancreas has to deal with meals and intense physical activity. It has to respond effectively to these disturbances. The use of control algorithms such as MPC, PID, or fuzzy logic-based has improved the responsiveness of fully automated APs (Claudio Cobelli, Renard, and Kovatchev, 2011). APs tests have simulations using mathematical models that mimic the glucose-insulin dynamic of a T1DM patient. The mathematical models use the pathophysiological knowledge of the disease and complement the simulations of the

artificial pancreas robustness tests (Claudio Cobelli, Federspil, et al., 1982). These principles are part of the next chapter as it describes the development of better controller algorithms. It also describes physiological models used for closed-loop controls strategies assessment against disturbances such as exercise and meals.

Chapter 3

STATE OF THE ART

Mathematical models take into account the hormone that regulates the blood glucose levels, insulin (Richard N Bergman, Finegood, and Ader, 1985; Hovorka, Canonico, et al., 2004) and others also take into account the glucagon (Sorensen, 1985), a hormone that stimulates the breakdown of glycogen into glucose. The models can group by their complexity. Models like the Bergman "Minimal" model (Richard N Bergman, Finegood, and Ader, 1985) are less complex than Hovorka's model (Hovorka, Canonico, et al., 2004) and the Sorensen's model (Sorensen, 1985). These are part of simulations, automatic control, and test for new therapies for diabetes (Lema-Perez, Aguirre-Zapata, and Garcia-Tirado, 2015). These models mimic the response of the BGLs of a T1DM patient. Therefore, these models integrate into simulations of the components of Artificial Pancreas such as the CGM sensor, insulin pump, and the controller algorithms to test different configurations of these systems to improve patients' life (see Figure 3.1) (Claudio Cobelli, Renard, and Kovatchev, 2011).

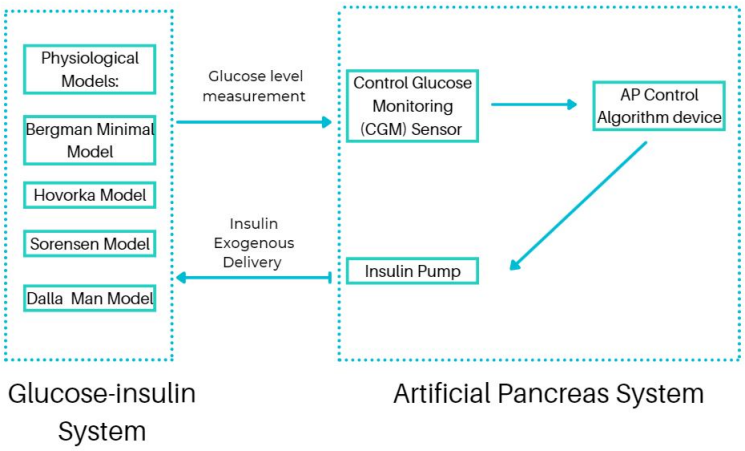

Figure 3.1: Graphical representation of physiological models or glucose-insulin/glucagon systems integrated with Artificial pancreas system. Own elaboration from Cobelli et al.(2011).

The general Artificial Pancreas design considers devices that T1DM patients commonly use to control their BG levels, CGM sensors, and insulin pumps. Control

algorithms use their data to deliver correct amounts of insulin, glucagon, or both to regulate BG levels.In other words, a closed-loop system requires an actuator or the insulin pump, a continuous glucose monitor (CGM) sensor, and control validation. This control validation (controller) is to obtain a low tolerance for mistakes. It needs sensor validation, a robustness test under uncertainty, and a glucose-insulin dynamic model, for insulin-only therapy (see Figure 3.2).

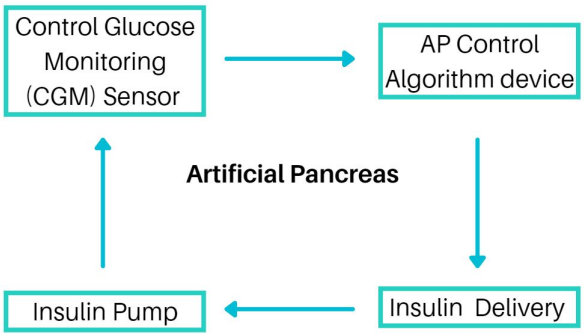

Figure 3.2: General Hardware design of a Closed Loop Artificial Pancreas. Own elaboration from Cobelli et al.,(2011).

First, there is a layered structure of the AP control algorithm (Del Favero, Toffanin, et al., 2019), which separates functionalities among modules, which allows independent development and solving integration hurdles. It describes from the bottom the physical layer (hardware), physical layer interface (software for hardware management), safety layer (software module), control layer (software computing, topic of this section), and at the top, the adaptation layer (adjusting standard therapy parameters). In advance, the types of control layer commonly used in AP are MPC, PID, and fuzzy logic (FLC).

3.1 Systems of glucose-insulin dynamics

This section shows the model known as the Minimal Model, then the Hovorka model, and the complex Sorensen Model. These mathematical models explain glucose-insulin dynamics and are the most cited in the literature (Panunzi et al., 2020). These models can be used with other models to improve human activities simulation such as eating and exercising. Therefore, the extension of these models is also detailed.

3.1.1 Bergman Minimal Model

The Minimal Model designed by Bergman et al. 1989 aimed at describing the pancreatic responsiveness and insulin sensitivity of a T1DM patient (González, Voos, and Darouach, 2015) in Figure 3.3. This model bases upon the physiology knowledge available at the time (Richard N Bergman, 2021; Pacini, Finegood, and Richard N Bergman, 1982; Richard N Bergman, Finegood, and Ader, 1985) and analysis of a frequently sampled intravenous glucose tolerance test (IVGTT). This Minimal Model is considered a method to analyzes the plasma glucose and insulin dynamics during an IVGTT (R. N. Bergman, Phillips, and C. Cobelli, 1981).

The model consists of two-linear differential equations, or two compartments, for insulin kinetics in plasma and the effects of insulin and glucose itself on glucose restoration after perturbation by intravenous injection (Richard N Bergman, 1989; Richard N Bergman, 2021).

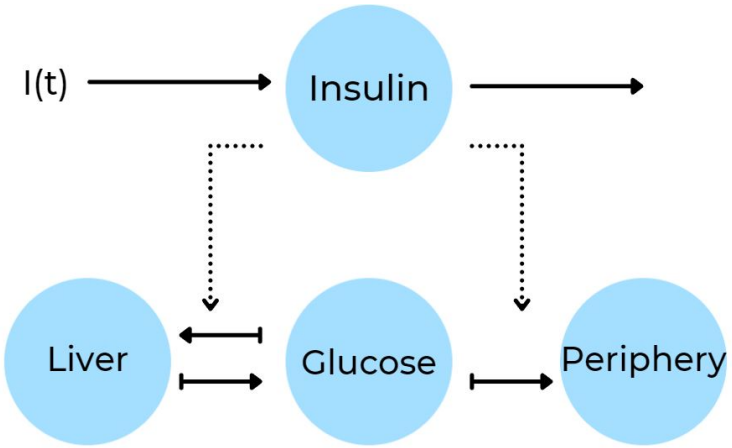

Figure 3.3: Schematic flow diagram for glucose kinetics of Bergman Minimal Model (Richard N Bergman, 2021).

First-order equation 3.1 assumes that the insulin secreted enters the interstitial fluid (ISF) compartment, represented by "X" . Then, ISF insulin exits remote compartment by the first-order process $\frac{dG}{dt}$ in equation 3.2.

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3\big(I(t) - I_b\big) \tag{3.1}$$

The rate of return of glucose to basal after injection in equation 3.2 includes an insulin-dependent component, X(t). Glucose dynamics (Eq. 3.2) includes the term S_G for glucose effectiveness. Glucose effectiveness (Richard N Bergman, 2021) is

the ability of glucose to normalize its concentration on its own.

$$\frac{dG(t)}{dt} = -\big(p_1 + X\big(t\big)\big)G\big(t\big) + p_1 G_b \tag{3.2}$$

After injection, the ability to normalize glucose on its own depends on insulin action (S_I) and glucose effectiveness (S_G). Bergman (2021) represent mathematically S_G as the partial derivative of glucose disappearance on glucose and insulin and results in the ratio of two parameters of the minimal model: $\frac{p_3}{p_2}$. Following IV glucose infusion, the time courses of plasma glucose G(t) and insulin I(t) were determined experimentally. The parameters of this model are determined through experimental studies of intravenous glucose tolerance test (in table 3.1).

Table 3.1: Description of parameters of Bergman Minimal Model (Welch et al., 1990; Richard N Bergman, 2021).

Parameter	Description	Unit
$G(t)$	Serum glucose concentration	mg/dL
$X(t)$	Concentration of insulin in a compartment remote from plasma	$1/min$
$I(t)$	Plasma insulin concentration	mU/L
G_b	Baseline glucose concentration	mg/dL
I_b	Baseline insulin concentration	mU/L
p_1	The fractional ability of glucose to lower its concentration in plasma independent of increased insulin	unitless
p_2	Fractional transport coefficient of insulin out the remote compartment	unitless
p_3	Fractional transport coefficient of insulin in the remote compartment	unitless

3.1.2 Hovorka et al. Model

The "Hovorka model" has compartment-base divided in three subsystems. Consists of a glucose subsystem, insulin subsystem and an insulin action subsystem, shown in figure 3.4.

The glucose subsystem has two compartments, described by:

(3.3)
$$\frac{dQ_1(t)}{dt} = -(\frac{F_{01}}{V_G G(t)} + X_1(t))Q_1(t) + k_{12}Q_2(t) - F_R + U_G(t) + EGP_o(1 - X_3(t))$$

$$\frac{dQ_2(t)}{dt} = X_1(t)Q_1(t) - (k_{12} + X_2(t))Q_2(t)y(t)G(t) = \frac{Q_1(t)}{V_G} \tag{3.4}$$

The insulin subsystem has two compartments, S_1 and S_2, representing absorption of insulin administered subcutaneously and the plasma insulin concentration. The insulin action subsystem has three compartments described by:

$$\frac{dX_1}{dt} = -k_{a1}X_1(t) + k_{b1}I(t) \tag{3.5}$$

$$\frac{dX_2}{dt} = -k_{a2}X_2(t) + k_{b2}I(t) \tag{3.6}$$

$$\frac{dX_3}{dt} = -k_{a3}X_3(t) + k_{b3}I(t). \tag{3.7}$$

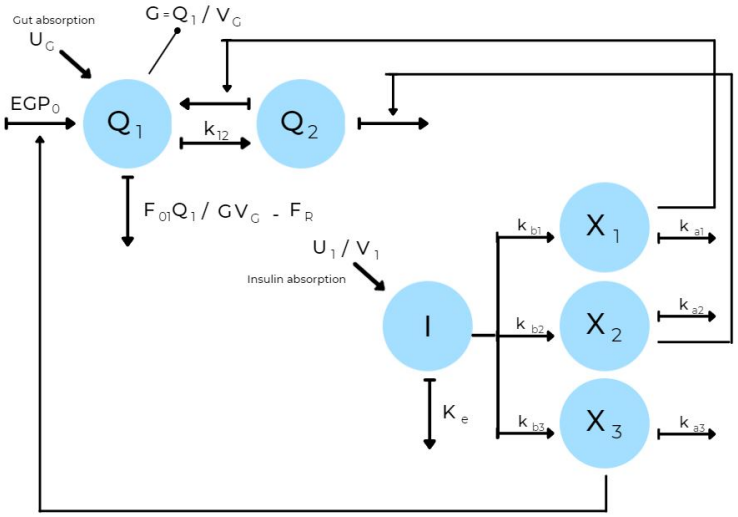

Figure 3.4: Schematic flow diagram for glucose and insulin subsystems of Hovorka et al. (2002).

Each parameter used in the differential equations is described in table 3.2. These parameters were obtained from labeled IVGTT data (Hovorka, Shojaee-Moradie, et al., 2002).

Table 3.2: Description of parameters of Hovorka model (Hovorka, Shojaee-Moradie, et al., 2002; Hovorka, Canonico, et al., 2004).

Parameter	Description	Unit
$Q_1(t)$	Mass of glucose in accessible compartment	$mmolL^{-1}$
$Q_2(t)$	Mass of glucose in non-accessible compartment	$mmolL^{-1}$
k_{12}	Transfer rate from Q_1 to Q_2	min^{-1}
k_{a1}, k_{a2}, k_{a3}	Deactivation rate constants	min^{-1}
k_{b1}, k_{b2}, k_{b3}	Activation rate constants	min^{-2} per mU/L
$I(t)$	Plasma insulin	mU/L
I_b	Basal plasma insulin	mU/L
EGP_o	Endogenous glucose production	$mmol/min$
F_{01}	Total non-insulin-dependent glucose flux	$mmol/min$
$G(t)$	Total glucose concentration	$mmol/L$
$U(t)$	Bolus dose of administered glucose	$mmol/min$
$X_1(t)$	Remote effect of insulin on glucose transport/distribution	min^{-1}
$X_2(t)$	Remote effect of insulin on glucose disposal	min^{-1}
$X_3(t)$	Remote effect of insulin on EGP	min^{-1}
k_e	Insulin elimination from plasma	min^{-1}
V_I	Insulin distribution volume	Lkg^{-1}
V_G	Glucose distribution volume	Lkg^{-1}
F_R	Renal glucose clearance	$mmolL^{-1}$

It considers that the regulation of glucose is represented by plasma glucose dynamics represented by the masses of glucose in all compartments and insulin action dynamics represented by the effect of insulin on glucose transport, disposal and endogenous glucose production (EGP) (Nath et al., 2018).

Nowadays, it serves to implement nonlinear MPC in clinical trials of closed-loop insulin therapy. It lies between simplicity of the Bergman Minimal Model and the complexity of a more physiologically based models such as that of Sorensen (Sorensen, 1985).

3.1.3 Sorensen's Physiological Model

In 1985, John T. Sorensen published a model with nineteen nonlinear differential equations to model the glucose-insulin dynamics (Sorensen, 1985). His model is based on differential concentration balances in the brain, heart, lungs, liver, kidney

and periphery organs involved in the glucose and insulin interactions, shown in figure 3.5.

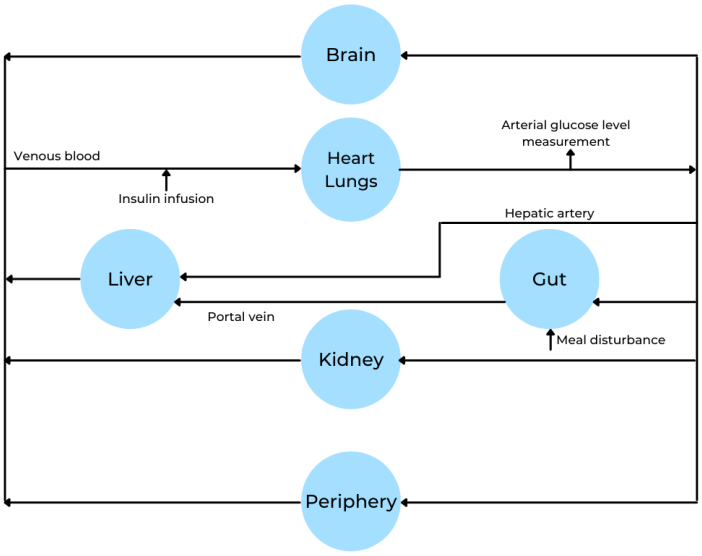

Figure 3.5: Schematic flow diagram for compartments of Sorensen (1985). Own elaboration from Sorensen (1985)

This model also incorporates glucagon, which is another regulatory hormone, and its effects. Furthermore, this model's equations is divided into three subsystems (glucose, insulin and glucagon). The subsystems of insulin and glucose are modeled for the brain, heart and lungs, liver, gut, kidney and periphery compartments (muscles and adipose systems) (see Figure 3.5). While the glucagon is modeled as a single compartment with one single nonlinear differential equation. Its parameters are obtained on the basis of literature research, 135 parameters including the initial conditions of the state variables (Panunzi et al., 2020).

In addition, the derived mass balance equations considered serve to estimate the rate of exchange for any given substance (insulin or glucagon), with metabolic sinks and metabolic sources according to the physiological response of the body.

This system's output is the arterial glucose allowing accurate glucose levels and considers inputs like intravenous insulin infusion and a glucose input through a meal.

Some of the limitations that this model has is that it does not have the ability to simulate the influence of amino acids (during meal intake), epinephrine effects on glucagon and insulin ratio and the effects of exercise (Al-Hashmi, 2007). However,

this model has been revised and extended with effects of exercise by Lenart and Robert S. Parker (2002).

Furthermore, it also was extended with the meal model by the gastric emptying done by Lehmann and Deutsch (1992), introduced by Parker et al. (2000).

3.1.4 Comparison of Bergman, Hovorka and Sorensen physiological model

Regarding to the level of detail, the models can be minimal (coarse) or maximal (fine-grain) (Lema-Perez, Aguirre-Zapata, and Garcia-Tirado, 2015). Differences in the number of differential equations primarily reflect the degree of body compartmentalization employed (Table 3.3). Therefore, the more ODEs, the more complex the model is.

Table 3.3: Comparison of mathematical complexities of physiologic models of glucose metabolism

Models	Mathematical Complexity		
	Differential Equations	Parameters	Nonlinear Functions
Minimal Model	3	8	2
Hovorka Model	9	17	-
Sorensen Model	22	135	19

In addition, the Bergman nor the Hovorka model captures the changes in glucose-insulin dynamics due to exercise (Roy and Robert S. Parker, 2007). Many researchers use these models for the development of control algorithms, but because of its complexity the Sorensen model only few authors use it (Panunzi et al., 2020).

These models have been extended to take into account other disturbances like meal intake and exercise. With the extension of meal models and exercise models, the disturbance testing of AP is possible, and discussed in the next section.

Furthermore, this glucose-insulin models serve as the foundation for the metabolic simulators. For instance, the University of Virginia (UVa)/Padova metabolic simulator, an accepted by the U.S. Food and Drug Administration simulator, with a large cohort of subjects with inter-subject variability allows extensive and robust studies. In addition, subcutaneous glucose sensors and insulin infusion pumps are also involved in the simulation (Rashid et al., 2019).

3.2 Meal Intake models

The performance of the controller depends on the meal model used and also on the model of the diabetic patient (Dua, F. J. Doyle, and Pistikopoulos, 2006).

3.2.1 Dalla et al. Model

It is a pharmaco-kinetic model that aims to describe the physiological events that follow meal administration for non-diabetic and diabetic patients. The dynamics of the model can be divided into a glucose subsystem, insulin subsystem, liver, gastrointestinal tract, muscle and adipose tissues and β-cells (Nath et al., 2018). Described mathematically a model of the gastric system (Dalla Man, Camilleri, and Claudio Cobelli, 2006).

$$\frac{dq_1}{dt} = u - k_{emp}q_1 \tag{3.8}$$

$$\frac{dq_2}{dt} = k_{emp}(q_1 - q_2) \tag{3.9}$$

$$\frac{dG_{gut}}{dt} = k_{emp}q_2 - k_{abs}G_{gut} \tag{3.10}$$

where q_1 is the mass of carbohydrate in the stomach compartment, u is the meal input, k_{emp} is the rate constant for gastric emptying, q_2 is the mass of carbohydrate in stomach of the compartment two, k_{abs} is the rate constant absorption from the gut, and G_{gut} is the mass of carbohydrates in the gut.

3.2.2 Fisher Model

Fisher (1991) extends the Bergmann Model with the rate of intestinal absorption following a meal as an exogenous glucose input. It also depends on the amount of carbohydrate disturbance (Fisher, 1991).

$$D(t) = \begin{cases} \beta e^{(a(t-t_{time}))}, & \text{if } t \geqslant t_{meal} \\ 0, & \text{if} t \leqslant t_{meal} \end{cases}$$

where, t_{meal} represents the time at which the meal begins digestion. The parameter a represents the absorption rate of the meal, while β represents the size of the meal.

3.2.3 Lehmann and Deutsch Meal Model

Their model aims to simulate the transitory phases after an insulin regimen or diet that lead to a steady-state glycaemic profile of an insulin-treated diabetic patients (Lehmann and Deutsch, 1992).

They assume a patient lacking of endogenous insulin secretion. Contains a single compartment representing extracellular glucose and blood glucose with inputs of

intestinal absorption and hepatic glucose production. Then, the glucose is first removed by the utilization of red blood cells and the central nervous systems then by liver and periphery such as muscles and adipose tissue.

According to Lehmann and Deutsch 1992, the rate of the absorption of glucose through the gut wall RG_{abs}, (mg/min) is given by:

$$RG_{abs} = K_{gabs} G_{gut}, \tag{3.11}$$

where G_{gut} is the amount, in mg, of glucose in the gut after the ingestion of meal. Defined as:

$$\frac{dG_{gut}}{dt} = RG_{empt} - K_{abs} G_{gut}.$$

The RG_{empt} is the rate of gastric emptying which bases on a trapezoidal form where the rate rises and saturates to a maximum value ($V-_{max}$) and then fall to zero where rise and fall are ramp function (Lehmann and Deutsch, 1992). K_{abs} is the constant rate for glucose absorption given by $1h^{-1}$.

It has much slower initial dynamics and smaller glucose excursions. When there is a postprandial period, the liver uptakes 25% of the absorbed glucose from the gut after a meal, until the glycogen reservoir is filled or until the postprandial period is ended (Hernández-Ordoñez and Campos-Delgado, 2008).

3.3 Exercise Models

As explained before, exercise induces metabolic changes in the body, such as the drop in plasma insulin concentration form its basal level, increase of hepatic glucose release, elevated hepatic glycogenolysis (Roy and Robert S. Parker, 2007).

For the quantification of exercise indices, the percentage of the maximum oxygen consumption rate (PVO_2^{max}) which is the proposed by (Lenart and Robert S Parker, 2002). The VO_2^{max} the mL of oxygen consumed per minute per kg of bodymass and it is defined by Ficks equation:

$$VO_2^{max} = Q(C_aO_2 - C_vO_2)$$

where Q is the cardiac output of the heart, C_aO_2 is the arterial oxygen content and C_vO_2 is the venous oxygen content. The second term is then the difference in oxygen content between arterial and venous blood (Rai and Sen, 2016; Bowen, Benson, and Rossiter, 2019). In basal state, this difference is around 4mL Oxygen per 100 mL of blood, and at maximal exercise intensity it gets closer to 16 mL (Lavie et al., 2016). Furthermore, the cardiac output can be calculated by multiplying the stroke

volume (amount of blood pumped from the left ventricle in a beat) and the heart rate (beats per minute) (Malek and Coburn, 2008). This value can be calculated in sport laboratories in a controlled environment with cardiopulmonary exercise cycling or treadmill tests and these test can more reliable (Mann, Lamberts, and Lambert, 2013). However, nowadays there are other methods such as fitness watches and online calculators (Eades et al., 2021; Firstbeat Technologies Ltd., 2014).

The traditional approach has been to prescribe exercise intensity as PVO_2^{max} or maximum heart rate (HRmax) and these methods remain common in the literature.

3.3.1 Roy and Parker Model

Roy and Robert S. Parker (2007) extended the Bergman minimal Model with the exercise effect as follows:

$$\frac{dI}{dt} = -nI(t) + p_4 u_1(t) - I_e(t); \tag{3.12}$$

$$\frac{dX}{dt} = -p_2 X(t) + p_3(I(t) - I_b); \tag{3.13}$$

$$\begin{aligned}\frac{dG}{dt} = p_1(G(t) - G_b) - X(t)G(t) + \frac{W}{Vol_G}(G_{prod}(t) \\ -G_{gly}(t)) - \frac{W}{Vol_G}G_{up}(t) + \frac{u_2(t)}{Vol_G};\end{aligned} \tag{3.14}$$

$$\frac{dG_{prod}}{dt} = a_1 PVO_2^{max}(t) - a_2 G_{prod}(t); \tag{3.15}$$

$$\frac{dG_{up}}{dt} = a_3 PVO_2^{max}(t) - a_4 G_{up}(t); \tag{3.16}$$

$$\frac{dI_e}{dt} = a_5 PVO_2^{max}(t) - a_6 I_e(t); \tag{3.17}$$

where I_e is the rate of insulin removal due to exercise, G_{up} and G_{prod} represent the rate of glucose uptake and hepatic glucose production. W is the weight of the patients. G_{gly} is the decline of glycogenolysis rate during prolonged exercise due to depletion of liver glycogen stores (Roy and Robert S. Parker, 2007). The latter decrease when the energy expenditure threshold (A_{th}) is exceeded. A_{th} is a function of exercise intensity and duration, represented by a linear equation:

$$A_{th} = -1.1521(u_3(t))^2 + 87.47u_3(t) \tag{3.18}$$

Therefore, the glycogenolysis during exercise is mathematically represented as:

$$\frac{dG_{gly}}{dt} = \begin{cases} 0, & A(t) < A_{th} \\ k, & A(t) \geqslant A_{th} \\ -\frac{G_{gly}}{T_1}, & u_3(t) = 0 \end{cases}$$

Where $A(t)$ is $u_3(t)$ (exercise intensity) integrated, which is calculated by the following equations:

$$\frac{dA}{dt} = \begin{cases} u_3(t), & u_3(t) > 0 \\ -\frac{A(t)}{0.001}, & u_3(t) = 0 \end{cases}$$

Hence, once A(t) reaches A_{th}, the rate of change of glycogenolysis rate starts to decline at a rate given by k because of the depletion of available liver glycogen stores. They take into account the increased glucose uptake by the working tissues and the hepatic glucose release that increases with the work intensity (Wahren et al., 1971). As well as the glycogenolysis rate during exercise.

3.4 Control Algorithms

By control algorithm, it means the algorithms used to control coordinate, and optimize a process, in this case insulin delivery. It analyzes the error between a process variable and a setpoint (Shen and S. Chen, 2012). The error, is applied as feedback to generate a control response to bring the controlled process variable closer to the setpoint. This feedback control is applied in AP, which takes the measurements from the CGM sensor and makes calculated adjustments to keep the blood glucose levels within a set range by means of a "final control element", such as an insulin pump (Hajizadeh et al., 2019a).

3.4.1 Model Predictive Control Algorithm

Model Predictive Control algorithm computes, at each control step, the sequence of control actions that is predicted to be the most effective, i.e. optimal according to a predefined cost function (Del Favero, Toffanin, et al., 2019). It is the most suitable for the design control systems with delays and constraints (Huyett et al., 2015).

MPC adds naturally in the design process a compensation for delays by means of feed-forward action, same as constraint handling (Magni et al., 2007).

The MPC is a basic strategy that is able to involve many different types of models and objective functions (Bequette, 2012). For instance, this controller has been enhanced to an Adaptive MPC with a Run-to-Run approach (R2R) (Toffanin et al., 2017) and test *in silico* with the University of Virginia and Padova (UVa/Padova) simulator's 100 virtual subjects in a realistic month scenario. The basal insulin delivery, carbohydrate-to-insulin ratio (CR), a Correction Factor, and bodyweight (BW) were used for control tuning and individualization. As a result, there was a reduction of overshoots detected after the meal approach and a reduced BG variability after months of using the R2R. Its performance indices improved day-by-day showing a good monotone trend. This study demonstrated that an adaptive AP might be the key for outpatient studies because this strategy showed a great potential to capture intra- and inter-day glucose variability.

Del Favero et al.(2019) proposes a modular controller composed of a Safety Supervision Module (SSM) and the MPC, called the Modular Model Predictive control (mMPC). The Modular architecture of the AP is in Fig. 3.6. This modification in clinical trials with inpatient and outpatient settings is showing promising outcomes. Their AP with an mMPC performed well in maintaining BG in target, and patients spent no time in hypoglycemia overnight and after diner (M. Breton et al., 2012). Later, they compared mMPC to an adaptive mMPC (A-mMPC) in real-life testing. The A-mMPC consists of SSM, MPC, and the run-to-run (R2R) algorithm (a strategy devoted to daily updates). A-mMPC showed good performance, but it was not statistically significantly different to mMPC (Del Favero, Toffanin, et al., 2019).

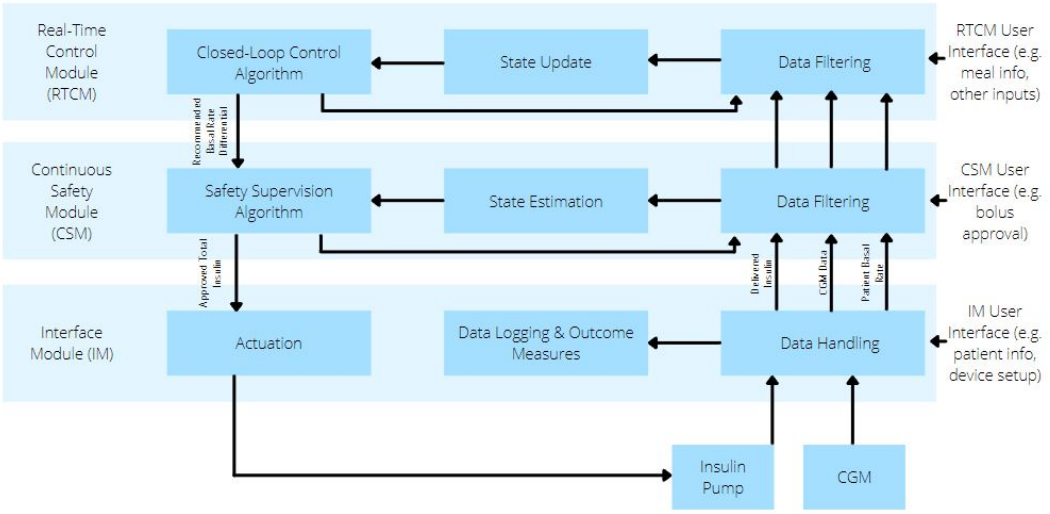

Figure 3.6: Modular architecture for Del Favero et al. (2019) Artificial Pancreas study. Taken from S. D. Patek et al., 2012 (2012).

The mMPC controller compared with the MPC-R2R strategy mentioned before, as an early-stage prototype with 18 TD1M patients in free-living conditions (Messori et al., 2017) faced normal daily activities, including exercise, during one month. The R2R-AP significantly improved the glucose control performance during the night. Although, this study did not specify whether the patients did or not exercise because of very limited interaction with patients due to telemedicine reports. Nevertheless, the results showed no time-in-hypoglycemia for both controllers demonstrating that this is a promising step for exercise response control in patients with T1DM and AP development.

Recently, another research team (Song et al., 2020) tested a learning type MPC algorithm (L-MPC) in a clinical trial that lasted eight days, combining two days of Open Loop therapy and six days of Closed Loop therapy. The L-MPC combines the MPC algorithm with an iterative learning control (ILC). ILC learns from an individual's lifestyle on a day-to-day basis for better daily glycemic control. The set-point or glucose target for the MPC control algorithm will be updated using ILC. They added exercise or alcohol to test the robustness. Each participant was part of 20 minutes of moderate-intensity physical activity, riding a stationary bicycle. On a different day, each participant drank 50 ml of beer with an alcohol content of 4%. This system showed a good performance and robustness in glycemic control during exercise and alcohol consumption and did not cause frequent or severe hypoglycemia.

The metrics of comparisons between each study reviewed in this section are in table 3.4. This table summarizes the strategy used by each research team and its overall outcomes. The overall outcomes are measured in the percentage that the patient had a hypoglycemic event and the time that it spent on the target range, normally between 70 mg/dl and 180 mg/dl. Using the MPC strategy without exercise, the time in target range is higher than with exercise (Toffanin et al., 2017). The free living conditions of a patient consider small walks, unannounced meals or snacks, with mMPC and R2R the patient has more time in the target range (Messori et al., 2017; Del Favero, Boscari, et al., 2016).

Table 3.4: AP with MPC and exercise studies reviewed.

Authors	Modification	Exercise consideration	Overall Outcomes
Del Favero, Toffanin, et al., 2019	MPC + SSM = MMPC	Free Living Conditions	time in target (70-180 mg/dl) : $74\% \pm 13\%$; time in hypo (below 70 mg/dl): $[0\%, 3.1\%]$
Del Favero, Boscari, et al., 2016	MMPC vs SAP	Intense physical activity for 90-120 minutes	time in target (70-180 mg/dl): $56\% \pm 13.5\%$; time in hypo (below 70 mg/dl):$2\%(1.2 - 4.5)$
Toffanin et al., 2017	MPC + R2R	No Exercise	time in target (70-180mg/dl): $84.34\% \pm 30.76\%$; time in hypo(below 70 mg/dl): 0%
Messori et al., 2017	mMPC vs R2R-MPC	Free Living Conditions	time in target (70-180mg/dl): $61.82\% \pm 11.12\%$ vs. $66.90\% \pm 13.34\%$; time in hypo(below 70 mg/dl): $2.01\% \pm 1.69\%$ vs. $2.12\% \pm 1.33\%$
Song et al., 2020	ILC + MPC = LMPC	Alcohol and Moderate physical activity	time in target (70-180mg/dl): $64.0\% \pm 23.6\%$ and $62.0\% \pm 23.3$; time in hypo(below 70 mg/dl): $0\% \pm 0\%$ and $0\% \pm 0\%$

3.4.2 Proportional-Integer-Derivative Control Algorithm

It can automatically apply accurate and responsive correction to a control function, which makes it very suitable for glycemic control. Therefore, this algorithm can restore the glucose level, for instance, to the desired one with minimal delay and overshoot by increasing or not the output. However, the PID algorithm varies in design, tuning, and implementation in different ways (Bequette, 2013).

Sometimes only the proportional-derivative (PD) term is used as a controller. For instance, Beneyto et. al. (2018) proposed a novel hybrid AP with an automatic insulin infusion algorithm. This AP based the insulin-only controller on the PD and carbohydrates (CHO) suggestions done by the negative feedback controller with a predictive PD. The integral term discarded of the CHO loop minimizes the risk of hypoglycemia. This approach tested *in silico* adults used an exercise/disturbance model that increases the glucose uptake during and after an exercise session characterizing the aerobic exercise. Concluding that, this closed-loop CHO control strategy can prevent the majority of BG decreases. However, it still depends on the patient's response to the alarms. Table 3.5 describes more studies with PID algorithms facing exercise.

Furthermore, Ramprasad et al.(2004) design a robust PID based on Sorensen's and Parker's models where both single and multiple meals are considered.

Similarly, Ramkissoon et al. (2019) used a PD controller with sliding mode reference conditioning (SMRC) and insulin feedback (IFB) to develop and test *in silico* an exercise-induced hypoglycemia reduction algorithm (EHRA). They tested the EHRA with unannounced and the controller-only with announced and unannounced exercises using the UVa/Padova simulator extended with an exercise model. EHRA successfully triggered disturbance rejection exercise-induced hypoglycemia mitigation actions when it detected aerobic exercise. With announced exercise, the system gives a dose of carbohydrates to the patient but, it remains the same regardless of exercise intensity. However, the algorithm depended on accurate CGM readings. In addition, due to parameters not modeled, such as insulin formulations and their respective delay and the likelihood of inaccurate CGM readings happening in real life, some conclusions of the effectiveness of their approach are inconclusive.

On the other hand, Huyett et al. (2015) did a model-based tuning to adjust the different insulin sensitivities of the patients and a third-order discrete-time model structure that adequately captured the behavior of insulin action on the blood glucose concentration (see Figure 3.7). The personalized factor added to the model gain,

an Internal model control (IMC), is a tuning method that allows PID parameters to be calculated directly from the process model. Researchers added to the PID controller an anti-reset windup protection (AWP) (adjusts the integration based on the situation) strategy and an IFB (imitates the physiology of the human body). This system tested *in silico* tunned the PID controller for a robust stability and performance analysis. Their study showed that the intraperitoneal implanted AP system's faster insulin transport and action, along with more rapid glucose sensing, allows the PID controller to maintain excellent glycemic control. Although the system did not include exercise models, the modifications allow the system better control both large but temporary disturbances and small but persistent disturbances. So, this approach might function right with exercise models.

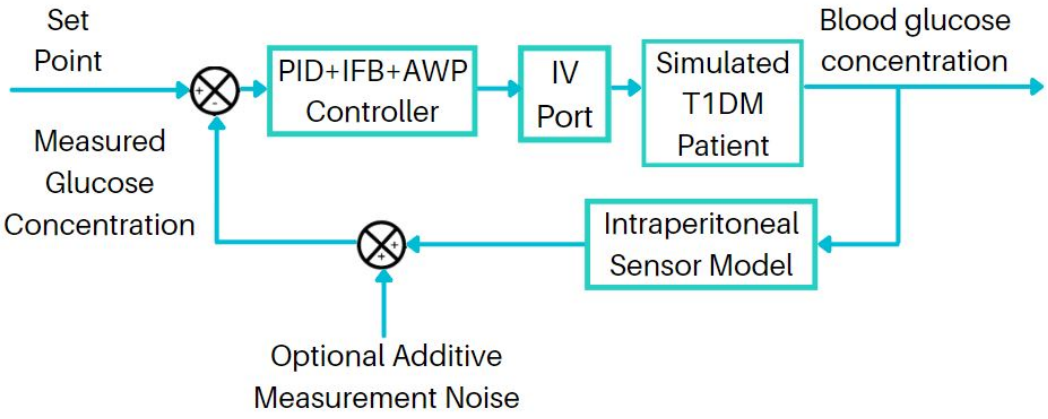

Figure 3.7: Block diagram representation of the simulation done by Huyett et al. (2015). Taken from Huyett et al. (2015).

Table 3.5 summarizes the studies reviewed in this section. The different PID strategies used has improved the time in target range of the patient. The studies reviewed have used different exercise models to test a PD strategy (Beneyto et al., 2018; Ramkissoon et al., 2019) with a promising time in target range. Quirós et al. (2018) has used an PID strategy with patients performing anaerobic and aerobic exercise for different amount of time, and have presented very good results with few hypoglycemic events.

Table 3.5: PID AP and exercise studies reviewed.

Authors	Modification	Exercise consideration	Overall Outcomes
Huyett et al., 2015	PID + IMC+anti-reset windup+IFB	No	time in target (80-140mg/dl): $78.0\% \pm 6\%$; time in hypo(below 70 mg/dl): $0\% \pm 0\%$
Beneyto et al., 2018	PD + SAFE + IFB + CHO	Exercise Model	time in target (70-180mg/dl): $92.4\%(90.1 - 97.0)$ daytime and $98.9\%(98.1 - 99.2)$ nightime ; time in hypo (below 70 mg/dl): $0.9\%(0.2-2.2)$ daytime and $0.9\%(0.3 - 1.2)$ nighttime
Quirós et al., 2018	PID + SMRC	Aerobic and Anaerobic Exercise	time in target (70-180mg/dl): $89.8\% \pm 18.6\%$ and $75.9\% \pm 27.6\%$; time in hypo (below 70 mg/dl): $2.5\% \pm 6.3\%$ and $1\% \pm 3.6\%$
Ramkissoon et al., 2019	PD + SMRC +IFB	Exercise Model	time in target (70-180mg/dl) [median (25th%, 75th%)]: $93.6\%(90.8, 93.9)$; time in hypo(below 70 mg/dl): $0.1(0.0, 0.1)$

3.5 Applications for self-monitoring of blood glucose levels

Mobile phone apps for health self-management can communicate with different types of sensors. In addition, they are able to transfer data securely to relatives and health care personnel and summarize different factors. These can encourage patients to self-manage for longer periods, enabling them to achieve healthy outcome (Årsand et al., 2015).

The mobile smartphone technology offers innovative strategies that could improve the self-management of patients with chronic diseases and especially diabetes (Doupis et al., 2020). In 2011, the World Health Organization (WHO) defined mobile health (mHealth), a component of eHealth, as the "medical and public health

practice supported by mobile devices" (WHO, 2011). The use of mHealth technology increases access to health-related information for both patients and healthcare providers and also facilitating remote patient monitoring (Klonoff, 2013).

A mHealth application for T1DM patients could eliminate complicated calculations, handwritten logbooks and long-lasting search for evaluation of the nutritional content of foods. Furthermore, a personalized treatment approach could improve patient's quality of life and glycemic control (Chatzakis et al., 2019).

Prediction Models of blood glucose would allow to generate alerts is hypoglycemia or hyperglycemia is about to occur. If the prediction of BGL is accurate enough, it would prevent complications and would improve the quality of life of patients. On the other hand, another approach to help T1DM is through insulin calculators, there are few applications that provide this service (Doupis et al., 2020). Although many applications designed to achieve these goals have reached the market because of their efficacy and safety (Doupis et al., 2020; Chatzakis et al., 2019).

For instance, the Intelligent Diabetes Management (IDM) application links to a website, records glucose levels, proposed carbohydrate intakes, and planned activities, and suggests the appropriate insulin doses. It possesses an insulin dose calculator with the option of varying the insulin for small or large meals, together with an insulin grid system to adjust for differing glucose levels at that time or by those using any combination of these methods (Ryan et al., 2017).

Furthermore, Doupis et al. (2020) reviews apps that have been tested with diabetic patients in different settings and have shown promising results. The results include improvement of the median HbA1c levels and the prevention of hypoglycemic effects.

The described applications include the GoCARB mobile application (Rhyner et al., 2016) that helps patients calculate the amount of carbohydrates about to consume. This application could facilitate the calculation of insulin needed since it is hardest to do (Chatzakis et al., 2019; Rhyner et al., 2016). This application has been tested in a multicenter setting. However, there were no significant change over time in relation to self-efficacy, self-care activities, and quality of life (Doupis et al., 2020).

3.6 Summary

This chapter reviews the state of the art of some of the components of an AP's first in silico trial like the patient model, the control strategy to correctly deliver the insulin dose. Finally, it describes another approach to help patients to deliver the

right amount of insulin, with mobile applications that patients use to calculate the insulin delivery according to the patient diabetic data.

Table 3.6: Summary of revision of the state of the art

Revision of the state of the art		
Physiological Mathematical Models that explain glucose-insulin dynamics and most cited in the literature.	Bergman Minimal Model	Section 3.1
	Hovorka Model	Section 3.1
	Sorensen Model	Section 3.1
Meal Models to simulate the response of TD1M patients to exogenous glucose infusion and carbohydrates.	Dalla et al. Model	Section 3.2
	Fisher et al. Model	Section 3.2
	Lehmann and Deutsch Model	Section 3.2
Exercise Model to simulate the response of T1DM patients to aerobic exercise.	Roy and Parker Model	Section 3.3
Control Algorithms to close the loop between patient and insulin delivery.	Model Predictive Control (MPC)	Section 3.4
	Proportional-Integer-Derivative (PID) Control	Section 3.4
Diabetes Diary Applications for patients to monitor and control their BGLs at home.	Applications for Self-Monitoring of BGLs	Section 3. 5

Chapter 4

MATERIALS AND METHODS

This chapter describes the development of closed-loop insulin delivery systems using mathematical models such as the Bergman Minimal Model (Richard N Bergman, Finegood, and Ader, 1985). The Bergman Minimal Model is used because of its simplicity and flexibility with disturbances such as meals and exercise. For meals disturbances testing (section 4.2), an extended version of the Minimal Model proposed by (Palma, 2013) is used. Then, this model is joined with PID (section 4.3) and MPC (section 4.4) closed-loop strategy for insulin delivery. For physical activity and meal disturbances (section 4.5), the Roy and Robert S. (2007) described in chapter 3 is used. Then this model is implemented with a PID closed-loop insulin delivery strategy (section 4.6). Finally, the data collected from the simulations and testing of closed-loop strategies are used to develop a personalized app (section 4.7) for a virtual patient, simulated in section 4.5, this app stores the patient's entries in a database and also suggest an insulin amount according to the patient's meals or physical activity.

4.1 Pancreas Artificial simulation components

The artificial pancreas consists of mainly three components: insulin pump, continuous glucose monitor sensor, and controller algorithm to mimic the sugar control with little human interference. In addition, the current technology of CGMs allows to send the measurements to mobiles and this data can be analyzed by medical care and the patient for a better control (Kesavadev et al., 2020). It functions in a closed loop as follows (see figure 4.1):

1. The CGM sensor measures blood glucose levels and sends the measurements to a controller algorithm,
2. the algorithm analyzes the data and computes the required insulin dose or glucagon dose.
3. the insulin pump delivers the insulin instructed by the algorithm

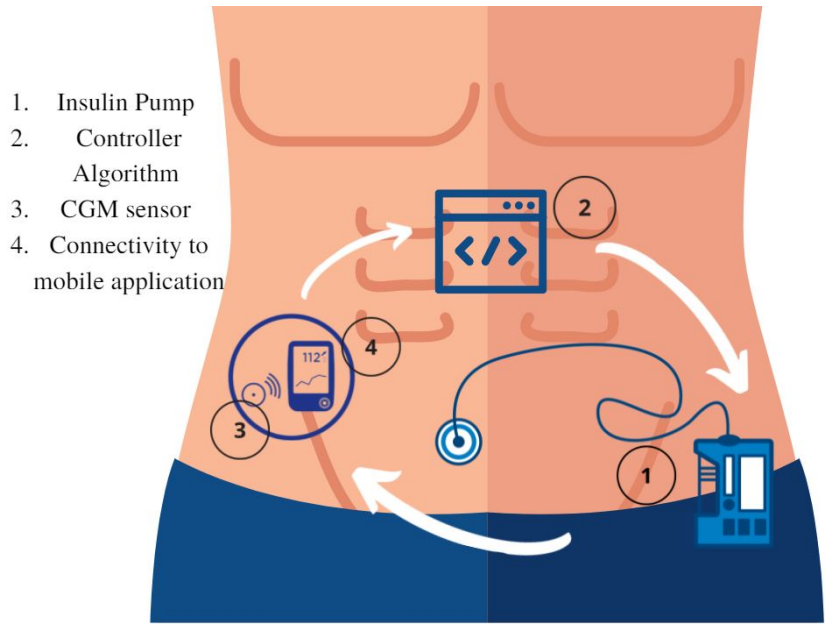

Figure 4.1: Representation of the components of a closed-loop or Artificial Pancreas therapy. Own elaboration from Cobelli et al.(2011).

The artificial pancreas is revolutionizing the treatment of Type 1 Diabetes Mellitus. However, it is important to perform clinical tests before commercial closed-loop systems are available and widespread. This tests start by in silico intervariability and robustness tests (Wilinska and Hovorka, 2008). These in silico tests include the simulation of one or many T1DM patients with different characteristics. These virtual patients are taken from the mathematical models such as the minimal model to more complex models as the Sorensen. For variability, various parameters are changed in each subject simulated, facilitated by metabolic simulators such as the one developed by the UVa/Padova. For robustness, many disturbances can be added, such as exercise or meals (Huyett et al., 2015).

Furthermore, control algorithms need to be tested for a reliable adaptation to a particular patient and be safe to operate with a minimal risk of low and high glucose levels (Kesavadev et al., 2020).

4.2 Extension of the Bergman Minimal Model

Bergman et al. (1985) developed the “minimal model” to analyze the plasma glucose and insulin dynamics during an IVGTT. Modifications have been made to the original Bergman model to incorporate various physiological effects on glucose and insulin (Roy and Robert S Parker, 2006).

4.2.1 Extended Bergman Minimal Model with Meal Disturbance

The model is taken from Palma R. (2013). The model is simulated with Simulink Tools and a Matlab S-Function. It is an extended version of the Bergman minimal Model. It uses the equations of the minimal model, such as 3.1 and 3.2, in chapter 3. In addition, a term form mass of carbohydrates in the gut to model the meal effects on BGLs. Therefore, the extended model main formulas are:

$$\dot{G} = -p_1(G - G_b) - S_i X G + \frac{f k_{abs}}{V_G} G_{gut} \tag{4.1}$$

$$\dot{X} = -p_2(X - I - I_b) \tag{4.2}$$

$$\dot{I} = -u - k_e I \tag{4.3}$$

Equation 4.1 models the glucose dynamics with the effects of meal, where:

- p_1 is the glucose effectiveness,
- G_b is the basal or steady state of plasma glucose,
- S_i is the insulin effectiveness,
- f is the carbohydrates fraction available for absorption,
- K_{abs} is the carbohydrates absorption rate into the bloodstream from the gut.
- V_G is the volume of the plasma glucose distribution.

Equation 4.2 models the insulin dynamics, where p_2 is the remote insulin clearance fractional rate and I_b is the basal plasma insulin concentration. In addition, equation 4.3 models the subcutaneously injected rapid-acting insulin u as an impulse function and k_e is the insulin clearance rate from the plasma.

In addition, this model uses the Dalla Man et al. (2006) mathematical model of the gastrointestinal tract, these equations are Equation 3.8, 3.9 and 4.4. The meals are modeled as impulse responses for the Equation 4.4. For a meal that contains a mass of carbohydrates of D.

$$G_{gut} = D(\beta e^{-k_{abst}} - (\beta + \gamma t)e^{-k_{empt}t}). \tag{4.4}$$

The steady-states were obtained from Hedengren et al. (2014). This are calculated in the absence of meal and setting the left side of equations 4.1 and 4.2 to zero in order to obtain G and X. Then, for the appearance of rapid-acting insulin as a step increase in the plasma insulin.

For the insulin infusion rate of 2 micro-U/min, the steady state vector is:

$$x_0 = \begin{bmatrix} 112.4400 & 22.2230 & 22.2220 & 11.1110 & 11.1110 & 166.6700 \end{bmatrix}'.$$

And for an insulin infusion rate of 3 micro-U/min:

$$x_0 = \begin{bmatrix} 76.2159 & 33.3333 & 33.3333 & 16.6667 & 16.6667 & 250.0000 \end{bmatrix}'.$$

Figure 4.2 shows the schematic of the Simulink modelling of the extended Bergmanm Model with meal disturbances, and an open-loop therapy with exogenous insulin input. Where the exogenous insulin in a constant input, the meal disturbance is an impulse response with a lag, and snacks are added as a sinuous disturbance to the model.

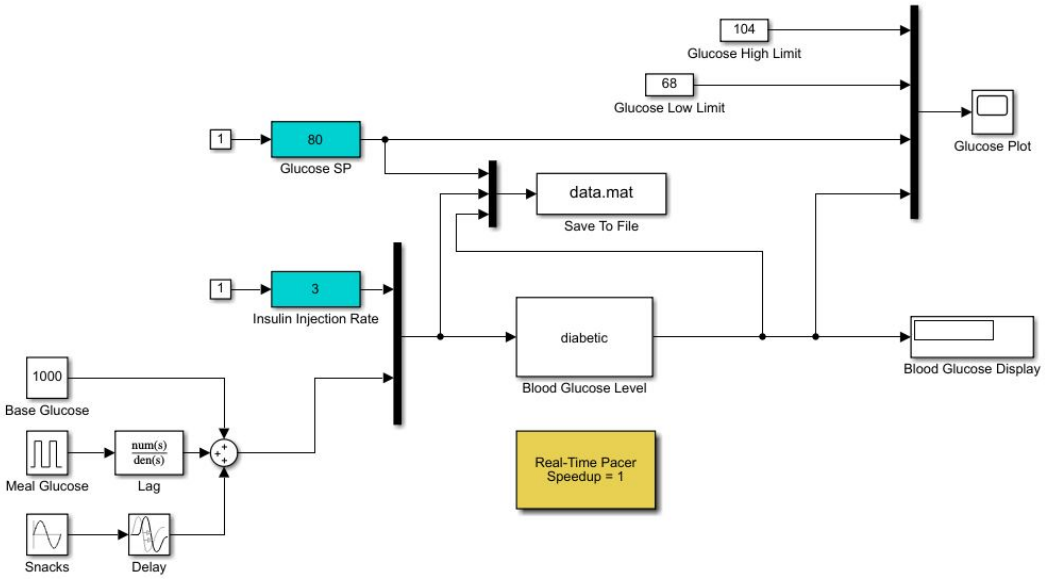

Figure 4.2: Schematic flow diagram for extended Bergmann Model with meal disturbance and Snacks (Hedengren et al., 2014).

The diabetic block contains the physiological model coded in a Matlab S-function. In return, this blocks gives the blood glucose levels taking into account the disturbance added and its effects. Then it is saved in m-file called data.mat. The complete code of the diabetic patient can be found at Annex A.

4.2.2 Extended Bergman Minimal Model with effects of Exercise disturbance

The model of Roy and Robert S. Parker (2007) is used for this simulation where the initial state vector is:

$$x_0 = \begin{bmatrix} 80 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}'$$

This model assumes that the average blood glucose level of the patient is 80 mg/dl (first term of the initial state vector), no insulin is remotely injected initially, and there is no insulin production by the patient. The exercise intensity is at 0, glucose production and uptake rate is also 0. Exercise intensity and energy expenditure is 0. Finally, it also assumes that there is no glycogenolysis occurring initially.

This simulation has three inputs, the exogenous insulin, the exogenous glucose as impulse response and the exercise intensity as impulse response as well. The differential equations are the ones described in the chapter 3: Equations 3.12-3.17. And the rate of glycogenolysis is also added as well as the integrated exercise intensity in the Matlab S- Function.

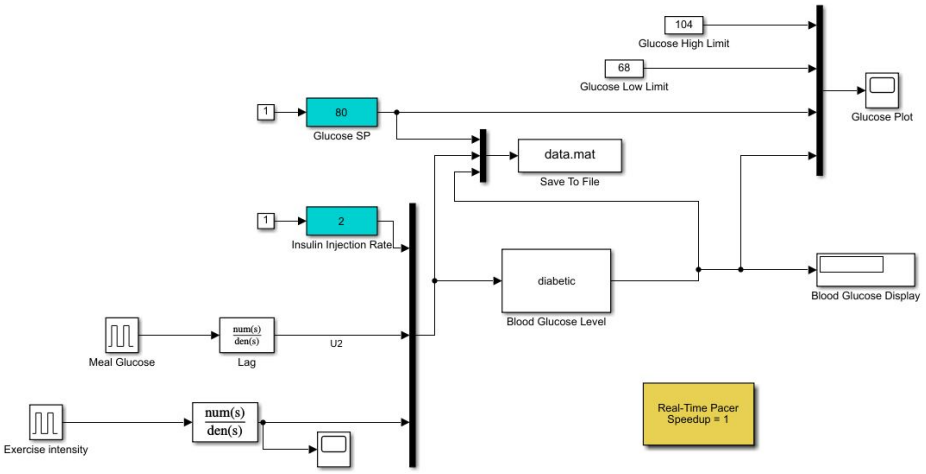

Figure 4.3: Schematic of Simulink of the Extended Physiological Bergmann Model with exercise and meals. Own elaboration from Hedengren et al. (2014)

The parameters of the model of Roy and Parker (2007) described in section 3.3 were used for this simulation, and are described in table 4.1.

The parameters for the exercise model used were estimated using nonlinear least squares (Roy and Robert S. Parker, 2007) for equations 3.15-3.17 and the equation for the rate of glycogenolysis. As for the equations from the Bergman Minimal

Table 4.1: Parameters used to model exercise and meal ingestion in a diabetic type 1 patient from Roy and Robert S. Parker (2007).

Parameter	Value	Unit
p_1	0.035	min^{-1}
p_2	0.05	min^{-1}
p_3	0.000028	$ml/\mu U min^2$
p_4	0.098	ml^{-1}
n	0.142	min^{-1}
Vol_G	117.0	dl
G_b	80.0	mg/dl
a_1	0.00158	$mg/kgmin^2$
a_2	0.056	min^{-1}
a_3	0.00195	$mg/kgmin^2$
a_4	0.0485	min^{-1}
a_5	0.00125	$\mu U/mlmin$
a_6	0.075	min^{-1}
k	0.0108	$mg/kgmin^2$
T_1	6.0	min

Model (equations 3.12-3.14), the parameters were already defined in (Richard N Bergman, Finegood, and Ader, 1985). The complete code of the diabetic patient with meals and exercise can be found at Annex B.

4.3 Closed Loop Insulin Delivery with MPC controller

This sections explains the use of Simulink and Matlab for the modelling of the components of a closed-loop insulin delivery system. These components are the controller algorithm (MPC in this case), the insulin dosage delivered to the patient, and the continuous measurement of blood glucose levels (see Figure 4.4). It is important to remark that there is no modelling of the delays of insulin pump and the CGM. Therefore, the system relies in accurate measurement of BGLs (for the feedback action) and rapid insulin pump action.

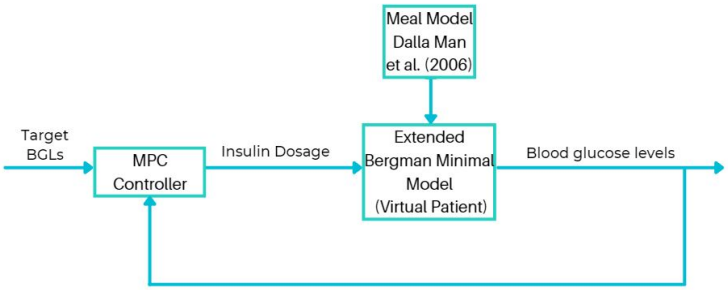

Figure 4.4: Schematic representation of the extended Bergmann Model with meal disturbances. Own elaboration from Cobelli et al. (2011)

In addition, a meal model is added to the Minimal Model to test the response of BGLs and MPC controller to meals and snacks. The meal and snacks are counted as mass of carbohydrates explained in section 4.2.1. The code in APMonitor coding language can be found at Annex C.

4.3.1 Closed Loop Insulin Delivery with MPC controller against meal disturbance

The extended Bergmann Model with meal disturbance is used for the simulation and test of a closed-loop insulin therapy. This therapy will deliver the necessary amount of insulin so the patient does not experience and hyper- or hypoglycemic event. The therapy is an Artificial Pancreas that closes the loop of patient and insulin delivery system. To deliver the right of insulin a MPC controller algorithm is used program with the APmonitor server (*Artificial pancreas simulation study* 2014). Advanced process monitor (APMonitor) is a modeling language for differential algebraic (DAE) equations (Hedengren et al., 2014). It is a free web-service or local server for solving representations of physical systems in the form of implicit DAE models. It can be used for nonlinear model predictive control (Ramlal, Allsford, and Hedengren, 2007). In this section, it is used to solve the model predictive control algorithm using the parameter and conditions in Table 4.2.

Table 4.2: MPC controller Modeling with APmonitor

MPC controller Modeling		
Model Parameters	tau	1.5
	K_p	-20
	K_d	0.05
Initial Conditions	u_0	3
	x_0	80
	d_0	1000
Linear First order equation for MPC		
$tau\frac{dx}{dt} = -(x - x_0) + K_p(u - u_0) + K_d(d - d_0)$ (4.5)		

The model equation 4.2 adjusts the insulin delivery. Where tau is time of response of the controller to the inputs (1.5). K_p is the gain that is necessary so the insulin to regulates the blood glucose near the set-point which is 80 mg/dl. K_p is then set to -20. K_d is the process gain for the disturbance, the meal model.

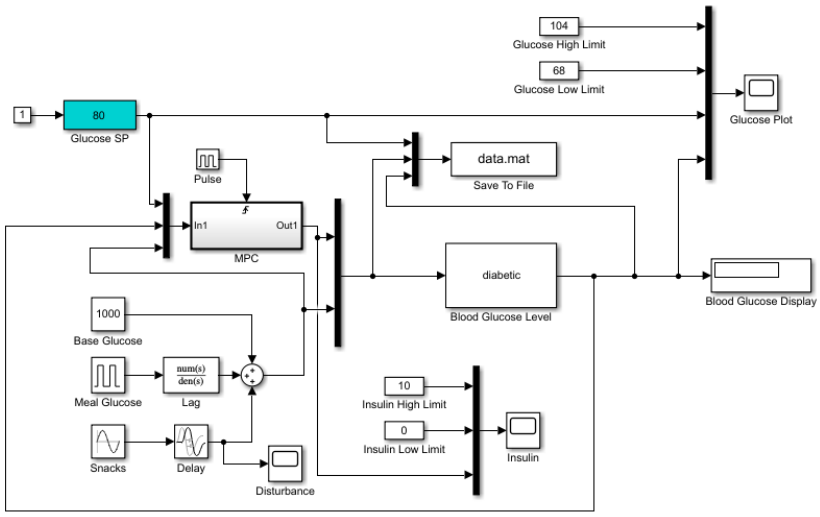

Figure 4.5: Schematic flow diagram for AP with meal disturbance and Snacks. From Hedengren et al. (2014).

The exogenous insulin input (u_0) is constantly 3 mU/min, as if the patient is on continuous subcutaneous insulin infusion. Then, it is added as a block in Simulink with the physiological model as shows Figure 4.5.

4.4 Closed Loop Insulin Delivery with PID controller

This sections explains the use of Simulink and Matlab for the modelling of the components of a closed-loop insulin delivery system. These components are the

controller algorithm (PID in this case), the insulin dosage delivered to the patient, and the continuous measurement of blood glucose levels. As stated in the last section, there is no modelling of the delays of insulin pump and the CGM. Therefore, the system relies in accurate measurement of BGLs and rapid insulin pump action.

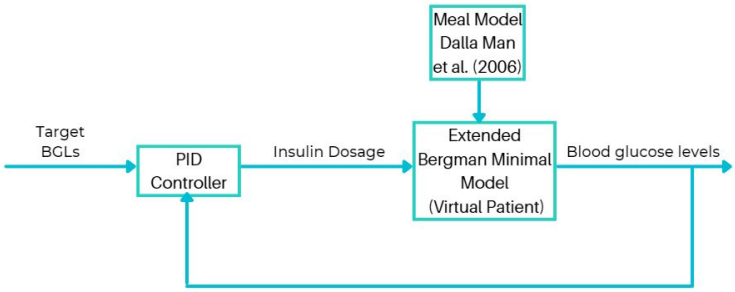

Figure 4.6: Schematic representation of closed-loop insulin delivery with PID controller with meal disturbance and Snacks. Own elaboration from Rhee et al. (2017).

In section 4.3.1, the closed-loop insulin delivery is tested with meal disturbances such as snacks and three meals using the Dalla Man et al.(2006) model (see Figure 4.6). In addition, it is possible to use the Extended Bergman Minimal Model with exercise by Roy and Robert S. Parker (2007) to test the controller with disturbances such as physical activity (see Figure 4.7), in section 4.3.2.

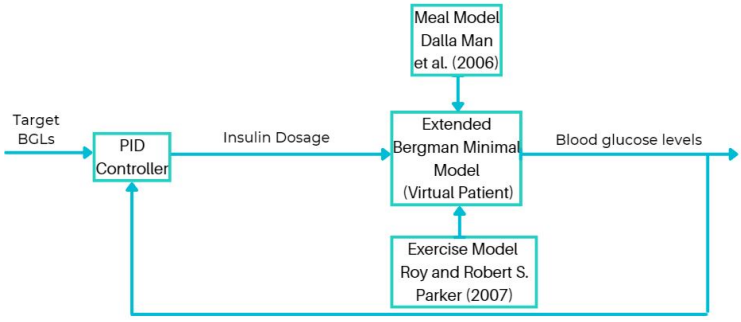

Figure 4.7: Schematic flow diagram for AP with meal disturbance and Exercise. Own elaboration from Rhee et al.,(2017).

4.4.1 Closed Loop Insulin Delivery with PID controller against meal disturbance

The extended Bergman model with meal disturbance is used for the simulation and test of a closed-loop insulin therapy. This therapy will deliver the necessary amount

of insulin so the patient does not experience and hyper- or hypoglycemic event. The therapy is an Artificial Pancreas that closes the loop of patient and insulin delivery system. To deliver the right of insulin a PID controller tool of Simulink is used. The PID form is parallel so the controller output is the sum of the proportional, integral, and derivative actions, weighted independently by P, I, and D, respectively (The MathWorks, 2021). Therefore, it is implemented as Equation 4.6.

$$C_{par}(s) = P + I\frac{1}{s} + D\frac{N}{1 + N\frac{1}{s}} \tag{4.6}$$

The proportional (P) controller parameter is set to -0.05, the integral (I) is set to -0.1, the derivative (D) is set to zero, and the filter coefficient (N) is set to 100. The Integrator initial condition is 2 (considering that the exogenous insulin input is still constantly 2 mU/min) because the minimal model that all the necessary insulin is infused exogenously. The filter initial condition is 0. The output is limit to 10 mU/min of insulin delivery.

A back-calculation anti-windup method unwinds the integrator when the block output saturates by feeding back to the integrator the difference between the saturated and unsaturated control signal. The Kb parameter specifies the gain of the anti-windup feedback circuit (The MathWorks, 2021). And it has a back-calculation anti-windup method with a coefficient (Kb) of 1.

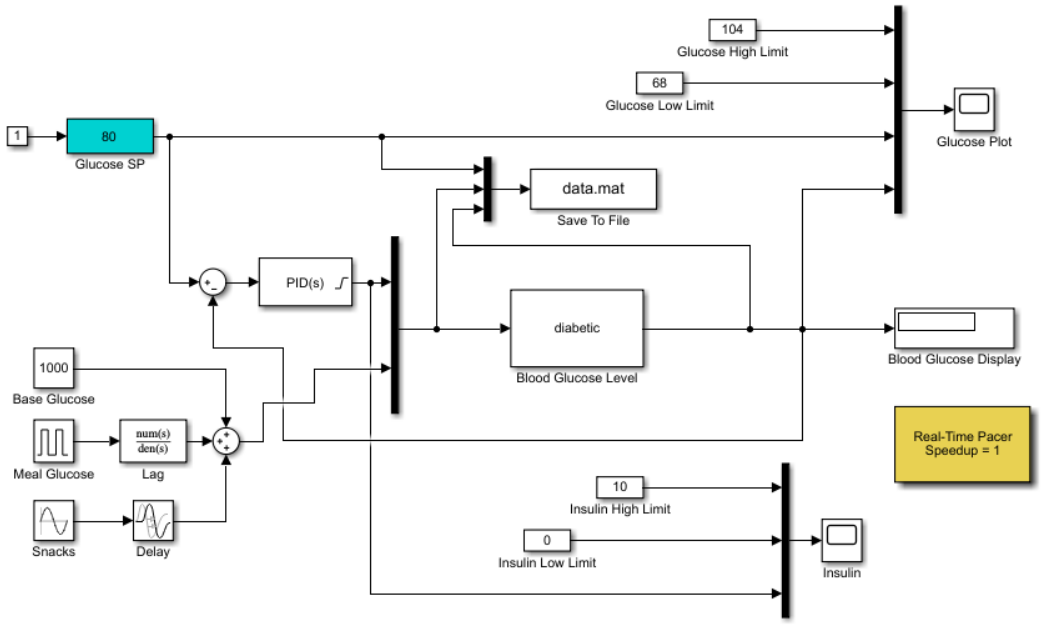

Figure 4.8: Schematic flow diagram for AP with meal disturbance and Snacks (Hedengren et al., 2014).

Figure 4.8 shows the schematic of the physiological model explained in the section before integrated with PI-controller artificial pancreas. Where the Insulin delivery is controlled by the PI algorithm. This model is taken from the documentation of APMonitor (Hedengren et al., 2014).

4.4.2 PID Controlled Insulin therapy with extended Bergman Minimal Model with effects of Exercise disturbance and meals

Insulin-only controllers have shown poor performance, mainly due to the lack of a control action that counteracts the metabolic effect of exercise, such as higher glucose uptake by muscles. In particular, the initial decrease in glucose levels usually observed after the start of aerobic exercise is a challenge for insulin-only AP systems, because the only possible action is to arrest insulin infusion which is probably completely ineffective (Quirós et al., 2018).

Here, the PI controller designed is similar to the one used for meals. The proportional (P) controller parameter is set to -1, which this action is independent of the integral and derivative actions. The integral (I) is set to -0.01, the derivative (D) is set to zero, and the filter coefficient (N) is set to 100. The integrator initial condition is 3 mU/min because the minimal model that all the necessary insulin is infused exogenously, as the patient is using continuous subcutaneous insulin infusion. The

filter initial condition is 0. The output is limit to 10 mU/min of insulin delivery.

And it has a back-calculation anti-windup method with a coefficient (Kb) of 1. This method unwinds the integrator when the block output saturates by feeding back to the integrator the difference between the saturated and unsaturated control signal. The Kb parameter specifies the gain of the anti-windup feedback circuit (The MathWorks, 2021). In addition, it counts with internal model control which allows the PID parameters to be calculated directly from the process model. This PID controller is tested with exercise and three meals with Simulink (see Figure 4.9).

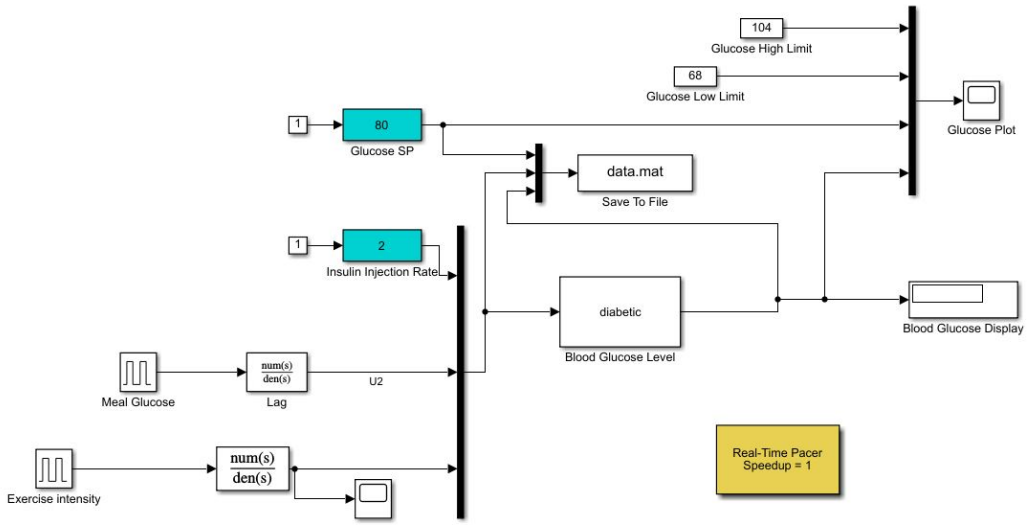

Figure 4.9: Schematic of Closed Loop Insulin Therapy PID Controlled and the Extended Physiological Bergman Model with exercise and meals during 24 hours

In addition, the same PID controller it simulated with snacks as well, the same sinusoidal disturbance as described in section 4.3 and 4.2. Snacks of 10 grs of carbohydrates are added (see Figure 4.10).

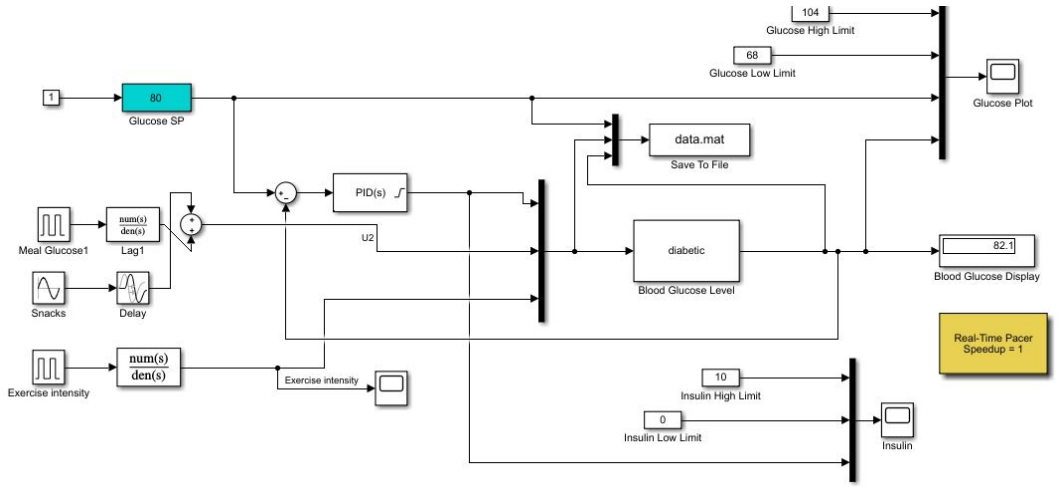

Figure 4.10: Schematic of Closed Loop Insulin Therapy PID Controlled and the Extended Physiological Bergman Model with exercise, meals and unannounced snacks during 24 hours

4.5 Mobile Application for Self-Monitoring of BGL

The application (app) had two phases: data gathering and the design of the app. The data used for personalizing the app is from the simulations of a virtual patient of 70 kg with T1DM under a PID controller in section 4.5. The design of the application used the Django platform, a high-level Python web framework.

The application can serve as a diary for a T1DM patient to monitor its Blood Glucose Levels. It serves for patients that use use carbohydrate counting or insulin sensitivity correction systems and patients that use fixed doses of insulin for mealtimes. It will store in database, the blood glucose level set point or target, the measured blood glucose, the carbohydrates in meals ingested, and it can register the physical activity as well. In addition, it will suggest an insulin dose depending the amount of carbohydrates or physical activity. It also contains advises to maintain a healthy life style.

A feature of the application is that it uses a k-nearest neighbor (KNN) model for regression was used to predict insulin bolus necessary to get to a desired BGL set-point. KNN is a classification method based on the k-closest training examples in the feature space. It is known to be strong when large datasets and low dimensions are used (Kramer, 2013). KNN is a basic type of instance-based learning and assumes that all instances are points in n-dimensional space (Saxena, Khan, and Singh, 2014). It compares feature vectors of different points in a space region and

classifies them. Furthermore, KNN regression is a similar method where the set of data is very large in comparison to classification.

This method has been used successfully classifying diabetic patients (Karegowda, Jayaram, and Manjunath, 2012) and diabetes related data (Jaafar and Ali, 2005; Christobel and Sivaprakasam, 2013).

For this purpose, the Diabetes Diary Application uses the glucose set-point, the latest blood glucose measured, the amount of carbohydrates in the meal about to ingest or the PVO_2^{max} of the exercise intensity about the perform. Using python libraries such as pandas and numpy. The data obtained from the simulations described in previous section. The data is obtained from the virtual patient of 70 kg under a PID controlled insulin delivery.

Next, the data is split into training (80%) and testing data (20%). For this the library from scikit-learn and its function *train_test_split* is used to create the test data (X_train and X_test) and the target data (Y_train and Y_test) which is the glucose prediction. This data is picked randomly. In total, the data used for training comprises 3848 elements. And the test data has 962 elements.

The KNN regressor function is from the library *sklearn.neighbors*. Then, a KNN model is created and trained with the selected training data and target values. The code for the training and testing can be found in Annex D.

Then, as an effort to integrate this glucose predictor into the application. This application would be a personalized app for a patient of 70 kg. Therefore, it would work as a diary for a better diabetes monitoring (See Figure 4.11) that would save the entries in a database.

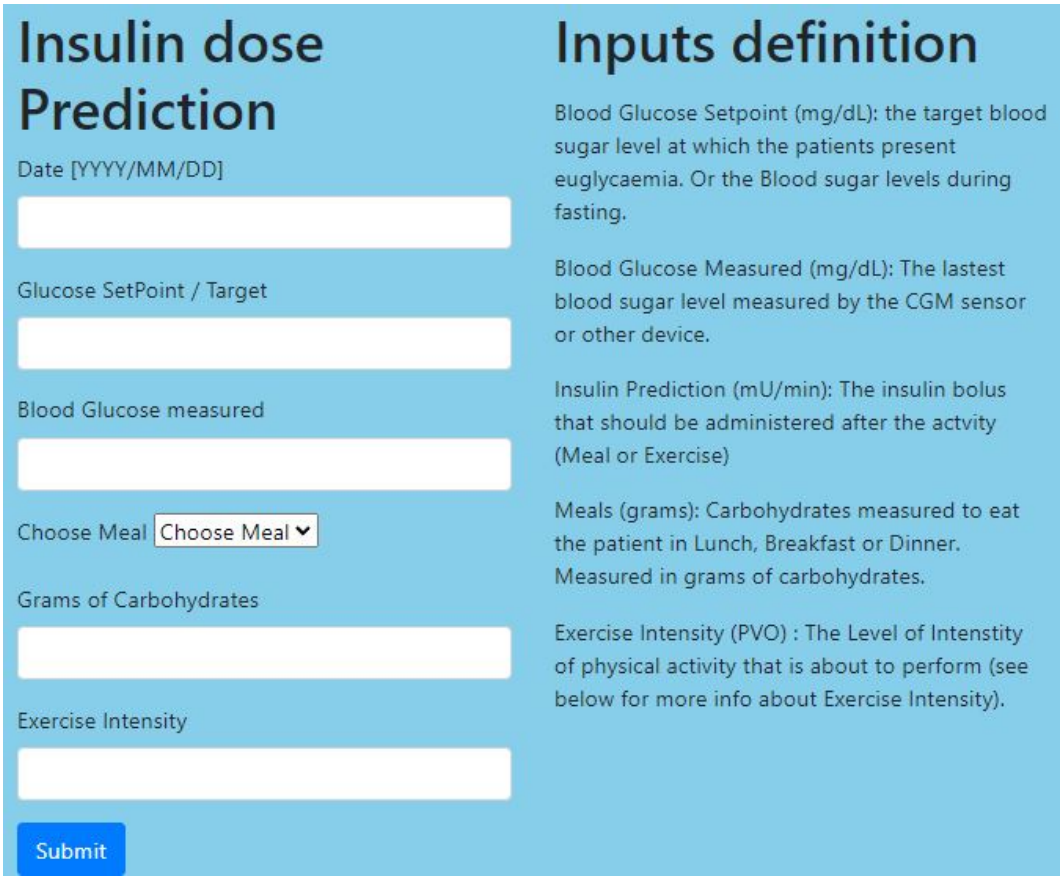

Figure 4.11: Web Application Diary Entries with Django python framework

Chapter 5

RESULTS

The results of the simulations set up in the last chapter are described in this chapter. The results of simulation are plotted to visualize the insulin and glucose dynamics in the virtual patient of 70 Kg. In addition, the different disturbances described in the last chapter are included in the plot as the appear throughout the simulated day. Furthermore, the plots showed allow to see the response of the described therapies against said disturbances. Finally, numerical outcomes are detailed to assess the performance of the therapy and to compare them. The section 5.1 describes the results of the simulation of the Minimal Model extended with meal disturbance. Then, the performances and plots of the PID and MPC based insulin therapies are described in section 5.2 and 5.3, respectively. The results pf extended minimal model with meals and exercise are in section 5.4, followed by the PID therapy used to respond to exercise in section 5.5. A comparison between the described therapies is in section 5.6. Finally, the results of the personalized app for the virtual patient is in section 5.6.

5.1 Extension of the Bergman Minimal Model

5.1.1 Extended Bergman Minimal Model with Meal Disturbance

The simulation of this model shows that an uncontrolled Type 1 diabetes might cause elevated blood sugar levels and a prolonged state of hyperglycemia after meals ($> 140mg/dL$). Since, this model assumes that the only source of insulin is exogenously, a 3 micro-U/min is administered constantly. However, it is not enough to prevent the rise of BGLs during meals.

The time that the glucose absorption after every meal last is about an hour. The amount of carbohydrates is of 50 g of carbohydrates for breakfast, lunch and dinner. The meals are deliver six hours apart as an impulse response (see Figure 5.1). And the BGLs rise after very meal to dangerous hyperglycemic levels.

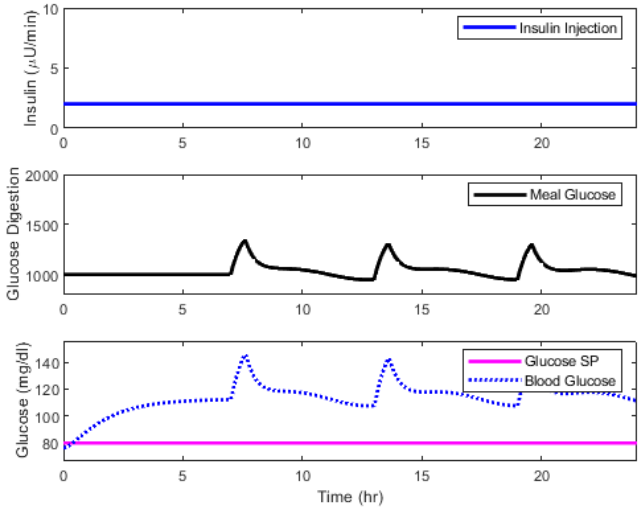

Figure 5.1: Simulation of Extended Physiological Bergmann Model with meals and snacks during 24 hours

5.1.2 Extended Bergman Minimal Model with effects of Exercise disturbance

A Light physical activity of 40% PVO_2^{max} of intensity is simulated using the extended Bergman model. And as Figure 5.2 shows the blood glucose levels drop as the intensity rises.

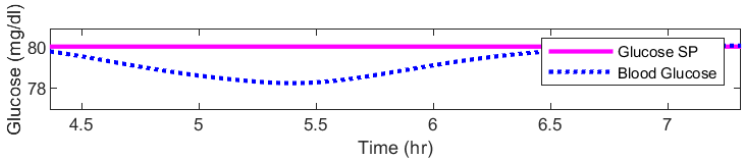

Figure 5.2: Simulation of exercise during 1 hour

The physical activity was simulated during an hour, in which it reaches the highest intensity and drops blood glucose levels. However, as the exercise intensity rises the glucose levels drop lower. Then, the exogenous glucose input is from meal ingestion of 50 grams of carbohydrates for breakfast, lunch and dinner (see Figure 5.3).

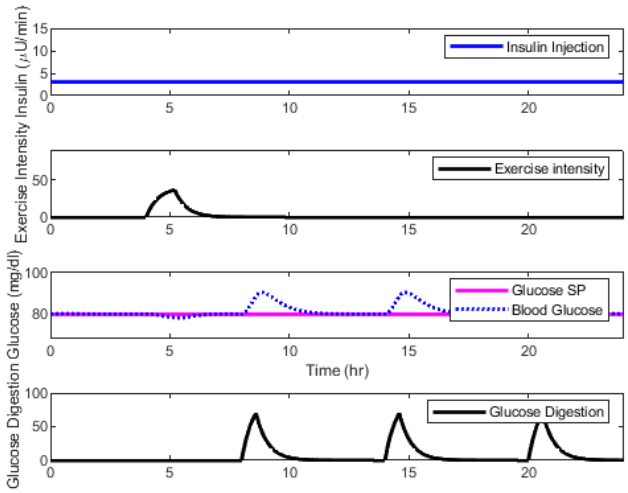

Figure 5.3: Simulation of exercise during 1 hour and three meals

5.2 Closed Loop Insulin Delivery with MPC controller against meal disturbance

In this scenario the MPC controller shows better performance than the PID controller in the number hypo- or hyperglycemic events during the 24 hours (see Figure 5.4). The amount of carbohydrates is of 50 g of carbohydrates for breakfast, lunch and dinner.

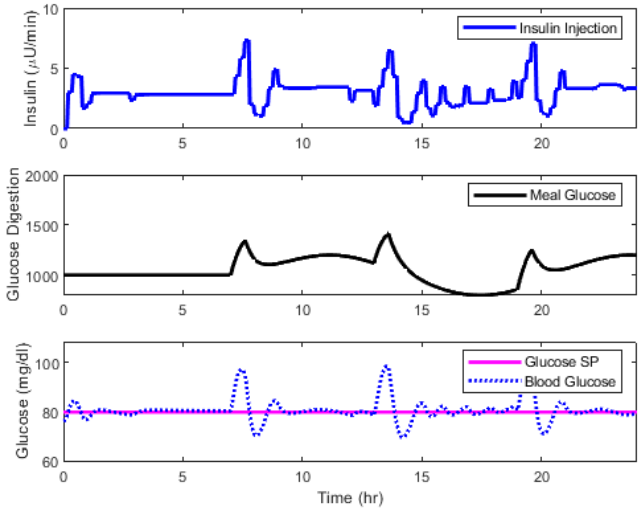

Figure 5.4: MPC therapy performance with meal disturbance and Snacks during 24 hours (Hedengren et al., 2014).

Table 5.1: Overall outcomes of MPC Control Strategy

Number of Events	Blood Glucose Level (mg/dl)	Event
189	>70	Target Range
290	>80	Around Setpoint
3	<70	Hypoglycemic
0	>100	High Blood Sugar Level
0	>110	Hyperglycemic
Total = 481	80.80	Average Blood Glucose Level

The MPC strategy showed more time in range (around 90% of the day), and 3 events of hypoglycemia (see table 5.1).

5.3 Closed Loop Insulin Delivery with PID controller

5.3.1 Closed Loop Insulin Delivery with PID controller against meal disturbance

The closed loop insulin therapy is able to maintain the BGLs close to the set-point (80 mg/dl) by adjusting the insulin doses during meals and after meals. The amount of carbohydrates is of 50 g of carbohydrates for breakfast, lunch and dinner, the same way explained in section 2.1.

However, during this simulation the controller caused three hypoglycemic events (BGLs lower than 70 mg/dl) of around 1 hour each after every meal and during the snack. The snack disturbance is simulated as a sinusoidal function to test the controller with unannounced disturbances such a snacks (see Figure 5.5).

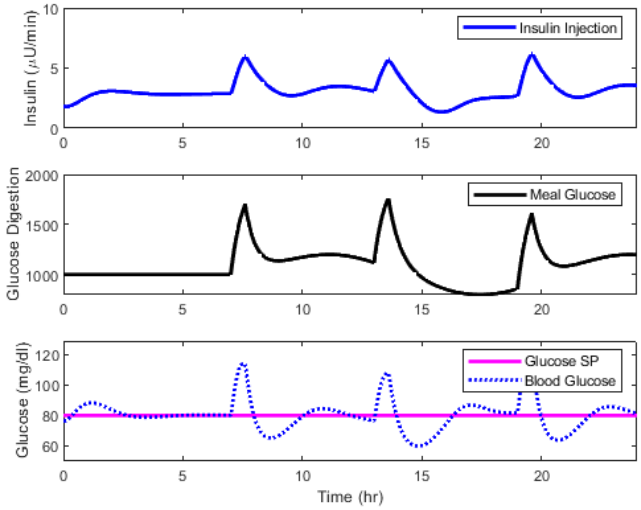

Figure 5.5: AP performance with meal disturbance and Snacks during 24 hours (Hedengren et al., 2014).

In a day of Closed-loop PID control insulin delivery therapy, 16% of the events of the day were hypoglycemic, and 9% were hyperglycemic (see Table 5.2).

Table 5.2: Overall outcomes of PID Control Strategy

Number of Events	Blood Glucose Level (mg/dl)	Event
169	>70	Target Range
198	>80	Around Setpoint
79	<70	Hypoglycemic
31	>100	High Blood Sugar Level
15	>110	Hyperglycemic
Total= 481	80.6308482	Average Blood Glucose Level

5.3.2 Closed Loop Insulin Delivery with PID controller against meals and Exercise disturbance

The therapy is applied to a day in which the patients does exercise of 40% PVO_2^{max} intensity at the beginning of the day, then eats three times a day of 50 grams of carbohydrates. The meals are identified by the peaks in glucose digestion, and the exercise is identified by the plot of exercise intensity in Figure 5.6.

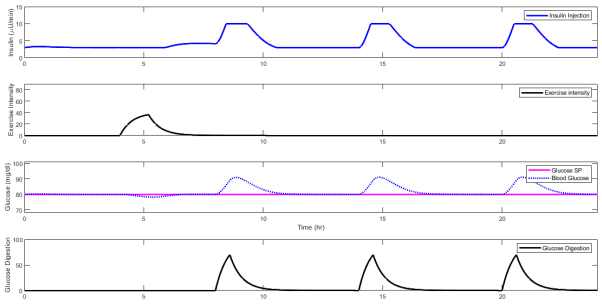

Figure 5.6: Closed Loop Insulin Therapy for exercise during 1 hour and meals

The PID controller is able to respond in time during meals to prevent dysglycemia and prevents the drop in the BGLs during exercise. This simulation does not include snacks. It is able to maintain the BGLs of the patients under the set-point during 38.66% of the day and above the set-point during 61.74% of the day (see Table 5.3).

Table 5.3: Overall outcomes of PID Control Strategy against meals and exercise

Number of Events	Blood Glucose Level (mg/dl)	Event
186	>70	Target Range
297	>80	Around Setpoint
0	<70	Hypoglycemic
0	>100	High Blood Sugar Level
0	>110	Hyperglycemic
Total = 481	80.83	Average Blood Glucose Level

Next, this PID strategy showed a good performance against 10 gr of snacks during the day (see Figure 5.7). It presented no hypoglycemic or hyperglycemic events during the simulation day. It stayed under the set-point (80 mg/dl) during 27.6% of the day, and above the set-point during 72.55% of the day (see table 5.4).

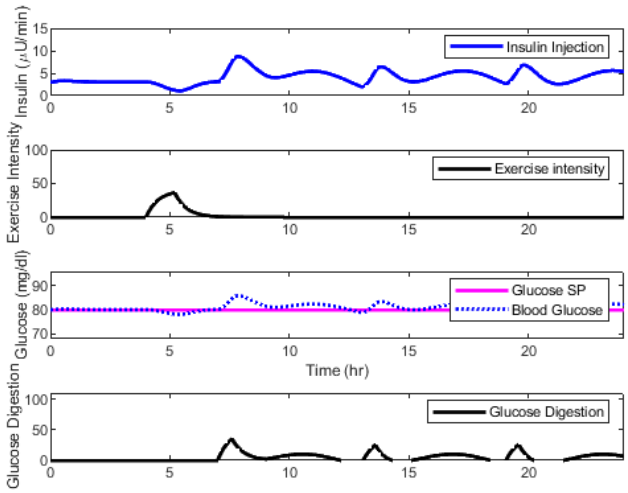

Figure 5.7: Closed Loop Insulin Therapy for exercise during 1 hour, meals and 10gr of snacks

Table 5.4: Overall outcomes of PID Control Strategy against meals, exercise and snacks

Number of Events	Blood Glucose Level (mg/dl)	Event
133	>70	Target Range
349	>80	Around Setpoint
0	<70	Hypoglycemic
0	>100	High Blood Sugar Level
0	>110	Hyperglycemic
Total = 481	80.98	Average Blood Glucose Level

5.4 Diabetes Diary Web Application

For the Diabetes Diary-Calculator (DDC) Application, the user makes its entries, it will predict the insulin bolus needed (see Figure 5.8) and then save the entries into the database (see Figure 5.9).

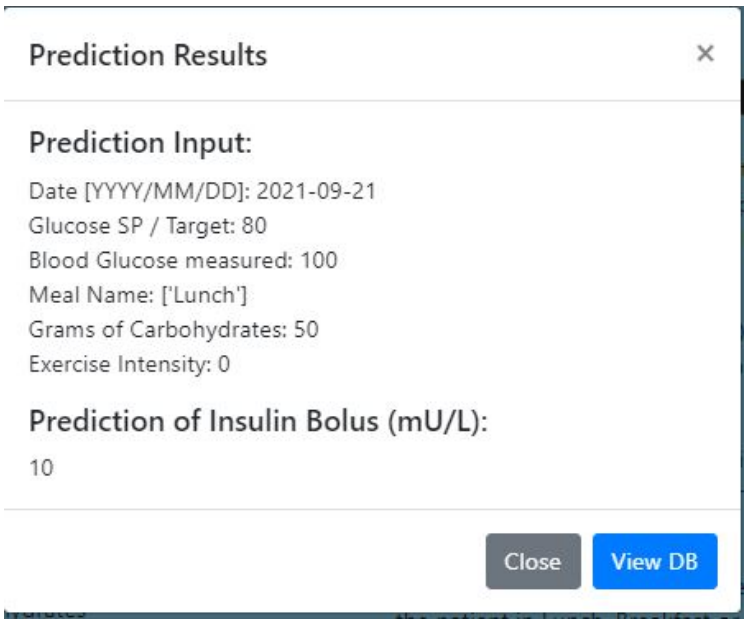

Figure 5.8: Prediction result after user entries

Prediction Results

#	Date	Glucose SP	Insulin	Meal Name	Amount of Carbs	Exercise Intensity	Glucose
1	Sept. 14, 2021	80.0	2.0	None	1000.0	0.0	97.34880000000001
2	Sept. 14, 2021	80.0	2.0	None	1000.0	0.0	97.34880000000001
3	Sept. 14, 2021	80.0	2.0	None	1000.0	0.0	97.34880000000001
4	Sept. 14, 2021	80.0	2.0	None	1000.0	0.0	97.34880000000001
5	Sept. 14, 2021	80.0	2.0	None	1000.0	0.0	97.34880000000001
6	Sept. 14, 2021	80.0	2.0	None	1000.0	0.0	97.34880000000001
7	Sept. 14, 2021	90.0	3.0	None	1000.0	0.0	97.34880000000001
8	Sept. 14, 2021	80.0	3.0	None	1000.0	0.0	97.34880000000001
9	Sept. 14, 2021	80.0	3.0	None	2000.0	0.0	97.34880000000001
10	Sept. 14, 2021	80.0	3.0	2.0	1000.0	3.0	97.34880000000001
11	Sept. 14, 2021	80.0	2.0	['2']	1000.0	40.0	97.34880000000001
12	Sept. 14, 2021	70.0	2.0	[]	1000.0	30.0	97.34880000000001

Figure 5.9: Web Application Database of Entries with Django python framework

For the model evaluation the mean squared error (MSE) and mean absolute error (MAE) are used. The error of the training data is:

- MSE = 0.06119348262778453
- MAE = 0.08958584189189192
- RMSE = 0.24737316472848167

This mean that according to the MAE, the prediction is approximately 0.06 away from the true prediction. Mean squared error, and consequently root mean squared error (RMSE) mean that the mean error of the model is 0.24.

Furthermore, with the test data, the model is evaluated on how it would work in a real scenario:

- MSE = 0.11092742887507659
- MAE = 0.13958012806652803
- RMSE = 0.333057696015385

This results shows that the model is 0.06 way from the true prediction and has a lower mean error.

Chapter 6

DISCUSSION

Two strategies, taken from Hedengren et al. (2014), were tested with meals and snacks using the same virtual patient. Between these two, the MPC strategy proved to be the most economical in terms of use of insulin but it is slow to react to the disturbance. The PID therapy has a better time of response but expensive in use of insulin. Furthermore, there were not hyperglycemic events using the MPC therapy, but the PID therapy could not prevent 79 events of hypoglycemia after the snack (see Table 6.1).

In addition, the proposed PID therapy, used to face 40% of exercise intensity, meals and snacks, is the most expensive in terms of insulin. However, it has a fast time of response and prevents hypoglycemic and hyperglycemic events (see Table 6.1).

Furthermore, a performance and cost analysis is performed, showing that the MPC approach against meals is the most cost effective but takes more time to react than the PID therapy. The metrics considered to compare the control algorithms implemented in this thesis project show that the PID controller that faces meals and exercise could perform better in a real setting than the other controllers. The PID controller has a good time of response, and can withstand exercise without putting the patient at risk of hypoglycemia or hyperglycemia.

It is important to remark that the PID selected as the best performer against disturbances did not use the same physiological model as the others. However, other authors have compared the PID controller with others using the same physiological model and have also shown good results.

For instance, a similar comparison is made in a study (Tang and Y. Wang, 2017) to develop an economic bihormonal (insulin and glucagon) AP System based on Switching Control strategies. Tang and Y. Wang, (2017) proposed a switching Dynamic R-parameter Economic Model Predictive Control (R-EMPC) to reduce costs of insulin, improve control performance and reduce error. They used the meal model and glucose model from Hovorka et al. (2004) and other models for insulin and glucagon. As a result, they proved that the R-EMPC decreases the costs of insulin and glucagon. However, the measurement of insulin used in a day is in different unit to the one obtain in this thesis project. Furthermore, it also proves

that the MPC controller can significantly prevent hypoglycemic and hyperglycemic events when meals are programmed.

Hajizadeh et al. (2019) proposed an adaptive MPC algorithm to improve the response to meal and physical activity of Artificial Pancreas. This controller is tested using a multivariable simulator based on the Hovorka model. The aerobic exercise is estimated using metabolic equivalent (MET) values. The test is carried out during 3 simulation days and showed very good results (see Table 6.1). Although, they do not specify the amount of insulin used in a day, they state that the algorithm optimizes the insulin dosage. Furthermore, they proved that an adaptive MPC controller could potentially face an active lifestyle of a T1DM patient.

Romanski et al. (2019) used the Sorensen Model with extensions made by Lenart et al. (2002) and Hernández-Ordoñez et al. (2008) to test a PID controller with a feedforward compensator (FFC). These extensions of the Sorensen model for physical activity measure it using MET values. They used a similar proportional gain of -0.5 for a set-point of 100 mg/dl. They tested the PID-FFC controller with different %PVO intensities. The PID-FFC controller showed improvements in time in hypoglycemia. With 60 %PVO, showed no hypoglycemia events. And as the intensity increased to 70%, the virtual patient experienced 21 minutes in hypoglycemia. Hypoglycemia increased in time to 87 minutes with 80% PVO. The simulation is done during 300 minutes not a day. Furthermore, it proves that a PID controller can respond very well to high-intensity exercise too.

Patek et al. (2007) used the Dalla Man et al. (2006) to compare a linear quadratic Gaussian-based control to the PID control. They compared the control strategies using 100 in silico subjects. As a result, they have favorable performances, showing equal average BG maximum, and significantly lower risks for hypoglycemia. Insulin doses were comparable in both methods, hinting at limitations of purely reactive control algorithms. This study proves that PID could be used with other meal models and show favorable results.

Interestingly, using a similar approach to the Huyett et al. (2015) explained in section 3.4.2 , with an Internal model control (IMC), an anti-reset windup (adjusts the integration based on the situation) strategy and an IFB (imitates the physiology of the human body). This PID control strategy prevented hyperglycemic events during exercise and meal intake.

Furthermore, Rodriguez-Herrero et al. (2010) used the Lehmann and Deutsch

(1992) glucose dynamic mode along with other models to complete the glucose-insulin dynamic to compare a inversor controller and a PID controller. They use noise to mimic the delays and inaccuracies from CGMs. However, the controller apply insulin in different ways. The inversor controller administer higher insulin rates after the meal, while PID administer more insulin before and during the meal intake. This shows that PID controller behavior is linear and limits the prevention of hyperglycemic events after the meal, because of the delays by subcutaneous measurement and subcutaneous insulin absorption. The overall results are in table 6.1.

Table 6.1: Performance Comparisons.
* Same Physiological Model used

Therapy	Insulin Amount per day	Time of reaction (min)	Hypoglycemic Events	Hyperglycemic Events
PID against meals and snacks* (Proposed)	1503.2883 mU	3	16.42%	3.11%
MPC against meals and snacks*(Proposed)	1443.2939 mU	12	0.62%	0
PID against meals, exercise and snacks (Proposed)	1959.1333 mU	3	0	0
Switching R-EMPC against meals (Tang and Y. Wang, 2017)	43.38 U	-	0	0
Adaptive MPC against unannounced meals and exercise (Hajizadeh et al., 2019a)	-	-	0	11.07%
PID-FFC against %PVO 70 (Romanski et al., 2019)			7%	
PID against meals (Stephen D. Patek et al., 2007)			8.73%	14.2%
PID against meals (Rodrıguez-Herrero et al., 2010)	36.1 IU		2.5%	69

The MPC and PID controller algorithms were simulated with meal intake and showed good performance in maintaining the blood glucose around a target range. However, these simulations did not consider the delay and misreading (noise) that the continuous glucose monitor could have while measuring blood sugar levels and send them to the device. Besides, the closed loop of insulin delivery is achieved

thanks to the continuous glucose monitoring (CGM) sensor (Saiti et al., 2020). Therefore, both therapies PID rely in the accuracy and rapid response of the CGM for the insulin pump deliver the right amount of insulin.

When noise is not considered, the results may be inconclusive. For instance, Ramkissoon et al. 2019 used a PD controller with sliding mode reference conditioning (SMRC) and insulin feedback (IFB) to develop and test *in silico* an exercise-induced hypoglycemia reduction algorithm (EHRA). However, as in this case, the algorithm depended on accurate CGM readings, due to parameters not modeled, such as insulin formulations and their respective delay and the likelihood of inaccurate CGM readings happening in real life, some conclusions of the effectiveness of their approach are inconclusive.

In addition, this PID therapy used for exercise is applied to an application which is meant to be a diary for T1DM patients. It would be personalized for a 70 kg patient since the PVO_2^{max} and is that of a patient of 70 kg. However, there are other mobile application for the continuous monitoring of BGLs such as MySugr (Payne, 2015), which monitors the user's glucose, meals, physical activity and medications, estimates the glycated hemoglobin and helps the patient calculate their insulin bolus. The proposed application counts with an algorithm of machine learning such as K-nearest neighbor regressor to help said patient to calculate the right amount of insulin.

Furthermore, the DDC web application is compared to the commercially available mobile apps in table 6.2. Diabeo is an application promoted by Voluntis and provides a bolus calculator validated by an algorithm for insulin dosage adjustments based on premeal BG, carbohydrate intake, and anticipated physical activity. It can also adjust insulin/carbohydrate ratio and basal insulin doses or insulin pump infusion rates based on postprandial or fasting glucose levels with an algorithm (see table 6.2). It enables the patient to upload data to a Web site for a teleconsultation with a professional. It was initially reported for use by patients with T1DM, but can also be used for T2DM. It is currently available only in Europe (Charpentier et al., 2011).

The application called Diabetes Diary is for patients with T1DM. Developed by the Norwegian Centre for Integrated Care and Telemedicine. Its functions are in table 6.2 and allows wireless transfer of BG values to the mobile phone from BG meter via Bluetooth. It identifies the events by the amount of carbohydrate ingested, time of day, physical activity, which aids decisions regarding food and medicine. It is available in Europe only (Drincic et al., 2016).

The Diabetes Interactive Diary is an application promoted by Meteda. It serves as a diary for BG, insulin administrations, physical activity, and notes. The health care professionals have to set the CR, correction factor, and target BG level. This would be very similar to the application proposed in thesis project. This app obtained a CE mark in Europe and is available through the Apple App store in Italy only (Rossi et al., 2010).

Finally, Glooko application also serves as transmission device for BG meters, CGMs, and insulin pumps that work with an HIPAA-compliant server, and shares data with the patient's care team. Glooko function are in table 6.2. Patients can use it to enter carbohydrate intake, insulin doses, and exercise. The app contains a nutrition database to help the carbohydrate counting. Glooko is an FDA-cleared app, but no outcome studies have been published (Drincic et al., 2016).

Table 6.2: Commercially available mobile medical apps for T1DM management

Application	**Authors**	**Stage**	**Function**
Diabetes Diary Calculator (DDC) (Proposed)		Early Development	-Insulin Dose calculator -Database of insulin doses, BGLs, exercise and meals -Advices
Diabeo	Voluntis	Developed in France. CE marked in EU	-Bolus Calculator -Adjustment for exercise -Basal bolus pattern recognition -Real-time feedback
Diabetes Diary	Norwegian Centre for Integrated Care and Telemedicine	Developed in Norway. CE marked in EU	-Bolus Calculator -Tracking of BGLs, insulin, food and activity -Database to facilitate decision making
Diabetes Interactive Diary	Meteda	Developed in Italy. CE marked in EU	-Book for blood sugar, insulin dosing, and events -Nutritional database for counting carbohydrates -Food exchange data -Insulin dose calculator -Physical activity diary -Annual screening reminder -SMS to diabetes provider.
Glooko	iOS and Android	FDA cleared in United States	-Integrates health and fitness apps -Nutrition database for CHO counting -Data sharing with providers -Analytics data on clinic population for providers -Hypoglycemia prediction algorithms -Reminders

Chapter 7

CONCLUSIONS

This chapter gives the final conclusions that can be inferred from this thesis work and the challenges for future investigations in order to improve what has been obtain. In addition, it shows the scientific disclosure form this work.

7.1 Conclusions

This thesis project proved that prolonged exercise causes problems to the patient's safety when it is not regulated, in chapter 5. The study of physiological systems is a hard issue due to their nonlinear behavior which makes it harder to regulate. Advanced control strategies must be applied and sometimes, there is no technology to accomplish it.

Nonetheless, in this thesis project, potential outcomes have been obtained, from a modification of the minimal model, and applying control theory, the development of a PID controller that has the ability of impeding the glucose system to become unstable. This PID controller can compensate the effects of exercise and meal intake. Answering the hypothesis set in chapter 1.

This thesis project describes, in chapter 3, the mathematical models, exercise effects, and closed-loop insulin delivery systems used to compensate for the exercise and meal effects. Chapter five describes the implementation of the extended versions of the Bergman Minimal Model. From the implementation of the mathematical model of exercise, it is concluded that because of the simplicity and flexibility of the minimal model, the effects are visible and controllable. However, as the complexity of the model increases, the control strategies have to be more elaborate such as the one implemented by Romanski et al. (2019).

It also compares MPC and PID control strategies compensation of the effects of the meals on blood glucose level simulated and prevent a hypo-hyper glycemic event in chapter 4. The comparison from MPC and PID control strategies can conclude that the PID controller developed can optimize the insulin usage and compensate the exercise effects. PID control strategies have also been tested with different physiological models and shown good results facing announced and unannounced disturbances.

Furthermore, in order to improve a T1DM patient's life, a personalized self-monitoring mobile application is developed in order to help calculate the adequate amount of insulin dose and keep record of the blood glucose levels, physical activity and carbohydrate intake. In comparison to already market-available app, it could help patients blood glucose levels control and help doctors make better decisions based on the patient's profiles saved on the app.

7.2 Future Works

For future works, the proposed PID therapy could be test with more in silico patients with different weights, glucose set-points and insulin demands. In order to make the PID controller more robust, the intervariability of in silico patients is needed (Claudio Cobelli, Renard, and Kovatchev, 2011). This could make the mobile application available for more diverse patients. Furthermore, the app could connect the care team of the patient to deliver alerts to them and help the patient change treatment when it is needed.

7.3 Scientific disclosure

Presented Manuscript in: IEEE International Conference on Machine Learning and Applied Network Technologies (ICMLANT 2021). With the work entitle: "Implementation of MPC and PID Control Algorithms to the Artificial Pancreas for Diabetes Mellitus Type 1: Diabetes diary calculator (DDC) web application."

Submitted Manuscript in: IEEE Xplore. With the work entitle: "Implementation of MPC and PID Control Algorithms to the Artificial Pancreas for Diabetes Mellitus Type 1: Diabetes diary calculator (DDC) web application."

Submitted Manuscript in: Journal of Medical Engineering & Technology. With the work entitle: "Artificial Pancreas and Exercise: current developments in controllers and trials"

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Appendix A

S-FUNCTION FOR DIABETIC PATIENT WITH MEAL INTAKE

```
function [sys,x0,str,ts,simStateCompliance] = diabetic(t,y,u,
   flag)

switch flag,

    %%%%%%%%%%%%%%%%%%
    % Initialization %
    %%%%%%%%%%%%%%%%%%
    case 0,
        [sys,x0,str,ts,simStateCompliance]=mdlInitializeSizes();

        %%%%%%%%%%%%%%%
        % Derivatives %
        %%%%%%%%%%%%%%%
    case 1,
        sys=mdlDerivatives(t,y,u);

        %%%%%%%%%%
        % Update %
        %%%%%%%%%%
    case 2,
        sys=mdlUpdate(t,y,u);

        %%%%%%%%%%
        % Outputs %
        %%%%%%%%%%
    case 3,
        sys=mdlOutputs(t,y,u);

        %%%%%%%%%%%%%%%%%%%%%%%
        % GetTimeOfNextVarHit %
```

```
        %%%%%%%%%%%%%%%%%%%%%%%
    case 4,
        sys=mdlGetTimeOfNextVarHit(t,y,u);

        %%%%%%%%%%%%%%
        % Terminate %
        %%%%%%%%%%%%%%
    case 9,
        sys=mdlTerminate(t,y,u);

        %%%%%%%%%%%%%%%%%%%%
        % Unexpected flags %
        %%%%%%%%%%%%%%%%%%%%
    otherwise
        DAStudio.error('Simulink:blocks:unhandledFlag', num2str(
            flag));

end

% end sfuntmpl

%
%===================================
% mdlInitializeSizes
% Return the sizes, initial conditions, and sample times for
    the S-function.
%===================================
%
function [sys,x0,str,ts,simStateCompliance]=mdlInitializeSizes()

%
% call simsizes for a sizes structure, fill it in and convert
    it to a
% sizes array.
%
```

```
% Note that in this example, the values are hard coded. This is
    not a
% recommended practice as the characteristics of the block are
   typically
% defined by the S-function parameters.
%
sizes = simsizes;

sizes.NumContStates = 6;
sizes.NumDiscStates = 0;
sizes.NumOutputs = 1;
sizes.NumInputs = 2;
sizes.DirFeedthrough = 0;
sizes.NumSampleTimes = 1; % at least one sample time is needed

sys = simsizes(sizes);
%
% initialize the initial conditions
% SS for insulin injection of 2.0.
%x0 = [112.4400 22.2230 22.2220 11.1110 11.1110 166.6700]';
% SS for insulin injection of 3.0.
x0 = [ 76.2159 33.3333 33.3333 16.6667 16.6667 250.0000]';

%
% str is always an empty matrix
%
str = [];

%
% initialize the array of sample times
%
ts = [0 0];

% Specify the block simStateCompliance. The allowed values are:
% 'UnknownSimState', < The default setting; warn and assume
   DefaultSimState
```

```
% 'DefaultSimState', < Same sim state as a built-in block
% 'HasNoSimState', < No sim state
% 'DisallowSimState' < Error out when saving or restoring the
   model sim state
simStateCompliance = 'UnknownSimState';

% end mdlInitializeSizes

%==================================
% mdlDerivatives
% Return the derivatives for the continuous states.
%==================================
%
function sys=mdlDerivatives(t,y,u)
%
% Model source:
% R. Palma and T.F. Edgar, Toward Patient Specific Insulin
   Therapy: A Novel
% Insulin Bolus Calculator. In Proceedings Texas Wisconsin
   California Control
% Consortium, Austin, TX, Feb. 7-8, 2011.
%
% Expanded Bergman Minimal model to include meals and insulin
% Parameters for an insulin dependent type-I diabetic

% Inputs (2):
% Insulin infusion rate
ui = u(1); % micro-U/min

% meal disturbance
d = u(2);

% States (6):
% In non-diabetic patients, the body maintains the blood
   glucose level at a
```

```
% range between about 3.6 and 5.8 mmol/L (64.8 and 104.4 mg/dL)
    .
g = y(1,1); % blood glucose (mg/dl)
x = y(2,1); % remote insulin (micro-u/ml)
i = y(3,1); % insulin (micro-u/ml)
q1 = y(4,1);
q2 = y(5,1);
g_gut = y(6,1); % gut blood glucose (mg/dl)

% Parameters:
gb = 291; % Basal Blood Glucose (mg/dL)
p1 = 3.17e-2; % 1/min
p2 = 1.23e-2; % 1/min
si = 2.9e-2; % 1/min * (mL/micro-U)
ke = 9.0e-2; % 1/min
kabs = 1.2e-2; % 1/min
kemp = 1.8e-1; % 1/min
f = 8.00e-1; % L
vi = 12.0; % L
vg = 12.0; % L

% Compute ydot:
sys(1,1) = -p1*(g-gb) - si*x*g + ...
    f*kabs/vg * g_gut + f/vg * d; % glucose dynamics
sys(2,1) = p2*(i-x); % remote insulin compartment dynamics
sys(3,1) = -ke*i + ui; % insulin dynamics
sys(4,1) = ui - kemp * q1;
sys(5,1) = -kemp*(q2-q1);
sys(6,1) = kemp*q2 - kabs*g_gut;

% convert from minutes to hours
sys = sys*60;
% end mdlDerivatives

%
%==================================
```

```
% mdlUpdate
% Handle discrete state updates, sample time hits, and major
    time step
% requirements.
%==================================
%
function sys=mdlUpdate(t,y,u)

sys = [];

% end mdlUpdate

%
%==================================
% mdlOutputs
% Return the block outputs.
%==================================
%
function sys=mdlOutputs(t,y,u)

y1 = y(1);

sys = [y1];

% end mdlOutputs

%
%==================================
% mdlGetTimeOfNextVarHit
% Return the time of the next hit for this block. Note that the
     result is
% absolute time. Note that this function is only used when you
    specify a
% variable discrete-time sample time [-2 0] in the sample time
    array in
% mdlInitializeSizes.
```

```
%==================================
%
function sys=mdlGetTimeOfNextVarHit(t,y,u)

sampleTime = 1; % Example, set the next hit to be one second
    later.
sys = t + sampleTime;

% end mdlGetTimeOfNextVarHit

%
%==================================
% mdlTerminate
% Perform any end of simulation tasks.
%==================================
%
function sys=mdlTerminate(t,y,u)

sys = [];

% end mdlTerminate
```

Appendix B

S-FUNCTION FOR DIABETIC PATIENT WITH MEAL INTAKE AND EXERCISE

```
function [sys,x0,str,ts,simStateCompliance] = diabetic(t,y,u,
   flag)

switch flag

    %%%%%%%%%%%%%%%%%
    % Initialization %
    %%%%%%%%%%%%%%%%%
    case 0,
        [sys,x0,str,ts,simStateCompliance]=mdlInitializeSizes();

        %%%%%%%%%%%%%%
        % Derivatives %
        %%%%%%%%%%%%%%
    case 1,
        sys=mdlDerivatives(t,y,u);

        %%%%%%%%%%
        % Update %
        %%%%%%%%%%
    case 2,
        sys=mdlUpdate(t,y,u);

        %%%%%%%%%%
        % Outputs %
        %%%%%%%%%%
    case 3,
        sys=mdlOutputs(t,y,u);

        %%%%%%%%%%%%%%%%%%%%%%%
```

```
        % GetTimeOfNextVarHit %
        %%%%%%%%%%%%%%%%%%%%%%%
    case 4,
        sys=mdlGetTimeOfNextVarHit(t,y,u);

        %%%%%%%%%%%%
        % Terminate %
        %%%%%%%%%%%%
    case 9,
        sys=mdlTerminate(t,y,u);

        %%%%%%%%%%%%%%%%%%%
        % Unexpected flags %
        %%%%%%%%%%%%%%%%%%%
    otherwise
        DAStudio.error('Simulink:blocks:unhandledFlag', num2str(
            flag));

end

% end sfuntmpl

%
%==================================
% mdlInitializeSizes
% Return the sizes, initial conditions, and sample times for the
    S-function.
%==================================
%
function [sys,x0,str,ts,simStateCompliance]=mdlInitializeSizes()



sizes = simsizes;

sizes.NumContStates = 9;
sizes.NumDiscStates = 0;
```

```
sizes.NumOutputs = 1;
sizes.NumInputs = 3;
sizes.DirFeedthrough = 0;
sizes.NumSampleTimes = 1; % at least one sample time is needed

sys = simsizes(sizes);
%
% initialize the initial conditions
x0 = [80 0 0 0 0 0 0 0 0]';

% str is always an empty matrix
%
str = [];

%
% initialize the array of sample times
%
ts = [0 0];

% Specify the block simStateCompliance. The allowed values are:
% 'UnknownSimState', < The default setting; warn and assume
   DefaultSimState
% 'DefaultSimState', < Same sim state as a built-in block
% 'HasNoSimState', < No sim state
% 'DisallowSimState' < Error out when saving or restoring the
   model sim state
simStateCompliance = 'UnknownSimState';

% end mdlInitializeSizes

%=====================================
% mdlDerivatives
% Return the derivatives for the continuous states.
%=====================================
%
function sys=mdlDerivatives(t,y,u)
```

```
% Inputs (2):
% Insulin infusion rate
ui = u(1); % micro-U/min

% meals
d = u(2);

%u3*pvo
ex = u(3);


% States (6):
g = y(1,1); % blood glucose (mg/dl)
x = y(2,1); % remote insulin (micro-u/ml)
i = y(3,1); % insulin (micro-u/ml)
PVO = y(4,1);
gprod = y(5,1);
gup = y(6,1);
ie = y(7,1);
at = y(8,1);
ggly = y(9,1);


% Parameters:
gb = 80; % Basal Blood Glucose (mg/dL)
vg = 117.0; % dL
n = 0.142;
p4 = 0.098;
p2 = 0.05;
p3 = 0.000028;
p1 = 0.035;
a1 = 0.00158;
a2 = 0.055;
si = 2.9e-2;
a3 = 0.00195;
```

```
a4 = 0.0485;
a5 = 0.00125;
a6 = 0.075;
f = 8.00e-1;
k =0.0108;
T1 = 6;
W = 70; %Kg
ib = (p4/n)*ui ;
Ath = -1.1521*(ex^2) + 87.471*ex;

% Compute ydot:
sys(1,1) = -p1*(g-gb) -x*g + (W/vg)*(gprod - ggly) - ...
    W/vg * gup + d/vg ;

sys(2,1) = - p2*x + p3*(i-ib);

sys(3,1) = -n*i + p4*ui - ie;

sys(4,1) = -0.8*PVO + 0.8*ex;

sys(5,1) = a1*PVO - a2*gprod;

sys(6,1) = a3*PVO - a4*gup;

sys(7,1) = a5*PVO - a6*ie;

sys(8,1) = ex - at/0.001;

if at > Ath
   sys(9,1) = 0;
elseif at > Ath
   sys(9,1) = k;
else
   sys(9,1)= -ggly/T1 >0;
end
% convert from minutes to hours
```

```
sys = sys*60;
% end mdlDerivatives

%
%=======================================
% mdlUpdate
% Handle discrete state updates, sample time hits, and major
   time step
% requirements.
%=======================================
%
function sys=mdlUpdate(t,y,u)

sys = [];

% end mdlUpdate

%
%=======================================
% mdlOutputs
% Return the block outputs.
%=======================================
%
function sys=mdlOutputs(t,y,u)

y1 = y(1);

sys = [y1];

% end mdlOutputs

%
%=======================================
% mdlGetTimeOfNextVarHit
% Return the time of the next hit for this block. Note that the
   result is
```

```
% absolute time. Note that this function is only used when you
   specify a
% variable discrete-time sample time [-2 0] in the sample time
   array in
% mdlInitializeSizes.
%=============================================
%
function sys=mdlGetTimeOfNextVarHit(t,y,u)

sampleTime = 1; % Example, set the next hit to be one second
   later.
sys = t + sampleTime;

% end mdlGetTimeOfNextVarHit

%
%=============================================
% mdlTerminate
% Perform any end of simulation tasks.
%=============================================
%
function sys=mdlTerminate(t,y,u)

sys = [];

% end mdlTerminate
```

Appendix C

APMONITOR MODEL OF A MPC CONTROLLER FOR BLOOD GLUCOSE LEVELS WITH MEAL INTAKE AS A DISTURBANCE

```
Constants
  ! model parameters from step test
  tau = 1.5
  Kp = -20
  Kd = 0.05

  ! initial conditions
  u0 = 3
  x0 = 80
  d0 = 1000

Parameters
  u = u0 ! insulin injection rate
  d = d0 ! disturbance (meal)

Variables
  x = x0 ! blood glucose level

Equations
  ! linear, first order equation
  tau * $x = -(x-x0) + Kp * (u-u0) + Kd * (d-d0)
```

Appendix D

CODE FOR THE INSULIN PREDICTION OF THE DDC APPLICATION

```
from pandas import read_csv
from sklearn.model_selection import train_test_split
from sklearn.svm import SVC
from sklearn.metrics import accuracy_score
import pandas as pd
import numpy as np
df = pd.read_csv(r"f:\Tesis\database1a.csv")

X=df.drop(["time","insulin"],axis=1)
y=df["insulin"]
X_train, X_test, y_train, y_test = train_test_split(X, y,
   test_size=0.2, random_state=123)

X_train.shape
(3848, 4)

X_test.shape
(962, 4)

from sklearn.neighbors import KNeighborsRegressor

model = KNeighborsRegressor()

model.fit(train_scaled, y_train)

KNeighborsRegressor()

from sklearn.metrics import mean_squared_error
from sklearn.metrics import mean_absolute_error
```

```
mse = mean_squared_error(y_train, model.predict(train_scaled))
mae = mean_absolute_error(y_train, model.predict(train_scaled))
from math import sqrt

print("mse␣=␣",mse,"␣&␣mae␣=␣",mae,"␣&␣rmse␣=␣", sqrt(mse))
mse = 0.06119348262778453 & mae = 0.08958584189189192 & rmse =
    0.24737316472848167

test_mse = mean_squared_error(y_test, model.predict(test_scaled)
    )
test_mae = mean_absolute_error(y_test, model.predict(test_scaled
    ))
print("mse␣=␣",test_mse,"␣&␣mae␣=␣",test_mae,"␣&␣rmse␣=␣", sqrt(
    test_mse))
mse = 0.11092742887507659 & mae = 0.13958012806652803 & rmse =
    0.333057696015385

pd.to_pickle(model,r"f:\Tesis\knearestneighbor3.pickle")
```