CONTROL AND MODELING TECHNIQUES IN BIOMEDICAL ENGINEERING: THE ARTIFICIAL PANCREAS FOR PATIENTS WITH TYPE 1 DIABETES

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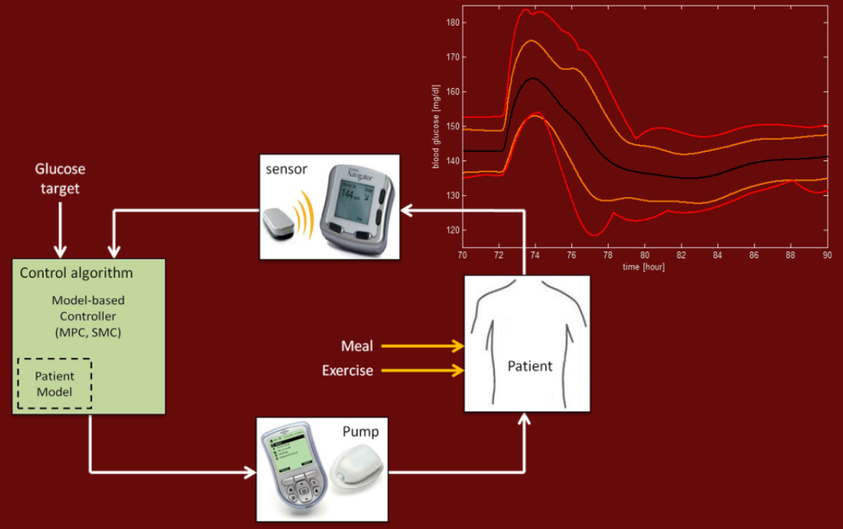
ABOUT THIS THESIS:

The artificial pancreas is an automated closed-loop control system that is applied for glucose regulation in subjects with Type 1 Diabetes Mellitus, who suffer severe lack of insulin production. The artificial pancreas has the potential to reduce the frequency and severity of the diabetes complications and improve the patients' quality of life. However, blood glucose control is still a challenging problem in biomedical engineering, since there exist several factors that significantly hinder the performance of the closed-loop control.

This thesis presents different control strategies for the closed-loop artificial pancreas, which are based on Model Predictive Control (MPC) and Sliding Mode Control (SMC). More specifically, multiple MPC with linear models and gain scheduling, SMC with linear and nonlinear models, and MPC with nonlinear model, have been developed. All control strategies use the subcutaneous route for glucose monitoring and insulin delivery. The proposed control strategies combine more than one linear/nonlinear control and modeling approaches in one structure. The main idea behind such combined approaches is to make use of the virtues of each approach while reducing the effects of their drawbacks. The control strategies have been tested and validated in simulations, where two mathematical models have been used to represent patients with Type 1 Diabetes. The control strategies are tested in different conditions, such as the presence of meal disturbance, inter-patient and intra-patient variability, time-delay, and sensor errors.



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AMJAD HISHAM AHMAD ABU-RMILEH

Control and Modeling Techniques in Biomedical Engineering: The Artificial Pancreas for Patients with Type 1 Diabetes

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DOCTORAL THESIS

Control and Modeling Techniques in Biomedical Engineering: The Artificial Pancreas for Patients with Type 1 Diabetes

AMJAD HISHAM AHMAD ABU-RMILEH

2013

University of Girona

Doctoral Thesis

Control and Modeling Techniques in Biomedical Engineering: The *Artificial Pancreas* for Patients with Type 1 Diabetes

Amjad Hisham Ahmad Abu-Rmileh

Directed by:

Prof. Dr. Marc Saez Zafra
Dr. Winston Garcia-Gabin

A dissertation submitted to the University of Girona in fulfillment of the requirements of the degree of Doctor of Philosophy (PhD)
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Universitat de Girona

Prof. Dr. Marc Saez Zafra, Director of the Research Group on Statistics, Econometrics and Health (GRECS), University of Girona, Spain; and Dr. Winston Garcia-Gabin, Department of Automatic Control, Royal Institute of Technology (KTH), Sweden

CERTIFY

That the thesis titled “Control and Modeling Techniques in Biomedical Engineering: The Artificial Pancreas for Patients with Type 1 Diabetes”, presented by **Amjad Hisham Ahmad Abu-Rmileh** to obtain a “doctoral degree”, has been completed under our supervision and meets the requirements to opt for an *International Doctorate*.

Prof. Dr. Marc Saez

Dr. Winston Garcia-Gabin

Girona, November 2013

Universitat de Girona

Prof. Dr. Marc Saez Zafra, Director of the Research Group on Statistics, Econometrics and Health (GRECS), University of Girona, Spain; and Prof. Dr. Winston Garcia-Gabin, Department of Automatic Control, Royal Institute of Technology (KTH), Sweden

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Prof. Dr. Marc Saez

Dr. Winston Garcia-Gabin

Girona, November 2013

Compendium of Publications

This thesis is presented as a compendium of the following publications, which will be referred to in the text by their Arabic numerals:

- Chapter 4

  Publication 1: Amjad Abu-Rmileh and Winston Garcia-Gabin. "A gain-scheduling model predictive controller for blood glucose control in type 1 diabetes." *IEEE Transactions on Biomedical Engineering* 57, no. 10 (2010): 2478-2484. (DOI: 10.1109/TBME.2009.2033663)
  Journal Citation Report (JCR) - Impact factor: **2.278**, Quartile: **Q2**

- Chapter 5

  Publication 2: Amjad Abu-Rmileh and Winston Garcia-Gabin. "Feedforward-feedback multiple predictive controllers for glucose regulation in type 1 diabetes." *Computer Methods and Programs in Biomedicine* 99, no. 1 (2010): 113-123. (DOI: 10.1016/j.cmpb.2010.02.010)
  Journal Citation Report (JCR) - Impact factor: **1.516**, Quartile: **Q1**

- Chapter 6

  Publication 3: Amjad Abu-Rmileh, Winston Garcia-Gabin, and Darine Zambrano. "Internal model sliding mode control approach for glucose regulation in type 1 diabetes." *Biomedical Signal Processing and Control* 5, no. 2 (2010): 94-102. (DOI: 10.1016/j.bspc.2009.12.003)
  Journal Citation Report (JCR) - Impact factor: **1.000**, Quartile: **Q3**

- Chapter 7

  Publication 4: Amjad Abu-Rmileh, Winston Garcia-Gabin, and Darine Zambrano. "A robust sliding mode controller with internal model for closed-loop artificial pancreas." *Medical and Biological Engineering and Computing* 48, no. 12 (2010): 1191-1201. (DOI: 10.1007/s11517-010-0665-3)
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- Chapter 8

  Publication 5: Amjad Abu-Rmileh and Winston Garcia-Gabin. "Wiener sliding-mode control for artificial pancreas: A new nonlinear approach to glucose regulation." *Computer Methods and Programs in Biomedicine* 107, no. 2 (2012): 327-340. (DOI: 10.1016/j.cmpb.2012.03.001)
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- Chapter 9

  Publication 6: Amjad Abu-Rmileh and Winston Garcia-Gabin. "Hypoglycemia Prevention in Closed-Loop Artificial Pancreas for Patients with Type 1 Diabetes." *Diabetes - Damages and treatments* (2011), Everlon Rigobelo (Editor): 207-226, InTech (ISBN: 978-953-307-652-2)

- Chapter 10

  Publication 7: Amjad Abu-Rmileh and Winston Garcia-Gabin. "Detection and Prevention of Hypoglycemia in Automated Insulin Delivery Systems for Type 1 Diabetes Patients." *Advances in Medicine and Biology* 44 (2012), Leon V. Berhardt (Editor): 249-266, Nova Science Publishers (ISBN: 978-1-62100-961-0)

Abstract

Diabetes is one of the world's main causes of death and disability due to the increasing number of patients with diabetes worldwide. Recent developments of Continuous Glucose Monitoring sensors and insulin pumps give hope for the development of an artificial pancreas. The artificial pancreas is an automated closed-loop control system that is applied for glucose regulation in subjects with Type 1 Diabetes Mellitus, who suffer severe lack of insulin production. The artificial pancreas has the potential to reduce the frequency and severity of the diabetes complications and improve the patients' quality of life. However, blood glucose control is still a challenging problem in biomedical engineering, since there exist several factors that significantly hinder the performance of the closed-loop control. These factors include: the inherent complexity of the glucose regulation system (e.g. the presence of nonlinearities, the high intra and inter-patient variability), the inaccurate and noisy measurements of the glucose sensors, the time-delay associated to the subcutaneous glucose sensing and insulin delivery, and the presence of different sources of disturbance and uncertainty that interfere with glucose control (e.g. stress, meal, exercise).

This thesis presents different control strategies for the closed-loop artificial pancreas, which are based on Model Predictive Control (MPC) and Sliding Mode Control (SMC). More specifically, multiple MPC with linear models and gain scheduling, and SMC with linear and nonlinear models, have been developed. All control strategies use the subcutaneous route for glucose monitoring and insulin delivery. The proposed control strategies combine more than one linear/nonlinear control and modeling approaches in one structure. The main idea behind such combined approaches is to make use of the virtues of each approach while reducing the effects of their drawbacks.

The control strategies have been tested and validated in simulations (*in silico* validation). For the *in silico* testing, two mathematical models (the UVa simulator and the Hovorka model) have been used, simulating patients with Type 1 Diabetes Mellitus (virtual patients). The control strategies are tested in different conditions, such as the presence of meal disturbance, inter-patient and intra-patient variability, time-delay, and sensor errors.

The thesis also reviews the state of the art in hypoglycemia prevention and detection techniques in the closed-loop artificial pancreas. Hypoglycemia is the major adverse effect of insulin therapy, and therefore, minimizing the risk of hypoglycemia, by applying different control and detection techniques, is often considered in the development of the artificial pancreas.

Resumen

La diabetes es una de las principales causas de muerte y discapacidad a nivel mundial debido al creciente número de pacientes con diabetes. El reciente desarrollo de los sensores de monitoreo continuo de glucosa y las bombas de insulina dibujan un panorama alentador para el desarrollo de un páncreas artificial. El páncreas artificial es un sistema automatizado de control en bucle cerrado que se aplica para la regulación de la glucosa en pacientes con diabetes mellitus tipo 1, que padecen un grave déficit de producción de insulina. El páncreas artificial tiene el potencial de reducir la frecuencia y gravedad de las complicaciones de la diabetes y mejorar la calidad de vida de los pacientes. Sin embargo, el control de la glucosa en sangre sigue siendo un problema difícil en el ámbito de la ingeniería biomédica, debido a la existencia de diferentes factores que dificultan significativamente el rendimiento del control de bucle cerrado. Entre estos factores cabe destacar: la complejidad inherente al sistema de regulación de la glucosa (por ejemplo, la presencia de no linealidades, el alto grado de variabilidad intra e inter-paciente), las medidas inexactas y ruidosas de los sensores de glucosa, el retardo asociado a la vía subcutánea de detección de glucosa y administración de insulina, y la presencia de diferentes fuentes de perturbación e incertidumbre que interfieren con el control de glucosa (por ejemplo, estrés, comidas, ejercicio).

Esta tesis presenta diferentes estrategias de control para el páncreas artificial de bucle cerrado, que se basan en control predictivo basado en modelo (Model Predictive Control - MPC) y el control por modo deslizante (Sliding Mode Control - SMC). Más específicamente, múltiples MPC con modelos lineales y planificación de ganancia, y SMC con modelos lineales y no lineales, se han desarrollado. Todas las estrategias de control utilizan la vía

subcutánea para el monitoreo de la glucosa y la administración de insulina. Las estrategias de control propuestas combinan más de un método (lineal y/o no lineal) de control y modelado en cada estructura. La idea principal detrás de estos enfoques combinados es hacer uso de las virtudes de cada enfoque al tiempo que se reducen los efectos de sus desventajas. Las estrategias de control han sido probadas y validadas en simulaciones (validación *in silico*). Para los ensayos *in silico*, dos modelos matemáticos (el simulador UVA y el modelo de Hovorka) se han utilizado, simulando los pacientes con diabetes mellitus tipo 1 (pacientes virtuales). Las estrategias de control se ensayan en diferentes condiciones, tales como la presencia de perturbación por ingesta de comida, variabilidad inter- e intra-paciente, retardo, y errores del sensor.

La tesis también analiza el estado del arte en las técnicas de prevención y detección de hipoglucemia en el páncreas artificial de bucle cerrado. La hipoglucemia es el principal efecto adverso de la terapia de insulina, y por lo tanto, la reducción al mínimo del riesgo de hipoglucemia, mediante la aplicación de diferentes técnicas de detección y de control, se contempla a menudo en el desarrollo del páncreas artificial.

Resum

La diabetis és una de les principals causes de mort i discapacitat a nivell mundial a causa del creixent nombre de pacients amb diabetis. El recent desenvolupament dels sensors de monitorització continua de glucosa i les bombes d'insulina dibuixen un panorama encoratjador pel desenvolupament d'un pàncrees artificial. El pàncrees artificial és un sistema automatitzat de control en bucle tancat que s'aplica per la regulació de la glucosa en pacients amb diabetis mellitus tipus 1, que pateixen un greu dèficit de producció d'insulina. El pàncrees artificial té el potencial de reduir la freqüència i gravetat de les complicacions de la diabetis i millorar la qualitat de vida dels pacients. No obstant això, el control de la glucosa en la sang segueix sent un problema difícil en l'àmbit de l'enginyeria biomèdica, a causa de l'existència de diferents factors que dificulten significativament el rendiment del control de bucle tancat. Entre aquests factors cal destacar: la complexitat inherent al sistema de regulació de la glucosa (per exemple, la presència de no linealitats, l'alt grau de variabilitat intra i inter-pacient), les mesures inexactes i sorolloses dels sensors de glucosa, el retard associat a la via subcutània de detecció de glucosa i administració d'insulina, i la presència de diferents fonts de pertorbació i incertesa que interfereixen amb el control de glucosa (per exemple, estrès, menjars, exercici).

Aquesta tesi presenta diferents estratègies de control pel pàncrees artificial de bucle tancat, que es basen en control predictiu basat en model (Model Predictive Control - MPC) i el control en mode lliscant (Sliding Mode Control - SMC). Més específicament, múltiples MPC amb models lineals i planificació de guany, i SMC amb models lineals i no lineals, s'han desenvolupat. Totes les estratègies de control utilitzen la via subcutània per al monitoratge de la glucosa i l'administració d'insulina. Les estratègies

de control proposades combinen més d'un mètode (lineal i/o no lineal) de control i modelatge en cada estructura. La idea principal darrere d'aquests enfocaments combinats és fer ús de les virtuts de cada enfocament alhora que es redueixen els efectes dels seus desavantatges. Les estratègies de control han estat provades i validades en simulacions (validació *in silico*). Per als assajos *in silico*, dos models matemàtics (el simulador UVA i el model de Hovorka) s'han utilitzat, simulant els pacients amb diabetis mellitus tipus 1 (pacients virtuals). Les estratègies de control s'assagen en diferents condicions, com ara la presència de pertorbació per ingesta de menjar, variabilitat inter- i intra-pacient, retard, i errors del sensor.

La tesi també analitza l'estat de l'art en les tècniques de prevenció i detecció d'hipoglucèmia en el pàncrees artificial de bucle tancat. La hipoglucèmia és el principal efecte advers de la teràpia d'insulina, i per tant, reduir al mínim el risc d'hipoglucèmia, mitjançant l'aplicació de diferents tècniques de detecció i control, es considera sovint en el desenvolupament del pàncrees artificial.

To my parents who are always there for me.

To my family and all those who supported me through the University years.

To the little ones who always gave me hope.

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Amjad Abu-Rmileh

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Contents

Abbreviations

The following list provides the abbreviations that are frequently used throughout the thesis text.

AP	Artificial Pancreas
BG	Blood Glucose
BLA	Best Linear Approximation
CGM	Continuous Glucose Monitoring
CHO	Carbohydrates
$CSII$	Continuous Subcutaneous Insulin Infusion
$CVGA$	Control Variability Grid Analysis
$FF-FB$	Feedforward-Feedback
FRF	Frequency Response Function
GS	Gain Scheduling
GSC	Gain Scheduling Control
$GS-MPC$	Gain Scheduling Model Predictive Control
IMC	Internal Model Control
$IMC-SMC$	Internal Model Control Sliding mode Controller
$LMPC$	Linear Model Predictive Control
$MDII$	Multiple Daily Insulin Injections
MPC	Model Predictive Control
$MMPC$	Multiple Model Predictive Control
PID	proportional-integral-derivative
$PNLSS$	Polynomial Nonlinear State-Space
SC	Subcutaneous
SD	Standard Deviation
SMC	Sliding Mode Control
SP	Smith Predictor
$SP-SMC$	Smith Predictor Sliding Mode Control
$T1DM$	Type 1 Diabetes Mellitus
$T2DM$	Type 2 Diabetes Mellitus
WM	Wiener Model
$WM-SMC$	Wiener Model Sliding Mode Control

Part I

General Introduction

Chapter 1

Introduction

This chapter provides a brief background on the glucose regulation problem in diabetes, introduces the objectives of the thesis and presents the structure of the thesis's book.

1.1 Background

Diabetes is a chronic disease that is characterized by the fact that the body does not produce or properly use insulin. Diabetes Mellitus is a long-term condition, which results in elevated blood glucose levels as a consequence of the body's failure to effectively control the usage and storage of glucose. According to the International Diabetes Federation (IDF) there are 366 million people with diabetes worldwide [1]. There are two major types of diabetes: type 1 and type 2. Type 1 diabetes (insulin-dependent diabetes mellitus) usually appears suddenly during childhood or adolescence. Type 2 diabetes (non insulin-dependent diabetes mellitus) comes on gradually, generally in people aged over 40. Diabetes Mellitus is strongly associated with macro-vascular complications, such as coronary, cerebral and peripheral vascular diseases, as well as with micro-vascular complications like retinopathy, nephropathy and neuropathy. These long term complications result in increasing disability, reduced life expectancy and enormous health costs for virtually every society. In 2011, an estimated 4.6 million people died from consequences of diabetes [1].

In type 1 diabetes (T1DM), which is insulin-dependent diabetes (IDDM), the pancreas

cannot produce the necessary amount of insulin to control the glucose levels and, thus, there is a control failure. In non-insulin dependent, or type 2 diabetes (NIDDM), the pancreas is able to produce insulin, however, the secreted insulin is either not enough or the body is unable to use the insulin properly (insulin resistance). Therefore, drug therapy is needed to control the remaining functionality of the glucose regulation system. In the case of T1DM patients, control can only be achieved with insulin therapy due to pancreatic failure.

The intensive insulin therapy, with the goal of maintaining blood glucose levels close to the normal range, proved to effectively delay the onset and slow the progression of diabetic retinopathy, nephropathy, and neuropathy in patients with insulin-dependent diabetes mellitus [2]. The current insulin therapy for T1DM patients is based on discrete blood glucose measurements and multiple daily insulin injections (MDII) or a continuous subcutaneous insulin infusion (CSII). The use of sensors and CSII pumps systems in an open-loop combination has resulted in better clinical outcomes than conventional MDII therapy [3].

Given the inability of current therapies to achieve satisfactory glycemic control, the development of continuous glucose monitoring (CGM) sensors and the increasing use of CSII pumps, the development of an artificial pancreas (a biomedical device performing closed-loop control of blood glucose) is viewed as a promising solution for glycemic control in T1DM. The artificial pancreas automatically delivers insulin to maintain blood glucose levels within the desired range, prevents hypoglycemia, minimizes the need for patient intervention in the therapy and gives higher flexibility for patients in daily life (e.g. meal times and quantities, physical activity). By achieving good glycemic control, the artificial pancreas will also reduce the occurrence and severity of diabetes complications. The artificial pancreas has three main components: a glucose sensor, an insulin pump, and a control algorithm linking between the sensor measurements and the pump to calculate the required insulin input.

1.2 Motivation

Diabetes is one of the most serious health problems of our time. In addition to its significant mortality rate, the direct healthcare costs of diabetes and its related compli-

cations range from 2.5% to 15% of annual healthcare budgets worldwide [4]. Therefore, from quality of life and economic perspectives, it is very important for diabetic patients to regulate their blood glucose level tightly, keeping it within the acceptable range of 70-180 mg/dL [5], by using insulin therapy. Closed-loop insulin delivery by the artificial pancreas gives hope to achieving the desired glycemic control in T1DM, resulting in less long-term medical complications, as well as avoiding hypoglycemic and hyperglycemic incidents.

The development of a closed-loop artificial pancreas has been a continuously growing research topic for more than four decades. Different clinical and simulation studies have demonstrated the feasibility of such an automated system, where several classical and advanced control algorithms have been tested as possible candidates to close the control loop [6–11]. However, a closed-loop system is not yet commercially available, and blood glucose control in T1DM is still a challenging problem in biomedical engineering. Glucose regulation in T1DM encompasses several sources of errors and uncertainty that convert the design of a control algorithm for the artificial pancreas into a very tough task: (1) the inherent complexity of the insulin-glucose system which includes the presence of nonlinearities, and time-varying and patient-specific dynamics; (2) inaccurate and noisy sensor measurements; (3) modeling errors and uncertainty; (4) time-delay in glucose sensing and insulin delivery; (5) different sources of disturbance that affect the glucose level, such as meal intake, stress and physical activities.

An adequate control algorithm must be capable of handling these physiological and technical challenges while still providing acceptable performance. Currently, the main challenges that the progress of the artificial pancreas faces are the development of a reliable closed-loop control algorithm and the availability of a robust and accurate glucose sensor [12–14].

1.3 Objectives

The main objective of the thesis is to design, validate and compare advanced model-based control techniques for the closed-loop regulation of blood glucose in type 1 diabetes. The proposed control strategies, namely Model Predictive Control (MPC) and Sliding Mode Control (SMC), are applied to complex nonlinear mathematical models

that represent the physiological glucose regulation system in diabetic patients (*virtual patients*). Mainly, the proposed control strategies will be focusing on the use of models that are derived from input-output information generated from comprehensive physiological models. First, large and reduced-order linear models are used, and then, a nonlinear modeling approach is proposed to improve the control performance by using a data-driven nonlinear model in the control algorithm design.

The designed control strategies will take into account most of the limitations observed in the direct application of industrial control approaches to the problem of glucose regulation; the principles of biomedical engineering will be taken into account in order to adapt and modify the structure of industrial controllers so as to be applicable to biomedical control problems like diabetes. Therefore, each of the designed control algorithms is a combination of two control techniques; MPC is combined with a gain scheduling scheme to deal with system nonlinear gain, while SMC is used in a Smith predictor structure to reduce the effect of system time-delay. The idea behind such 'combined' approaches is to make use of the advantages of each technique while reducing the effect of their drawbacks.

Since the quality of model-based control highly depends on the accuracy of the used model, obtaining an accurate, as good as possible, model is an essential step to achieve the objective of the thesis. Therefore, other objectives of the thesis are:

- Assessment of the quality and the reliability of the linear modeling framework, that is frequently used in closed-loop glucose regulation.

- Identification of a nonlinear control-oriented model that represents the glucose regulation system more accurately than linear models, and consequently, improves the control performance. Model identification is based on the available input-output data of the patient (i.e. data-driven model).

- The development of a new sliding mode control law in which the Wiener model, that consists of a linear dynamic part and static nonlinear part, is employed in the mathematical formulation of the control law.

- Testing the control algorithms under realistic conditions, in order to make the simulation tests mimic, as close as possible, the real-life conditions of a diabetic patient.

1.4 Organization of the Thesis

This thesis is organized in 12 chapters, based on the aforementioned compendium of seven scientific publications:

Chapter 1 is an introductory chapter. The general background of the work, the research motivation and the thesis objectives are outlined in this chapter.

In **Chapter 2** an overview of the theoretical background is given, which forms the basis of development of the thesis. The physiological background of diabetes mellitus is provided to familiarize the reader with the subject. On the basis of that, the closed-loop control algorithm and the patient mathematical modeling will be presented. Both topics form the core of this thesis, and are two main research topics in the field of artificial pancreas and automated glucose regulation.

In **Chapter 3**, the mathematical models that will be used to describe the diabetic patient are presented. Two nonlinear first principle models are selected: the model developed by Dalla-Man and coworkers [15], and the model developed by Roman Hovorka and his colleagues [16]. These are the most commonly used physiological models in the artificial pancreas research in the past few years [6, 17, 18].

In **Chapter 4 - Publication 1**, a combination between multiple linear MPC and gain scheduling (GS-MPC) scheme is designed and applied to a benchmark nonlinear model (i.e. the Dalla-Man virtual patient). The controller is provided with asymmetric penalties in the cost function, which penalizes hypoglycemia more than hyperglycemia since the former is more life-threatening in short term. The idea of feedforward control, that can be used to counteract the effect of known sources of disturbances (such as meal intake in the glucose control problem) is also introduced in the chapter. The GS-MPC proved to be more effective than stand-alone MPC in regulating the glucose levels; due to the controller ability to deal with the nonlinear gain of the model.

In **Chapter 5 - Publication 2**, the GS-MPC approach is designed for another nonlinear model (i.e. the Hovorka virtual patient) which exhibits a higher level of nonlinearity, and more realistic testing conditions are used to test the controller (e.g. time-varying dynamics is considered).

In **Chapter 6 - Publication 3**, a nonlinear robust controller based on the variable structure sliding mode control (SMC) is presented, while a simple linear model is used to build the controller. The SMC controller is merged into a Smith Predictor time-compensation structure (a special configuration of Internal Model Control). The combined SP-SMC approach harvests the advantages of each control structure, while reducing their drawbacks. The Dalla-Man model is used as a virtual patient. The concepts and the use of external dynamic and static feedforward control are discussed in the chapter. Also, the structure of the IMC Smith predictor and its working principles are given in Chapter 6.

In **Chapter 7 - Publication 4**, the SP-SMC strategy is extended to a higher order model to make it able to deal with the higher nonlinearity shown in the Hovorka virtual patient.

In **Chapter 8 - Publication 5**, the linear modeling approach is replaced by a Wiener block-oriented model. A new approach, including the identification protocol, the mathematical development and the validation of the control algorithm, based on the nonlinear Wiener model, is proposed.

In **Chapter 9 - Publication 6** and **Chapter 10 - Publication 7**, the state of the art in hypoglycemia detection and prevention techniques is reviewed. Hypoglycemia is the most feared complication of insulin therapy, therefore, hypoglycemia prevention should be listed among the primary goals of the closed-loop artificial pancreas. In order to achieve this goal, different detection and prediction algorithms, alarms and safety techniques are being developed to tackle the problem of hypoglycemia.

In **Chapter 11**, a general discussion is given on the obtained control and modeling results.

Finally, **Chapter 12** provides general conclusions on the work done, and summarizes the major scientific contributions of the thesis. The chapter ends by highlighting the

directions of future work.

Chapter 2

T1DM: Control and Modeling

This chapter presents the elements involved in the glucose regulation problem in diabetes. First, the mechanism of glucose regulation in healthy persons is summarized. Then, the differences between the diabetic patient and the healthy person are explained in order to indicate the elements of the required control scheme. Finally, the previous work performed in the area of glucose control, with respect to modeling and closed-loop control, is briefly reviewed in order to provide the necessary background before discussing the research completed in this thesis.

2.1 Glucose regulation

Comprehensive discussions on glucose metabolism and the complications associated with glucose control can be found in specialized textbooks on physiology, endocrinology and diabetes mellitus [20, 21]. This section gives a general summary so as to provide a basic understanding of the main processes and hormones involved in glucose control.

The human body uses glucose as a primary source of energy. Glucose molecules are broken down within cells in order to synthesize Adenosine Triphosphate (ATP) molecules, energy-rich molecules that drive numerous processes in living cells. Therefore, glucose is the primary metabolite required for the body to function properly. Glucose molecules are delivered to the cells by the bloodstream, either to be used as ATP or for energy storage (depending on the target tissue). Therefore, to ensure a constant supply of

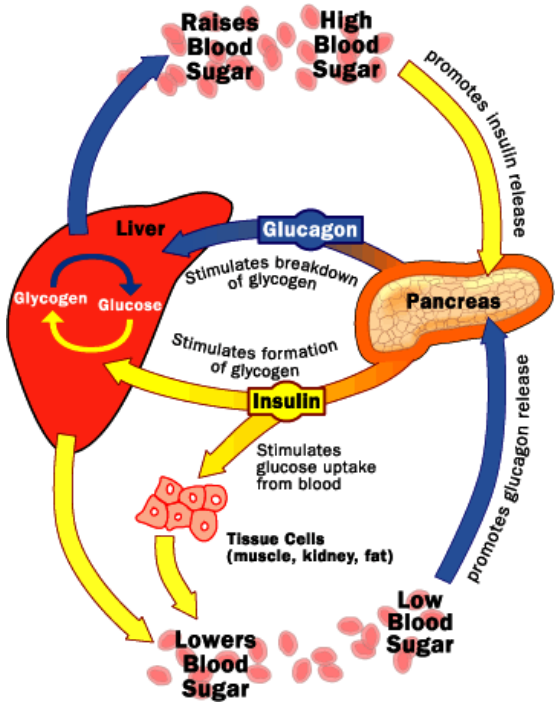

Figure 2.1: Feedback in blood glucose regulation [19]

glucose to the cells, it is important that relatively constant glucose levels are present in the bloodstream. In a healthy subject, blood glucose (BG) level is normally maintained within a relatively narrow range (70-110 mg/dL) by complex negative feedback control systems that track changes in the body and activate mechanisms that reverse the changes to restore body conditions to their normal levels. Negative feedback mechanisms are essentially important in glucose regulation to guarantee the balance between glucose entering the bloodstream and glucose being consumed by the body.

Glucose regulation is mediated primarily by the actions of two pancreatic hormones, namely insulin and glucagon (Figure 2.1). These hormones are secreted by the endocrine cells in the islets of Langerhans in the exocrine tissue of the pancreas. The β-cells secrete insulin, while glucagon is secreted by the α-cells. When the blood glucose rises to a high level (usually after a meal intake), the β-cells respond by secreting insulin. Insulin metabolic effects include: (1) stimulation of body cells to increase their rate of glucose uptake from the blood; (2) increase the cellular utilization of glucose as an energy source; (3) stimulation of glycogenesis (formation of glycogen from glucose in

liver and skeletal muscle cells); and (4) catalyze the fat synthesis from glucose in liver cells and adipose tissue. These effects of insulin cause the blood glucose level to return to the normal range.

On the other side, when blood glucose levels fall below normal (for instance, between meals, in fasting conditions, due to exercise, or during starvation), insulin secretion is inhibited and, at the same time, the α-cells of the pancreas respond by secreting glucagon, another hormone that functions in the opposite direction of insulin. Glucagon has the following effects (mainly on the liver cells): (1) stimulation of the breakdown of glycogen (glycogenolysis) back to glucose, which is then released into the bloodstream, preventing glucose levels from falling too low; (2) increase the breakdown of fats to fatty acids and glycerol in the adipose tissue and, consequently, the release of these substances into the bloodstream; and (3) stimulation of glucose synthesis in the liver (from glycerol absorbed from the blood) and glucose release into the blood. These effects cause blood glucose to increase to normal levels. Such feedback control actions of insulin and glucagon maintain blood glucose within tight limits, guaranteeing a constant supply of glucose to body tissues. In addition to insulin and glucagon, there are other hormones that can influence blood glucose levels. The most important are epinephrine, cortisol, and growth hormone. All of these are counter-regulatory hormones that work against the action of insulin and can increase blood glucose levels.

2.2 Diabetes

Under normal conditions, glucose is by far the main stimulus for insulin secretion. When blood glucose levels increase, insulin levels will increase as well, establishing a classical negative feedback system that keeps the glucose level within a narrow range. In Diabetes Mellitus, glucose metabolism is impaired by either lack of insulin secretion or reduced sensitivity (i.e. increased resistance) of the cells to insulin.

Due to lack of insulin or insulin resistance, glucose cannot be efficiently utilized nor stored by most cells of the body. As a result, blood glucose levels rise (i.e. hyperglycemia occurs), and the cells utilization of fat and proteins as energy source increases leading to the release of free fatty acids, cholesterol and phospholipids into the bloodstream. The accumulation of these substances in blood is associated with damages, dysfunction

and failure of various organs in the body. Sustained hyperglycemia is associated with acute ketoacidosis, micro-vascular and macro-vascular diseases [20]. Ketoacidosis, due to accumulation of ketons from fat and protein breakdown in the blood, can be life-threatening if left untreated, leading to coma and death.

2.2.1 Types of Diabetes

Regarding the classification of the disease, there are two main types of diabetes:

Type 1 Diabetes Mellitus (T1DM): in T1DM, pancreatic β-cells are destroyed by an erroneous autoimmune reaction in the body. Thus, insulin secretion is reduced to a very low level (down to 10% of normal). At this production level, insulin cannot decrease the blood glucose level. The blood glucose increases even more because of another missing effect of insulin, namely the inhibition of the secretion of glucagon (which stimulates the glycogen breakdown into glucose) when the blood glucose level is high. The blood glucose level in T1DM patients can be as high as 300-1200 mg/dL, 8-10 times higher than the level in a healthy person. When glucose level goes above 180 mg/dL, the kidneys start to release glucose in the urine. The symptoms of T1DM include tiredness, hunger and weight loss. Patients suffering from T1DM are dependent on receiving external insulin doses because nothing is secreted. Therefore this type is also called insulin-dependent diabetes mellitus (IDDM).

Type 2 Diabetes Mellitus (T2DM): in contrast to type 1 diabetes patients, in type 2 diabetes the pancreas is able to produce insulin. However, the secreted insulin is not able to affect the cells of the body to increase their uptake of glucose. Thus, people suffering from type 2 diabetes are insulin resistant. Over time, the number of β-cells start to decrease due to overloading, and then, the type 2 diabetics should be treated with drugs to increase the insulin sensitivity. If these drugs are not sufficient, external insulin has to be injected like in T1DM. T2DM is the most common type of diabetes.

During the last two decades, the prevalence of diabetes has increased dramatically and the disease is now a worldwide public health problem. Worldwide there are about 366 million people who are diabetics. The number is expected to rise to about 552 million by year 2030 [1]. The disease and its complication had a cost of at least 465 billion dollars in terms of healthcare expenses in 2011. Diabetes is among the ten-leading causes of

death in the world. These are alarming facts that justify the need for research in this area.

2.2.2 Current Treatment of Diabetes

Since the insulin-producing cells in T1DM are destroyed, the treatment of T1DM is based on daily administration of external insulin. While the number, amount and timing of the insulin doses are adjusted according to the characteristics of each patient, T1DM treatment can be classified, according to the insulin regime and the monitoring (measurement) of blood glucose levels, in: Conventional Therapy (CT) and Intensive Therapy (IT). The CT includes one or two daily insulin injections, self-monitoring of glucose in blood or urine, and dietary control and exercise. Generally, this therapy does not include daily adjustments of the insulin dose. On the other hand, the IT consists of multiple insulin injections (three or more times a day), or insulin delivery through a pump, and testing the blood glucose by pricking the fingers for blood six or more times. The dose can be adjusted according to self-monitoring of glucose levels, diet and anticipation of the exercise intensity.

The Diabetes Control and Complications Trial (DCCT) [2] studied the types of therapy and demonstrated the benefits of intensive glycemic control in T1DM. The study proved that microvascular and some macrovascular complications of T1DM could be reduced by intensive glycemic control. However, the increased risk of hypoglycemia associated to the intensive insulin therapy has limited the clinical use of such a therapy, because of the imperfections of available treatment regimes [22]. The two main modalities currently used for insulin administration are MDII and CSII pumps. In fact, all the current treatments still strongly depend on the patient's daily decisions about the insulin therapy, while many factors should be considered (e.g. current blood glucose level, blood glucose target, insulin sensitivity, meal time and composition and physical activities). This treatment regime can add strict limitations on the patients' lifestyle and is prone to errors. As a result, many diabetic patients do not, or are not able to maintain tight blood glucose control, subjecting themselves to significant short and long term complications.

Therefore, one major problem with current treatment is that there is no interaction between the glucose monitoring system and the insulin pump to automate the treatment in a stable and robust way. Due to the problems of current treatment, several attempts to develop an automated closed-loop control system of blood glucose have been made in the past and are still undergoing today.

2.2.3 Glucose Monitoring

Typically, glucose is monitored using a glucose meter, which is a small portable device. Testing glucose level with a traditional meter requires a person to take a small blood sample by pricking the finger, place the sample on a test strip, and insert the strip in the device. The existing meters either use electrochemical or optical reflectometry principles to measure the glucose level [8]. Most of these glucose meters employ an enzyme-based (glucose oxidation) electrochemical method for glucose detection. The test should be repeated multiple times daily. The current glucose meters provide instant (discrete) information, and don't consider the dynamics (e.g.variations in levels and trends) of glucose between tests, limiting their ability in achieving the desired glycemic control.

The DCCT recommended a strict monitoring of blood glucose levels to keep the glucose concentration within the safest range possible. Such monitoring is possible by using continuous glucose monitoring (CGM) devices: sensor technologies that provide continuous measurements of glucose levels, and emit reading every 1-5 minutes [3]. Most CGM devices consist of a sensor that is usually inserted into the subcutaneous tissue, a monitor to display the information, and a transmitter that transmits the sensor data to the monitor. CGM can provide information to: (1) detect hypoglycemic and hyperglycemic events as well as wide fluctuations in glucose levels (glycemic variability), and (2) predict impending hypoglycemia [23]. CGM devices can help patients and doctors to make adjustments to therapy and facilitate the development of therapeutic strategies that take into account the real-time dynamics of the blood, such as the time response of glucose as a function of meal intake and/or insulin dose and the rate of change of the measured glucose signal.

2.2.4 Insulin pumps

The CSII pump is the most accurate way to mimic normal insulin secretion because basal insulin rates can be programmed in multiple segments throughout a 24-hour period [24]. Patients can handle metabolic changes related to daily conditions (e.g. eating, exercise, illness, varying work schedule, etc.) by modifying insulin availability on an hourly basis. The CSII pump is a small device that patients wear outside their body, and can deliver insulin to the patient at a continuous rate. The device consists of a mechanical pump, a disposable container for the insulin within the pump, and a disposable infusion set consisting of a cannula and soft thin tubing used to connect the cannula and the insulin container. The cannula at the end of the tubing can be easily inserted with a single needle-stick under the skin to deliver the insulin to the subcutaneous tissues.

The amount of insulin a patient needs varies depending on the time of the day, food intake and activity level. A steady (basal) amount of insulin is needed throughout the day for normal bodily functions, and an additional dose is needed when eating or exercising. With traditional insulin injections, it is hard to ensure that the basal rate is being maintained during the day and that the basal insulin is not being consumed in eliminating the effect of meals. On the other hand, insulin pumps can be programmed according to each patient conditions, and can provide the two different amounts of insulin needed (Figure 2.2). The pump is programmed to deliver a small predetermined basal rate of insulin continuously to the patients to ensure a constant glucose range between meals and while patients sleep. The second type of insulin delivery is not a regular amount, but instead a bolus dose of fast-acting insulin to counter a patient's current condition. This dose is usually given at meal time, but can also be given if the patient's glucose level is too high.

Modern pumps can accurately track the remaining insulin-on-board (IOB) for safer use of bolus insulin. IOB is an empirical method used to estimate how much insulin is still active from previous doses. IOB is represented by decay curves of insulin action with different durations (2-8 hours). Insulin pumps include the IOB option that helps calculating the next required insulin dose while reducing the risk of overdosing and hypoglycemia [25]. New insulin pumps can also estimate the prandial (meal-time)

insulin required for a meal [24]. The dose is calculated by the patient entering to the pump the blood glucose reading at the time and the expected carbohydrate intake. The pump calculates how much previous prandial insulin is still active, and provides the patient with a suggested dose which the patient may activate or skip. Although CSII pumps have several advantages over the MDII therapy, in the sense of convenience, easy bolusing, accurate carbohydrate counting and precise dose adjustment, the pumps are still operating in open-loop, requiring the patient's intervention to set the basal infusion rate and deliver meal-time boluses based on their blood glucose level.

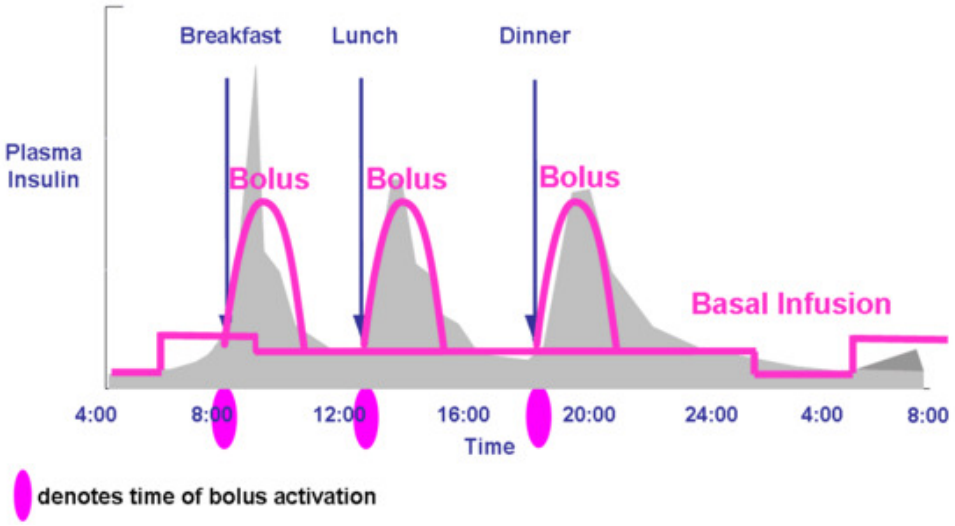

Figure 2.2: Administration of fast-acting insulin by CSII - gray background represents the physiologic insulin levels seen in healthy persons. The basal insulin component can be altered based on changing basal insulin requirements [24].

Currently, the use of CSII pumps is increasing, and a number of CGM devices have received regulatory approval. Although the CGM sensors and CSII pumps systems still have some problems, their use in an open-loop combination resulted in better clinical outcomes than the MDII therapy [3, 13]. Therefore, ongoing efforts are aimed at closing the control loop by linking continuous blood glucose measurement with automatically controlled insulin pumps, with the final goal of developing an artificial pancreas [23].

2.3 Closed-Loop Control in Diabetes

2.3.1 The Artificial Pancreas

As previously mentioned, in healthy subjects glucose is regulated through a closed-loop feedback system. In T1DM, the control loop is broken due to the absence of insulin. Therefore, a natural way of replacing the broken loop is by using an external closed-loop control system for glucose regulation. Currently, the inexistence of an outer 'artificial' loop to replace the natural one makes diabetic patients regulate their blood glucose in an open-loop manner, using the available systems of glucose monitoring and insulin delivery. Although the treatment is supervised by medical staff, mishandled (uncontrolled) situations often appear, resulting in hyperglycemia and hypoglycemia which are both dangerous, with the latter being more life-threatening in the short term, leading, for example, to loss of consciousness and coma. Therefore, arguably, the most complex component of blood glucose regulation is the control domain.

In the case of glucose regulation by a closed-loop system, also known as an artificial pancreas, the glucose levels are monitored continuously, which results in a continuous insulin infusion calculated by a computing algorithm, without the need for patient input (Figure 2.3). The artificial pancreas has three main components [6, 11]: a glucose sensor, a pump for insulin, and a control algorithm which is able to determine 'automatically' the required insulin dose under real-life conditions (e.g. in the presence of meal and exercise, or during the night).

Compared to the currently used insulin therapy, the artificial pancreas has the potential to achieve: (1) lower glycemic variability; (2) less hypoglycemic risk; (3) less pain from pricking the skin to check glucose and deliver insulin; and (4) less overall patient effort [23] with a higher flexibility in lifestyle. However, till now no commercially available artificial pancreas system does exist. With the significant improvements in the CGM sensor and CSII pumps components, the development of an adequate control algorithm to close the loop is vital for the progress of the artificial pancreas.

2.3.2 Control Algorithms

To be able to close the loop, and thus make the glucose control scheme an automatic one, a set of decision rules (i.e. algorithm) for insulin administration, mainly based on the monitored glucose level, is required. Several attempts have been made to design such a control algorithm using a wide spectrum of approaches in control theory. Several reviews have already extensively discussed the glucose control algorithms developed since 1960s up to the present time (see for example [6–11, 17, 18, 26–28]). For this reason, only a brief overview of the existing closed-loop control algorithms will be given in this chapter, indicating the most relevant ones.

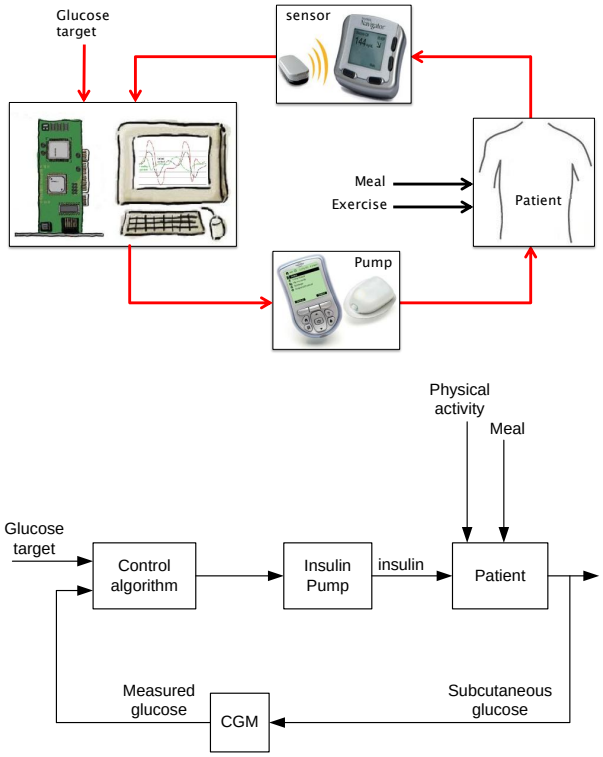

Figure 2.3: Closed-loop Artificial Pancreas - Upper: Intuitive sketch, Lower: System block diagram

Attempts to close the control loop started in 1960s by *Kadish* in 1964, who used an on-off system with intravenous insulin and glucose (or glucagon) infusion based on con-

tinuous glucose measurements in the diabetic patient. In 1974, *Albisser* developed one of the first control equations based on curve fitting. This algorithm was later modified and formed the basis for the algorithm used in Biostator, the first commercial device for automated glucose control [8]. The Biostator also used the intravenous (IV) route for glucose monitoring and insulin delivery (i.e. IV-IV route), where the control algorithm calculates the insulin dose using a sigmoidal glucose-insulin response curve [8]. The adopted IV-IV approach has the disadvantage of being highly invasive, and it can not be used on a daily basis. The development of fast-acting insulin analogues (e.g. insulin lispro, insulin aspart, or insulin glulisine) and less (or minimally) invasive glucose sensors have made more feasible the use of the subcutaneous route (SC-SC) which is much less invasive than the IV-IV route, since insulin delivery and glucose measurements are done at the subcutaneous tissues.

Subsequently, various control algorithms have been proposed, ranging from classical approaches such as Proportional-Integral-Derivative (PID), advanced control algorithms like Model Predictive Control (MPC), run-to-run, Iterative Learning Control (ILC), adaptive control, robust H_∞ and Sliding Mode Control (SMC) approaches, to soft-computing algorithms like fuzzy and neural network control. Most of these control algorithms have been tested in simulations [6, 17, 18], while some approaches have been tested on animals and even on diabetic patients [29–35].

The PID control strategy is one of the most widely used algorithms in the field of glucose regulation. In its simple formulation, the control law of PID depends on the output error (i.e. difference between measured and desired glucose level) and its proportional-integral-derivative behavior. Such an algorithm is preferred because it is based on mathematical calculations and no detailed knowledge of the patient's behavior is required. Also, the PID algorithm shows similarity with the multiphase insulin response of the natural β-cells [34]. In [34] a PID algorithm was tested in preliminary clinical closed-loop trial, using the subcutaneous control route. Subsequent modifications have been adopted in the algorithm, such as the use of an *Insulin feedback* term to minimize the administration of insulin based on an estimation of the insulin in blood [36]. In a recent clinical study [33], the insulin feedback has been used to improve the PID controller response in avoiding hypoglycemia after breakfast, and the desired performance was achieved. However, the controller is still not completely able to avoid hypoglycemia.

In the PID control, the integral action causes the amount of delivered insulin to be much higher than needed, resulting in overdosing and increased risk of hypoglycemia (especially in postprandial conditions) [7, 37]. Thus, the PD (Proportional-Derivative) control algorithm is expected to perform better than PID in avoiding low glucose levels [7]. Another disadvantage of PID control is its unsatisfactory performance in regulating systems with time-delay. Thus, the physiological and technological time-delays in the SC-SC route will result in a poor control performance for the PID algorithm.

The limitations of PID control and other classical approaches have motivated the study of solutions based on more advanced control approaches, such as model predictive control (MPC). Most recent studies and reviews suggest that MPC algorithms are especially well suited for a closed-loop artificial pancreas [6, 7, 11, 14, 18, 38]. As its name indicates, MPC is a model-based control approach that employs a model of the patient to predict future glucose levels. To calculate the insulin dose, the MPC algorithm solves an optimization problem by minimizing a quadratic cost function at every sampling time. Generally, the cost function includes terms that penalize the set-point error (i.e. the difference between predicted future blood glucose level and the desired reference trajectory), and the insulin delivery rate. The main advantage of this control algorithm, over pure reactive feedback control like PID, is its ability to predict future glucose excursions and, therefore, to be able to act in an anticipatory manner to avoid hypoglycemic and hyperglycemic episodes. Another advantage of MPC is its ability to deal with constraints on the inputs and outputs of the system.

MPC performance depends largely on the ability of the model to accurately predict future glucose levels based on the current state and available measurements. Several configurations of MPC have been studied, based on linear and nonlinear models of the glucose regulation system [6, 18]. MPC is frequently implemented with other techniques (e.g. parametric programming [39, 40], iterative learning control [41], gain scheduling [42, 43]), to enhance its overall performance. MPC strategies have been tested in different clinical studies [30–32, 44, 45]. The studies concluded that MPC algorithms are well suited for glucose control under fasting and overnight conditions in T1DM patients. The studies showed that the artificial pancreas is superior to open-loop control in preventing overnight hypoglycemia, where significant reduction in overnight hypoglycemia episodes was observed with closed-loop control in comparison with standard therapy.

Also, during closed-loop period, the blood glucose level was within the target glycemic range for a longer time period, with reduced frequency of low glucose values.

As mentioned above, PID and MPC are by far the most common used control algorithms [6, 7, 11, 18]. In this thesis, MPC and SMC control strategies will be designed and tested in simulations, using mathematical models to represent the diabetic patient. More into the details, variations of the MPC algorithm (namely, multiple linear MPC with gain scheduling, and nonlinear MPC), and robust control based on SMC algorithms are proposed in the thesis. While MPC is frequently used in the literature, SMC is presented as an alternative to PID control algorithms. The SMC approach is as simple as PID in its formulation, yet presenting higher level of robustness, and giving an explicit relation between the control algorithm and the patient model. The general concepts of both MPC and SMC algorithms will be briefly presented in the following subsections.

Finally, since hypoglycemia is the major adverse effect of insulin therapy, hypoglycemia prevention is often considered among the primary goals of the closed-loop artificial pancreas. In order to achieve this goal, different detection and prediction algorithms, alarms and safety techniques are being developed to tackle the problem of hypoglycemia. Techniques like insulin-on-board (IOB) [46, 47], insulin feedback [36], meal detection algorithms [46, 48] and hypoglycemia alarms [49, 50] have been also developed and tested within the structure of the artificial pancreas control scheme to improve the system performance and reduce the risk of life-threatening hypoglycemia. Reviews about the state of the art in hypoglycemia detection and prevention techniques are given in Chapters 9 and 10 of the thesis.

2.3.3 Model Predictive Control

Model predictive control (MPC) is a control strategy that has developed considerably over the past few years. MPC is fundamentally based on a model of the system to be controlled. The main purpose is to keep an output $y(t)$ at a reference value or setpoint, $r(t)$. A model is used to predict the future system outputs, based on the past and current values and on the proposed optimal future control actions (Figure 2.4). These control actions are calculated by optimizing a cost function where the future tracking error is considered, as well as the system constraints, if any. MPC employs a receding

horizon strategy; a repeated displacement of the time horizon. At each time step, only the first control signal in the calculated sequence is applied to the system, with the rest of the sequence being discarded. The prediction horizon (H_p) of MPC determines how far ahead the model predicts the output, while the control horizon (H_c) determines how far ahead the algorithm determines the moves of the control action (Figure 2.4). Typically, the control horizon is chosen to be smaller than the prediction horizon, and the manipulated variable remains constant for the remaining $H_p - H_c$ sampling instants.

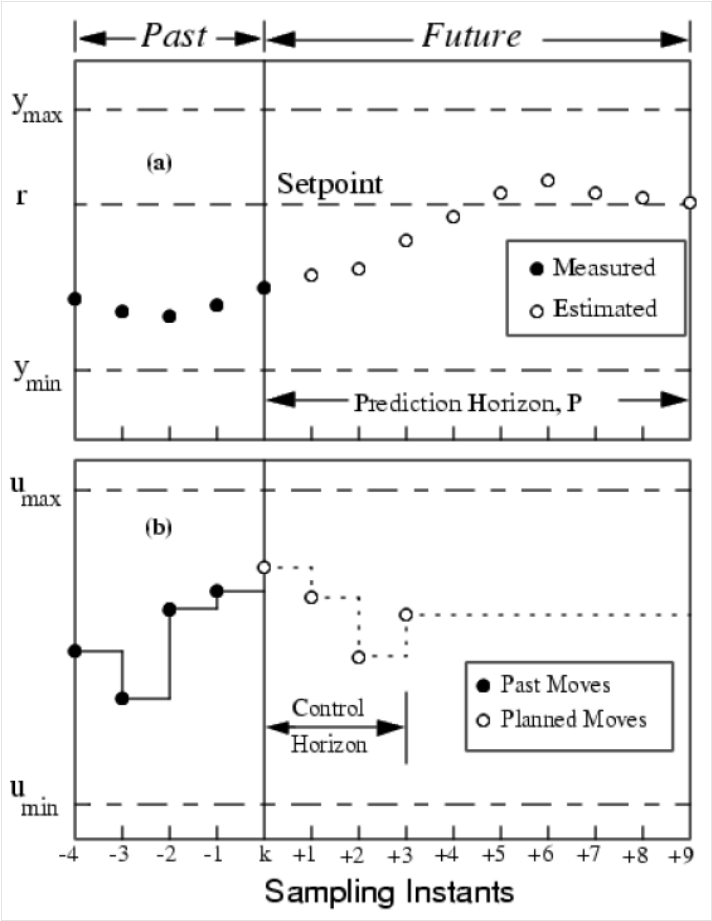

Figure 2.4: Principle of Model Predictive Control [51]

MPC has many virtues that make it a competitive candidate for the blood glucose control problem. (1) The prediction property of MPC allows for anticipatory and careful

insulin delivery to avoid large fluctuations in blood glucose levels. (2) The applicability of MPC to systems with long time-delays can be useful to overcome the physiological delays associated to the subcutaneous route [38]. (3) Compensation for dead time, which exists in the glucose problem also (i.e. delay in CGM tubing, and time course between the insulin infusion and the glucose response). (4) Implicit introduction of feedforward control action to compensate for known sources of disturbance affecting the system, such as meal intake. (5) Constraints handling on system inputs and outputs; such constraints can be very critical when dealing with the human body, and allow for satisfying hardware specifications of the insulin pump. These advantages of MPC over classical feedback control, along with its proved stability and robustness [52–54], have promoted the use of MPC in the field of automated insulin delivery. Different MPC schemes have been used in artificial pancreas research, where the applicability of such a control strategy is demonstrated, see for instance [14, 55–60].

For the design of a linear MPC, a linearized approximation (i.e. model) of the nonlinear system (i.e. virtual patient) should be obtained. A general representation of a dynamic nonlinear system is given by:

$$\begin{aligned} \dot{x}(t) &= f_1(x(t), u(t), v(t), d(t)) \\ y(t) &= f_2(x(t), u(t), v(t), d(t)) \end{aligned} \tag{2.1}$$

where, in the glucose control problem, $x(t)$ is the states vector (which represents the memory of the system, and includes the common dynamics present in the different outputs of the system), $u(t)$ is the insulin input, $v(t)$ is the meal intake disturbance (measurable disturbance), $d(t)$ is the unmeasured disturbance (e.g. sensor errors), and $y(t)$ is the measured glucose level (see equation 3.20 in section 3.4). When implementing the MPC algorithm, state-space realization is the most convenient since it can be easily extended to multivariable and nonlinear systems [61]. Therefore, the MPC is designed using the state-space representation of the linear system. The discrete linearized state-space (prediction model) obtained from the nonlinear virtual patient's model can be written as:

$$\begin{aligned} x(k+1) &= Ax(k) + B_u u(k) + B_v v(k) + Ed(k) \\ y(k) &= Cx(k) + D_v v(k) + D_d d(k) \end{aligned} \tag{2.2}$$

where $A_{n\times n}$, $B_{n\times 1}$, $E_{n\times 1}$, $C_{1\times n}$, and $D_{1\times 1}$ are the matrices of the discrete linear model, n is the model order, $x(k)$, $u(k)$, $y(k)$, $v(k)$, and $d(k)$ are the discrete linear equivalents of the variables in (2.1).

The objective of the predictive control system is to bring the predicted output vector, $Y(k) = [\hat{y}(k+1)\ \ \hat{y}(k+2)\ \ \dots\ \ \hat{y}(k+H_p)]^T$, as close as possible to the desired setpoint (reference signal). This objective is then translated into an optimization process to find the 'best' control moves sequence such that an error function between the reference and the predicted output is minimized. To do so, the control action $u(k)$ is governed by the optimization of a cost function, penalizing predicted output deviations and control signal along predetermined prediction horizons. In this thesis, the proposed MPC strategy (see Chapters 4 and 5) employs an asymmetric cost function and soft output constraints. The used cost function, J, is defined as:

$$\min_{\Delta u} J = \sum_{j=1}^{H_p} \|w^y(\hat{y}(k+j|k) - r(k+j))\|^2 + \sum_{j=1}^{H_c} \|w^{\Delta u}(\Delta u(k+j-1))\|^2 + q\varepsilon^2 \quad (2.3)$$

Subject to:

$$\begin{aligned} u_{min} \le u(k) \le u_{max} \\ \Delta u_{min} \le \Delta u(k) \le \Delta u_{max} \\ y_{min} - \varepsilon\Omega_{min} \le y(k) \le y_{max} + \varepsilon\Omega_{max} \end{aligned} \quad (2.4)$$

where $\hat{y}(k+j|k)$ is the j-step prediction of the output based on data up to instant k, $r(k+j)$ is the reference glucose level, Δu is the input increment ($\Delta u(k) = u(k) - u(k-1)$), H_p and H_c are the prediction and control horizons, $w^{\Delta u}$ and w^y are weights on the control action increments and the error between $y(k)$ and $r(k)$ respectively, ε is a slack variable used for output constraints softening, q is the weight on the slack variable ε, $u_{min/max}$, $\Delta u_{min/max}$ and $y_{min/max}$ are the constraints imposed on the input, input increments, and output respectively, and Ω_{min}, Ω_{max} are the relaxation variables.

Hard output constraints may cause infeasibility in the optimization problem (e.g. because of unpredicted disturbances, or model mismatch), therefore, ε is defined for output constraints softening [62]. The weight q on ε penalizes the violation of the constraints. The larger q with respect to input and output weights, the more the constraint violation is penalized.

The cost function in (2.3) is asymmetric; the lower and upper output constraints are subjected to unequal relaxation bands, and therefore, the constraints have different levels of softness. The unequal softness levels are achieved by introducing the nonnegative relaxation variables Ω_{min}, Ω_{max} which represent the concern for relaxing the corresponding constraint [51]; the larger Ω, the softer the constraint. The reason for using such an asymmetric cost function is that, in diabetes therapy, the performance requirement of a controller has an asymmetric nature, as hypoglycemic events are much less tolerable than hyperglycemia. Since hypoglycemia is viewed to be more life-threatening in short term, the control algorithm should be more aggressive in avoiding hypoglycemic events than in correcting hyperglycemic events. Satisfying such requirement with the use of a conventional cost function, that imposes the same weight on hypoglycemic and hyperglycemic events, would be difficult. Therefore, an asymmetric cost function MPC is used to minimize the hypoglycemic risk (especially in the postprandial period). The constrained optimization problem in (2.3) and (2.4) is solved using a quadratic programming (QP) solver. The QP solver *qpdantz* in $MATLAB^{©}$ uses the Dantzig-Wolfe's active set method to find the optimum.

2.3.4 Sliding mode control

Sliding mode control (SMC) is a robust and simple procedure to synthesize controllers for linear and nonlinear processes based on the principles of variable structure control (VSC). The controller structure changes in response to the changing state of the system in order to obtain the desired response. The SMC algorithm includes the following steps: (1) choosing a sliding (switching) surface, $s(t)$, along which the controlled system can slide to its desired final value. The sliding surface divides the phase plane into regions where the function $s(t)$ has different signs. (2) By using an appropriate control law: (a) make the system reach the switching surface (*reaching phase*), and (b) keep the system state trajectory on the switching surface for the subsequent period (*sliding phase*). The structure of the controller is intentionally altered as its state crosses the surface in accordance with the prescribed control law.

The biggest advantage of SMC is its robustness and insensitivity to variation in system parameters, external disturbances and modeling errors [63, 64]. This can be achieved by forcing the system onto the desired surface, and subsequently maintaining the system

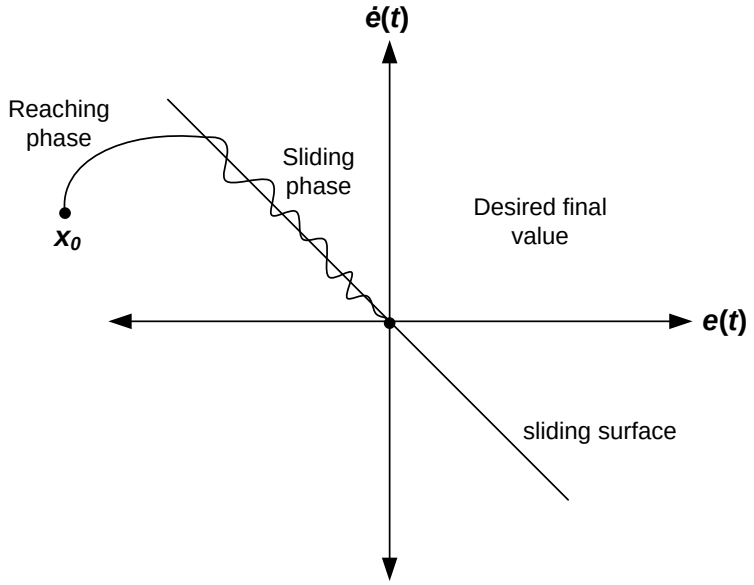

Figure 2.5: Sliding Mode Control

state trajectory on this surface. Once reached the surface, the system is insensitive to external disturbance and variations in parameters. Such control strategy is suitable for different types of systems due to its ability to deal with modeling errors, nonlinearities, time-varying behavior and disturbances.

The first step in SMC design is to define the surface $s(t)$, along which the system can slide to its desired final value. In general, $s(t)$ represents the system behavior during the transient period, and therefore, it must be designed to represent the desired system dynamics (e.g. stability and tracking performance). Here, the sliding surface presented in [65, 66] is used, which is an integral-differential error function:

$$s(t) = \left(\frac{d}{dt} + \lambda\right)^n \int_0^t e(\tau)d\tau \tag{2.5}$$

where n is the system order, $e(t)$ is the tracking error and λ is a tuning parameter, which helps to shape $s(t)$. This term is selected by the designer. This surface is often used because it provides a good performance in practical applications of sliding mode controllers [64, 67].

The SMC control law contains two parts: a continuous part, $u_{C_{fb}}(t)$, and a discontinuous part, $u_{D_{fb}}(t)$. The total feedback control action, $u_{fb}(t)$, is given by:

$$u_{fb}(t) = u_{C_{fb}}(t) + u_{D_{fb}}(t) \tag{2.6}$$

$u_{C_{fb}}(t)$ is responsible for maintaining the controlled system dynamics on $s(t)$, which represents the desired closed-loop behavior. The method normally used to generate the equivalent SMC law $u_{C_{fb}}(t)$ is the Filipov construction of the equivalent dynamics [66]. The method consists in satisfying the sliding condition, and substituting it into the system's dynamic equations to obtain the control law $u_{C_{fb}}(t)$. The nonlinear part $u_{D_{fb}}(t)$ is used to bring the system onto the sliding surface, and it represents the switching element in the SMC control law. Typically, $u_{D_{fb}}(t)$ is designed on the basis of a relay-like function (e.g. the signum function).

The control objective is to ensure that the controlled variable is driven to its reference value. This means that, in the stationary state, $e(t)$ and its derivatives must be zero. This requirement is achieved by satisfying the following sliding condition:

$$\frac{ds(t)}{dt} = 0 \tag{2.7}$$

After selecting $s(t)$, attention must be drawn to the design of the control law that drives the controlled variable to its reference value, and satisfies the sliding condition (2.7). The formulation of first and second order SMC control laws is presented in more details in Chapters 6 and 7.

In this thesis, the SMC strategy is designed in a Smith predictor structure, which has good time-delay compensation features. The Smith predictor (SP) is a special configuration of Internal model control (IMC), where the system model becomes an explicit part of the controller, and the time-delay can be compensated for. The resulting SP-SMC combination is a robust, simple control strategy with time-delay compensation features. The SMC part provides robustness and clear relation between model and controller parameters. The SP part makes it possible to avoid the increased complexity of the SMC that would result from time-delay approximation (i.e. increased controller order). Also, the SP structure is used due to its good properties in reducing the effect of system time-delay. The design of the SP-SMC and the formulation of the control laws are described in more details in Chapters 6 and 7.

2.4 Models of the Glucose Regulation System

Motivated by the need to study the physiological system and analyze its response to a wide range of control and disturbance signals without subjecting the real patient to risk, several mathematical models have been developed to describe the glucose regulation system in T1DM [11]. These models are essential for testing and validating the artificial pancreas in simulation studies (i.e. *in silico*) before putting it into clinical use with real patients. Also, these models are critical for the design of the closed-loop control algorithms (for both clinical and *in silico* trials), since most of the currently proposed controllers are model-based, where the artificial pancreas regulates the glucose level based on the glucose measurements and the mathematical model of the patient that is used to design the controller.

Two classes of models are employed in the field of glucose regulation: physiological models and empirical models. Physiological models are first principle models, in the form of differential and algebraic equations, based on existing knowledge and hypotheses regarding the underlying physiological system. Since the 1960s [8], several physiological models with different structures and degrees of complexity are being used to describe the glucose regulation system in T1DM, mainly in terms of insulin-glucose and meal-glucose relationships. Among the models that have been frequently used to represent the diabetic patient in artificial pancreas studies are: the *Meal model* [15, 68], *Hovorka model* [16, 55], the *minimal model* [69], *Fabietti model* [70], and *Sorensen model* [71]. Extensive reviews on available models can be found in [8, 11, 17]. Some of these models have been implemented in simulation environments designed to support the development of the closed-loop artificial pancreas [72, 73]. Physiological models are better suited for simulation of the system and representing the virtual patient for testing and validating controllers. However, these models are of limited usability in control and prediction algorithms design, due to their complex structure and the high number of parameters involved. From a practical perspective, it is very difficult (or even impossible) to identify the parameters in the structure based on the available input-output data of each patient.

On the other hand, empirical models, or data-driven models, develop a functional relationship between input (e.g. insulin and meal) and glucose based on empirical observations (i.e. collected patient data) by using system identification methods. These

models do not provide insight into the physiological system, but they explicitly address inter-patient variability since the data-driven model is specific to each individual patient's dynamics. Empirical models are more suitable for real-time parameter estimation and updating due to their simple structure in comparison with complex physiological models. Therefore, the implementation of control algorithms based on these models will be easier as the model structure is easily identifiable from the available patient data [17]. To represent the diabetic patient for control and prediction purposes, a wide range of empirical models has been developed based on linear and nonlinear system identification techniques, such as autoregressive moving average (ARMA) linear regression, autoregressive moving average with exogenous input (ARMAX) linear regression, nonlinear Wiener model identification [74], subspace-based identification, fuzzy logic, Volterra series and artificial neural networks (ANN) models (see reviews in [17, 75, 76]).

In this thesis, two nonlinear physiological models are used to represent the diabetic patients. Namely, the model developed by Hovorka and coworkers [16, 55, 77], and the model proposed by Dalla-Man and coworkers [15, 68, 78] are employed in the simulation studies to generate the data for the identification of control-relevant empirical models, and to test the proposed control algorithms under different simulation scenarios. The next chapter provides a detailed discussion on these models.

2.5 Challenges in Glucose Control

As previously mentioned, the closed-loop control of blood glucose has been a topic of continuous research for nearly 50 years. The technological improvements in subcutaneous glucose sensing and insulin delivery have improved the glycemic control results in T1DM patients and brought the artificial pancreas closer to reality. However, until now, only a limited number of artificial pancreas prototypes has been developed and tested in clinical trials, and there are still various challenges and difficulties that justify the research on advanced control algorithms:

- The complexity of the glucose regulation system, the presence of nonlinearities, time-varying and patient-specific dynamics. Due to the inherited nonlinearity of the glucose regulation system, the used algorithms and models need to be

complex and nonlinear in order to resemble the real physiological process [10]. Time-varying insulin sensitivity (i.e. the body's ability to respond to insulin) is believed to be a major challenge for both modeling and control. Therefore, obtaining an accurate model to represent the system is believed to be a very critical aspect.

- The need for control algorithm individualization (i.e. tuning for each patient), due to the fact that large inter-patient and intra-patient variability exist among diabetic patients.
- The presence of significant sources of disturbances that affect glucose levels such as meals, physical activity and stress.
- The time-delay associated to the subcutaneous route (SC-SC), where the control algorithm should deal with delays for the administrated insulin to take effect and for the actual blood glucose level to be measured. These time-delays can be time-varying, depending on the patient conditions, making the situation even more complicated.
- The noise, accuracy and reliability issues in the CGM devices.
- The insulin effect: insulin is the input controlled by the control algorithm and it decreases the glucose level. Once delivered, insulin can not be removed from the body. Till now, there is no other action to counteract the effect of insulin and reduce the risk of hypoglycemia. The use of glucagon infusion has been proposed as a possible solution in limited studies [32].

The above-mentioned challenges indicate that the design of a robust closed-loop control algorithm, that can handle different sources of error and disturbance, is an essential step for the progress of the artificial pancreas. Intensive research and validation efforts are still required before a fully developed artificial pancreas system might be used by diabetic patients in their daily life.

Chapter 3

Virtual Patient Models

3.1 Introduction

Preclinical testing trial is a critical step to evaluate the performance and robustness of closed-loop control algorithms. Recently, *in silico* environments are being increasingly used for control algorithm testing [72, 73, 79], and have shown ability to replace the animals' trials step in the development of clinical tools, while providing realistic results and covering a wider range of the variability observed among diabetic population [72]. These environments have as main building block a model that describes the T1DM patient (virtual subject). Many models have been investigated for *in silico* studies; these models range from simple linear models (e.g. Ackerman model), to nonlinear models (Bergman, and De Gaetano models), and comprehensive mathematical models (e.g. Cobelli, Sorensen, Hovorka, and Dalla-Man models) [8, 17]. Detailed analysis and simulations of different patient models' responses can be found in [17]. In this chapter, the models used to represent the diabetic patient, as well as the model of subcutaneous glucose sensor are described in detail.

3.2 Dalla-Man model

The *Meal model*, developed by Dalla-Man and coworkers in [15, 68], consists of a network of glucose and insulin compartments linked by the control of glucose on insulin secretion

and by the action of insulin on glucose utilization and endogenous production. Later on, some modifications have been introduced into the Dalla-Man model in order to simulate the metabolic conditions in T1DM [78]; the β-cells subsystem in the original models, which is inactive in the case of diabetes, is replaced by the subcutaneous insulin subsystem to model the dynamics of external insulin infusion in patients with T1DM [78, 80].

The model has been implemented in a simulation environment (UVa T1DM simulator) that has been accepted by the Food and Drug Administration (FDA) as a substitute for animals' trial in preclinical testing of closed-loop Artificial Pancreas control algorithms [72]. In addition to the patient model, the simulator incorporates two other models: a sensor-related errors model, to account for sensor noise, and measurements' errors [72, 81], and a model for the subcutaneous insulin pump. The UVa simulator has been used to develop several control algorithms [6, 18, 40, 42, 58, 82, 83]. A brief description of the model units and subsystems is given in the following (adapted from [15, 58, 68, 78]):

3.2.1 Intestinal glucose absorption

Glucose intestinal absorption is modeled by a three-compartment model:

$$\begin{aligned}
\frac{dQ_{sto1}(t)}{dt} &= -k_{gri}Q_{sto1}(t) + m(t) \\
\frac{dQ_{sto2}(t)}{dt} &= -k_{empt}Q_{sto2}(t) + k_{gri}Q_{sto1}(t) \\
\frac{dQ_{gut}(t)}{dt} &= -k_{abs}Q_{gut}(t) + k_{empt}Q_{sto2}(t) \\
Q_{sto}(t) &= Q_{sto1}(t) + Q_{sto2}(t) \\
Ra(t) &= \frac{f_{abs}k_{abs}Q_{gut}(t)}{BW}
\end{aligned} \tag{3.1}$$

where Q_{sto} is the amount of glucose in the stomach (Q_{sto1} in solid, Q_{sto2} in liquid phase), Q_{gut} is the glucose amount in the intestine, k_{gri} is the rate of grinding, k_{abs} is the rate constant of intestinal absorption, f_{abs} is the fraction of intestinal absorption which actually appears in the plasma, $m(t)$ is the amount of glucose (mg/min) from digested meal, BW is the body weight, Ra is the glucose rate of appearance in plasma and k_{empt} is the rate constant of gastric emptying which is a time-varying nonlinear function of Q_{sto} [68].

3.2.2 Glucose subsystem

3.2.2.1 Glucose kinetics

A two-compartment model is used to describe glucose kinetics:

$$\begin{aligned}\frac{dG_p(t)}{dt} &= -k_1 G_p(t) + k_2 G_t(t) + EGP(t) + Ra(t) - U_{ii} - E(t)\\ \frac{dG_t(t)}{dt} &= k_1 G_p(t) - k_2 G_t(t) + U_{id}(t)\\ G(t) &= \frac{G_p(t)}{V_G}\end{aligned} \tag{3.2}$$

where G_p and G_t (both in mg/kg) are glucose amounts in plasma and rapidly equilibrating tissues, and in slowly equilibrating tissues, respectively, EGP is the endogenous glucose production, $E(t)$ is the renal excretion, U_{ii} and U_{id} are the insulin-independent and insulin-dependent glucose utilizations, respectively, and k_1 and k_2 are the rate constants, V_G is the distribution volume of glucose and $G(t)$ (mg/dL) is the plasma glucose level.

3.2.2.2 Glucose renal excretion

The renal excretion represents the glucose fraction which is eliminated by the kidneys, when glucose level exceeds a certain threshold k_{e2}:

$$E(t) = max\{0, k_{e1}(G_p(t) - k_{e2})\} \tag{3.3}$$

where k_{e1} (min^{-1}) is the renal filtration rate.

3.2.2.3 Endogenous glucose production

EGP comes from the liver, where a glucose reservoir, as glycogen, exists. EGP is inhibited by high levels of glucose and insulin:

$$EGP(t) = max\{0, k_{p1} - k_{p2} G_p(t) - k_{p3} I_d(t)\} \tag{3.4}$$

where k_{p1} is the extrapolated EGP at zero glucose and insulin, k_{p2} is liver glucose effectiveness, k_{p3} is a model parameter describing the insulin action on the liver, and

I_d is the delayed insulin signal, that is given as:

$$\frac{dI_1(t)}{dt} = -k_i I_1(t) + k_i I(t)$$
$$\frac{dI_d(t)}{dt} = -k_i I_d(t) + k_i I_1(t) \tag{3.5}$$

where $I(t)$ is plasma insulin level and k_i is the rate parameter accounting for the delay between insulin signal and insulin action.

3.2.2.4 Glucose utilization

Glucose utilization consists of two components: an insulin-independent glucose utilization U_{ii}, which represents the glucose uptake by the brain and erythrocytes, and an insulin-dependent component U_{id}, which depends nonlinearly on glucose level in the tissues:

$$U_{id}(t) = V_m(X(t))\frac{G_t(t)}{K_m + G_t(t)} \tag{3.6}$$
$$\frac{dX(t)}{dt} = -p_{2u}X(t) + p_{2u}(I(t) - I_b) \tag{3.7}$$

where V_m is a linear function of the interstitial fluid insulin (i.e. the remote insulin signal), $X(t)$, which is a function of plasma insulin $I(t)$. I_b is the basal insulin level, and p_{2u} is the rate constant of insulin action on peripheral glucose utilization. The insulin-independent glucose utilizations U_{ii} is assumed constant and equal to F_{cns} [15].

3.2.3 Subcutaneous insulin

To account for the subcutaneous insulin infusion in diabetic patients, a two compartment model is introduced to describe the subcutaneous insulin kinetics:

$$\frac{dS_1(t)}{dt} = u(t) - (k_{a1} + k_d)S_1(t), \quad \frac{dS_2(t)}{dt} = k_d S_1(t) - k_{a2}S_2(t) \tag{3.8}$$

where $u(t)$ $(pmol/kg/min)$ represents the flow of administrated insulin, S_1 represents the polymeric insulin, and S_2 is the compartment of monomeric insulin in subcutaneous tissues, k_d is the degradation constant of polymeric insulin, k_{a1} and k_{a2} are absorption rate constants.

3.2.4 Insulin system

The insulin coming from the subcutaneous compartments enters the bloodstream and is degraded in the liver and in the periphery as follows:

$$\begin{aligned} \frac{dI_\ell(t)}{dt} &= -(m_1 + m_3)I_\ell(t) + m_2 I_p(t) \\ \frac{dI_p(t)}{dt} &= -(m_2 + m_4)I_p(t) + m_1 I_\ell(t) + k_{a1}S_1(t) + k_{a2}S_2(t) \\ I(t) &= \frac{I_p(t)}{V_I} \end{aligned} \tag{3.9}$$

where I_p and I_ℓ are the insulin masses in plasma and liver, respectively, V_I is the distribution volume of insulin and m_1, m_2, m_3, m_4 are rate parameters.

3.2.5 Subcutaneous glucose

Finally, to model the subcutaneous glucose dynamics, a first order system, with a rate constant k_{sc}, is used to describe the relation between plasma glucose, $G(t)$, and the subcutaneous glucose concentration, $G_{sc}(t)$:

$$\frac{dG_{sc}(t)}{dt} = -k_{sc}G_{sc}(t) + k_{sc}G(t) \tag{3.10}$$

3.3 Hovorka model

The nonlinear model developed by Hovorka and coworkers [16, 55] is the second model selected to represent the virtual diabetic patient. It is a physiological model validated with experimental data. The model consists of several subsystems; a subsystem of glucose kinetics, a subsystem of carbohydrate absorption, a subsystem of insulin actions, and a subsystem of subcutaneous insulin absorption and kinetics. The insulin actions describe the effect of insulin on glucose transport, removal and endogenous production, and are described by the insulin sensitivities. The model shows a good trade-off between simplicity and accuracy, and it is being used in clinical and *in silico* trials for the artificial pancreas research [31, 37, 40, 44, 74, 84, 85]. A summary of the model's subsystems and equations is given in this section (adapted from [55, 73]).

3.3.1 Glucose absorption subsystem

A two-compartments model, with identical transfer rate constants, is used to describe the carbohydrates (CHO) breakdown and absorption as glucose into the bloodstream.The gut absorption rate, $U_G(t)$ $(mmol/min)$, is given by:

$$U_{\mathrm{G}}(t) = \frac{M_G A_G\, t\, e^{-t/t_{\mathrm{max},G}}}{t^2_{\mathrm{max},G}} \tag{3.11}$$

where M_G is the amount of CHO digested, A_G is the CHO bioavailability of the meal, and $t_{\mathrm{max},G}$ is the time-of-maximum appearance rate of glucose in the accessible glucose compartment (see equation 3.12 below).

3.3.2 Glucose subsystem

3.3.2.1 Glucose kinetics

The glucose kinetics is represented by a two-compartments system:

$$\begin{aligned} \frac{dQ_1(t)}{dt} &= -F^c_{01}(t) - x_1(t)Q_1(t) + k_{12}Q_2(t) - F_R(t) + U_{\mathrm{G}}(t) + EGP_0(1 - x_3(t)) \\ \frac{dQ_2(t)}{dt} &= x_1(t)Q_1(t) - (k_{12} + x_2(t))Q_2(t) \\ G(t) &= \frac{Q_1(t)}{V_G} \end{aligned} \tag{3.12}$$

where $Q_1(t)$ and $Q_2(t)$ represent the masses of glucose in the accessible (where measurements are made) and non-accessible compartments, k_{12} represents the transfer rate constant from the non-accessible to the accessible compartment, V_G is the distribution volume of the accessible compartment, $G(t)$ is the plasma glucose concentration and EGP_0 represents the endogenous glucose production extrapolated to the zero insulin concentration. $F^c_{01}(t)$ is the total non-insulin-dependent glucose consumption, and $F_R(t)$ is the renal glucose clearance above the glucose threshold of 9 $mmol/L$ (about 160 mg/dL).

3.3.2.2 Glucose renal clearance

The glucose fraction eliminated from the blood by the kidney is defined as:

$$F_R(t) = \begin{cases} 0 & \text{if } G(t) < 9 \ mmol/L \\ 0.003(G(t) - 9)V_G & \text{if } G(t) \geq 9 \ mmol/L \end{cases} \tag{3.13}$$

3.3.2.3 Glucose utilization

The total non-insulin-dependent glucose flux (corrected for the ambient glucose concentration) is defined as:

$$F_{01}^c(t) = \begin{cases} \frac{f_{01}G(t)}{4.5} & \text{if } G(t) < 4.5 \ mmol/L \\ f_{01} & \text{if } G(t) \geq 4.5 \ mmol/L \end{cases} \tag{3.14}$$

3.3.3 Insulin subsystem

The subcutaneous absorption of insulin is described by a two-compartments system:

$$\frac{dS_1(t)}{dt} = u(t) - \frac{S_1(t)}{t_{\text{max,I}}}, \quad \frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{\text{max,I}}} - \frac{S_2(t)}{t_{\text{max,I}}} \tag{3.15}$$

where $u(t)$ represents the administration (bolus and infusion) of insulin, $t_{\text{max,I}}$ is the time-to-maximum insulin absorption, and $S_1(t)$, $S_2(t)$ are the insulin masses in the accessible and nonaccessible subcutaneous compartments. The insulin absorption rate (i.e. appearance of insulin in plasma), $I_{ex}(t)$, is given by:

$$I_{ex}(t) = \frac{S_2(t)}{t_{\text{max,I}}} \tag{3.16}$$

Thus, the plasma insulin concentration, $I(t)$, is described by:

$$\frac{dI(t)}{dt} = \frac{I_{ex}(t)}{V_I} - k_e I(t) \tag{3.17}$$

where k_e is the fractional elimination rate from plasma, and V_I is the insulin distribution volume.

3.3.4 Insulin actions subsystem

Plasma insulin concentration has an effect on glucose transport from plasma to tissues, hepatic glucose production and peripheral glucose disposal. These actions are modeled as follows:

$$\begin{aligned}\frac{dx_1(t)}{dt} &= -k_{a1}x_1(t) + k_{a1}S_{IT}I(t)\\ \frac{dx_2(t)}{dt} &= -k_{a2}x_2(t) + k_{a2}S_{ID}I(t)\\ \frac{dx_3(t)}{dt} &= -k_{a3}x_3(t) + k_{a3}S_{IE}I(t)\end{aligned} \tag{3.18}$$

where $x_1(t)$ represents the effects of insulin on glucose distribution/transport, $x_2(t)$ represents the effect on glucose disposal and $x_3(t)$ is the effect on endogenous glucose production. k_{a1}, k_{a2}, and k_{a3} are the deactivation rate constants, and S_{IT}, S_{ID}, and S_{IE} are insulin sensitivities for transport, disposal and endogenous glucose production.

3.3.5 Subcutaneous glucose

At steady state, the subcutaneous glucose concentration $G_{sc}(t)$ is highly correlated with the plasma glucose $G(t)$. However, in the dynamic state, it follows the changes in plasma glucose with some delay. Again, a first order model is used to describe the subcutaneous glucose kinetics [73]:

$$\frac{dG_{sc}(t)}{dt} = -\frac{1}{t_{sc}}(G_{sc}(t) + G(t)) \tag{3.19}$$

where t_{sc} is the transfer time constant. In this thesis, a $t_{sc} = 10$ min is used for the Hovorka virtual patients.

3.4 Subcutaneous glucose sensor

In order to simulate more realistically the behavior of a diabetic patient who uses an artificial pancreas, it is necessary to consider, beside the glucose level in the subcutaneous tissues, the measurement errors related to the subcutaneous sensor. For this

purpose, the model developed in [81] is used to describe the sensor-related errors. Thus, the CGM signal, $y(t)$ is given as:

$$y(t) = G_{sc}(t) + \varepsilon(t) \tag{3.20}$$

$$\varepsilon(t) = \xi + \mu \sinh\left(\frac{\sigma(t) - \gamma}{\beta}\right) \tag{3.21}$$

$$\sigma(t) = 0.7(\sigma(t-1) + \nu(t)) \tag{3.22}$$

where $\varepsilon(t)$ is a non-white sensor error generated using an autoregressive moving average (ARMA) time series model. The ARMA model is driven by $\nu(t)$ which is assumed to be white noise with zero mean and unity covariance. The model developers in [81] assume that the sensor errors are not normally distributed. Therefore, the nonlinear Johnson transformation in (3.21) is used to bias the distribution of the errors generated in (3.22) from normal. ξ, μ, β and γ are the parameters of Johnson distribution [81]. Note that $G_{sc}(t)$ in (3.20) is the subcutaneous glucose level obtained from Dalla-Man (3.10) or Hovorka (3.19) virtual patients.

Part II

Publications and Results

Chapter 4

Publication 1: A Gain Scheduling Model Predictive Controller for Blood Glucose Control in Type 1 Diabetes

This chapter corresponds to the publication:
Amjad Abu-Rmileh and Winston Garcia-Gabin. "A gain-scheduling model predictive controller for blood glucose control in type 1 diabetes." *IEEE Transactions on Biomedical Engineering* 57, no. 10 (2010): 2478-2484. DOI: 10.1109/TBME.2009.2033663.

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Abstract

This paper presents a control strategy for blood glucose (BG) level regulation in type 1 diabetic patients. To design the controller, model-based predictive control scheme has been applied to a newly developed diabetic patient model. The controller is provided with a feedforward loop to improve meal compensation, a gain-scheduling scheme to account for different BG levels, and an asymmetric cost function to reduce hypoglycemic risk. A simulation environment that has been approved for testing of artificial pancreas control algorithms has been used to test the controller. The simulation results show a good controller performance in fasting conditions and meal disturbance rejection, and robustness against model-patient mismatch and errors in meal estimation.

Keywords

Gain scheduling (GS); model predictive control (MPC); type 1 diabetes mellitus (T1DM)

Chapter 5

Publication 2: Feedforward-feedback multiple predictive controllers for glucose regulation in type 1 diabetes

This chapter corresponds to the publication:
Amjad Abu-Rmileh and Winston Garcia-Gabin. "Feedforward-feedback multiple predictive controllers for glucose regulation in type 1 diabetes." *Computer Methods and Programs in Biomedicine* 99, no. 1 (2010): 113-123. DOI: 10.1016/j.cmpb.2010.02.010.

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Abstract

Type 1 diabetic patients depend on insulin therapy to maintain blood glucose levels within safe range. The idea behind the “Artificial Pancreas” is to mimic, as close as possible, the functions of the natural pancreas in glucose sensing and insulin delivery, by using closed-loop control techniques. This work presents a model-based predictive control strategy for blood glucose regulation in diabetic patients. The controller is provided with a feedforward loop to improve meal compensation, a gain scheduling scheme to improve the controller performance in controlling the nonlinear glucose–insulin system, and an asymmetric cost function to reduce the hypoglycemic risk. Simulation scenarios with virtual patients are used to test the designed controller. The obtained results show a good controller performance in fasting conditions and meal disturbance rejection, and robustness against measurements errors, meal estimation errors, and changes in insulin sensitivity.

Keywords

Artificial pancreas; Gain scheduling; Model predictive control; Asymmetric cost function; Type 1 diabetes mellitus

Chapter 6

Publication 3: Internal model sliding mode control approach for glucose regulation in type 1 diabetes

This chapter corresponds to the publication:
Amjad Abu-Rmileh, Winston Garcia-Gabin, and Darine Zambrano. "Internal model sliding mode control approach for glucose regulation in type 1 diabetes." *Biomedical Signal Processing and Control* 5, no. 2 (2010): 94-102. DOI: 10.1016/j.bspc.2009.12.003.

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Abstract:

Patients with type 1 diabetes require insulin therapy to maintain blood glucose levels within safe ranges since their pancreas is unable to complete its function. The development of a closed-loop artificial pancreas capable of maintaining normoglycemia during daily life will dramatically improve the quality of life for insulin-dependent diabetic patients. In this work, a closed-loop control strategy for blood glucose level regulation in type 1 diabetic patients is presented. A robust controller is designed using a combination of internal model and sliding mode control techniques. Also, the controller is provided with a feedforward loop to improve meal compensation. A simulation environment designed for testing the artificial pancreas control algorithms has been used to evaluate the controller. The simulation results show a good controller performance in fasting conditions and meal disturbance rejection, and robustness against model–patient mismatch and meal estimation errors.

Keywords

Artificial pancreas; Internal model control; Sliding mode control; Type 1 diabetes mellitus

Chapter 7

Publication 4: A robust sliding mode controller with internal model for closed-loop artificial pancreas

This chapter corresponds to the publication:
Amjad Abu-Rmileh, Winston Garcia-Gabin, and Darine Zambrano. "A robust sliding mode controller with internal model for closed-loop artificial pancreas." *Medical and Biological Engineering and Computing* 48, no. 12 (2010): 1191-1201. DOI: 10.1007/s11517-010-0665-3.

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Abstract

The study presents a robust closed-loop sliding mode controller with internal model for blood glucose control in type-1 diabetes. Type-1 diabetic patients depend on external insulin delivery to keep their blood glucose within near-normal ranges. Closed-loop artificial pancreas is developed to help avoid dangerous, potentially life-threatening hypoglycemia, as well as to prevent complication-inducing hyperglycemia. The proposed controller is designed using a combination of sliding mode and internal model control techniques. To enhance postprandial performance, a feedforward controller is added to inject insulin bolus. Simulation studies have been performed to test the controller, which revealed that the proposed control strategy is able to control the blood glucose well within the safe limits in the presence of meals and measurements errors. The controller shows acceptable robustness against changes in insulin sensitivity, model–patient mismatch, and errors in estimating meal’s contents.

Keywords

Artificial pancreas; Internal model control; Sliding mode control; Type-1 diabetes mellitus

Chapter 8

Publication 5: Wiener sliding-mode control for artificial pancreas: a new nonlinear approach to glucose regulation

This chapter corresponds to the publication:
Amjad Abu-Rmileh and Winston Garcia-Gabin. "Wiener sliding-mode control for artificial pancreas: A new nonlinear approach to glucose regulation." *Computer Methods and Programs in Biomedicine* 107, no. 2 (2012): 327-340. DOI: 10.1016/j.cmpb.2012.03.001.

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Abstract

Type 1 diabetic patients need insulin therapy to keep their blood glucose close to normal. In this paper an attempt is made to show how nonlinear control-oriented model may be used to improve the performance of closed-loop control of blood glucose in diabetic patients. The nonlinear Wiener model is used as a novel modeling approach to be applied to the glucose control problem. The identified Wiener model is used in the design of a robust nonlinear sliding mode control strategy. Two configurations of the nonlinear controller are tested and compared to a controller designed with a linear model. The controllers are designed in a Smith predictor structure to reduce the effect of system time delay. To improve the meal compensation features, the controllers are provided with a simple feedforward controller to inject an insulin bolus at meal time. Different simulation scenarios have been used to evaluate the proposed controllers. The obtained results show that the new approach outperforms the linear control scheme, and regulates the glucose level within safe limits in the presence of measurement and modeling errors, meal uncertainty and patient variations.

Keywords

Artificial pancreas; Sliding mode control; Type 1 diabetes mellitus; Wiener model

Chapter 9

Publication 6: Hypoglycemia Prevention in Closed-Loop Artificial Pancreas for Patients with Type 1 Diabetes

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11

Hypoglycemia Prevention in Closed-Loop Artificial Pancreas for Patients with Type 1 Diabetes

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1. Introduction

The current chapter addresses the problem of hypoglycemia in type 1 diabetes from biomedical and control engineering points of view. It gives a general introduction to the artificial pancreas system, and the risk of hypoglycemia in closed-loop insulin treatment. Then, it provides a review on the state of the art in hypoglycemia control, and the recent approaches in dealing with hypoglycemia in closed-loop artificial pancreas systems. Next, different control techniques that can be used to minimize the risk of hypoglycemia and improve the control outputs are presented.

Since the Diabetes Control and Complications Trial (DCCT), tight glycemic control has been established as the control objective in the treatment of patients with type 1 diabetes mellitus (T1DM) (DCCT Research Group (1993)), except if some contraindication exists. However, there still lacks a universal, efficient and safe system able to normalize the glucose levels of patients. The intensive insulin therapy required to achieve the tight glycemic control, based on the injection of basal and bolus insulin to reproduce its physiological secretion, has as counteraction an increase in the risk of significant and severe hypoglycemia with all their consequences. Therefore, hypoglycemia is considered as one of the major limiting factors in achieving tight glycemic control in T1DM (Cryer (2008)).

With the inability of conventional therapy to achieve satisfactory glycemic control, and the development in continuous glucose monitoring (CGM) systems and the increasing use of insulin pumps, the idea of developing an artificial pancreas is viewed as the ideal solution for glycemic control in T1DM (Bequette (2005); Hovorka et al. (2006); Kumareswaran et al. (2009)). The artificial pancreas is an automated closed-loop system that maintains blood glucose levels within the desired range and prevents hypoglycemia, while minimizing or eliminating the need for patient intervention. The artificial pancreas replaces the β-cells functions in glucose sensing and insulin delivery. It consists of three main components (Figure 1): a glucose sensor to measure glucose concentration, a pump for insulin delivery, and a closed-loop control algorithm to bridge between the glucose measurements and the dose of insulin to be delivered. As other medical devices, the architecture of closed-loop

artificial pancreas should include strict safety measures implemented as safety module or supervision system, to evaluate the performance of the control algorithm and apply fault detection techniques (Doyle III et al. (2007)).

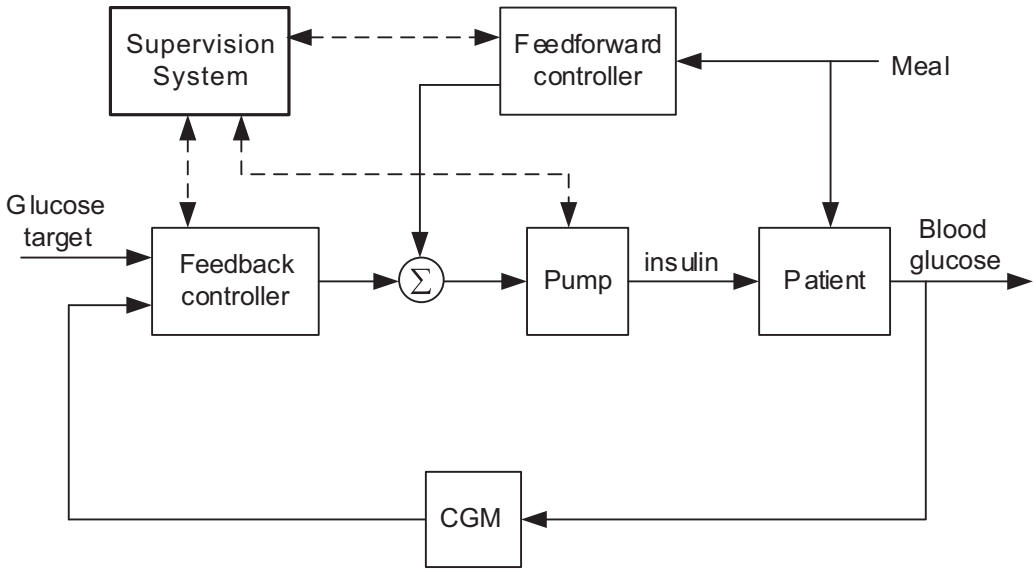


Fig. 1. Artificial pancreas components with patient in the loop. Control algorithm may use feedback or feedforward-feedback control loops

Closed-loop control of blood glucose has been a subject of continuous research for more than 40 years, however, till now no commercially available product does exist. The continuous subcutaneous insulin infusion (CSII) pumps are being widely used, and a number of CGM systems have received regulatory approval (Kumareswaran et al. (2009)). Although the sensors and pumps systems still have some limitations, their use in an open-loop combination resulted in better clinical outcomes over conventional injections therapy (Klonoff (2005); Kumareswaran et al. (2009)). Thus, the primary limitations to develop such an artificial pancreas are the development of reliable closed-loop control algorithms, and the availability of robust and precise glucose sensors. However, recent research in the development of the artificial pancreas suggests that types of the automatic glucose control system are likely to come to market in the near future.

1.1 Patient modeling

The artificial pancreas automatically regulates the blood glucose level based on the glucose measurements, the insulin infusions and in model-based control approaches, on the mathematical insulin-glucose model (diabetic patient model) used to design the controller. Also, these models are essential for testing and validating the artificial pancreas in simulation studies (i.e. *in-silico*) before putting it into clinical use with real patients. Thus, one essential task in the development of artificial pancreas is to obtain a model of T1DM patient, which can help in the development of a closed-loop control system.

Several models with different structures and degrees of complexity are being used to describe the glucoregulatory system - mainly as insulin-glucose and meal-glucose relationships - in T1DM. Most of these are first principle models represented by differential and algebraic equations and based on existing knowledge and hypotheses regarding the underlying physiological system. Among the models that have been frequently used to represent the

diabetic patient in artificial pancreas studies are: the *Meal model* (Dalla Man et al. (2006; 2007)), *Hovorka model* (Hovorka et al. (2004; 2002)), the minimal model (Bergman et al. (1979)), and *Sorensen model* (Sorensen (1985)). Extensive reviews on available models can be found in Chee & Fernando (2007) and Cobelli et al. (2009). Some of these models have been implemented in simulation environments designed to support the development of the closed-loop artificial pancreas (Kovatchev et al. (2009); Wilinska et al. (2010)).
Due to the complex nature of the insulin-glucose system, different empirical models have been proposed to relate insulin input to glucose response (see for example Eren-Oruklu et al. (2009b); Finan et al. (2009)). Empirical models develop a functional relationship between insulin and glucose based on empirical observations (i.e. collected patient data). These models do not describe the physiological model, but they explicitly address inter-patient variability since the data-driven model is specific to individual patient dynamics. Empirical models are more suitable for real-time parameter estimation and updating due to their simple structure in comparison with complex first order models.

1.2 Control problems

The feasibility of closed-loop artificial pancreas systems and their advantage over conventional treatment has been proved in several clinical studies (Atlas et al. (2010); Clarke et al. (2009); Hovorka et al. (2010); Steil et al. (2011; 2006); Weinzimer et al. (2008)), and a wide spectrum of control algorithms has been proposed to close the control loop, including classical and modern control strategies. Many reviews on closed-loop algorithms are available, see for example (Bequette (2005); Chee & Fernando (2007); Doyle III et al. (2007); El-Youssef et al. (2009); Takahashi et al. (2008)).
However, blood glucose control in T1DM is still one of the difficult control problems to be solved in biomedical engineering. In addition to the inherent complexity of glucoregulatory system, which includes the presence of nonlinearities, and time-varying and patient-specific dynamics, there exist other problems, such as noisy measurements, limitations of the models used to develop the control algorithms, as well as the limitations of the subcutaneous route used for glucose sensing and insulin delivery (e.g. technological and physiological delays and subcutaneous tissues dynamics). The aforementioned challenges make it very difficult to find a general and reliable solution to the nonlinear problem of glycemic control. Therefore, the design of a robust closed-loop control algorithm is an essential step for the progress of the artificial pancreas.
For closed-loop artificial pancreas system to be optimal and replicate the normal insulin secretion, the insulin therapy should respect the fact that hypoglycemia is not a naturally occurring episode in T1DM. Also, hypoglycemia is believed to be more dangerous in short term than hyperglycemia. Therefore, in order to achieve tight control while not substituting the problem of hyperglycemia for the life-threatening hypoglycemia, the insulin therapy in T1DM should be optimized so that it reduces the risk of hyperglycemic events in both frequency and magnitude, without provoking significant or severe hypoglycemia as a result of excessive or ill-timed insulin infusion.

2. Hypoglycemia in closed-loop artificial pancreas

Hypoglycemia is the most common complication of insulin therapy in T1DM and continuously limits the efforts to improve glycemic control. Therefore, hypoglycemia prevention should be unavoidably considered among the main objectives in the development of the closed-loop artificial pancreas systems. Severe hypoglycemia episodes are a

well-known cause of death in diabetic patients, and are more commonly seen during the night than during the day. Given that the first generations of the artificial pancreas are not expected to achieve complete regulation of the glucose levels during the 24 hours period, first generations of the artificial pancreas might be focusing on critical aspects like preventing hypoglycemia episodes during night (Hovorka et al. (2010)).
Currently, the vast majority of closed-loop artificial pancreas works focuses on the achievement of tight control during daily life conditions (i.e. 24 hours control), and therefore addresses both hyper- and hypoglycemia in fasting and postprandial conditions. Various strategies are employed in these works to avoid fasting, postprandial and nocturnal hypoglycemia. Mostly, the control algorithms use changes in the target blood glucose to adjust the doses of insulin to prevent hypoglycemia (i.e. higher target glucose level during night and postprandial periods) (Eren-Oruklu et al. (2009a); Marchetti et al. (2008); Weinzimer et al. (2008)). In other works, hypoglycemia prediction algorithms were tested, and short-term suspension of insulin pump was used as safety approach when hypoglycemia is predicted (Lee & Bequette (2009)). Also, variations in insulin sensitivity during the day (due to the 24 hours circadian cycle in insulin sensitivity), have been considered in the design of artificial pancreas control algorithms, and used to adjust the basal insulin requirements during the day (Garcia-Gabin et al. (2009); Steil et al. (2003); Wang et al. (2009)).
Another strategy used to avoid hypoglycemia is the double hormone closed-loop system, which uses glucagon infusion in response to low glucose levels. In T1DM, insulin deficiency is often accompanied by the loss of glucagon secretory response to hypoglycemia. Furthermore, insulin therapy causes even more degradation in the functionality of other counterregulatory hormones (Briscoe & Davis (2006)), and consequently, results in higher possibility for hypoglycemic risk. Different artificial pancreas studies have demonstrated that glucagon infusion significantly reduces the risk of insulin-induced hypoglycemia in T1DM (Castle et al. (2010); El-Khatib et al. (2009; 2010); Ward et al. (2008)).

2.1 Overnight hypoglycemia control

Overnight closed-loop insulin delivery has received great interest because it addresses the critical problem of nocturnal hypoglycemia. Furthermore, prevention of nocturnal hypoglycemia and achieving good control overnight can help in improving the quality of glycemic control during the day (Hovorka et al. (2010)) (e.g. starting the day with acceptable glucose levels). A number of clinical and *in-silico* studies attempts to deal with the hypoglycemia prevention - mainly nocturnal hypoglycemia - as the primary control objective. In (Wilinska et al. (2009)), a manual closed-loop insulin delivery system was employed during night period using model predictive control (MPC) algorithm and CGM measurements (CGM readings were provided to the MPC by medical staff), and aimed at regulating glucose level overnight to avoid nocturnal hypoglycemia. In (Hovorka et al. (2010)), the system was tested in a clinical study with children and adolescents. Earlier version of this MPC algorithm was tested in previous clinical study to evaluate its control and prediction performance during fasting conditions (Shaller et al. (2006)). An automated closed-loop insulin delivery system was tested in a multinational clinical trial (Bruttomesso et al. (2009); Clarke et al. (2009)). The system used a personalized MPC algorithm developed in (Magni et al. (2007)). The system was developed completely *in-silico* and then tested in the clinical trial.
The studies concluded that the MPC algorithm is well suited for glucose control under fasting and overnight conditions in T1DM patients. The studies showed that the artificial pancreas is superior to open-loop control in preventing overnight hypoglycemia where significant

reduction in overnight hypoglycemia episodes was observed with closed-loop control in comparison with standard therapy. Also, during closed-loop period, the blood glucose level was within the target glycemic range for a longer time period, and the frequency of low glucose values was reduced.

2.2 Hypoglycemia alarm systems

Beside control algorithms, several algorithms for hypoglycemia detection and prediction are proposed as alarm systems to avoid hypoglycemia. The progress in CGM systems has made it possible to develop such real-time algorithms to reduce the hypoglycemic risk. These algorithms can be used to detect occurring hypoglycemia or warn about a pending hypoglycemic episode. The algorithms are based mainly on a combination of CGM data and a set of defined threshold of glucose and glucose rate of change. Different estimation and prediction approaches (e.g. linear and statistical prediction, Kalman filter optimal estimation, time series, etc.) have been proposed to develop these algorithms (Buckingham et al. (2009); Cameron et al. (2008); Hughes et al. (2010); Palerm et al. (2005); Sparacino et al. (2007)). Nguyen et al. (2009) used a specialized sensor (*Hypoglycemia monitor*) for nocturnal hypoglycemia detection, based on bayesian neural networks approach. The sensor measures specific physiological parameters continuously trying to detect the hypoglycemic events. In Skladnev et al. (2010), a data fusion approach was used to enhance the hypoglycemia alarm of CGM systems. The CGM information (data and alarms) was fused with autonomic nervous system responses that were detected by the specialized *Hypoglycemia monitor*. The data fusion method was able to improve nocturnal hypoglycemia alarms, and reduced the number of undetected hypoglycemic events.

Hypoglycemia prediction/detection algorithms are usually coupled with specific supporting actions to improve their efficiency in preventing hypoglycemia. Different actions have been proposed, such as gradual insulin attenuation (Hughes et al. (2010)), pump suspension (Buckingham et al. (2009); Lee & Bequette (2009)), glucose infusion (Choleau et al. (2002)), and audible (Buckingham et al. (2009); Weinzimer et al. (2008)) or visual (Hughes et al. (2010)) alarms to alert the patient about actual or impending hypoglycemia. The statistical and linear hypoglycemia predictors with pump suspension algorithm proposed in (Buckingham et al. (2009)) were used in a clinical study, and proved to be effective in preventing hypoglycemia without provoking rebound hyperglycemia after the suspension of the pump.

3. Hypoglycemia prevention by control algorithm improvement

To improve the performance of the closed-loop system, and significantly reduce the risk of hypoglycemia, the control system of the artificial pancreas can be augmented with different control techniques. Such techniques can be introduced either by modifying the controller structure (i.e. internal), or by implementing the additional technique separately (i.e. external component). The increased cost or complexity that could be added to the system by incorporating such techniques can be justified by the improved performance of the system in dealing with life-threatening hypoglycemia. Both external and internal techniques have been tested and proved to provide satisfactory results, and to outperform the stand-alone closed-loop controllers.

3.1 Model predictive control

Several studies have concluded that model predictive control (widely known as MPC) is expected to be the core of closed-loop control algorithm in the near future artificial pancreas.

Therefore, MPC is discussed in some details in this chapter. MPC is a control strategy that has developed considerably over the past few decades. Basically, MPC is based on a model of the system to be controlled. The model is used to predict the future system outputs, based on the past and current values and on the proposed optimal future control actions. These actions are calculated by optimizing a cost function where the future tracking error is considered, as well as the system constraints if any (Maciejowski (2002)). MPC employs a receding horizon strategy; repeated displacement of the time horizon, while only applying the first control signal in the calculated sequence at each time step, with the rest of the sequence being discarded.
MPC has many virtues that make it a competitive candidate for the blood glucose control problem: (1) The prediction nature of MPC allows for anticipatory and careful insulin delivery to avoid large fluctuations in glucose levels. Such feature is important for avoiding overdosing and hypoglycemic risk. (2) The ability of MPC to handle constraints on system inputs and outputs is a major advantage of MPC over other control strategies. These constraints are very critical when dealing with the human body, and allow to satisfy hardware specifications of the insulin pump. (3) The applicability of MPC to systems with time delays can be useful to overcome the physiological and technological delays associated with the subcutaneous route. (4) MPC allows the introduction of feedforward control action to compensate for known sources of disturbance affecting the system, such as meal intake. These advantages of MPC over other control strategies have promoted the use of MPC in the field of insulin delivery. Different MPC schemes are being used in artificial pancreas research, where the applicability of such control strategy has been demonstrated in *in-silico* studies (see for instance (Abu-Rmileh et al., 2010a; Dua et al., 2009; Grosman et al., 2010; Hovorka et al., 2004; Lee & Bequette, 2009; Magni et al., 2007; Parker et al., 1999)), and clinical trials as mentioned earlier.

3.2 Unequal penalization

Closed-loop control schemes can be designed so that unequal penalties are used upon hyperglycemia and hypoglycemia. The reason for such unequal penalties is that in diabetes therapy, the performance requirement of a controller has asymmetric nature, as hypoglycemic events are much less tolerable than hyperglycemia. Since hypoglycemia is believed to be more life-threatening in the short term, the control algorithm should be more aggressive in avoiding hypoglycemic episodes than in correcting hyperglycemic events.
MPC is one control strategy that permits to incorporate this kind of unequal penalization. To achieve such requirements of asymmetrical response, an asymmetric cost function is used in the optimization algorithm in MPC. The asymmetric cost function imposes different weight on hypoglycemia than on hyperglycemia, in contrast to conventional cost functions that impose the same weight on hypoglycemic and hyperglycemic events. As stated before, MPC calculates the insulin control action u_k, by optimizing a quadratic cost function, penalizing predicted output deviations and control signal along some prediction horizons. The asymmetric cost function has the form:

$$\min_{\Delta u} J = \sum_{j=1}^{N_p} \|w^y(\hat{y}(k+j|k) - r(k+j))\|^2 + \sum_{j=1}^{N_u} \|w^{\Delta u}(\Delta u(k+j|k)\|^2 + q\varepsilon^2 \quad (1)$$

Subject to the following constraints:

$$\begin{aligned} u_{min} \leq u_k \leq u_{max} \\ \Delta u_{min} \leq \Delta u_k \leq \Delta u_{max} \\ y_{min} - \varepsilon\Phi_{min} \leq y_k \leq y_{max} + \varepsilon\Phi_{max} \end{aligned} \tag{2}$$

where $\hat{y}(k+j|k)$ is the j-step prediction of the output on data up to instant k, $r(k+j)$ is the target glucose level, Δu is the insulin input increment, N_p and N_u are the prediction and control horizons, and $w^{\Delta u}$, w^y are weights on the insulin increments and the error between $y(k)$ and $r(k)$ respectively, ε is a slack variable used for output constraints softening (to avoid infeasibility problems in the optimization), q is the weight on the slack variable ε, $u_{min/max}$, $\Delta u_{min/max}$ and $y_{min/max}$ are the constraints imposed on the input, input increments, and output respectively, and Φ_{min}, Φ_{max} are the relaxation variables.

The cost function in equation (1) is asymmetric in the sense that the lower and upper output constraints are subjected to unequal relaxation bands and therefore, the constraints have different levels of softness. The unequal softness levels could be achieved by introducing the nonnegative relaxation variables Φ_{min}, Φ_{max} which represent the concern for relaxing the corresponding constraint; the larger Φ, the softer the constraint. MPC with asymmetric cost function was tested with different diabetic patient models, and showed an excellent ability to minimize the hypoglycemic events, especially in postprandial period (Abu-Rmileh & Garcia-Gabin (2010a;b); Kirchsteiger & Del Re (2009)). Kirchsteiger & Del Re (2009) give a comparison between symmetric and asymmetric cost function MPC's, where the latter shows superior performance in avoiding hypoglycemia.

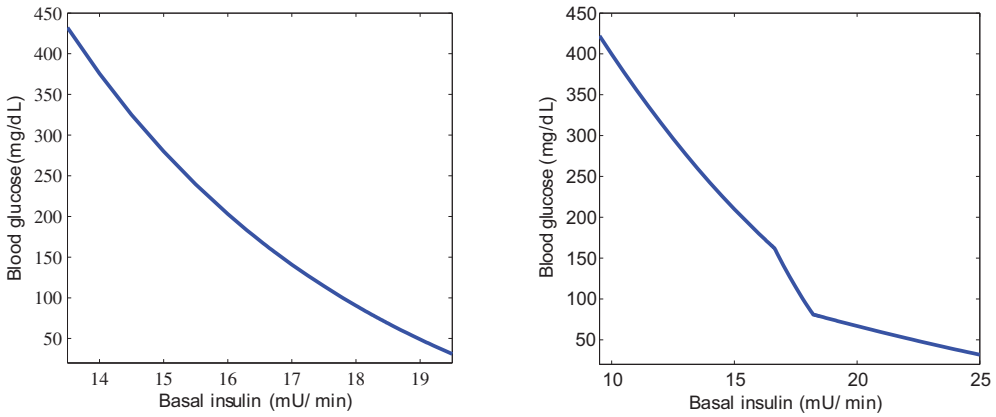
In Dua et al. (2009), a multi-programming MPC is used, and provided with different techniques to avoid hypoglycemia. In the multi-programming approach, the optimization problem in MPC is solved by searching for optimal solution within some valid regions (search regions) defined by the constraints and the parameters of the cost function. The main advantage of the multi-parametric MPC is that it provides the same performance as traditional MPC with lower computational load. The controller is provided with asymmetric cost function, and higher priority is given to the satisfaction of constraints imposed on hypoglycemia. Another type of asymmetric performance is presented in Grosman et al. (2010) to minimize the undesirable hypoglycemic and hyperglycemic events. The proposed MPC uses a glycemic zone rather than a fixed glucose level as a target (Zone-MPC). Three different zones are defined (permitted, lower, and upper zones), where the control objective is adjusting the insulin input to maintain glucose level within the permitted zone.

3.3 Gain scheduling

Gain scheduling (GS) is a well-known technique for controlling nonlinear systems by linear controllers. Briefly, GS is one of the simplest forms of adaptive control that employs different control structures in the different operating ranges of the nonlinear system. In glucose control, GS was inspired from the natural pancreas where the level of insulin activity varies between different glycemic ranges; being dominant in the hyperglycemic range, in balance with glucagon action in normoglycemia, and almost inactive in the hypoglycemic range where glucagon is dominant.

From an engineering perspective, a simple nonlinearity test (e.g. steady state insulin-glucose relationship) can be used to show that insulin has a nonlinear effect on blood glucose in different glycemic ranges (see Figure 2). Linear control algorithms are intended to control

linear systems, and they usually offer poor results when used to control nonlinear systems in regions far from where the linear model used was obtained. Therefore, nonlinear control or multiple linear controllers should be applied to handle each glycemic range separately and mimic the natural pancreas secretions. The use of multiple linear controllers by gain scheduling approach is discussed here, while nonlinear control is addressed later in this chapter.



(a) Smooth nonlinearity (*Meal model*) (b) Strong nonlinearity (*Hovorka model*)

Fig. 2. Nonlinear steady-state insulin-glucose behavior in different models of diabetic patients

The idea behind using the GS strategy in artificial pancreas is to use multiple linear controllers to deal with the system nonlinear behavior and maintain the ability of handling each glycemic range separately according to its dynamics. Since most of the closed-loop control strategies use insulin only, the control algorithm should provide the different levels of insulin activity in different glycemic ranges by employing the GS technique. GS scheme requires the assignation of scheduling parameters that can be used to select the suitable linear controller for each range. The GS strategy overcomes the limitations of the linear control approach which is only valid in the neighborhood of a single operating point, and provides a performance similar to nonlinear controllers with lower complexity.
A simplified diagram of the GS control is shown in Figure 3. As it can be seen in the figure, the measured glucose level is used as a scheduling variable, and also delivered to the controllers box as feedback signal. The controllers receive the desired glucose level (glucose target) to calculate the required insulin based on the difference between target glucose and CGM measurements, and the glycemic range defined by the GS selection. A control approach combining linear MPC with GS was tested in (Abu-Rmileh & Garcia-Gabin (2010a;b)), and proved to enhance the performance of the closed-loop controller in avoiding hypoglycemia.

3.4 Meal announcement

Regulation of blood glucose level after a meal is one of the main challenges for the fully developed artificial pancreas. Meals usually lead to a significant glucose flux into the blood stream. If feedback control is used to eliminate the meal effect, the controller reacts only after a rise in glucose has occurred and been detected by the CGM sensor. Elevated glucose level can lead to insulin overdosing, resulting in postprandial hypoglycemia (Steil et al. (2006)).

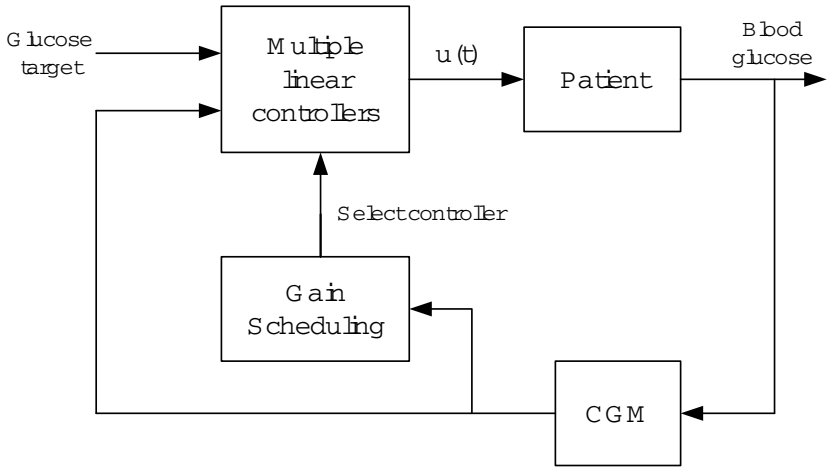


Fig. 3. Gain scheduling control scheme; the CGM output is delivered to the controllers box as a feedback signal, and to GS to select the controller to be used.

To avoid the limitation of purely reactive feedback control action and improve the controller response against meal effect, feedforward control (i.e. meal announcement) can be used. Feedforward is a well-known control technique used to eliminate the disturbance effect when the source of disturbance can be measured. In blood glucose control, the meal intake can be viewed as a known source of disturbance, and feedforward control can be used for meal announcement. In case information is given to the artificial pancreas system about the upcoming meal (size and time), a feedforward scheme may be implemented to deliver additional meal-time insulin bolus (Figure 1).
For the design of the feedforward controller, the effect of meal on blood glucose level should be modeled. The system model (insulin-glucose) in the feedforward element describes or predicts how each change in insulin will affect glucose, while the disturbance model (meal-glucose) is used to describe or predict how each change in meal will affect glucose. Let G_s and G_d be the system and disturbance models respectively, the feedforward control u_{ff} is calculated as:

$$u_{ff} = -\frac{G_d}{G_s} \times Meal \tag{3}$$

Feedforward controllers can range from simple scaling multipliers (static feedforward) to sophisticated differential equations (dynamic feedforward). Dynamic models give a better description of actual system and disturbance behaviors, often achieving improved disturbance rejection performance. However, the dynamic feedforward can be difficult to obtain and implement. In specific control algorithms such as MPC, the feedforward control signal can be calculated by the controller itself rather than using a separate feedforward controller. If the meal effect is included in the prediction model of the MPC, the controller predicts the future glucose levels as a function of insulin-glucose dynamics, CGM measurements, and meal information. Consequently, the meal effect on blood glucose will be considered in calculating the future insulin dose (i.e. predictive feedforward). In this controller configuration, the insulin dose has two parts: feedback insulin delivered in fasting conditions, and feedforward insulin bolus used at meal time to obtain better meal compensation.

The different configurations of feedforward (static, dynamic, and predictive) are being used in the artificial pancreas research, and their feasibility in improving the overall controller performance has been demonstrated in different clinical and simulation studies (Abu-Rmileh & Garcia-Gabin (2010a;b); Abu-Rmileh et al. (2010b); Lee & Bequette (2009); Marchetti et al. (2008); Weinzimer et al. (2008)). Since the feedforward action starts to deliver insulin before the meal effect appears in the CGM feedback loop, lower fluctuations in glucose levels are observed, with higher percentage of time within the acceptable glycemic range. An example of the improved performance achieved with feedforward control is shown in Figure 4. Finally, it should be mentioned that meal announcement must be done carefully, since an excess of insulin or badly-timed bolus may induce undesirable hypoglycemia episodes.

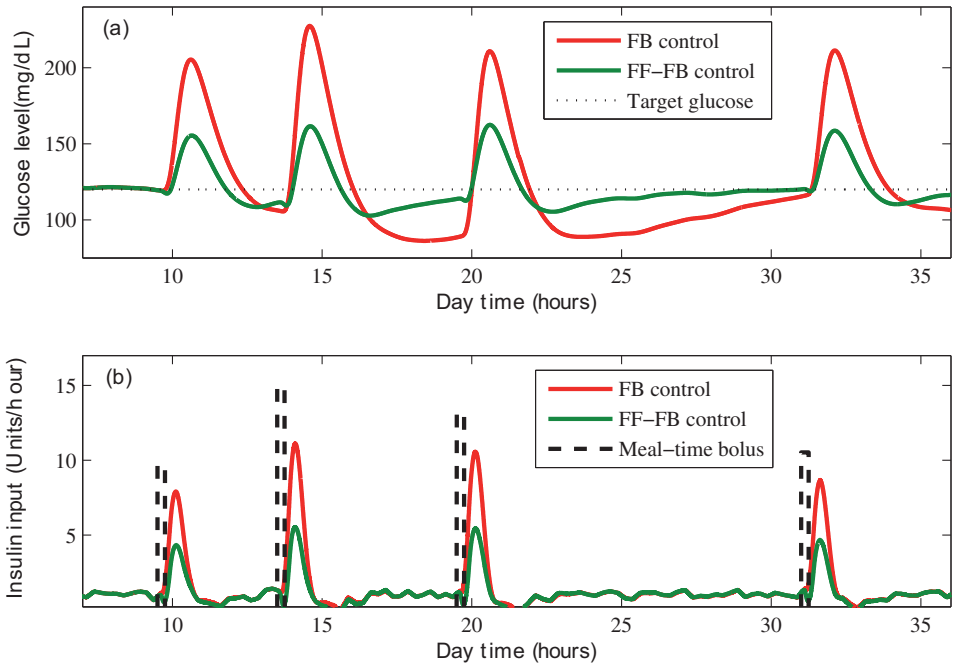


Fig. 4. Feedback (FB) vs. feedforward-feedback (FF-FB) control performance, (a) glucose level (b) insulin input

3.5 Meal detection

Beside feedback and feedforward control, meal detection techniques can be used to deal with meal challenge. Although feedforward-feedback control achieves better results than feedback alone, it is not uncommon that patients forget to announce upcoming meals. Therefore, a system for meal compensation that does not require information from the patient, would be preferable. The CGM measurements along with a set of thresholds on glucose levels and glucose rates of change (i.e. first and second derivative), can be used to build meal detection/compensation algorithms. When a meal is detected, the algorithm can be used to initiate extra meal-time insulin dose, or to activate an alarm for the patient. The meal-time dose can be delivered as insulin bolus or micro boluses, or a gain scheduling scheme can be used to adjust the controller output when a meal is detected. Meal detection and CGM-activated insulin dose remove the need for patient's interventions, and make the closed-loop artificial pancreas fully automatic. Meal detection algorithms also reduce the

hypoglycemic risk produced by erroneous insulin bolus or skipped meal, which may occur in the case of feedforward meal announcement.
Three main types of meal detection algorithms currently exist. A voting scheme is used in (Dassau et al. (2008)) to detect meals based on a combination of four different methods for calculating glucose rates of change. Another algorithm is proposed in (Lee & Bequette (2009); Lee et al. (2009)), where the meal detection algorithm is developed by using a finite impulse response filter and a set of threshold values. The algorithm estimates the meal size at the time of detection. Since the main objective of the development of meal detection algorithms is the application to closed-loop artificial pancreas, Lee & Bequette (2009) tested the design algorithm in combination with a MPC closed-loop controller, and demonstrated that meal detection strategy is efficient and outperforms the stand-alone feedback control scheme. Cameron et al. (2009) presented a probabilistic and evolving algorithm to detect the meal and predict its shape, and to estimate the total appearance of glucose from the meal. The algorithm has proved to enhance the meal-compensation ability of the feedback controller.

3.6 Time delay compensation

It is well-known that the time delay in the subcutaneous route is a major challenge in the development of the artificial pancreas (Hovorka (2006)). Both physiological and technological delays exist in glucose sensing and insulin delivery. Such time delays can result in poorly controlled glucose since hypoglycemia can be induced and remains undetected for a significant time period. In an attempt to eliminate or minimize the effect of time delay, closed-loop control structures with time-delay compensation features can be used to improve the control outputs and reduce the hypoglycemic risk produced by physiological and technological delays.
Smith predictor structure is a control scheme that presents good properties in controlling systems with long time delay. The idea behind Smith predictor is to incorporate the system model within the closed-loop control structure (i.e. the system model becomes an explicit part of the controller). Thus, the design of Smith predictor scheme requires a model of the system dynamics and an estimate of the system time delay t_0. In the Smith predictor scheme, there are two parallel paths for the control signal $u(t)$ (see Figure 5); one passing through the real system (the patient), and one passing through the model of the system G_s. The function of the parallel path containing the model is to generate the difference $e_m(t)$ between the actual system output $y(t)$ and a model-based prediction of the control signal effect on the system output $y_m(t)$. The Smith predictor uses the model to predict the delay-free response of the system $y_m^-(t)$. Then, it compares this prediction to the target glucose level $r(t)$ to decide what control actions are needed. To avoid drifting and reject external disturbances, the Smith predictor also compares the actual system output with a prediction that takes the time delay into account. The error $e_m(t)$ contributes to the overall error signal $e(t)$ delivered to the feedback controller.
The Smith predictor structure has been recently used in artificial pancreas studies (Abu-Rmileh et al. (2010a;b)). With an initial estimation of the time delay, the Smith predictor shows the ability to minimize the effect of time delays and the associated risk of hypoglycemia, and to enhance the controller performance. As mentioned before, the MPC strategy, which has been extensively studied in artificial pancreas applications, is another competitive control algorithm with inherited ability to deal with system time delays (Hovorka (2006)).

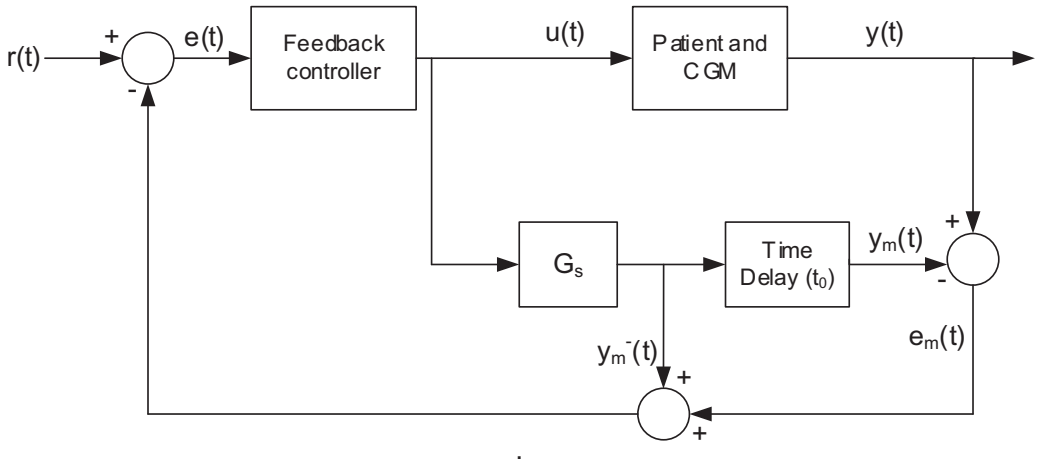


Fig. 5. Smith predictor control structure for time-delay compensation

3.7 Insulin on board and insulin feedback

As discussed previously, the use of subcutaneous route faces a challenging problem represented by the delayed insulin action. The effect of subcutaneous insulin may remain active over an extended time period (3-5 hours) after administration. Insulin on board (IOB) is a term used to describe how much insulin is still active from previous doses. Modern insulin pumps include the IOB option that helps in calculating the next required insulin dose. Therefore, IOB curves (time-action profiles) can be used in the development of artificial pancreas control algorithms to consider the effect of previous insulin, and provide a type of safety measure to avoid the problem of overdosing and the associated hypoglycemia. Ellingsen et al. (2009) developed a MPC scheme with IOB constraints. The IOB was used as dynamic safety constraints with a set of curves, to account for the time profile of delayed insulin action. Lee et al. (2009) used the IOB safety constraints in an integrated control scheme for the artificial pancreas that includes MPC strategy, meal detection algorithm, IOB constraints, and pump suspension option to avoid hypoglycemia.

Another technique used to reduce insulin infusion is the *insulin feedback*, initially introduced by Steil et al. (2004). The algorithm aims at reproducing as close as possible the insulin secretion from the natural pancreas. The idea behind this technique is to consider that a part of previous insulin is still active, and can cause further reduction in glucose level. Based on a pharmacokinetic model (Steil et al. (2006)), the algorithm estimates the plasma insulin level, and reduces the output of a proportional-integration-derivative (PID) controller by using the insulin feedback term, that is proportional to the estimated plasma insulin. Different versions of the algorithm have been used in clinical studies (Steil et al. (2011; 2006); Weinzimer et al. (2008)). In a recent study (Steil et al. (2011)), the insulin feedback has been used to improve the PID controller response in avoiding hypoglycemia after breakfast, and has achieved the desired performance.

3.8 Nonlinear modeling and control

Since the effect of insulin is nonlinear across the different glycemic ranges, the use of nonlinear models able to describe this nonlinear behavior would facilitate the design of more robust nonlinear control strategies, to handle the difference between glycemic ranges and their insulin requirements. Nonlinear models are more flexible in capturing complex behavior than the linear models, and consequently, the nonlinear control strategies are considered to be more suitable for this type of systems than linear control strategies. Therefore, nonlinear

control is believed to be more appropriate for the closed-loop artificial pancreas, and will enhance hypoglycemia prevention features of closed-loop systems due to its ability to provide particular insulin profile for each glycemic region. However, the identification of nonlinear models is still a challenging task in the artificial pancreas research. In order to be used in closed-loop control, such nonlinear model should be sufficiently accurate to capture the main system behavior and nonlinearity, while being relatively simple to be identified from the available data such as CGM measurements, and insulin and meal information.

Nonlinear control strategies like nonlinear MPC (NMPC) and sliding mode control (SMC), have shown superior performance over classical linear controllers in the blood glucose control problem. Most of the available MPC strategies are based on a linear model of the system. For systems that are highly nonlinear, the performance of a linear MPC can be poor. This has motivated the design of the NMPC, where a more accurate nonlinear model of the system is used for prediction and optimization. NMPC has been used in a number of artificial pancreas studies (Hovorka et al. (2010; 2004); Schlotthauer et al. (2005); Trajanoski & Wach (1998)).

SMC is a nonlinear robust procedure to synthesize controllers for linear and nonlinear systems. The design of SMC algorithm includes two main steps. 1) Choosing a switching (sliding) surface, along which the system can slide to its desired final value. The sliding surface is designed so that it describes the desired system dynamics. The sliding surface divides the phase plane into regions where the switching function has different signs. 2) By using appropriate control law: make the system reach the switching surface *(reaching phase)*, and keep it on the surface *(sliding phase)*. The structure of the controller is intentionally altered as its state crosses the surface in accordance with a prescribed control law. SMC exhibits good robustness against parameter variations, modeling errors and disturbances.

SMC algorithms have been employed successfully in different *in-silico* studies of artificial pancreas (Abu-Rmileh et al. (2010a;b); Kaveh & Shtessel (2008)). The combination between SMC and Smith predictor used in (Abu-Rmileh et al. (2010a;b)) is simple in its formulation and implementation, yet has some good features such as accuracy and robustness, insensitivity to internal and external disturbances, time-delay compensation and finite time convergence. These features make the proposed control algorithm suitable for the blood glucose problem which incorporates many sources of uncertainty and disturbances, and imposes some specific time requirements to avoid hypoglycemia and extended hyperglycemia. Other nonlinear control and modeling techniques have been used in the artificial pancreas research. Brief descriptions of frequently used approaches are given here, while comprehensive reviews are provided in Bequette (2005); Chee & Fernando (2007); El-Youssef et al. (2009); Takahashi et al. (2008)).

As mentioned before, the glucoregulatory system is nonlinear and difficult to model mathematically. Therefore, empirically-based and model-free control techniques such as fuzzy and neural network systems would be key components in artificial pancreas control systems. Fuzzy systems are based on the idea that input-output relationships are not crisp, but can change gradually from one state to the next, and partial membership rather than crisp membership can be used to adjust the control action. Fuzzy logic control takes the input variables and maps them into fuzzy levels by sets of membership functions. Each input variable has determined value's degree of membership in a fuzzy set. The process of converting crisp input values to fuzzy values is called *fuzzification*. The fuzzy controller makes decisions for what action to take based on a set of rules. The set of rules are built generally based on expert knowledge. The input signal is processed applying the corresponding rules and generating a result for each, then combining the results of these rules. Finally, the fuzzy

controller output is obtained via *defuzzification* combining result back into a specific crisp control output value. Different fuzzy control schemes have been implemented in artificial pancreas studies (see for example Atlas et al. (2010); Campos-Delgado et al. (2006); Ibbini (2006); Ibbini & Massadeh (2005)). In Atlas et al. (2010), a personalized fuzzy logic controller has been validated clinically, and proved to minimize hyperglycemic peaks while preventing hypoglycemia.

Neural networks are modeling techniques that result in a nonlinear model based on experimental data. It is a black-box model organized in sequential layers containing neurons. The network output is obtained as a weighted sum of inputs through the hidden layers. The weights are found during a training process by minimizing the error between desired and network output. Neural networks show excellent adaptation and learning ability. Neural networks deal with the blood glucose problem without explicit description of the exact model of the insulin-glucose system. Such approach is very useful in irregular situations (e.g. patients have a disease or abnormal conditions) that limit the usability of normal models (Takahashi et al. (2008)). Neural networks have been used to obtain insulin-glucose models for the design of nonlinear closed-loop controllers (El-Jabali (2005); Schlotthauer et al. (2005); Takahashi et al. (2008); Trajanoski & Wach (1998)). A combination between fuzzy logic and neural network (neuro-fuzzy) control strategy was applied by Dazzi et al. (2001) in clinics, and proved to provide superior glycemic control compared to conventional algorithms, with hypoglycemic events reduced to half.

Adaptive control is another approach used for glucose regulation. The complexity of glucose control mechanism highlights the need for an adaptive control algorithm to compensate for variations in patient dynamics (e.g. time-varying insulin sensitivity, stress and physical exercise) or disturbances by adapting the controller and model parameters to the changing patient conditions (Eren-Oruklu et al. (2009a); Hovorka (2005)). Adaptive control includes several configurations that allow not only outputs of the controller to be changed over time, but also the method by which those outputs are generated; the controller continuously monitors its own adaptation through a defined metric, and is capable of altering its own control scheme to better meet the adaptation criterion. For blood glucose control, different adaptation schemes have been employed (Chee & Fernando (2007)), in systems that use the sensor measurements to track the changes in glucose dynamics and update the controller structure to assign the required insulin regime. In model-based adaptive control, patient model is used to predict future glucose levels based on current and past insulin infusions. The model parameters are continuously updated and used in the control algorithm to calculate the required insulin. Adaptive control strategies have the ability to individualize the control scheme and/or patient model to represent the inter- and intra-patient variability. Adaptive schemes have achieved safe control while avoiding hypoglycemia in spite of all the challenges facing the closed-loop artificial pancreas (Eren-Oruklu et al. (2009a); Shaller et al. (2006)).

4. Conclusions

Closed-loop insulin delivery by the artificial pancreas gives hope to achieve tight glycemic control in T1DM by reducing the risk of hypoglycemia while solving the problem of hyperglycemia. The prevention of life-threatening hypoglycemia is considered as a possible goal for the first generation of the artificial pancreas before reaching the fully developed device that mimics the function of natural pancreas in night, fasting and prandial conditions. The closed-loop system can be subjected to different modifications to implement control techniques that reduce the risk of hypoglycemia. The feasibility of some of these techniques

has been tested and proved to improve the performance of the closed-loop control and reduce the hypoglycemia episodes. Other techniques are still under study.

While partial results obtained in different artificial pancreas studies are promising, several aspects regarding the fully developed artificial pancreas are still open, and further improvements are needed. Obtaining models from patient's input-output data using advanced modeling techniques is recommended for blood glucose control. Nonlinear identification of insulin-glucose models for control is desirable. Development of advanced control techniques is needed due to the nonlinear behavior, unmodeled disturbances, delay and inaccuracy in measurements, together with modeling errors and patient variability.

Another required improvement is the modeling of different meal contents, since most of the available models are restricted to carbohydrates effect. Using multiple variable control (i.e. considering insulin, glucagon, exercise, stress, etc.), and incorporating the effect of insulin sensitivity change during the day in the control algorithm design, would increase the reliability of models in representing the real conditions of the diabetic patient, and consequently, improve the overall performance of the designed artificial pancreas.

Although the nonlinearity in the insulin-glucose system is quite obvious, the available hypoglycemia detection and prediction algorithms do not consider the nonlinear nature of the system through the different glycemic ranges (Chan et al. (2010)). Taking into account the nonlinearity of the system would be a possible way to enhance the performance of the algorithms and increase their effectiveness in preventing hypoglycemia (Chan et al. (2010)). The inclusion of IOB effect in predicting future hypoglycemic episodes could be another technique to improve the feasibility of these algorithms (Buckingham et al. (2009)). Finally, improving the accuracy and reliability of CGM systems is an essential task, since both control algorithms and hypoglycemia alarms depend widely on CGM measurements. Poorly functioning sensor increases the risk of system-induced and undetected hypoglycemia, while accurate sensor improves the control quality and reduces the risk.

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Chapter 10

Publication 7: Detection and Prevention of Hypoglycemia in Automated Insulin Delivery Systems for Type 1 Diabetes Patients

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Abstract

This chapter presents some key techniques that proved to be efficient in reducing the risk of hypoglycemia in automated insulin-delivery systems used in type 1 diabetes therapy. The insulin therapy of type 1 diabetes has as major drawback, namely the increased risk of drug-induced hypoglycemia, with all of its complications. Therefore, hypoglycemia is considered as one of the main challenges in the treatment of the disease. The artificial pancreas brings hope to achieve better glycemic control, reduce the occurrence of hypo- and hyperglycemia, and avoid the complications of diabetes and insulin therapy. Different techniques can be integrated within the structure of the artificial pancreas to improve the performance of the system, and significantly reduce the risk of hypoglycemia. The current chapter discusses five major techniques that can be used in integrated artificial pancreas systems, to detect and prevent the life-threatening hypoglycemia and its consequences. These techniques include: hypoglycemia alarms,asymmetric penalization in control, insulin-on-board (IOB) constraints, insulin feedback, and meal detection algorithms. Different configurations of these techniques have been tested in the artificial pancreas research, and proved to provide satisfactory results in predicting and preventing hypoglycemia. The chapter first briefly introduces the idea of the artificial pancreas, then, the hypoglycemia detection and prevention techniques are discussed in detail.

Part III

Discussion and Conclusions

Chapter 11

General Discussion

The increasing number of patients with diabetes makes it one of the major health problems worldwide. Blood glucose regulation in type 1 diabetes is still a challenging biomedical engineering problem. Patients are extremely diverse in their dynamics, and in addition, their characteristics are time-varying. Inter- and intra-patient variability, nonlinearity of the physiological system, modeling errors and mismatch between the models used to develop the control algorithms and the real patients, as well as the limitations of the subcutaneous route used for glucose sensing and insulin delivery (e.g. physiological delays and subcutaneous tissues dynamics), make it very difficult to find a general and reliable solution to the nonlinear problem of glycemic control.

With the inability of conventional therapy to achieve satisfactory glycemic control, and the development in continuous glucose monitoring (CGM) systems and the increasing use of insulin pumps, the idea of developing an artificial pancreas is viewed as the ideal solution for glycemic control in T1DM [7, 13, 86]. The artificial pancreas is an automated closed-loop system that maintains blood glucose levels within the desired range and prevents hypoglycemia, while minimizing or eliminating the need for patient intervention. The artificial pancreas replaces the β-cells functions in glucose sensing and insulin delivery. It consists of three main components: a glucose sensor to measure glucose concentration, a pump for insulin delivery, and a closed-loop control algorithm to bridge between the glucose measurements and the dose of insulin to be delivered.

Closed-loop control of blood glucose has been a subject of continuous research for more

than 40 years, however, till now no commercially available product does exist. The continuous subcutaneous insulin infusion (CSII) pumps are being widely used, and a number of CGM systems have received regulatory approval [13]. Although the sensors and pumps systems still have some limitations, their use in an open-loop combination resulted in better clinical outcomes over conventional injections therapy [3, 13, 23]. Thus, the primary limitations in the progress of such an artificial pancreas are the development of advanced robust closed-loop control algorithms, and the availability of reliable and precise glucose sensors. However, recent research in the development of the artificial pancreas suggests that types of the automatic glucose control system are likely to come to market in the near future.

This thesis presented control strategies for the closed-loop artificial pancreas, which are based on Model Predictive Control and Sliding Mode Control. The proposed control strategies adopted the subcutaneous route for glucose monitoring and insulin delivery. Each of the control strategies combined more than one linear/nonlinear control and modeling approaches in one structure, in an attempt to make use of the virtues of each approach while reducing the effects of their drawbacks. The control algorithms have been tested and validated in simulations, where two mathematical models have been used to represent the diabetic patients. Different scenarios, such as the presence of meal disturbance, inter-patient and intra-patient variability, time-delay and sensor errors, have been considered to study the performance of the developed control strategies.

In Chapters 4 and 5, a first control scheme for closed-loop regulation of blood glucose was presented. A model-based predictive control strategy with a gain scheduling scheme was developed and tested with virtual diabetic patients. The control algorithm tackled the problem of patient nonlinearity by using multiple linear models/controllers to handle the difference between glycemic ranges. Although the proposed control scheme applies a well-known control strategy (linear MPC), it is provided with additional features that give it advantage over other approaches commonly used in controlling the nonlinear patient [28, 87]. These features are mainly the gain scheduling technique, the asymmetric cost function, and the incorporation of meal information in the prediction model to calculate the feedforward insulin dose. The control algorithm is provided with the gain scheduling scheme, which selects between the different linear controllers, to improve the controller performance in controlling the nonlinear system. The asymmetric

cost function is used in the optimization problem to reduce the hypoglycemic risk [87], and the feedforward control loop is implemented to improve the meal compensation features and to avoid high glycemic levels in the postprandial conditions.

In Chapter 4, the model predictive control algorithm with gain scheduling, GS-MPC, was applied to the blood glucose control problem in T1DM using the Dalla-Man model, implemented in the UVa simulator, as a (virtual) diabetic patient under test. The designed controller is evaluated *in silico*; simulations with virtual diabetic subjects are used to test and tune the controller. The 10 adults in the UVa simulator are considered for controller testing and validation. In Chapter 5 the idea of GS-MPC (also named as MMPC) was applied to the Hovorka virtual patients. The Hovorka patient model shows a stronger nonlinear steady-state behavior than the UVa patients (see Figure 2 in Chapter 9 - page 113). The main sources of such nonlinearity are the saturation (activation/deactivation) behavior of some model parameters, and the insulin actions [55]. The stronger nonlinear nature of the Hovorka patient indicates that it would be difficult to achieve good control properties by a simple linear controller. A linear model-based controller with a single linearized model is expected to perform well only in the neighborhood of the linearization point (i.e. in a specific operating range). However, the performance of such a controller will degrade considerably in other operating ranges where the nonlinear system exhibits different dynamics. Thus, the use of the gain scheduling MPC with multiple linear models is believed to be even more justifiable in the case of the Hovorka virtual patient.

To apply the linear GS-MPC to the nonlinear Dalla-Man and Hovorka patients, linearized 'approximations' of the nonlinear patient models in Chapter 3 were obtained in the different glycemic ranges. The obtained linearized models were used to design the family of the MPC controllers. The gain scheduling scheme was used to choose among the three controllers depending on the measured glucose level. The applicability and the performance of the proposed control scheme have been evaluated *in silico*. Several simulation scenarios with the virtual patients were used to test the proposed control algorithm. The obtained results show a good controller performance in the presence of different sources of disturbance and errors.

The prediction ability of the MPC, enforced by effects of the gain scheduling scheme and the asymmetric cost function, resulted in a good controller performance and 'adap-

tation' to different glucose ranges, so that neither hypoglycemic events nor elevated hyperglycemia have been observed during simulation, although big size meals have been used. A good level of robustness against meal over- and under- estimation errors has been demonstrated. Also, the GS-MPC controller has shown good performance against inter- and intra-patient variability and model-patient mismatch. In addition, while the GS-MPC has been driven by the CGM sensor, that can produce measurements errors up to 30 mg/dL, the controller has been able to nicely reject the effects of sensor errors. In order to validate the proposed GS-MPC controller under extreme conditions, the controller in Chapter 4 has been tested with a virtual patient that is represented by a mathematical model which is completely different from the one used during the controller design. The GS-MPC achieved good control, and maintained the Hovorka patient within the 70-180 mg/dL range, although the patient is represented by a model that is totally different from the one implemented in the GS-MPC (the linearized version of the Dalla-Man model).

Although the GS-MPC achieved good performance under different operating conditions, it is still difficult to personalize such a control strategy in practice, since it is based on a linearized version of the full nonlinear patient models. Models with large dimensions are difficult to obtain from the available patient data. Therefore, the practical use of such a control strategy will depend on the implementation of an average patient model obtained from a population of patients. Using a linearized or a nonlinear average patient to develop an efficient MPC and then apply it to a population of virtual patients, can work well in *in silico* tests as a first step in the development of the artificial pancreas control algorithm. But when applied to real patients, the results obtained with such an approach are not always satisfactory (see for example the results of the clinical trials in [45]). Also, the tuning parameters of the controller are not directly related to the patient model, which makes the controller tuning procedure difficult to perform. Therefore, there is a need for a control strategy that employs a reduced order model, and has a clear relation between controller and model parameters to facilitate the tuning of the controller. The use of reduced-order models requires the control strategy to be able to handle modeling errors (i.e. robust control algorithm); Chapters 6 and 7 addressed such an approach.

In Chapters 6 and 7, the use of sliding mode control in closed-loop glucose regulation was discussed. The chapters presented the design of the robust nonlinear sliding mode control algorithm, in a linear model-based scheme with time-delay compensation features. The rationale for this robust model-based approach is that it may provide a means to deal with different sources of errors and uncertainty that exist in the glucose control problem.

Chapter 6 considered the application of the proposed Smith predictor sliding mode control strategy (SP-SMC) to the Dalla-Man virtual patients in the UVa simulator, while Chapter 7 presented the design and testing of the SP-SMC control strategy with the Hovorka virtual patient. First and second order linear models were used to represent the patient (in the internal structure of the controllers), and to formulate the sliding mode control laws. A higher order model is used for the Hovorka patient because it has a higher order dynamics and shows a higher level of nonlinearity. According to SMC theory, the controller structure is based on the used model. Therefore, a different model order implies that the designed controller will be different. Also, the sliding surface used for the Hovorka patients is of higher order (second-order sliding surface instead of the first-order used for the UVa patient).

In order to test the SP-SMC controllers in realistic situations, sensor and meal announcement errors, intra- and inter-patient variability, patient-model mismatch, varying meal size and time, and variation in insulin sensitivity have been considered in the simulation scenarios. From the *in silico* tests, we observed that the SP-SMC achieves tight glycemic control with no hypoglycemic events. The ability of the SP-SMC strategy to deal robustly with the different sources of error and uncertainty in the simulation scenarios indicates that the controller would provide acceptable performance when dealing with other sources of disturbance, such as the influence of stress and physical activity on blood glucose, and the effect of meal contents other than carbohydrates (e.g., mixed meals).

It was shown that, in the ideal setting, when the feedforward control action is active, the SP-SMC outperforms the feedback-alone setting, with lower fluctuations in glucose levels and significantly lower risk of hypoglycemia. The SP-SMC algorithms achieved superior postprandial performance with the used of feedforward insulin, highlighting the limitations of purely reactive feedback control algorithms. The designed controllers

were able to handle large ($> \pm 25\%$) errors in the meal announcement without reaching the severe glycemic limits of 50 mg/dL and 280 mg/dL. From the simulation experiments, it could be observed that, with a good lower-order linear approximation of the nonlinear virtual patients, the SP-SMC strategy achieved tight glycemic control with no hypoglycemic events. In order to make the *in silico* trials as close as possible to realistic conditions, time varying insulin sensitivity has been considered in the case of the Hovorka patient. These sensitivity variations were ignored in the case of UVa patients, mainly due to the lack of flexibility of the used simulation environment.

The SP-SMC approach is a new control scheme to be applied in the closed-loop artificial pancreas. The SP-SMC strategy proposed in Chapters 6 and 7 is simple in its formulation and implementation, yet has several interesting features, such as: finite time convergence, robustness and accuracy, and insensitivity to internal and external disturbances. Another important feature of the proposed SP-SMC scheme is the direct relation between the controller structure and the model parameters; such explicit relation makes the tuning of the controller easier, a feature that is not common in other glucose control strategies (see for instance [39, 55, 58, 88]). Furthermore, the SP-SMC is a nonlinear controller that shows better performance with nonlinear systems than simple PID or linear MPC. These features of the SP-SMC strategy make it suitable for the glucose control problem which incorporates many sources of uncertainty and disturbance, and imposes some specific time requirements to avoid hypo- and hyperglycemia.

Still, the SP-SMC scheme need to be evaluated under more realistic conditions, where the parameters of the reduced-order model must be estimated from the available clinical data for each subject individually. Also, the controller performance in response to meal disturbance, containing other nutrients along with CHO, has to be studied. In this thesis, as in other works based on CHO metabolic models, such testing scenario is ignored due to the lack of suitable metabolic models.

Then, Chapter 8 was devoted to the use of nonlinear modeling approach for the design of the control algorithm in the artificial pancreas. The chapter showed how nonlinear control-oriented model might be used to improve the performance in the closed-loop regulation of blood glucose. In previous chapters, linear and nonlinear control strategies were applied to the glucose regulation problem in diabetes, where in both cases, linear

models (either obtained by linearization of the full nonlinear model or by identifying low-order process models) were used to design the model-based control strategies. The nonlinear behavior of the virtual patients has been handled either by using multiple linear controllers (as in the case of GS-MPC), or by designing a robust nonlinear controller that can handle significant levels of model-patient mismatch (as in the case of SP-SMC).

The inherent nonlinear behavior of the glucose regulation system motivated the move towards the nonlinear system identification framework in Chapter 8, to obtain a more accurate, nonlinear, control-oriented model. Furthermore, linear (model-based) controllers are intended to control linear systems, and they usually offer poor results when used to control nonlinear systems in regions far from where the used linear model was obtained. In this case, nonlinear models that are able to represent the system more accurately, could offer better controller performance. Therefore, the nonlinear modeling approach is adopted in Chapter 8. The nonlinear Wiener model was used as a novel modeling approach to be applied to the glucose control problem. The Wiener model was employed in the design of a robust Smith predictor sliding mode control (Wiener-based SP-SMC) strategy.

The structure of the nonlinear Wiener model, that includes the static nonlinearity, would facilitate the reduction of the control problem to a linear one by performing the inverse of the nonlinearity. Therefore, two configurations of the Wiener-based SP-SMC controller were developed and compared: a full nonlinear configuration and a linear configuration with static nonlinearity inversion. To explore their feasibility, the Wiener-based control algorithms were compared to linear model-based control schemes.

The Wiener-based control strategy is a novel nonlinear control approach in the closed-loop insulin delivery in T1DM, that combines sliding mode control, nonlinear Wiener model and Smith predictor structure. The static nonlinearity in Wiener model made it possible to represent the main nonlinear behavior of the insulin-glucose system in diabetic patients. The designed Wiener-based SP-SMC control strategies were evaluated *in silico* under different simulation conditions. The ability of the Wiener model to provide a very good approximation for the diabetic patients resulted in excellent closed-loop control performance. The nonlinear Wiener-SMC proved to be superior to the linear-SMC and linear-MPC in regulating the blood glucose levels. The features of the combined

SP-SMC structure (e.g. robustness, insensitivity to internal and external disturbances, finite time convergence, time-delay compensation and the use of reduced-order internal model), and the superior performance of the Wiener model in representing the virtual diabetic patient (compared to linear models) make the Wiener-based SP-SMC approach suitable for closed-loop glucose control in T1DM, where different sources of uncertainty, disturbance and nonlinearity should be handled by the control algorithm to achieve the desired glycemic control performance. The use of the Wiener model-based control strategies proved to be feasible, and the increased controller/model complexity was rewarding and justifiable, since the nonlinear model improved the quality of the control results. Subsequent improvements in the modeling and control results might be possible, by the identification of better approximations for the static nonlinearity (and its inverse) in the Wiener model.

Finally, Chapters 9 and 10 reviewed key techniques that proved to be efficient in reducing the risk of hypoglycemia in automated insulin-delivery systems used in T1DM therapy. The insulin therapy of type 1 diabetes has as major drawback, namely the increased risk of drug-induced hypoglycemia, with all of its complications. Therefore, hypoglycemia is considered as one of the main challenges in the treatment of the disease, and it continuously limits the achievement of tight glycemic control in T1DM [22]. Different techniques can be integrated within the structure of the artificial pancreas to improve the performance of the system, and significantly reduce the risk of hypoglycemia. Chapters 9 and 10 discussed major techniques that can be used in integrated artificial pancreas systems, to detect and prevent the life-threatening hypoglycemia and its consequences. These techniques include: insulin-on-board (IOB) constraints [46, 47], insulin feedback [36], meal detection algorithms [46, 48], hypoglycemia alarms [49, 50] and asymmetric penalization in control algorithms [42, 43, 87]. Different configurations of these techniques have been tested in the artificial pancreas research, and proved to provide satisfactory results in predicting and preventing hypoglycemia.

Chapters 9 and 10 also highlighted different aspects regarding the fully developed artificial pancreas that are still open, and where further improvements are needed. Among these topics exist: (1) the use of nonlinear data-driven modeling of diabetic patients, (2) studying the effect of different meal contents, (3) improving the accuracy and reliability of glucose sensors, (4) modeling the effect of factors other than meals and

insulin (e.g. glucagon, physical exercise, stress, variations in insulin sensitivity, etc.) in glucose regulation, (5) considering the nonlinearity of the physiological system to improve the effectiveness of hypoglycemia detection and prevention algorithms [89], and (6) the development of advanced control techniques that could deal with nonlinear behavior, unmodeled disturbances, delay and inaccuracy in measurements, together with modeling errors and patient variability.

Chapter 12

Conclusions and Future Work

12.1 Overview

Along the development of this thesis, work was devoted to model predictive control, sliding mode control, linear and nonlinear system identification methods and several aspects in the MATLAB programming to design a closed-loop control algorithm for the artificial pancreas in type 1 diabetes.

The main objective of the thesis was to design and validate advanced model-based control techniques for closed-loop regulation of blood glucose in type 1 diabetes. The proposed Model Predictive Control (MPC) and Sliding Mode Control (SMC) strategies, have been applied to complex nonlinear mathematical models that represent the physiological glucose regulation system in diabetic patients. Each of the designed control algorithms consisted of a combination of two control techniques; MPC is used in a gain scheduling scheme to deal with system nonlinearity, while SMC is combined with the Smith predictor structure to reduce the effect of system time-delay. The idea behind such 'combined' approaches was to make the control strategies more suitable for biomedical systems. Linear and nonlinear models have been used in the design of the model-based control algorithms.

Since obtaining an accurate model is an essential step for the design of model-based control, the thesis also addressed related problems, such as: (1) testing the quality and reliability of the linear modeling framework, that is frequently used in closed-loop glu-

cose regulation. It was shown that linear models are not able to reliably represent the nonlinear behavior of the glucose regulation system in the patient under wide operating conditions. Such observation should be taken into account in subsequent design steps in order to avoid the risk of model and control algorithm failure. (2) Application of nonlinear system identification techniques for the identification of control-relevant nonlinear models. The use of nonlinear models in model-based control strategies proved to be feasible, and the increased complexity in the used model was rewarding, since the nonlinear models improved the quality of the control results.

The control design started with the use of a linearized version of the complete nonlinear patient models. Although this approach yielded good simulation results, the use of model with large order is difficult to apply (as an individualized model) in practice. Then, reduced-order linear and nonlinear models have been used for controller synthesis. These models have also the advantage of being data-driven; the model is derived from input-output data of the patient. Such features make it possible to use these models in individualized model-based control strategies. The nonlinear model yielded better results in representing the diabetic patient, and improved the performance of the control algorithms.

In this thesis, it was shown that reduced-order SP-SMC strategies that are designed using the nonlinear Wiener model are suitable for closed-loop glucose regulation. These control algorithms: (1) are simple in structure, (2) have good time-delay compensation ability, (3) are based on reduced-order nonlinear models that can be identified for each patient, (4) robust against internal and external disturbances, and (5) have explicit relation between model and controller parameters (this feature simplifies the controller tuning for each patient). On the other hand, the use of multiple linear MPC with gain scheduling has the prediction ability that makes it more conservative in insulin dosing and more efficient in hypoglycemia prevention. Also, constraints handling in the MPC formation make it possible to deal with the insulin and glucose constraints that should be satisfied in the glucose control problem.

To conclude this work, the major contributions of the thesis and the directions of the future work will be highlighted in the following sections.

12.2 Major Contributions

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

- The proposed control schemes, that combine between more than one linear/nonlinear control and modeling approaches in one structure. The main idea of such combined control schemes is to take advantage of the virtues of each approach while reducing the effects of their drawbacks. The GS-MPC and SP-SMC are novel approaches introduced in the field of closed-loop glucose regulation in T1DM.
- Introducing the Wiener model as a novel approach in modeling the insulin-glucose system for control design purposes. Specifically, the combination of the Wiener model, SMC and Smith predictor collects different contributions:
  1. The idea of using nonlinear block-oriented model (Wiener model) in the design of robust nonlinear control structures (Smith predictor SMC) that also exhibit good time-delay compensation features.
  2. The synthesis of different Wiener-based controller configurations.
  3. The mathematical derivation of the Wiener-based SMC control laws.
- The considered testing and validation scenarios. Throughout the thesis, the control algorithms have been tested under harsh operating conditions that are usually ignored in the literature, such as big meal intakes, large estimation errors in the meal contents, changes in insulin sensitivity, inter-patient variability and the presence of combined sources of errors. Such scenarios are considered because they are frequently faced in the real-life conditions of diabetic patients.

12.3 Future Work

This thesis opens the way to many possible future developments, mainly related to the improvement of the proposed control and modeling approaches and their practical usage. Among the topics that have been recently initiated and would be addressed in future research:

- Incorporating supporting techniques (e.g. Insulin-on-board, meal detection algorithms, and hypoglycemia alarms) in the control scheme. Such techniques (as reviewed by the author in [28, 90]) are expected to further improve the good control results obtained by the nonlinear model-based SMC and MPC controller (especially in avoiding hypoglycemic episodes). Regarding the SP-SMC algorithm, the control scheme can be modified so that unequal penalties are used upon hyper- and hypoglycemia.

- Introducing the use of frequency domain analysis and identification techniques for the development of models and control algorithms for the artificial pancreas. Recently, we have used the frequency domain framework, in contrast to the time domain approach, for the characterization and analysis of the dynamics and nonlinearity of the glucose regulation system [91]. In this new approach, the idea of the best linear approximation (BLA) of nonlinear systems and the concept of nonlinear distortion (i.e. effect of system nonlinearity on linear modeling) are introduced, for the first time, in the field of diabetic patient modeling [91]. Such concepts are very useful when studying the reliability of linear models, and to emphasize the need for nonlinear data-driven models to represent the patient under widely-varying operating conditions. Based on the new frequency domain approach:

    1. Firstly, a full analysis of the dynamic and nonlinearity of the glucose regulation system has been performed, to study the differences between popular physiological models of the glucose regulation system [91]. The BLA of the nonlinear models and the level and type of nonlinearity are used in the comparative analysis. The analysis shows significant differences between the Dalla-Man and Hovorka patient models that are frequently used to represent the diabetic patients, and raises new questions regarding the reliability of the linear modeling framework. The analysis results indicate that the glucose regulation system in diabetics (as it is described by the Dalla-Man and Hovorka models) has a 'non-negligible' level of nonlinearity, and that the use of linear modeling framework may not provide satisfactory results under wide operating conditions (see results in [91]).

The steady-state behavior of both virtual patient models (Figure 2 in Chapter 9 - page 113) shows that there exists a difference between these models. However, both diabetic and healthy persons are almost always in a dynamic state, making the dynamic response analysis more relevant than the steady-state behavior. Therefore, we have presented the new analysis method to study and compare the dynamics and the nonlinearity in these models, using the frequency domain.

2. Then, motivated by the model analysis results and the better performance obtained by the nonlinear Wiener model-based SP-SMC algorithm, and starting from collected input-output data, frequency domain identification techniques have been used to identify a control-relevant nonlinear model that mimics the virtual patients very well, but with a much simpler mathematical description. The nonparametric estimate of the frequency response function (FRF) of the linear dynamics (or the BLA) of the nonlinear system is obtained, and then used as an initial step in the identification of nonlinear models. Different nonlinear frequency domain modeling techniques have been studied. The Wiener and the polynomial nonlinear state-space (PNLSS) models are used for the first time in modeling the insulin-glucose system, in a wide operating range. The quality and complexity of nonlinear models are compared to the linear approach. Then, the Wiener model, being the most control-relevant model, is used in the development of model-based closed-loop control algorithm. The obtained Wiener model and the BLA of the system are used in the design of closed-loop MPC algorithms for blood glucose regulation.

- Lately, we have started the use of Wiener model in the design of Wiener-based MPC, where the linear block of the Wiener model is used in the design of linear MPC, and a static nonlinearity is used to capture the nonlinear gain observed in the system. Such an approach retains the simplicity of linear MPC, while improving the performance of the feedback control scheme when dealing with system nonlinearity. The Wiener-based MPC is a novel approach in the field of closed-loop glucose control in T1DM. First obtained results show the ability of Wiener-MPC to regulate the glucose levels in different patients (with an average

model), and the ability to identify the Wiener model from available input-output data (for controller individualization), indicate that the Wiener-based MPC can be a good candidate to close the control loop in the artificial pancreas. Although control results are promising, more testing scenarios should be considered to get a more detailed insight into the control algorithm performance under various operating conditions.

- Considering the multiple inputs case of the nonlinear model, where the meal effect is also considered in the Wiener model. Such approach might be helpful to achieve better representation of the nonlinear glucose regulation system, and would be rewarding in the design of the feedforward control loop for meal compensation. First results already obtained show some improvement compared to multiple input linear models. However, such multiple input approach will increase the complexity of the model and the control algorithm. Currently, only the insulin input is taken into account, since it is the main control variable. Another approach that will be considered for feedforward design is the identification of the feedforward transfer function in frequency domain, using the nonparametric approach. Preliminary results indicate that such a method will eliminate the problem or realizability of the transfer function (as discussed in Chapter 7), since the user will be able to specify the orders of the fitted parametric transfer function.

- Extend the use of polynomial nonlinear state space (PNLSS) model in representing the glucose regulation system. The flexibility of PNLSS and its ability to model dynamic nonlinear behavior [92, 93], indicate that this model structure can be used to represent the inherently nonlinear glucose regulation system. Subsequently, the obtained model can be used in nonlinear control design for the artificial pancreas. Recently obtained results show the superior performance of PNLSS model over linear models in representing the insulin-glucose system. However, further improvement is still needed in the quality of the proposed PNLSS model.

- Using the Wiener model in different configurations of MPC, where the full Wiener model (linear and nonlinear blocks) are used in the prediction/optimization problem. The complexity and performance of such an approach should be compared to that of the Wiener-MPC with linear model and static nonlinearity inversion.

- Highlight the difference between the existing mathematical models of the glucose regulation system in T1DM, in an attempt to select which one approximates better the real system. This is important because big differences do exist between these models that try to simulate the same system. Other mathematical models of diabetic patients can be studied and analyzed using the developed frequency domain analysis method described in [91, 94, 95]. Also, the proposed frequency domain method should be further extended to the full problem, where noise sources (e.g. measurements noise) are presented in the measured output data.

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Appendices

This final section of the thesis contains two appendices with supplementary material. The first appendix is a paper presented in the invited session ‘‘Modeling Methods and Clinical Applications in Medical and Biological Systems II”, in the 18^{th} IFAC world congress, Italy 2011. The second appendix includes a CD-ROM with a draft version of different *MATLAB* and *SIMULINK* files used during the development of the thesis publications.

Appendix A

Smith Predictor Sliding Mode Closed-loop Glucose Controller in Type 1 Diabetes

This appendix corresponds to the publication:
Amjad Abu-Rmileh and Winston Garcia-Gabin. "Smith Predictor Sliding Mode Closed-loop Glucose Controller in Type 1 Diabetes." 18^{th} *International Federation of Automatic Control World Congress* (IFAC-WC). Milan, Italy (2011): 1733-1738. (DOI: 10.3182/20110828-6-IT-1002.01213).

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Smith Predictor Sliding Mode Closed-loop Glucose Controller in Type 1 Diabetes ⋆

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Abstract: Type 1 diabetic patients depend on external insulin delivery to keep their blood glucose within near-normal ranges. In this work, two robust closed-loop controllers for blood glucose regulation are developed to prevent the life-threatening hypoglycemia, as well as to avoid extended hyperglycemia. The proposed controllers are designed by using the sliding mode control technique in a Smith predictor structure. To improve meal disturbance rejection, a simple feedforward controller is added to inject meal-time insulin bolus. Simulations scenarios were used to test the controllers, and showed the controllers ability to maintain the glucose levels within the safe limits in the presence of errors in measurements, modeling and meal estimation.

Keywords: Artificial pancreas; biomedical control; sliding mode control; type 1 diabetes.

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a metabolic disease characterized by the pancreas inability to produce the glucose-regulating hormone, the insulin. Therefore, T1DM treatment consists mainly in administrating exogenous insulin to achieve near-normal glucose levels. If glucose is not carefully controlled within a tight range, chronic (e.g. cardiovascular diseases, nephropathy, and retinopathy), and acute (e.g. hypoglycemic coma) complications can occur. The progress in insulin pumps and continuous glucose monitoring (CGM) systems has encouraged the development of the artificial pancreas (Bequette [2005]). The artificial pancreas consists of a CGM, a closed-loop controller, and an insulin pump. The closed-loop artificial pancreas will improve the patients' quality of life (e.g. greater flexibility in meal times, carbohydrate (CHO) quantities, and physical activities), and will reduce the risk of T1DM complications.

A wide range of control algorithms was proposed to close the loop (extensive reviews are given in Bequette [2005], Chee and Fernando [2007], Takahashi et al. [2008]). However, there exist many physiological and technical factors that make it very difficult to find a general and reliable controller for the blood glucose (BG) control problem. These factors include the limitations of the subcutaneous (SC) route used for glucose sensing and insulin delivery (e.g. time delays and CGM measurement errors), system nonlinearity, and uncertainty in insulin-glucose system modeling. Such problems in the BG control highlight the need for an advanced controller. A controller that shows a level of robustness sufficient to deal with modeling errors and other sources of disturbance and uncertainty, and at the same time, has a predictive nature to deal with physiological and measurements delay, and to provide a proactive control action to avoid high fluctuations in BG.

In this work, a controller that uses a combination of the robust sliding mode control (SMC) and the Smith predictor (SP) structures, is proposed as a competitive candidate to achieve the required performance. The SP's prediction and time delay compensation virtues, and the robustness of SMC are merged in one structure (SP-SMC controller). To avoid the limitation of purely reactive control, and to improve the controller response against meal disturbance, a static feedforward control (i.e. meal announcement) is added to inject meal-time insulin bolus.

2. PATIENT MODELING

Different models with different structures and degrees of complexity are being used to describe the glucoregulatory system (see for instance Bergman et al. [1979], Hovorka et al. [2004], Dalla Man et al. [2007]) . In this work, two nonlinear models have been used to represent the diabetic patient *(virtual subject)*.

2.1 The Meal Model

The Meal model developed by Dalla Man and coworkers in Dalla Man et al. [2007] incorporates a complex network of compartments. The model considers that the glucose and insulin subsystems are interconnected by the control of insulin on glucose utilization and endogenous production. The glucose subsystem is described by a two-compartment model as is the insulin subsystem. Endogenous glucose production, glucose rate of appearance, and glucose utilization are the most important model unit processes. The model was modified to adapt for T1DM subjects, SC glucose measurements, and exogenous insulin delivery.

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The modified model was implemented in the UVa/Padova metabolic simulator (Kovatchev et al. [2009]), designed to support the development of closed-loop artificial pancreas. In addition to the patient model, the simulator incorporates a sensor-related errors model to account for sensor noise and measurements errors (Kovatchev et al. [2009]).

2.2 The Hovorka Model

The second model was developed by Hovorka and coworkers in Hovorka et al. [2002, 2004]. It is a physiological model validated with experimental data. It consists of three subsystems: the CHO absorption, the subcutaneous insulin absorption, and the glucose-insulin kinetics. The insulin actions describe the effect of insulin on glucose transport, removal and endogenous production. The model shows a good trade-off between simplicity and accuracy.

Subcutaneous glucose measurements The output of the model above is the glucose level in blood, $G_b(t)$. Therefore, due to our interest in using the SC route, it is necessary to consider the glucose level in SC tissue, and the CGM errors. The CGM signal, $y(t)$ is modeled with added errors and time delay ($\tau_{sc} = 10$ min):

$$y(t) = G_b(t - \tau_{sc}) + \varepsilon(t) \tag{1}$$

The model in Breton and Kovatchev [2008] is used to describe the sensor-related errors, and is given by:

$$\varepsilon(t) = \xi + \theta \sinh\left(\frac{\sigma(t) - \gamma}{\beta}\right) \tag{2}$$

$$\sigma(t) = 0.7(\sigma(t-1) + \nu(t)) \tag{3}$$

where $\varepsilon(t)$ is a non-white, non-Gaussian sensor error. ξ, θ, β and γ are the parameters of the Johnson distribution. $\nu(t)$ is white noise and (3) is the autocorrelation function.

2.3 Model Identification

The two models are used for controllers design and testing; data obtained from the nonlinear models are used in the identification of lower order linear models for controllers design, then, the designed controllers are tested with the nonlinear models. Although the Meal model has a more complex structure, the Hovorka model exhibits a more nonlinear behavior - due to the activation/deactivation nature of some model parameters. Also, the Hovorka model has a higher dynamic. Based on the results of the identification procedure and previous experience with the used models, the identified linear models have different orders and time delays. For the Meal model, a first order plus time delay (FOPTD) is used to represent the insulin-BG system:

$$G_{m1}(s) = \frac{Y_{m1}(s)}{U_1(s)} = \frac{K_{m1}}{\tau_{m1}s + 1} e^{-t_{0m1}s} \tag{4}$$

For the Hovorka model, a second order plus time delay (SOPTD) is identified to approximate the insulin-BG system:

$$G_{m2}(s) = \frac{Y_{m2}(s)}{U_2(s)} = \frac{K_{m2}}{(\tau_{m2}s + 1)(\tau_{m3}s + 1)} e^{-t_{0m2}s} \tag{5}$$

where $Y_m(s)$ and $U(s)$ are deviations of glucose level and insulin infusion from the chosen basal point (Y_0, U_0).

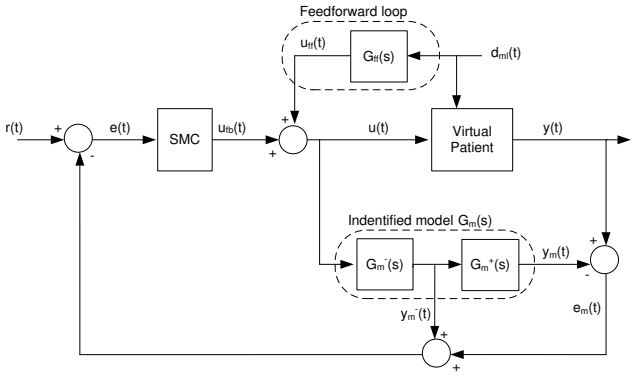

Fig. 1. Closed-loop SP-SMC with feedforward control.

$K_{m1,2}$ are the models gains, $\tau_{m1,2,3}$ are the time constants and $t_{0m1,2}$ are the time delays.

3. CONTROLLER ARCHITECTURE

3.1 The SMC & SP components

SMC is a simple procedure to synthesize robust controllers for linear and nonlinear processes based on principles of variable structure control (VSC). The design problem consists of selecting the parameters of each controller structure and defining the switching logic. The first step in SMC is to define a sliding surface $s(t)$, along which the process can slide to its desired final value. The sliding surface divides the phase plane into regions where the switching function $s(t)$ has different signs. The structure of the controller is intentionally altered as its state crosses the surface in accordance with a prescribed control law. SMC controller exhibits good robustness against parameter variations (Garcia-Gabin et al. [2010]), and has been used to design controllers based on its robustness against modeling errors and disturbances.

The SP scheme is a type of predictive controller for systems with pure time delay, that needs a model of the system dynamics and an estimate of its time delay t_0. In the SP structure, the control signal passes through two parallel paths (Figure 1); one passing through the real system (*the patient*), and the other through the identified model, $G_m(s)$. The parallel path containing the model is used to generate the difference $e_m(t)$ between the actual system output $y(t)$ and an estimation (model-based prediction) of the control signal effect on the system output $y_m(t)$. The SP scheme uses the model to predict the delay-free response of the system $y_m^-(t)$. Then, it compares this prediction to the desired setpoint to decide the required control action. To avoid drifting and reject external disturbances, the SP also compares the actual system output with a prediction that takes the time delay into account. The overall error signal $e(t)$ is delivered to the controller to calculate the needed adjustments.

3.2 SP-SMC Controller design

The main components of the proposed closed-loop controllers (e.g. feedback SMC, SP structure, and feedforward loop), and the variables used throughout the work are given in Figure 1.

First order SMC To design the first SP-SMC controller, the FOPTD transfer function in (4) is used. Given the model (4), it can be factorized in the following way:

$$G_{m1}(s) = G^{+}_{m1}(s)G^{-}_{m1}(s) \tag{6}$$

The first factor $G^{+}_{m1}(s)$ corresponds to terms of the model $G_{m1}(s)$ that lead to instability and realisability problems (e.g. term containing time-delay). The second one, $G^{-}_{m1}(s)$, corresponds to terms of the model that can be used to design the controller. This procedure eliminates all elements in the process model that can produce an unrealisable controller. $G^{-}_{m1}(s)$ eliminates the time-delay term from the model (4), and $G^{+}_{m1}(s)$ and $G^{-}_{m1}(s)$ are defined as

$$G^{+}_{m1}(s) = e^{-t_{0m1}s} \tag{7}$$

$$G^{-}_{m1}(s) = \frac{K_{m1}}{\tau_{m1}s + 1} \tag{8}$$

This factorization facilitates the SMC design because developing a SMC for systems with time delay requires using approximations for time delay (Camacho et al. [1999]). The first step to design a SMC is to define the surface $s(t)$. In general, the sliding surface represents the system behavior during the transient period, therefore, it must be designed to represent the desired system dynamics, for instance stability and tracking performance. In this work, the sliding surface presented in Camacho et al. [1999] is used:

$$s(t) = \left(\frac{d}{dt} + \lambda\right)^{n} \int_{0}^{t} e(\tau)d\tau \tag{9}$$

where n is the system order, $e(t)$ is the tracking error and λ is a tuning parameter, which helps to shape $s(t)$. This term is selected by the designer. This surface, consisting of the integral-differential error function, is frequently used because it provides a good performance in practical applications of SMC (Garcia-Gabin et al. [2010]). For the first-order system in (8), the sliding surface (9) will be:

$$s(t) = e(t) + \lambda \int_{0}^{t} e(\tau)d\tau \tag{10}$$

where the error $e(t) = r(t) - (y(t) - y_{m1}(t)) - y^{-}_{m1}(t)$, $r(t)$ is the glucose reference. $y_{m1}(t)$ is the glucose estimation using (4), $y^{-}_{m1}(t)$ is the glucose estimation using (8), and both are deviations variables from the basal point (y_0). The SMC control law contains two parts: a continuous part $u_{C_{fb}}(t)$, and a discontinuous part $u_{D_{fb}}(t)$, so that

$$u_{fb}(t) = u_{C_{fb}}(t) + u_{D_{fb}}(t) \tag{11}$$

The first of these is responsible for maintaining the controlled system dynamics on the sliding surface, which represents the desired closed-loop behavior. The method normally used to generate the equivalent SMC law $u_{C_{fb}}(t)$ is Filipov construction of the equivalent dynamics. It consists of satisfying the sliding condition and substituting it into the system dynamic equations; the control law is thereby obtained. The control objective is to ensure that the controlled variable is driven to its reference value. It means that, in the stationary state, $e(t)$ and its derivatives must be zero. This condition is satisfied when:

$$\frac{ds(t)}{dt} = 0 \tag{12}$$

Once the sliding surface has been selected, attention must be drawn to the design of the control law that drives the controlled variable to its reference value and satisfies (12). Applying the sliding condition (12) to (10):

$$\frac{ds(t)}{dt} = \frac{de(t)}{dt} + \lambda e(t) = 0 \tag{13}$$

and solving for the first derivative and considering the nominal case ($y(t) - y_{m1}(t) = 0$), we obtain

$$\frac{dy^{-}_{m1}(t)}{dt} = \frac{dr(t)}{dt} + \lambda e(t) \tag{14}$$

Then substituting (14) in the equivalent differential equation of the model (8), which is

$$\tau_{m1}\frac{dy^{-}_{m1}(t)}{dt} + y^{-}_{m1}(t) = K_{m1}u_{C_{fb}1}(t) \tag{15}$$

and solving for $u_{C_{fb}1}(t)$ to obtain the continuous part of the controller (Garcia-Gabin et al. [2010]):

$$u_{C_{fb}1}(t) = \frac{1}{K_{m1}}\left(\tau_{m1}\frac{dr(t)}{dt} + \tau_{m1}\lambda e(t) + y^{-}_{m1}(t)\right) \tag{16}$$

The expression for $u_{C_{fb}1}(t)$ can be simplified making zero the derivatives of the reference.

$$\frac{dr(t)}{dt} = 0 \tag{17}$$

The derivative computation in many controller implementations should be based on the value of the process variable itself. Because when setpoint changes (step changes), derivative on setpoint results in an undesirable control action called derivative kick (Smith and Corripio [1997]). Also, concerning practical implementation issues, a natural continuous approximation of the signum function is used for the discontinuous part $u_{D_{fb}}(t)$, to avoid the chattering problem (Garcia-Gabin et al. [2010]). This is the sigmoid-like function:

$$\text{sign}(s(t)) = \frac{s(t)}{|s(t)| + \delta}, \quad \delta > 0 \tag{18}$$

where δ is a tuning parameter used to reduce the chattering problem (a non-decreasing oscillatory component of finite amplitude and frequency). Finally, the resulting control law is given as:

$$u_{fb1}(t) = \frac{1}{K_{m1}}\left[\tau_{m1}\lambda e(t) + y^{-}_{m1}(t)\right] + K_{D1}\frac{s(t)}{|s(t)| + \delta} \tag{19}$$

Second order SMC To design the second controller, the SOPTD model in (5) is used. First, the model is factorized as follows:

$$G^{+}_{m2}(s) = e^{-t_{0m2}s} \tag{20}$$

$$G^{-}_{m2}(s) = \frac{K_{m2}}{(\tau_{m2}s + 1)(\tau_{m3}s + 1)} \tag{21}$$

The next step is to formulate the sliding surface. For the second order model in (21), the second order $s(t)$ is (Camacho et al. [1999]):

$$s(t) = \frac{de(t)}{dt} + \lambda_1 e(t) + \lambda_2 \int_0^t e(\tau)d\tau \tag{22}$$

where λ_1 and λ_2 are tuning parameters of $s(t)$. The next step is to formulate the control law for the second order SMC. From the sliding condition in (12):

$$\frac{ds(t)}{dt} = \frac{d^2e(t)}{dt^2} + \lambda_1 \frac{de(t)}{dt} + \lambda_2 e(t) = 0 \tag{23}$$

then solving for the highest derivative, and considering the nominal case ($y(t) - y_{m2}(t) = 0$):

$$\frac{d^2y_{m2}^-(t)}{dt^2} = \frac{d^2r(t)}{dt^2} + \lambda_1 \frac{de(t)}{dt} + \lambda_2 e(t) \tag{24}$$

Now, substituting (24) in the equivalent differential equation of the model (21):

$$\tau_{m2}\tau_{m3}\frac{d^2y_{m2}^-(t)}{dt^2} + (\tau_{m2} + \tau_{m3})\frac{dy_{m2}^-(t)}{dt} + y_{m2}^-(t) = K_{m2}u_{C_{fb}2}(t) \tag{25}$$

and solving for $u_{C_{fb}2}(t)$, gives the continuous part of the control signal:

$$u_{C_{fb}2}(t) = \frac{1}{K_{m2}}\left[\tau_{m2}\tau_{m3}\left(\frac{d^2r(t)}{dt^2} + \lambda_1\frac{de(t)}{dt} + \lambda_2 e(t)\right) + (\tau_{m2} + \tau_{m3})\frac{dy_{m2}^-(t)}{dt} + y_{m2}^-(t)\right] \tag{26}$$

Since a constant $r(t)$ is used, the first and second derivatives are equal to zero, and $u_{C_{fb}2}(t)$ can be further simplified. The final formulation of the control law of the second order SMC is:

$$u_{fb2}(t) = \frac{1}{K_{m2}}\left[\tau_{m2}\tau_{m3}\left(\lambda_1\frac{de(t)}{dt} + \lambda_2 e(t)\right) + (\tau_{m2} + \tau_{m3})\frac{dy_{m2}^-(t)}{dt} + y_{m2}^-(t)\right] + K_{D2}\frac{s(t)}{|s(t)| + \delta} \tag{27}$$

Following Camacho et al. [1999] and Garcia-Gabin et al. [2010], the following initial tuning parameters can be used to adjust the designed controllers:

$$\lambda = \frac{1}{\tau_{m1}}, \lambda_1 = \frac{\tau_{m2} + \tau_{m3}}{\tau_{m2}\tau_{m3}}, \lambda_2 = \frac{\lambda_1^2}{4} \tag{28}$$

For the discontinuous part of the controllers, the gain K_D will be selected so that $K_m K_D > 0$. This value must be high enough to cancel the disturbances. The initial values for $K_{D1,2}$ were selected as in (Garcia-Gabin et al. [2010]):

$$K_{D1} = \frac{1}{K_{m1}}, K_{D2} = \frac{1}{K_{m2}} \tag{29}$$

Feedforward controller Meals usually lead to a significant glucose flux into the blood. To achieve a better postprandial performance (i.e. avoid high glucose excursions after meal intakes), the SP-SMC is provided with a feedforward loop for meal announcement. Feedforward control is a well-known control technique to eliminate the effect of measurable sources of disturbance. In the BG problem, the meal CHO is considered as a known disturbance, and feedforward control can be used. The benefit of meal announcement in improving the postprandial performance has been verified in different studies (see for example Marchetti et al. [2008], Abu-Rmileh et al. [2010a,b]). To design a feedforward controller, the effect of meal CHO on BG level should be known or approximated. Two FOPTD models are identified to represent the CHO-BG system in the Meal and Hovorka models, $G_{ml1}(s)$ and $G_{ml2}(s)$ respectively. The general formula of the obtained transfer functions is given by:

$$G_{ml}(s) = \frac{Y_{ml}(s)}{D_{ml}(s)} = \frac{K_{ml}}{\tau_{ml}s + 1}e^{-t_{0ml}s} \tag{30}$$

where $Y_{ml}(s)$ is the glucose increment caused by the meal, $D_{ml}(s)$ is the CHO amount in the meal, K_{ml}, τ_{ml} and t_{0ml} are the model parameters. The objective of the feedforward controller $U_{ff}(s)$ is to eliminate the effect of $D_{ml}(s)$;

$$U_{ff}(s) = G_{ff}(s)D_{ml}(s) \tag{31}$$

Where $G_{ff}(s)$ is the transfer function of the feedforward element. For the Meal model, which is represented by another FOPTD model in the insulin-BG system (4), $G_{ff1}(s)$ is given by

$$G_{ff1}(s) = -\frac{G_{ml1}(s)}{G_{m1}(s)} = \frac{K_{ff1}(\tau_{m1}s + 1)}{\tau_{ml1}s + 1}e^{-t_{0ff1}s} \tag{32}$$

Where $K_{ff1} = -K_{ml1}/K_{m1}$, and $t_{0ff1} = t_{0ml1} - t_{0m1}$. Another formula that can be used is the static feedforward, which does not consider the dynamic behavior of $G_{m1}(s)$ and $G_{ml1}(s)$. Using static feedforward, $G_{m1}(s)$ and $G_{ml1}(s)$ are limited to their constant gain values, and the obtained static feedforward element will be a simple gain ratio multiplier:

$$G_{ff1}(s) \simeq -\frac{K_{ml1}}{K_{m1}} = K_{ff1} \tag{33}$$

The feedforward action is given by:

$$U_{ff1}(s) = K_{ff1}D_{ml1}(s) \tag{34}$$

For the Hovorka model, which is approximated by a SOPTD model in the insulin-BG system (5), $G_{ff2}(s)$ will be:

$$G_{ff2}(s) = \frac{K_{ff2}(\tau_{m2}s + 1)(\tau_{m3}s + 1)}{\tau_{ml2}s + 1}e^{-t_{0ff2}s} \tag{35}$$

where $K_{ff2} = -K_{ml2}/K_{m2}$, and $t_{0ff2} = t_{0ml2} - t_{0m2}$. The transfer function in (35) is unrealizable, and it should be approximated. When there are uncertainties in the lead-time constant and lag-time constant, then a better performance is obtained by using a static feedforward, since the performance of dynamic feedforward is affected by uncertainties in the time constants obtained by approximation(Smith and Corripio [1997]). Therefore, the static $G_{ff2}(s)$ and the static $U_{ff2}(s)$ will be:

$$G_{ff2}(s) \simeq -\frac{K_{ml2}}{K_{m2}} = K_{ff2} \tag{36}$$

$$U_{ff2}(s) = K_{ff2}D_{ml2}(s) \tag{37}$$

When feedforward is performed as a static bolus, the entire calculated insulin dose can be delivered into the

blood stream with the least possible delay. It was found that both dynamic and static feedforward improves the meal disturbance rejection, with the latter being superior (Abu-Rmileh et al. [2010a]). Thus, the static feedforward is adopted in this work. Finally, the total insulin dose delivered to the patient will be (as shown in Figure 1):

$$u(t) = u_{fb}(t) + u_{ff}(t) \tag{38}$$

4. RESULTS

4.1 In silico *testing*

To explore the applicability of the designed controllers, they have been tested with the nonlinear patient models, while the identified models served as internal models for the controllers. The simulations considered a 2-days testing period. For the first day, the meals were 55, 85, and 75 g of CHO at 9:30 AM, 1:30 PM, and 7:30 PM, respectively. In the second day, 60, 90, 85, and 55 g CHO were taken at 7:00 AM, 12:30 PM, 7:00 PM, and 10:00 PM, respectively. A constant target BG value of 120 mg/dl is used. The CGM signal is used to drive the controllers, while the BG level is used to evaluate their performance. The models and controllers parameters used in the simulations are given in Table 1. To evaluate the controllers performance in the presence of different sources of noise, disturbance and uncertainty, the simulation results are analyzed using the *Percentage within ranges* metrics. These metrics give the percentage of the testing period during which the patient's BG is within the acceptable (70-180 mg/dL), hypoglycemic ($<$ 70 mg/dL), and hyperglycemic ($>$ 180 mg/dL) ranges.

Table 1. Models and controllers parameters.

Parameter	Value	Units
K_{m1}	-0.3	mg/dL per pmol/min
τ_{m1}	200	min
t_{0m1}	100	min
K_{ff1}	0.57	pmol/mg
K_{D1}	-0.33	pmol/min per mg/dL
λ	0.0025	min^{-1}
K_{m2}	-19	mg/dL per mU/min
τ_{m2}	155	min
τ_{m3}	365	min
t_{0m2}	35	min
K_{ff2}	7.89	mU/mmol
K_{D2}	-0.526	mU/min per mg/dL
λ_1	0.014	min^{-1}
λ_2	4.923×10^{-5}	min^{-2}
δ	0.6	mg/dL

4.2 Testing scenarios

Feedback-Feedforward vs. Feedback SP-SMC To study the feasibility of the proposed controllers, two controllers' modes (fully automatic and semi-automatic) have been tested and compared. The fully automatic system (i.e. feedback-alone controller) does not need any input from the patient, and depends on the CGM signal only. The semi-automatic system needs the patient intervention to tell that a meal is coming up and the control algorithm needs to change (i.e. feedforward-feedback controller). The feedforward action is performed by injecting an insulin bolus (0-20) min before the meal. The feedback-alone setup is tested as a possible case where the SP-SMC should operate out of the nominal conditions (i.e. no meal announcement). From the results shown in Figure 2 and Table 2, a better performance is obtained when the feedforward control is active. Since the feedforward action starts to deliver insulin before the meals effect appears in the CGM feedback loop, lower hyperglycemic peaks and lower fluctuations in BG levels are observed. Without meal announcement, the feedback-alone controller is still able to achieve acceptable performance; no hypoglycemic events are detected, and only short periods of hyperglycemia are observed. Numerical results in Table 2 indicate that the semi-automatic feedforward-feedback SP-SMC shows a superior performance over the fully automatic feedback-alone configuration, highlighting the limitations of purely reactive controllers. Meal announcement provides better results, however, it is not uncommon that patients forget to activate the meal bolus. Therefore, meal detection algorithms are developed to improve the control outcomes without requiring patient intervention (Lee et al. [2009]).

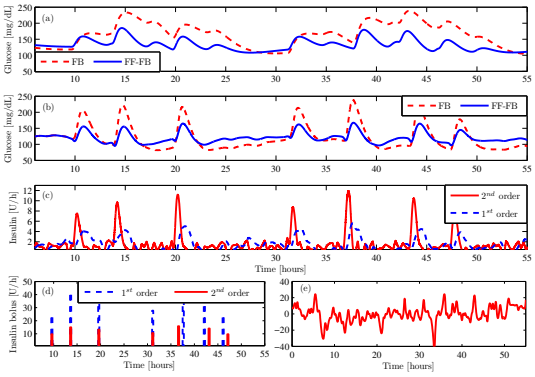

Fig. 2. Feedforward-feedback (FF-FB) vs. Feedback (FB) controllers' setups: (a) 1^{st} order SP-SMC with Meal model, (b) 2^{nd} order SP-SMC with Hovorka model, (c) insulin infusion, (d) feedforward bolus, (e) sensor errors (mg/dL).

Meal estimation errors Although the meal announcement is important to calculate the required feedforward control signal, the announcement may contain erroneous information about the meal contents. Therefore, the controller should have a good level of robustness against errors in estimating the meal CHO. The designed SP-SMC controllers have been tested with random over- and under-estimation errors up to 30% in meal announcement (the error is included in the controllers announcement while the correct meal is given to patient). Figure 3 shows the glucose levels obtained for the patients with the $\pm$30% errors. For the three scenarios (nominal meal, overestimation, and underestimation), the controllers are able to keep the BG level within the safe glycemic range during the testing period (See Table 2). The controllers performance is not affected by small and moderate estimation errors, while only minimum degradation is noticed near the boundaries of $\pm$30% errors.

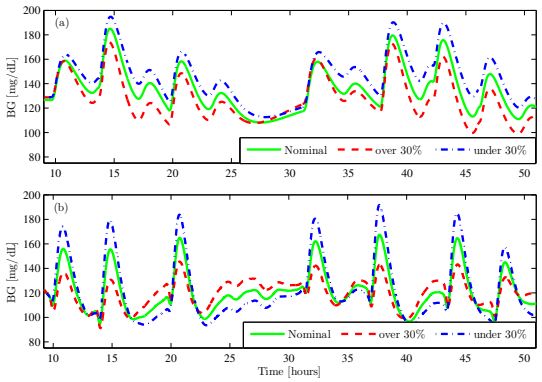

Fig. 3. BG profile with meal errors: (a) 1^{st} order SP-SMC with Meal Model, (b) 2^{nd} order SP-SMC with Hovorka model. Nominal meal (solid), 30% overestimation (dashed), 30% underestimation (dotted).

5. CONCLUSION

This study presented a closed-loop control approach for insulin delivery in T1DM based on SP-SMC methodology applied to virtual diabetic subjects. The proposed SP-SMC strategy is as simple as a PID controller in its formulation and implementation but has some advantages over it such as accuracy and robustness, insensitivity to internal and external disturbances, and finite time convergence. Such features make SP-SMC suitable for the BG control problem which incorporates many sources of uncertainty and disturbances, and imposes some specific time requirements to avoid hypo- and hyperglycemia. Another important feature of SP-SMC that is not common in other glucose controllers, is the direct relation between the controller structure and the model parameters. Such explicit relation facilitates the tuning of the controller. The conducted simulations indicate that, with a good lower-order approximation of the nonlinear model, the SP-SMC achieves tight glycemic control with no hypoglycemic events. Future work aims at testing the controllers' ability to deal with other sources of errors and uncertainty that exist in the glucose control problem.

Table 2. Controllers' performance assessment.

Controller	Mean BG (±SD)	% in 70-180 mg/dL	% >180 mg/dL
1^{st} ***order SP-SMC***			
without FF	145 (32)	80.7	19.3
with FF	127.7 (15.7)	97.6	2.4
with + 30 % error	125.1 (14.9)	100	0
with - 30 % error	131.6 (17.17)	94.1	5.9
2^{nd} ***order SP-SMC***			
without FF	119.9 (36.3)	89.7	10.3
with FF	120 (15.1)	100	0
with + 30 % error	120.1 (10.1)	100	0
with - 30 % error	121.8 (22.3)	97.2	2.8

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A. SMITH PREDICTOR SLIDING MODE CLOSED-LOOP GLUCOSE CONTROLLER IN TYPE 1 DIABETES

Appendix B

Supplementary material

Accompanying CD-ROM with a draft version of different *MATLAB* and *SIMULINK* files used during the development of the thesis publications.