UNIVERSITY of L'AQUILA
Faculty of Engineering
Master's Thesis

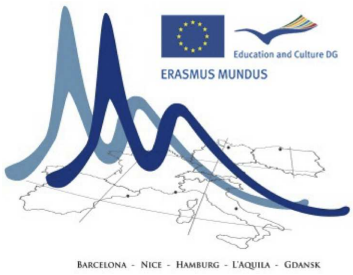
Glucose control by means of an observer-based control law

Advisor
Dr Pasquale Palumbo

Co-Advisor
Dr Pierdomenico Pepe

Candidate
Jude Dzevela Kong

Erasmus Mundus Masters Course
in
Mathematical Modeling in Engineering (MATHMODS)
Academic year: 2011-2012



Abstract

In this thesis, we consider the problem of tracking a desired plasma glucose evolution by meanss of subcutaneous insulin administration. A time-delay model is used to describe the glucose insulin homeostasis. This model takes into account also the pancreatic insulin release , which is not negligible in Type 2 diabetic patients. Only measurements of glycemia are considered: hence a nonlinear time observer for time-delay systems is used to estimates the plasma insulin concerntration.In line with the separation theorem, a nonlinear control law is proposed, based on the feedback linearization, which makes use of the observer estimations instead of the full state measurements. Simulations are performed in a virtual environment, and numerical results show the effectiveness of the proposed approach as well as that of the observer.

Dedication

To my Mother, Anastasia Bongyu
and to the Christains of St. Stefano Parish,
Pizzoli

Acknowledgments

I would like to express my deep appreciation and gratitude to the following people for the roles they played in making this work a reality.

The Almighty God for the wisdom and perseverance that he bestowed upon me during this research project, and indeed, throughout my life

Dr Pasquale Palumbo and Dr Pierdomenico Pepe, for making this research possible. Their support, guidance, advice throughout the research project, as well as their painstaking effort in proof reading the drafts, are greatly appreciated. Indeed, without their guidance, I would not have been able to put the topic together.

Professor Bruno Rubino, for his guidance during my masters study . I am forever indebted to his suggestions, support, encouragement, understanding and, in particular advice. Thank you Bruno.

The European Union for granting me the Erasmus Mundus Scholarship and German and Italian governments for awarding me the German- Italian grant. Without the finacial support from them I wouldnot had been able to go through my program.

The Mathmods staff for the knowledge they gave me that enabled me to put this peace of work together, the warm environment, and their continuous help and support.
My friends especially Kumar, for their encouragement especially at times when things were going tough

Last but not least, my family members for their love and best wishes, which despite of their physical absence has helped me in the successful completion of my study.

Contents

List of Figures

Chapter 1

The Problem and its Background

1.1 Introduction

Diabetes is a chronic disorder of impaired blood glucose control.Around 171 million people worldwide had diabetes in 2000. The number is expected to go up to 366 million by 2030 [28].It can be classified into two major categories : type 1 and type 2 diabetes.
Type 1 diabetes is caused by the autoimmune destruction of beta-cells in the pancreas, causing an absolute loss of insulin production by these cells. Type 2 diabetes is caused by insulin resistance in the body's cells, which essentially establishes a state of relative insulin deficiency [28]. The frequent high blood glucose levels found in diabetes patient is associated with a number of devastating long-term complications that may lead to amputation and systemic infection, as well as pathological changes of the eyes, kidneys, nerves, heart and blood vessels. In fact, individuals with diabetes have a 3 to 7.5 times greater incidence of death from cardiovascuar causes [51] . In addition, approximately 30% to 40% of all diabetics will develop diabetic nephropathy, and more than 75% of type 1 diabetics with nephropathy will eventually develop end-stage renal disease [51]. Yet, in the midst of such statistics, the Diabetes Control and Complications Trial (DCCT) has demonstrated that proper control of blood glucose levels reduces the risk of long-term complications of both type 1 and type 2 diabetes[28]. Insulin is a physiological hormone that works to lower the blood glucose concentration in the body. Since diabetics have a defect in their insulin pathway, their blood glucose levels can often be elevated above the normal glucose range for the blood, a term referred to as hyperglycemia. Normal blood glucose levels values vary depending on the time they are measured. A fasting blood glucose test carried out with no caloric intake for at least eight hours should return a glucose value between 3.9 and $5.5 mmol/L$[52]. A glucose measurement taken two hours after meal consumption (postprandial) is normal if it is between 3.9 and $8.1 mmol/L$ and a random blood glucose measurement should be between 3.9 and $6.9 mmol/L$ [52].
The basic procedure to cope with any malfunctioning of the endogenous insulin feedback action is exogenous insulin administration (in Type 1 diabetes only exogenous insulin is available, while in Type 2 exogenous insulin complements pancreatic production).
Subcutaneous or intravenous injection or infusions are the mean ways by which glucose control strategies are implemented. Control of glycemia by means of subcutaneous

insulin injections, with the dose adjusted on the basis of capillary plasma glucose concentration measurements, is by far more widely used than control by means of intravenous insulin, since the dose is habitually administered by the patients themselves (see [32]). Notwithstanding, in order to design closed-loop control strategies, the insulin absorption from the subcutaneous depot needs also to be taken into account.
Two approaches used in implementing a closed loop control strategy are: a model-less and a model-based approach. The first approach does not use a mathematical model of the glucose-insulin system, and provides an arbitrary (while possibly very effective) control rule for insulin infusion rate, based on experimental data: recent papers on this topic are mainly devoted to the application of PID controllers aiming to mimic the pancreatic glucose response (see [33, 34, 35, 36]).
Contrary to a model-less approach, a model-based approach presupposes sufficiently detailed knowledge of the physiology of the system under investigation. The advantages of a model-based approach are evident since, by using a glucose/insulin model, the control problem may be treated mathematically and optimal strategies may be determined. Clearly, the more accurate the model, the more effective is the control law.
Different approaches have been proposed, recently, based on nonlinear models such as the Minimal Model of Bergman et al. (1979) [20] and Toffolo et al. (1980) [37], or more exhaustive compartmental models like the ones of Cobelli et al. (1982)[38], of Sorensen et al. (1982) [39] and of Hovorka et al. (2007) [29] (see, e.g., papers on Model Predictive Control,[40], on nonlinear Model Predictive Control,[55], on Parametric Programming,[41], on Neural Predictive Control,[42], on H_∞ control,[40], on non-standard H_∞ control,[43, 44]). It has to been stressed that most of these approaches are based on the approximation of the original nonlinear model, provided by linearizion, discretization and model reduction (balanced truncation). An excellent review of the available models presently adopted for blood glucose regulation as well as the closed loop control methodologies and technical devices (blood glucose sensors and insulin pumps) may be found in [45].
In this thesis, a model based closed loop observer based control scheme is proposed. It is different from the previously mentioned model based approaches, which use nonlinear Ordinary Differential Equation (ODE) models, in that it uses a nonlinear Delay Differential Equation (DDE) model to describe the glucose/insulin regulatory system, reference to [4, 8]. Irrespective of the numerous proposed DDE models in the last 10 years, which allow a better representation of pancreatic Insulin Delivery Rate (IDR) (see e.g. [12] and references therein), their use is still lacking in the field of glucose control. First attempts were made in [5, 24], where an intra-venous insulin administration was designed to track a desired plasma glycemia, by means of a DDE model-based approach (DDE model taken from [8]). In this this thesis, we met the same purpose of tracking a desired glucose reference, this time by means of subcutaneous (instead of intra-venous) infusions. Mindful of this, the above mentioned model of the glucose-insulin regulatory system has been coupled to a linear model of the subcutaneous insulin absorption (see [6, 25], for an overview of the many different models of insulin absorption).We will adopt model 1 of table 1 in ([25]) for insulin absorption. Before now,the works done so far in designing a model-based glucose control have focus meanly on type 1 diabetic pa-

tients(who have essentially no endogenous insulin production and are very well described by suitably exploiting ODE models), there by avoiding the need to take pancreatic IDR into account. In this thesis we have taken into account spontaneous pancreatic IDR, thereby treating healthy, Type 2 diabetic and Type 1 diabetic patients in the same way. The glucose/insulin model we use to represent the natural dynamics of the system has been shown to exhibit a number of desirable characteristics (see [8])
Our designed control law, is based on recent results on differential geometry for time-delay systems (see [2, 46, 47]. We obtained an exact linearized input/output map by a nonlinear inner feedback which makes use of the state variables at present and delayed time. The control law is obtained without linearizing, by first order approximations, the system equations: this way, the control law here provided is meant to work also in case of large deviations from the desired final level, and not only for small deviations.Since our proposed control law depends on insulin and glucose measurements at the present and at a delayed time, and because insulin measurements are slower and more cumbersome to obtain, more expensive, and also less accurate than glucose measurements, a need exist to construct a control law that will not need to take into account the measurements of insulin in serum. This thesis makes use of a state observer for nonlinear time-delay systems in order to perform the glucose reference tracking by means of only glucose measurements. Most works concerning observers for time-delay systems consider the linear case (see, for instance, [49] and references therein). A review of recent works on observers for nonlinear time delay systems could be found in [50]. The observer, use in this thesis is the one proposed in [2, 47] for nonlinear time-delay systems.
To show the good performance of our designed control law, and the robustness of the observer, we implemented a virtual environment. This enabled us to test the insulin infusion programme. In fact, before arranging an in-vivo clinical setting of experiments (which are usually costly, time-consuming and confounded by ethical issues) in-silico tests need to be thoroughly carried out on a virtual patient (or even on a population of virtual patients), making it possible to evaluate a possibly exhaustive set of different scenarios, including cases of measurement error and other failures, [48].

1.2 Statement of Purpose of Problem

Despite the wide range of current diabetic treatments options available, research shows that the majority of people with diabetes are not keeping their glucose levels within the recommended ranges[53]. Despite the established importance of blood glucose self-monitoring in diabetes management, few patients actually measure their glucose levels after eating meals or overnight[54]. As a result, even patients with well-controlled type 1 diabetes regularly experience postprandial hyperglycemia or overnight hypoglycemia [54].Poor patient compliance with their diabetes management strategies may be partially attributed to burdensome nature of such treatment plans. In addition, due to the inability of insulin injections and current glucose lowering medications to precisely control blood glucose levels, even a fully compliant diabetic patient may not always be able to maintain their blood glucose levels within the recommended range.Due to the challenges

inherent in current diabetes management, there is a need to develop better treatments that will allow patients to maintain tight blood glucose levels without compromising their quality of life. The artificial pancreas shows promise in fulfilling this.
In line with the on going research work on artificial Pancreas, that is still at the prototype stage, this study aimed to design an observer-based control law for glucose control.
Specifically this study aimed to:

- Review the state of art of Artificial Pancreas
- Analyze some of the available Mathematical models for the glucose- insulin system.
- Design an observer based control law for glucose control using one of the models for the glucose insulin system and one of the models for insulin absorption in the subcutaneous layer.
- Present the state Observer that will be used to estimate insulin measurements
- Carry out simulations on a virtual patient on the basis of parameter estimates obtained from data related to an IVGTT experiment conducted on an obese patient, studied at the Catholic University of Rome, Department of Metabolic Diseases.
- Draw out logical conclusions from the simulations
- Make concrete proposals for further research work on artificial Pancreas.

1.3 Significance of the Study

This study will offer considerable hope to millions of patients with diabetes (Type 1 and 2) worldwide. If the designed control law is implemented together with the other components of the artificial Pancreas,it will offer diabetes' patients the possibility of managing their diabetes easily and enable them to attain an ideal blood glucose target without posing undue annoyances to they individuals' busy schedules.The control law, will help keep to the minimum, disease's devastating vascular, renal and nervous complications.Moreover, this work will not only provide significant benefits to diabetic patients, but also offer significant financial relief to a health care system which comprises burgeoning shares of our country's gross domestic product.

1.4 Scope and Delimitation

This study was delimited to designing a control law and implementing it, with the aim of tracking a desired blood glucose concentration.The implementation was done but on a virtual patient. The parameters for the model were obtained from the data of an experiment that was conducted only on a single obese patient in the department of Metabolic Disease of the Catholic University of Rome.

1.5 Framework

1.5.1 Blood glucose regulation

It is imperative for the body to always have a certain amount of glucose in the bloodstream as glucose is the mean source of energy for the central nervous system and the red blood cells. In a normal healthy person, the blood glucose is maintain between $3.9mmol/L$ and $6.9mmol/L$ by a complex neuro-hormonal control system which help ensures a balance between glucose entering the bloodstream after liver gluconeogenesis and intestinal absorption following meals and glucose uptake from the peripheral tissues. When a meal digestion or glycogen conversion causes the blood glucose to rise,the β cells of the pancreas will secret insulin into the blood stream when the blood and glucose flow into it. This insulin is delivered in boluses every 5 to 6 minutes. With the help of this insulin, in the form of a negative feedback loop, most of the glucose absorbed in the blood is removed and stored in the liver and muscles tissue as glycogen.The amylin that is released alongside insulin, helps prevent the release of glycagon from the pancreatic α cells and equally slows down gastric emptying.As the blood glucose level begins to fall and comes to a normal value, the β cells will stop releasing insulin and amylin.A further decreased in the blood sugar level below the normal value will cause the pancreatic alpha cells to release glucagon which helps the liver to release stored glucose into the blood stream. If the pancreas continue to release more glucagon, the quantity of glucose in the bloodstream will keep on going up to a point where we will have a positive error in the negative feedback loop and the β cells will be pushed to start producing insulin and amylin again. The three Pancreatic hormones work in harmony as a system to keep the blood glucose level within the required limit. These control interactions are usually referred to as insulin sensitivity and β cell responsitivity. Hence the glucose and insulin systems interact by feedback control signals to make sure the concentration of glucose in the blood stream stays at healthy levels at all times.Figure (1.5.1) shows the glucose-insulin control system for the non-diabetic subject.

1.5.2 Diabetes Mellitus

In case there is no insulin secretion or there is a decreased sensitivity of the tissue to insulin, the entry of glucose into skeletal, cardiac, smooth muscle and other tissues is decreased, as shown in figure (1.5.2). The only uptake of glucose that are unaffected by the absence of insulin are: the intestinal absorption, and glucose uptake by most of the brain and the red blood cells. If this is prolonged,blood glucose concentration starts fluctuating widely, leading to a syndrome called diabetes mellitus.The term diabetes therefore comprises a group of metabolic disorders characterized by an increase in blood glucose concentration (hyperglycemia), resulting from defects in insulin secretion, insulin action, or both. The most common types of diabetes are: Type 1 diabetes, in which there is an absolute deficiency of insulin secretion caused by an autoimmune destruction of the pancreatic β cells. Individuals with this extensive β cell destruction, and therefore no residual insulin secretion, require insulin for survival; and type 2 diabetes, caused by a combination of resistance to insulin action and inadequate compensatory in-

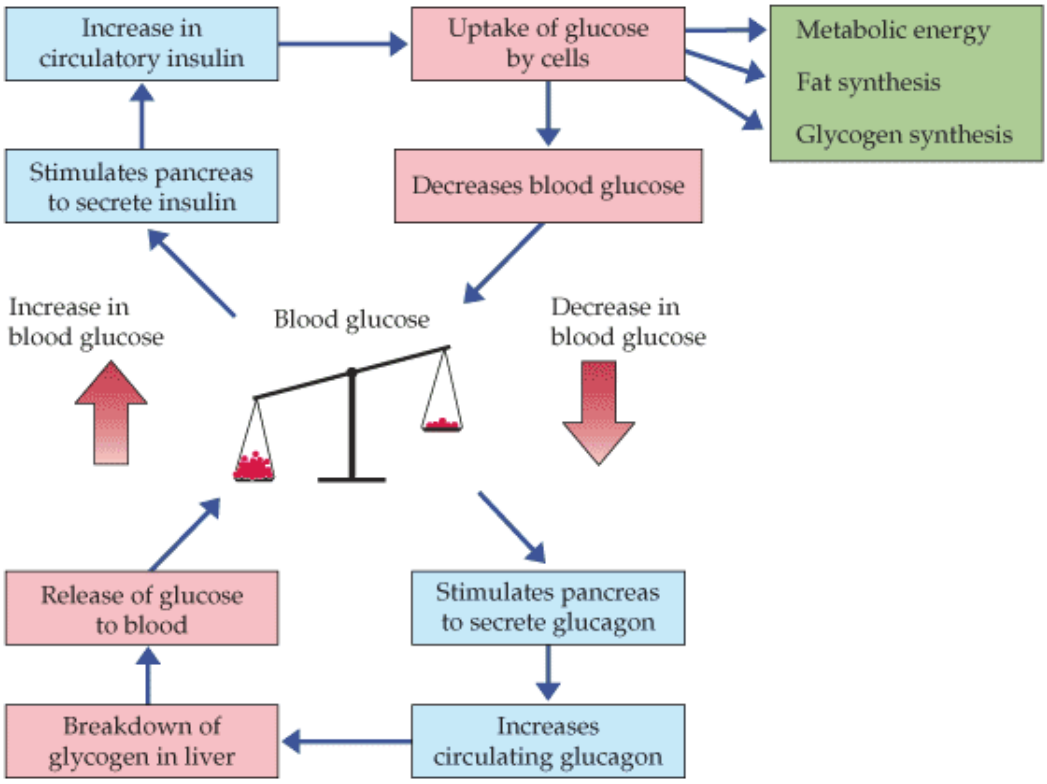


Figure 1.1: Glucose-insulin control system in a non-diabetic subject

sulin secretory response. These individuals have therefore insulin resistance and usually have relative (rather than absolute) insulin deficiency, in the face of increased levels of circulating insulin.Chronic hyperglycemia of diabetes is associated with multiple effects throughout the body associated with damage, dysfunction and failure of various organs. One basic procedure to cope with any malfunction of the endogenous insulin feedback action, is exogenous insulin administration. Focusing on tight blood glucose targets, the philosophy of insulin replacement is to mimic with injections the insulin secretion pattern in the non-diabetic person. Insulin in a non-diabetic person, is secreted into the portal circulation at two rates: a slow basal secretion throughout the 24 hours and an increased rate at meal times.The basal insulin concentration is capable of keeping a constant glucose concentration during fasting conditions and the prandial insulin doses is able to enhance an increased glucose uptake during and after meals.During the last decades,intensive insulin therapy has been strongly encouraged, following the results of the major Diabetes Control and Complications Trial [The Diabetes Control and Complications Trial Research Group, 1993] and follow-up Epidemiology of Diabetes Interventions and Complications [The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group, 2005] studies in order to keep blood glucose levels within the required range. However, insulin therapy may risk potentially severe induced hypoglycemia, resulting from too high levels of insulin, leading to loss of consciousness, coma and eventually death. Because of the

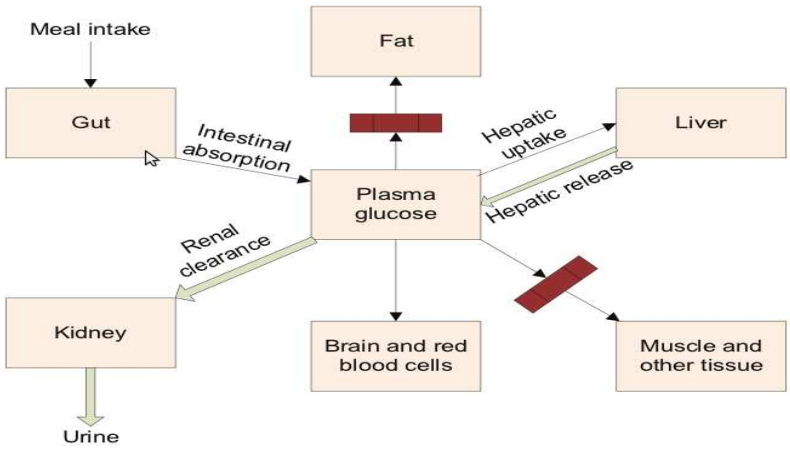


Figure 1.2: Plasma glucose homeostasis in insulin deficiency The heavy arrows indicate reactions that are accentuated. The red rectangles across arrows indicate reactions that are blocked

deficiencies of current diabetes treatments, there is a need to develop a new treatment modality for diabetes that will better succeed in helping patients maintain tight blood glucose control. One promising engineering feat is the development of an artificial pancreas that is programmed to provide physiologic insulin delivery, while keeping patients' blood glucose levels within the required range.

1.6 The Organization of this thesis

In Chapter (1), we gave an overview of the thesis, statement of purpose of the problem, significance of the study, delimitation and scope of the study and theoretical as well as conceptual frame work of the thesis. We looked at artificial pancreas with a greater focus on its state of art In chapter (2). Chapter (3) gives an analysis of some of the existing models for the glucose-insulin system. In chapter (4), we designed a control law for glucose control using one of the available models for the glucose insulin system and one of the models for insulin absorption. We went further in this chapter, to present the state Observer that will be used to estimate insulin measurements. We end the thesis with chapter (5) in which we carried out simulations on a virtual patient on the basis of parameter estimates obtained from data related to an IVGTT experiment conducted on an obese patient, studied at the Catholic University of Rome, Department of Metabolic Diseases. Logical conclusions are drawn from the simulations. Finally in this chapter, we made concrete proposals for further research work on artificial Pancreas.

Chapter 2

Artificial Pancreas

Definition 2.0.1. *The artificial pancreas is a technology in development to help people with diabetes automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.*

There are several important exocrine (digestive) and endocrine (hormonal) functions of the pancreas, but it is the lack of insulin production which is the motivation to develop a substitute. While the current state of insulin replacement therapy is appreciated for its life-saving capability,the task of manually managing the blood sugar level with insulin alone is arduous and inadequate.
The goals of artificial pancreas are:

- to improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia
- to ease the burden of therapy for the insulin-dependent.
- to mimic normal stimulation of the liver by the pancreas.

Some of the approaches under consideration are:

- the medical equipment approach- using an insulin pump under closed loop control using real time data from a continuous blood glucose sensor.
- the bioengineering approach- the development of a bio-artificial pancreas consisting of a biocompatible sheet of encapsulated beta cells. When surgically implanted, the islet sheet will behave as the endocrine pancreas and will be viable for years.
- the gene therapy approach- the therapeutic infection of a diabetic person by a genetically engineered virus which causes a DNA change of intestinal cells to become insulin-producing cells.

We will focus only on the medical equipment approach.

2.1 Closed loop Artificial Pancreas

It is an electro mechanical system that employs negative feedback to autonomously release insulin into the body in such a way that physiologically mimics the insulin producing activity of healthy pancreatic beta cells. The logic behind such a device is the idea that by delivering insulin into the body in the same way that a healthy pancreatic beta-cell would do, normal blood glucose levels can be achieved in a diabetic patient.[26] The artificial pancreas will ideally require very little manual input from the user, and thus also significantly decrease the treatment burden of diabetes. Due to their complete inability to produce insulin, patients with type 1 diabetes will be the main beneficiaries of an insulin-delivering artificial pancreas [27]. However, because type 2 diabetics become insulin dependent at later stages of their disease,it may be beneficial to these patients as well [28].

2.1.1 How the artificial Pancreas Works

The artificial pancreas essentially consists of three important components: a glucose sensor/monitor, an insulin pump to store and deliver insulin, and a control algorithm to compute the amount of insulin to be delivered and communicate between the sensor and the pump [28]. Figure (2.1.1) shows an overview of the three components that comprise a closed loop artificial pancreas and how these components interact with one another.

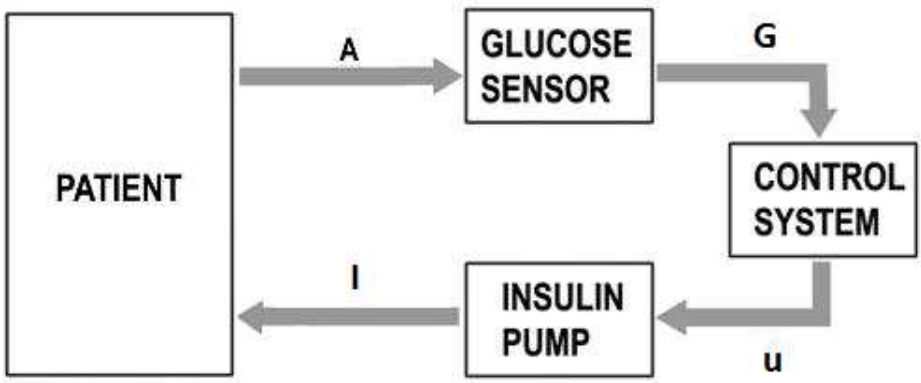


Figure 2.1: Artificial Pancreas

Before, during and after meals, as well as at night, glucose levels are continuously monitored by a sensor in a patient's blood or interstitial fluid. The glucose sensor determines the patient's blood or interstitial glucose concentration, and it sends this information to the control system of the artificial pancreas. The control system then uses a mathematical algorithm to compute the required insulin dosage that needs to be administered to return glucose levels back to baseline. This information is then forwarded to the insulin pump, which releases the appropriate amount of insulin into the bloodstream. There may also be a feature for the patient to manually program their insulin pump to inject themselves with a customized dosage of insulin if the need arises.

2.1.2 Insulin delivery Modes

There are two types of insulin delivery modes which can be implemented in an artificial pancreas: closed-loop or semi closed-loop. In a closed-loop insulin delivery system, the artificial pancreas will continuously and automatically deliver insulin to the patient without any manual input by the patient[28]. The artificial pancreas will simply continuously monitor the patient's glucose concentrations and autonomously deliver the appropriate insulin dose in order to keep the patient's glucose concentration within the normal range.
On the other hand, the artificial pancreas may also operate in a semi-closed-loop insulin delivery mode , where it will function completely autonomously, except for when the patient is intending to consume a meal or engage in exercise. During these times, the device will require the patient to provide it with information regarding the size and composition of their upcoming meal or the intensity level of their planned exercise regimen. The artificial pancreas then uses this information to immediately modify the amount of insulin being delivered to the patient in order to pre-compensate for the anticipated fluctuations in glucose concentration.

2.1.3 Body interface Designs for Sensor and Insulin Pump

There are three major types of artificial pancreas devices based on the location of the glucose sensor and insulin delivery pump within the body[28]:

- The subcutaneous (SC) sensing and SC delivery (SC-SC) system.
- The intravenous (IV) sensing and intraperitoneal (IP) delivery (IV-IP) system.
- The intravenous (IV) sensing and IV insulin delivery (IV-IV) system.

Each of the three categories of devices has their own distinct advantages and disadvantages. The SC-SC system has the advantage of being a minimally invasive system when compared to the IV-IP or IV-IV system. The minimally invasive nature of an SC-SC system gives it significant potential to achieve widespread application and, as a result, many of the current research efforts are devoted towards creating such a device. However, because SC-SC devices are inserted into the interstitial fluid of the subcutaneous tissue and not directly into the bloodstream, there are considerable delays associated with SC insulin delivery[28]. These delays are related to the time taken for newly injected insulin to migrate from the interstitial tissue, into the blood stream and the body's cells. In addition, there are also delays associated with glucose sensing in a SC-SC system, due to the time lag involved with glucose diffusing from the bloodstream into the subcutaneous interstitial fluid[29]. Due to the considerable delays associated with a SC-SC system, it currently appears that an SC-SC artificial pancreas will have difficulty operating in a completely closed-loop fashion, and users of an SC-SC device may have to manually enter in meal information to assist with insulin delivery [28].
The IV-IP system has lower insulin delivery delays when compared to an SC-SC system.

Nevertheless, the delays that remain are still substantial. For instance, there is an approximate delay of 70 minutes from the time that insulin is delivered intraperitoneally to when glucose levels noticeably drop in the blood. Additionally, there are minor glucose sensing delays associated with the IV glucose sensor. Another drawback of the IV-IP technology is that it is considerably more invasive than the SC-SC system, and can result in complications such as intravenous line infections and insulin pump occlusion [28].
The IV-IV artificial pancreas system is presently used only in special circumstances, such as in critically ill patients, surgical operations, or for research purposes. The benefit of this approach is that there are minimal insulin delivery delays (i.e., approximately 30 minutes due to the delay of insulin action in the blood), which facilitates the development of a fully closed-loop IV-IV system. The drawback of the IV-IV approach is that it is relatively invasive because it requires vascular access for both glucose monitoring and insulin delivery. As expected, IV-IV devices are also associated with a high risk of infection as well as biocompatibility issues[28].
Artificial pancreas control algorithms need to be adapted based on the continuous glucose sensing interface (subcutaneous, intra-peritoneal or intravenous) being employed, because of the associated differences in sensing delays between these interfaces. For instance, any algorithm designed to process interstitial (subcutaneous) glucose measurements will need to account for the delay between the change of blood and interstitial glucose levels when computing the insulin dosage to deliver. Similarly, control system algorithms need to be modified based on the different routes of insulin pump delivery because of their different insulin absorption rates

2.1.4 Current Artificial Pancreas devices

Today, artificial pancreas technology has developed to the point where there are a number of early models currently available in prototype forms. Three prominent prototype models are discussed here.

Medtronic Minimed

A SC-SC closed-loop artificial pancreas device has been developed using the Medtronic Minimed (Northbridge CA, US) continuous glucose monitoring system (CGMS), and Medtronic Paradigm insulin pump[30].
In one study of this device, 10 individuals with type 1 diabetes tested the device in a fully closed-loop insulin delivery mode over a 28-hour period. During the study, preprandial (before meal consumption) and postprandial glucose levels were measured at 5.6 $\pm$ 1.6 and 10.8 $\pm$ 2.6 mmol/L (mean $\pm$ SD). Patients with diabetes should aim to achieve preprandial blood glucose levels of 3.9 to 6.9$mmol/L$, and peak postprandial blood glucose levels of less than 10.0$mmol/L$. In total, 17 hypoglycemia events were observed, primarily after meals, suggesting excessive insulin secretion by the device. Under closed-loop control, glucose was within the range of 3.9 to 10.0$mmol/L$ 75% of the time.
A team from Yale carried out another study of this device in 17 well-controlled diabetics over a 34-hour period. During this study, a comparison was made between the effectiveness of the device operating in a fully closed-loop approach, and its operation in a

semi-closed-loop meal announcement mode, which included manual insulin delivery 10 to 15 minutes before meals. Better results were obtained with the device operating in meal announcement mode, with postprandial peak glucose values of 10.8 ± 2.6 mmol/L (vs. 12.6 ± 2.8 mmol/L for fully closed-loop) and mean glucose levels of 7.8 ± 2.6 mmol/L (vs. 8.3 ± 3.2 mmol/L for fully closed-loop).

Roche Diagnostics

An SC-SC artificial pancreas prototype has been developed by Roche Diagnostics GmbH (Manheim, Germany). The device operates in a semi closed-loop insulin delivery fashion with meal announcement, and employs a unique "empirical" control algorithm which administers an insulin bolus every 10 minutes according to a set of clinically derived rules. The prototype is designed to monitor subcutaneous interstitial glucose levels for up to 4 to 5 days[30]. The Roche system was tested on 12 type 1 diabetic subjects over a period of 32 hours and compared to results obtained with regular self-directed therapy. Overall, the device achieved similar mean glucose concentrations when compared to self directed therapy (6.9 vs. 6.2 mmol/L). The prototype reduced the number of hypoglycemia events per day from 3.2 to 1.1 per subject. In addition, during the evaluation, 60% of glucose readings obtained with the device were within the desired 5.0 to 8.3$mmol/L$ range, compared to only 45% of readings with self directed therapy.

EVADIAC Group

A fully closed-loop IV-IP device is being developed by the "Evaluation dans le Diabete du Traitement par Implants Actifs" (EVADIAC) group, a team of French doctors and researchers. Their artificial pancreas system employs an intravenous long term sensor system (LTSS) developed by Medtronic MiniMed. The LTSS, an enzymatic oxygen based sensor, is implanted in the superior vena cava through direct jugular access and is connected by a subcutaneous lead to an intraperitoneal insulin pump implanted in the abdominal wall. An external wireless transmitter receiver is used to communicate with the intraperitoneal pump [30].
The EVADIAC prototype was tested in four elderly type 1 diabetics over a 48 hour period. During this evaluation, blood glucose levels were within 4.4 to 13.3$mmol/L$, 84.1% of the time. In fact, excluding meals, glucose levels were below 13.3$mmol/L$ for 98%
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 pumps are being widely used, and a number of continuous glucose monitoring systems have received regulatory approval [31]. 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 [31, 32]. 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
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 Mathematical model for the Glucose Insulins system, 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 glucose insulin regulatory system. 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. Next we will take a look at some of the existing models.

Chapter 3

Mathematical Models for glucose-insulin system

Many Mathematical models have been developed for studying problems related to diabetes.These includes Ordinary Differential Equations (modeling), Delay Differential Equations (DDEs), Partial Differential Equations (PDEs) , Fredholm Integral Equations(FIEs), Stochastic Differential Equations (SDEs) and Integro Differential Equations (IDEs) (see [12] for more details about such models).In this chapter we will present an overview of some of the mathematical models appearing in the literature for use the study of problems related to diabetes.General approaches include the technique of compartment-split by introducing auxiliary variables in ODEs([13]), and modeling in delay differential equations by using explicit time delays in either discrete or distributed forms ([4, 15, 8]). Modeling by explicit delays is more natural and accurate, although the analysis is usually harder([4]).Models in the form of delay differential equations grouped according tp their functions include:

- Models used to analyze the ultradian insulin secretion oscillations
- Models used with dignostic tests
- Models related to insulin therapies
- Models taking intracellular activity of β cells into account

In this Chapter we present models of first and second category.

3.1 Ultradian Insulin Secretion Related Models

Insulin is released in a biphasic manner when the glucose concentration is raised from subthreshold to stimulatory levels, with a rapid peak at 2-4 min (first phase), a decrease lasting 10-15 min (pulsatile insulin secretion) followed by a gradual increase within the next couple of hours (50-120 minutes), Chew et al (2009) ([14]), (second phase, ultradian insulin secretion). As mentioned in ([14]), ultradian oscillations have been seen after meal ingestion during continuous enteral nutrition, and during intravenous

glucose infusion. Historically, it was in 1923 when rapid and slower oscillations in the peripheral concen- trations of glucose were reported by Karen Hansen and half a century later rapid oscillations in the peripheral insulin concentrations were demonstrated. As several authors mention, the precise mechanisms generating ultradian oscillations are not fully understood yet and the two most common mechanisms mentioned are:

- instability of the glucose-insulin feedback loop, where the insulin oscillations entrain those of glucose
- existence of an intrapancreatic pacemaker.

In this section, we present the ODEs models by Sturis et al (1991)([13]) and Tolić et al (2000) ([16]), that formed the basis of the DDEs models, the DDEs models by Drozdov and Khanina (1995)([17]), Li et al (2006)([18]) model in addition to Chen and Tsai (2009) ([19]) model.

3.1.1 Sturis et al (1991) ([13]) Compartmental-Split ODE Model

Based on two negative feedback loops describing the effects of insulin on glucose utilization and production and the effect of glucose on insulin secretion, the authors Sturis, Polonsky, Mosekilde and Van Cauter (1991) ([13]), developed a six dimensional ODE model. This model was later simplifies by Tolić , Mosekilde and Sturis (2000)([16]) . This model has been the basis of several DDE models. It has the following form:

$$
\begin{aligned}
\frac{dG(t)}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))f_4(I_i(t)) + f_5(x_3(t)) \\
\frac{dI_p(t)}{dt} &= f_1(G(t)) - E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_p} \\
\frac{dI_i(t)}{dt} &= f_1(G(t)) - E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_i} \\
\frac{dX_1(t)}{dt} &= \frac{3}{t_d}\left(I_p(t) - X_1(t)\right) \\
\frac{dX_2(t)}{dt} &= \frac{3}{t_d}\left(X_1(t) - X_2(t)\right) \\
\frac{dX_3(t)}{dt} &= \frac{3}{t_d}\left(X_2(t) - X_3(t)\right)
\end{aligned}
\tag{3.1}
$$

where G(t) is the mass of glucose, $I_p(t), I_i(t)$ the mass of insulin in the plasma and the intercellular space, respectively, V_p is the plasma insulin distribution volume, V_i is the effective volume of the intercellular space, E is the diffusion transfer rate, t_p , t_i are insulin degradation time constants in the plasma and inter-cellular space, respectively, G_{in} indicates (exogenous) glucose supply rate to plasma, and $X_1(t), X_2(t), X_3(t)$are three additional variables associated with certain delays of the insulin effect on the hepatic glucose production with total time t_d . $f_1(G)$ is a function modeling the pancreatic insulin production as controlled by the glucose concentration, $f_2(G)$ models insulin independent

glucose utilization (by the brain and nerves), $f_3(G)f_4(I)$ are functions modeling insulin dependent uptake (mostly due to fats and muscles cells) and $f_5(I)$ is a function modeling glucose production controlled by insulin concentration.
The glucose triggered time delay in the glucose insulin system is taken care of by breaking the insulin system into two separate compartments and the other one, the hepatic glucose production delay is fulfilled by the three auxiliary variables: X_1, X_2, X_3. This model simulated ultradian insulin secretion oscilations numerically.

3.1.2 Drozdov and Khanina (1995)([17]) Single Delay DDE Model

Drozdov and Khanina in 1995 proposed a model that uses a single explicit time delay instead of double delays in modeling ultradian oscillations in human insulin. The model equations are:

$$\begin{aligned}
\frac{dI_p(t)}{dt} &= f_1\left(\frac{0.1G(t)}{V_3}\right) - \left(\frac{E}{V_p} + \frac{1}{t_p}\right) I_p(t) + \frac{E}{V_i} I_i(t) \\
\frac{dI_i(t)}{dt} &= \frac{E}{V_p} I_p(t) - \left(\frac{E}{V_i} + \frac{1}{t_i}\right) I_i(t) \\
\frac{dG(t)}{dt} &= f_5\left(\frac{I_p(t-\tau_g)}{V_p}\right) - \frac{0.1G(t)}{V_g} f_4\left(\frac{I_i(t)}{V_i}\right) + G_{in} - P_0
\end{aligned} \tag{3.2}$$

Where P_0 is a constant, τ_g is the delay in glucose production and the model parameters have the same meaning as in equation (3.1).The functions f_1, f_4, f_5 are suitable functions modeling the same thing as in (3.1).
Numerical results were obtained for a number of G_{in} and τ_g values. Stability analysis is also presented in the paper. The claim is that for a very large and very small values of G_in the steady state is stable and ultradian oscillations do not arise, but for moderate G_{in} values, the steady state solutions become unstable and periodic oscillations of insulin and glucose occur.

3.1.3 The Two Explicit Time Delay Model Proposed by Li et al (2006)[18]

The authors consider two time delays; the first one, τ_1 to denote the total time delay from the time that the glucose concentration level is elevated to the moment that the insulin has been transported to the interstitial space and becomes 'remote insulin', the second one (τ_2) has to do with the delay of the effect of hepatic glucose production measured from the time that insulin has become 'remote insulin' to the moment that a significant change of hepatic glucose production occurs. The model is formulated by the

observation of the Law of Conservation. The model is given by

$$\begin{aligned}\frac{dG(t)}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t-\tau_2)) \\ \frac{dI(t)}{dt} &= f_1(G(t-\tau_1)) - d_i I(t)\end{aligned} \tag{3.3}$$

$$I(0) = I_0 > 0, G(0) = G_0 > 0, G(t) = G_0, t \in [-\tau_1, 0], I(t) = I_0, t \in [-\tau_2, 0], \tau_1, \tau_2 > 0$$

where $d_i > 0$ is the insulin clearance rate and I(t) is the insulin concentration. The other parameters are defined as above.
Numerical simulations including bifurcation analysis are given in the paper and comparisons are made to some existing models.Based on the bifurcation analysis, the authors suspect that the total time delay τ_1 is critically responsible for the oscillation. The total time delay is measured from the moment that the glucose concentration level starts to increase to the moment that the insulin has been transported to the interstitial space.

3.1.4 The Two Explicit Time Delay Model Proposed by Chen and Tsai (2009) [19]

The authors proposed a modified version of the Li et al (2006) and Li and Kuang (2007) ([15]) models with respect to the following:

- They use a variable glucose infusion function $G_{in}(t)$ instead of the constant G_{in} used in [18] throughout the simulation time, so that external inputs like food uptake can be simulated too.
- They introduce two additional functions f_6 and f_7 to provide the effects of hyperglycemia, with the rest of the functions $f_1 - f_5$ the same as in [18]
- They introduce two additional parameters α, β for the purpose of estimating the condition of major dysfunction of diabetes (α for insulin release from the pancreas, β for the ability of insulin-dependent glucose utilization - small β value indicates increasing severity of insulin resistance).
- They use $f_7(G(t) - 330)$ for describing the kidney glucose excretion rate above the urine threshold (330 $\frac{mg}{dl}$).
- They perform least squares estimation of the parameters $G_0, I_0, \tau_1, \tau_2, \alpha, \beta, d_i, t_m, m \in M$, where $m = 1, 2, 3$ and t_m are CHO (infused carbohydrate) times

The model equations are:

$$\begin{aligned}\frac{dG(t)}{dt} &= [G_{in}(t) + f_5(I(-\tau_2))f_6(G(t))] - [f_2(G(t)) + f_7(G(t) - 330)] - \beta f_3(G(t))f_4(I(t)) \\ \frac{dI(t)}{dt} &= \alpha f_1(G(t-\tau_1)) - d_i I(t)\end{aligned} \tag{3.4}$$

with

$$G_{in}(t) = \sum_{m \in M} G_m(t - t_m)u(t - t_m)$$

where where G(t), I(t) denote glucose and insulin concentrations respectively, $G_m(t - t_m), m \in M$ denotes the mth exogenous food uptake at $t_m, u(t - t_m)$ is a unit step function that has the unity value for $t \geq t_m$. $G_{in}(t)$ is the overall effective exogenous food uptake.

3.2 Models used with Diagnostic tests

A number of diagnostic tests have been developed to assess two indices important in metabolic research known as insulin sensitivity and glucose effectiveness and also the β cell function. An example of such diagnostic tests is the IVGTT (intravenous glucose tolerance test).
The intravenous glucose tolerance test (IVGTT) involves the intravenous administration of a bolus of glucose and the frequent sampling of glucose and insulin concentrations. Two noticeable differences in modeling IVGTT from the glucose-insulin regulation are that

- The large bolus intravenous glucose infusion causes the time delay of the hepatic glucose production insignificant and thus negligible; and
- The bi-phasic insulin secretion caused by the quick and direct stimulation of large bolus of glucose infusion in plasma.

These distinguish the modeling rationale from the ultradian oscillation. In this case, only one time delay should be considered.

Definition 3.2.1. *Insulin sensitivity is defined as the ability of insulin to enhance glucose effectiveness and glucose effectiveness, is the ability of glucose to promote its own disposal*

Several models have been proposed to interprete the IVGTT. Some of which are: the minimal model proposed by Bergman, Ider, Bowden and Cobelli (1979)([20]), the DDEs models of Panunzi, Palumbo, and De Gaetano (2007) ([8]), Giang, Lenbury, De Gaetano, Palumbo (2008) ([21]), and the integro- differential equation model of Palumbo, Panunzi, De Gaetano (2007) ([4]).

3.2.1 The Minimal model Proposed by Bergman et al(1979)([20])

The first IVGTT model is the minimal model and it has been widely utilized in many clinics and extended in various applications . The model is an ODE model formulated

in split compartment and is given by

$$\begin{aligned}\frac{dG(t)}{dt} &= -(b_1 + X(t))G(t) + b_1 G_b \\ \frac{dX(t)}{dt} &= -b_2 X(t) + b_3(I(t) - I_b) \\ \frac{dI}{dt} &= b_4[G(t) - b_5]^+ t - b_6(I(t) - I_b)\end{aligned} \tag{3.5}$$

with initial conditions $G(0) = b_0, X(0) = 0, I(0) = b_7 + I_b$. Here $G(t)[mg/dl], I(t)[U/ml]$ is the plasma glucose, insulin concentration at time $t[min]$, respectively. $X(t)[min^{-1}]$ stands for the auxiliary function representing insulin-excitable tissue glucose uptake activity that is assumed to be proportional to insulin concentration in a "distant" compartment. $G_b[mg/dl], I_b[U/ml]$ is the subjects baseline glycemia, insulinemia, respectively. $b_0[mg/dl]$ is theoretical glycemia at time 0 after the instantaneous glucose bolus intake. $b_1[min^{-1}]$ is the insulin-independent constant of tissue glucose uptake rate. $b_2[min^{-1}]$ is the rate constant describing the spontaneous decrease of tissue glucose uptake ability. $b_3[min^{-2}(U/ml)^{-1}]$ is the insulin-dependent increase in tissue glucose uptake ability, per unit of insulin concentration excess over the baseline. $b_4[(U/ml)(mg/dl)^{-1}min^{-1}]$ is the rate of pancreatic release of insulin after the intake of the glucose bolus, per minute per unit of glucose concentration above the "target" glycemia $b_5[mg/dl].b_6[U/ml]$is the first order decay rate for insulin in the plasma. $b_7[U/ml]$ is the plasma insulin concentration at time 0, above basal insulinemia, immediately after the glucose bolus intake.
While the minimal model has its features widely used in research, it has several drawbacks in mathematics as pointed out in ([22]). The parameter fitting is to be divided into two separate parts: first, using the recorded insulin concentration as given input data in order to derive the parameters in the first two equations in the model, then using the recorded glucose concentration as given input to derive the parameters in the third equation. However, the system is an integrated physiological dynamic system and one should treat it as a whole system and be able to conduct a single step parameter fitting process. Secondly, some of the mathematical results produced by this model are not realistic. Specifically, it can be shown that the minimal model does not admit an equilibrium and the solutions may not be bounded. Finally, the non-observable auxiliary variable $X(t)$ is artificially introduced to delay the action of insulin on glucose. An alternative and natural approach is to introduce explicitly the time delay in the model. To address these issues, De Gaetano and Arino proposed a so called dynamic model ([22]) with explicit delay in distributed form. Recently, Palumbo et al ([8]) built a discrete delay differential equation model to further study the short but complicated phenomenon. Although not able to confirm the conclusion analytically, the authors produced reasonable simulation profile with experimental raw data statistically ([4, 8])

3.2.2 Palumbo et al (2007) Model ([8]) and Palumbo et al (2007)([4])

In [8] the authors present 4 two-compartment models for the plasma glucose and the plasma insulin concentrations following an IVGTT, two without delay and two with

delay on insulin action (τ_i).For each model the glucose equation includes a second-order linear term describing insulin-dependent glucose uptake, expressed in net terms since it includes changes in liver glucose delivery and changes in glucose uptake, as well as a zero-order term expressing the net balance between a possible constant, insulin-independent fraction of hepatic glucose output and the essentially constant glucose utilization of the brain. A linear term for glucose tissue uptake may or may not be present, and the effect of plasma insulin on glucose kinetics may or may not be delayed. Variations in plasma insulin concentration depend on the spontaneous decay of insulin and on pancreatic insulin secretion. After the nearly instantaneous first phase insulin secretion, represented in the model by means of the initial condition, a delay term is considered; it represents the pancreatic second phase secretion and formalizes the delay with which the pancreas responds to variations of glucose plasma concentrations. In this paper,the authors identified a special case (the model A in the paper) as the best model under the Akaike Information Criterion (AIC), ('without first order plasma glucose elimination (K_{xgi}) and without delay on insulin action'). The model is given as follows.

$$\begin{aligned} \frac{dG(t)}{dt} &= -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G}, \\ \frac{dI(t)}{dt} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}f(G(t-\tau_g)) \end{aligned} \tag{3.6}$$

The parameters

$$T_{gh} = K_{xgi}I_bG_bV_g$$

,

$$T_{iGmax} = K_{xi}I_bV_If(G_b)$$

where

- $G(t)$ in [mM] denotes the plasma glycemia.
- $I(t)$ in [pM] denotes the plasma insulinemia.
- K_{xgi} in [$\text{min}^{-1}\,\text{pM}^{-1}$] is the rate of glucose uptake by insulin dependent tissues per pM of plasma insulin concentration.
- T_{gh} in [min^{-1} (mmol/kgBW)] is the net balance between hepatic glucose output and insulin independent zero-order glucose tissue uptake.
- V_G in [L/kgBW] is the apparent glucose distribution volume.
- K_{xi} in [min^{-1}] is is the apparent first order disappearance rate constant for insulin.
- T_{iGmax} in [min^{-1}(pmol/kgBW)] is the maximal rate of second phase insulin release.
- V_I in [L/kgBW] is the apparent insulin distribution volume.
- τ_g in [min] is the apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations.

- $t_{max,I}$ in [min] is the time to maximum insulin absorption
- The non linear function $f(\cdot)$ models the pancreas Insulin Delivery Rate as

$$f(G) = \frac{(\frac{G}{G^*})^\gamma}{1 + (\frac{G}{G^*})^\gamma}$$

.

- The γ in $f(\cdot)$ denotes the progressivity with which the pancreas reacts to circulating glucose concentrations.
- G^* and I^* are the steady state. G^* correspond to the glycemia at which the insulin release is half its maximal rate.

The authors proved that the unique steady state (G^*, I^*) is globally asymptotically stable when

$$\gamma \leq 1$$

under the condition

$$\frac{K_{xgi} I_b \gamma}{1 + (\frac{G_b}{G^*})^\gamma} \leq K_{xg} + K_{xgi} I_b$$

regardless of the length of the time delay. However this case only accounts for 3% of the experimental data the authors obtained. For more general cases, the authors have shown that there exists a bifurcation point $\tau_0 > 0$ such that the steady state is locally asymptotically stable when the delay is smaller than τ_0 .Evidently, delay dependent conditions for global stability are needed to improve the analysis.The authors also demonstrated that the insulin sensitivity index can be obtained in the same way as in the minimal model but it is more effective.
Recently, in Palumbo et al (2008) ([21]), the authors considered the most general of the 4 models of the family introduced in [8] (with first order plasma glucose elimination (K_{xg}) and with delay in insulin action (τ_i)) and deal with theoretical results concerning global stability under certain conditions on the parameters and the effect of the delays τ_i, τ_g on the oscillatory behavior of the solutions when $K_{xg} = 0$.If $K_x g = 0$ and $\tau_i = 0$ the DDE model of [21] reduces to that of [8].
In [4], the authors, Palumbo, Panunzi and De Gaetano considered a model that consists of a system of two coupled integro-differential equations where different choices of the convolution kernels result in a number of different models including DDEs with constant delay. The model equations are

$$\begin{aligned} \frac{dG(t)}{dt} &= -K_{xg} G(t) - K_{xgi} G(t) \tilde{I}(t) + \frac{T_{gh}}{V_G} \\ \frac{dI(t)}{dt} &= -K_{xi} I(t) + \frac{T_{iGmax}}{V_I} f(\tilde{G}(t)) \end{aligned} \tag{3.7}$$

where

$$\tilde{G}(t) = \int_0^{\tau_g} w_g(\theta) G(t - \theta)\, \mathrm{d}\theta$$

$$\tilde{I}(t) = \int_0^{\tau_i} w_i(\theta) I(t-\theta)\,\mathrm{d}\theta$$

and the kernels

$$w_g : [0, \tau_g] \to \mathbb{R}^+$$
$$w_i : [0, \tau_i] \to \mathbb{R}^+$$

non-negative square integrable functions sunch that

$$\int_0^{\tau_g} w_g(\theta) G(t-\theta)\,\mathrm{d}\theta = 1$$

,

$$\int_0^{\tau_i} w_i(\theta) I(t-\theta)\,\mathrm{d}\theta = 1$$

and there exist T_g, T_i such that

$$\int_0^{\tau_g} w_g(\theta) I(t-\theta)\,\mathrm{d}\theta \leq T_g < \infty$$

$$\int_0^{\tau_i} w_i(\theta) I(t-\theta)\,\mathrm{d}\theta \leq T_i < \infty$$

Kernel choices:

- $w_g(t) = \delta(t-\tau_g), w_i(t) = \delta(t-\tau_i)$
- $w_g(t) = \alpha_g^2 t e^{-\alpha_g t}, w_i(t) = \alpha_i^2 t e^{-\alpha_i t}$

In the first case above, the integro- differential system reduces to a DDE system of two equations with constant delays τ_g, τ_i

$$\begin{aligned} \frac{dG(t)}{dt} &= -K_{xg} G(t) - K_{xgi} G(t) I(t-\tau_i)(t) + \frac{T_{gh}}{V_G} \\ \frac{dI(t)}{dt} &= -K_{xi} I(t) + \frac{T_{iGmax}}{V_I} f(G(t-\tau_g))(t)) \end{aligned} \tag{3.8}$$

In the second case with $\tau_g = \infty, \tau_i = \infty$ chain trick, using a linear, the authors transformed the integro - differential equation system into a system of six ODEs.
The following theoretical results are presented in the paper: It is shown that the integro-differential system has positive solution and that it is persistent. Local stability is shown for the DDE system and the ODE system. Global stability is shown for the IDE system, depending upon a condition on parameter values

$$\frac{K_{xgi} I_b \gamma}{1 + (\frac{G_b}{G^*})^\gamma} \leq K_{xg} + K_{xgi} I_b$$

They remarked that the above condition is not satisfied for particular values making sense physiologically.
As seen above, there are several DDE insulin regulatory system models. Until 2009, non

of these model had bee used to control plasma glucose concentration. The first attempts were made by Palumbo (see palumbo et al (2009ab) ([5, 24]), using the IVGTT DDE models proposed by Palumbo et al (2007)([8]) and Palumbo et al (2007) ([4]).In these papers, the authors designed an intravenous insulin administration to track a desired plasma glycemia.The authors used the model below to design the control law.

$$\begin{aligned}\frac{dG(t)}{dt} &= -K_{xgi}G(t)I(t-\tau_i)(t) + \frac{T_{gh}}{V_G} \\ \frac{dI(t)}{dt} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}f(G(t-\tau_g))(t)) + u(t)\end{aligned} \tag{3.9}$$

where u(t) in $[pM/min]$ is the insulin delivery rate; ie. the control input with $G(\tau) = G_0(\tau), I(\tau) = I_0(\tau), \tau \in [-\tau_g, 0]$
In this thesis, we aim to achieve the same goal of tracking a desired glucose reference , by means of subcutaneous (instead of intravenous) infusion. Since Insulin will be administered subcutaneously in our case, we will take into account subcutaneous insulin kinetics. We will adopt model 1 of table 1 in Wilinska et al (2005) ([25]) for insulin absorption. Thus Insulin absorption in the subcutaneous layer is described as:

$$\begin{aligned}\frac{dQ_1}{dt} &= u(t) - K_{a1}Q_1 \\ \frac{dQ_2}{dt} &= K_{a1}Q_1 - K_{a1}Q_2\end{aligned} \tag{3.10}$$

where Q_1 and Q_2 represents insulin mass (mU) in the accessible and non-accessible subcutaneous compartments, respectively and K_{a1} is the transfer rate.

Chapter 4

A DDE-Model Based Approach to Glucose Control

The model that we will use to design our control law consist of the Palumbo et al (2007) model described in equation (3.6) coupled to the linear model of subcutaneous insulin absorption described in equation (3.10). The model equations are:

$$\begin{aligned}
\frac{dG(t)}{dt} &= -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G}, \\
\frac{dI(t)}{dt} &= -K_{xi}I(t) + \frac{T_{iGmax}}{V_I}f(G(t-\tau_g)), \\
\frac{dS_2(t)}{dt} &= \frac{1}{t_{max,I}}S_1(t) - \frac{1}{t_{max,I}}S_2(t), \\
\frac{dS_1(t)}{dt} &= -\frac{1}{t_{max,I}}S_1(t) + u(t),
\end{aligned} \tag{4.1}$$

Where

- $G(t)$ in [mM] denotes the plasma glycemia.
- $I(t)$ in [pM] denotes the plasma insulinemia.
- S_2 is the insulin mass in the accessible subcutaneous depot.
- S_1 in [pmol] is the insulin mass in the accessible subcutaneous depot.
- K_{xgi} in [$\text{min}^{-1}\,\text{pM}^{-1}$] is the rate of glucose uptake by insulin dependent tissues per pM of plasma insulin concentration.
- T_{gh} in [min^{-1} (mmol/kgBW)] is the net balance between hepatic glucose output and insulin independent zero-order glucose tissue uptake.
- V_G in [L/kgBW] is the apparent distribution of volume for glucose.
- K_{xi} in [min^{-1}] is is the apparent first order disappearance rate constant for insulin.

- T_{iGmax} in [min^{-1}(pmol/kgBW)] is the maximal rate of second phase insulin release.
- V_I in [L/kgBW] is the apparent distribution of volume for insulin.
- τ_g in [min] is the apparent delay with which the pancreas varies secondary insulin release in response to varying plasma glucose concentrations.
- $t_{max,I}$ in [min] is the time to maximum insulin absorption
- $u(t)$ in [pM/min] is the subcutaneous insulin delivery rate; ie. the control input.
- The non linear function $f(\cdot)$ models the pancreas Insulin Delivery Rate as

$$f(G) = \frac{(\frac{G}{G^*})^\gamma}{1 + (\frac{G}{G^*})^\gamma}$$

  .
- The γ in $f(\cdot)$ denotes the progressivity with which the pancreas reacts to circulating glucose concentrations.
- The G^* in [mM] is the glycemia at which the insulin release is half its maximal rate.

4.1 Properties of the Model

- It agrees with Mathematical Principles in that it exhibits satisfactory properties of solutions:
  - Positivity and boundedness of solution
  - stability of a unique equilibrium point

  (see [8] for the proof of the case with no exogenous input)
- It conforms to established physiological concepts.
  - It present a realistic Pancreatic IDR
- It maybe used for many closed loop control strategy on type 1 and type 2 diabetic patients.
- It can be adopted to perform clinical trials on healthy subjects
- It easy enough to be used to synthesize control laws
- It is statistically robust, in that, its parameters are statistically identifiable with very good precision by means of standard perturbation experiment(see [1] for the case of obese, insulin resistant subject and [4] for the case of a healthy subject).

4.2 Linearisation of the model and Derivation of the Control Law

We linearized the system by means of a state feedback and coordinate transformation (see [9]).The following definitions will be useful.

Definition 4.2.1. ***Lie Derivative:*** *The lie Derivative L_φ of a C^∞ function $\lambda(x)$ with respect to a C^∞ vector field φ is define as*

$$L_\varphi \lambda(x) := \langle \bigtriangledown \lambda(x), \varphi \rangle \tag{4.2}$$

Where $\bigtriangledown$ stands for the gradient operator.Moreover, the symbol $L^k_\varphi \lambda(x)$ means the k-times repeated iterations of $L_\varphi \lambda(x)$

$$L^k_\varphi \lambda(x) = L_\varphi (L^{k-1}_\varphi \lambda(x))(x) \tag{4.3}$$

$$L^0_\varphi \lambda(x) = \lambda(x) \tag{4.4}$$

Consider:

$$\begin{aligned} \dot{x} &= f(x(t)) + g(x(t))u(t) \\ y(t) &= h(x(t)) \\ x(0) &= x_0 \end{aligned} \tag{4.5}$$

where $h : \mathbb{R}^n \to \mathbb{R}$ is a C^∞ function and f is a C^∞ vector field on $\mathbb{R}^n$,

Definition 4.2.2. ***Relative degree of a nonlinear system:*** *The nonlinear system (4.5) has relative degree r, $(r \leq n)$ if the following holds:*

- $$L_g L^i_f h(x) = 0, i = 0, ..., r-2$$
- $L_g L^{r-1}_f h(x) \neq 0 \ \forall x \in B(x_0, \delta)$

Definition 4.2.3. ***Observability:*** *A system is said to be observable if, for any possible sequence of state and control vectors, the current state can be determined in finite time using only the output.*

Definition 4.2.4. ***Observability Matrix:*** *The observability matrix of (4.5) $Q(x)$ is defined as (see [9])*

$$Q(x) = (\frac{d}{dx}) \begin{pmatrix} h(x) \\ L_f h(x) \\ . \\ . \\ . \\ L^{n-1}_f h(x) \end{pmatrix} \tag{4.6}$$

Definition 4.2.5. ***State controllability:*** *Complete state controllability describes the ability of an external input to move the internal state of a system from any initial state to any other final state in a final time interval.*

Proposition 4.2.1. *The nonlinear system defined in equation*(4.5) *is said to be observable if* $dim(Q(x)) = n$

We will now apply the above definitions and propositions to our model to enable us linearize it and provide us with a feedback controller that stabilizes the system.
Let $G_{ref}(t)$ be the desired glucose reference signal to be tracked, which we assumed to be smooth and bounded.
Let

$$x(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \end{pmatrix} = \begin{pmatrix} G(t) \\ I(t) \\ S_2(t) \\ S_1(t) \end{pmatrix} \tag{4.7}$$

$$y(t) = G(t) - G_{ref}(t) \tag{4.8}$$

Define

$$z(t) = \phi(x) = \begin{pmatrix} z_1(t) \\ z_2(t) \\ z_3(t) \\ z_4(t) \end{pmatrix} = \begin{pmatrix} y(t) \\ y^{'}(t) \\ y^{''}(t) \\ y^{'''}(t) \end{pmatrix} = \begin{pmatrix} G(t) - G_{ref}(t) \\ \frac{d(G(t)-G_{ref}(t))}{dt} \\ \frac{d^2(G(t)-G_{ref}(t))}{dt^2} \\ \frac{d^3(G(t)-G_{ref}(t))}{dt^3} \end{pmatrix} \tag{4.9}$$

(4.9) stems from the fact that our system has a full relative degree.By using (4.9) we have the following results.

$$z_2(t) = \dot{z}_1(t) = -K_{xgi}G(t)I(t) + \frac{T_{gh}}{V_G} - \dot{G}_{ref}(t) \tag{4.10}$$

$$\begin{aligned} z_3(t) = \dot{z}_2(t) = -K_{xgi}\big(&-K_{xgi}G(t)I^2(t) + \frac{T_{gh}}{V_G}I(t) \\ &- K_{xi}G(t)I(t) + \frac{T_{iGmax}}{V_I}G(t)f(G(t-\tau_g)) \\ &+ \frac{1}{V_I t_{max,I}}G(t)S_2(t)\big) - \ddot{G}_{ref}(t) \end{aligned} \tag{4.11}$$

$$\begin{aligned} z_4(t) = \dot{z}_3(t) = -K_{xgi}\Big[&K_{xgi}^2G(t)I^3(t) - \frac{k_{xgi}T_{gh}}{V_G}I^2(t) \\ &+3K_{xgi}k_{xi}G(t)I^2(t) \\ &-\frac{3K_{xgi}T_{iGmax}}{V_I}G(t)I(t)f(G(t-\tau_g)) \\ &-\frac{3K_{xgi}}{V_I t_{max,I}}G(t)I(t)S_2(t) \\ &+2\frac{T_{gh}T_{iGmax}}{V_G V_I}f(G(t-\tau_g)) + \frac{2T_{gh}}{V_G V_I t_{tmax,I}}S_2(t) \end{aligned}$$

$$
\begin{aligned}
&+k_{xi}^2 G(t)I(t) - \frac{K_{xi}T_{iGmax}}{V_I}G(t)f(G(t-\tau_g)) \\
&-\frac{1}{V_I t_{max,I}}(K_{xi}+\frac{1}{t_{max,I}})G(t)S_2(t) \\
&+\frac{T_{iGmax}}{V_I}G(t)\frac{df(\alpha)}{d\alpha}\bigg|_{\alpha=G(t-\tau_g)}\frac{dG(\theta)}{d\theta}\bigg|_{\theta=t-\tau_g} \\
&+\frac{1}{V_I t_{max,I}^2}G(t)S_1(t) - 2\frac{K_{xi}T_{gh}}{V_G}I(t)\Bigg] - \frac{d^3G_{ref}(t)}{dt^3} \qquad (4.12)
\end{aligned}
$$

$$
\begin{aligned}
\dot{z_4}(t) &= -K_{xgi}\left(-K_{xgi}G(t)I(t)+\frac{T_{gh}}{V_G}\right) \\
&.\big[K_{xgi}^2 I^3(t) + 3K_{xgi}K_{xi}I^2(t) \\
&-\frac{3K_{xgi}T_{iGmax}}{V_I}I(t)f(G(t-\tau_g)) - \frac{3K_{xgi}}{V_I t_{max,I}}I(t)S_2(t) \\
&+k_{xi}^2 I(t) - \frac{K_{xi}T_{iGmax}}{V_I}f(G(t-\tau_g)) \\
&-\frac{1}{V_I t_{max,I}}(K_{xi}+\frac{1}{t_{max,I}})S_2(t) \\
&+\frac{T_{iGmax}}{V_I}\frac{df(\alpha)}{d\alpha}\bigg|_{\alpha=G(t-\tau_g)}\frac{dG(\theta)}{d\theta}\bigg|_{\theta=t-\tau_g} \\
&\frac{1}{V_I t_{max,I}^2}S_1(t)\Bigg] - K_{xgi} \\
&.\left(-k_{xi}I(t)+\frac{T_{iGmax}}{V_I}f(G(t-\tau_g))+\frac{1}{V_I t_{max,I}}S_2(t)\right) \\
&.\Bigg[3K_{xgi}^2 G(t)I^2(t) - \frac{2K_{xgi}T_{gh}}{V_G} + 6K_{xgi}I(t)K_{xi}G(t)I(t) \\
&-\frac{3K_{xgi}T_{iGmax}}{V_I}G(t)f(G9t-\tau_g)) - \frac{3K_{xgi}}{V_I t_{max,I}G(t)S_2(t)} \\
&+K_{xi}^2 G(t) - 2\frac{K_{xi}T_{gh}}{V_G}\Bigg] - K_{xgi}\left(\frac{df(\alpha)}{d\alpha}\bigg|_{\alpha=G(t-\tau_g)}\frac{dG(\theta)}{d\theta}\bigg|_{\theta=t-\tau_g}\right) \\
&.\Bigg[-\frac{3K_{xgi}T_{iGmax}}{V_I}G(t)I(t) + \frac{2T_{gh}T_{iGmax}}{V_G V_I} \\
&-\frac{K_{xi}T_{iGmax}}{V_I}G(t)\Bigg] - K_{xgi}\left(\frac{1}{t_{max,I}S_1} - \frac{1}{t_{max,I}}S_2(t)\right) \\
&.\left[-\frac{3K_{xgi}}{V_I t_{max,I}}G(t)I(t) - \frac{1}{V_I t_{max,I}}\left(K_{xi}+\frac{1}{t_{max,I}}\right)G(t) + \frac{2T_{gh}}{V_G V_I t_{max,I}}\right] \\
&-K_{xgi}\left[\frac{T_{iGmax}}{V_I}G(t)\frac{d^2f(\alpha)}{d\alpha^2}\bigg|_{\alpha=G(t-\tau_g)}\left(\frac{dG(\theta)}{d\theta}\bigg|_{\theta=t-\tau_g}\right)^2\right.
\end{aligned}
$$

$$+\frac{T_{iGmax}}{V_I}G(t)\frac{df(\alpha)}{d\alpha}\Big|_{\alpha=G(t-\tau_g)}\frac{d^2G(\theta)}{d\theta^2}\Big|_{\theta=t-\tau_g}$$
$$-\frac{1}{V-It^3_{max,I}}G(t)S_1(t)+\frac{1}{V_It^2_{max,I}}G(t)u(t)\Bigg]-\frac{d^4G_{ref}(t)}{dt^4} \tag{4.13}$$

From equations((4.10), (4.11),(4.12),(4.13)) we have that the dynamics of $z(t)$ is given by:

$$\dot{z}(t)=Az(t)+B\left(\alpha(*)-\frac{K_{xgi}}{V_It^2_{max,I}}G(t)u(t)\right) \tag{4.14}$$

where $\alpha(*)$, according to equation(4.13) is a suitable function of: $G(t), I(t), G(t-\tau_g), S_2(t), S_1(t)$,
$\frac{d^iG(\theta)}{d\theta^i}\Big|_{\theta=t-\tau_g}$ $i=1,2$
$G_{ref}(t), \frac{d^G_{ref}(t)}{dt^j}, j=1,...,4$
Thus, the (inner) feedback control law

$$u(t)=\frac{-\alpha(*)+v(t)}{-\frac{K_{xgi}}{V_It^2_{max,I}}G(t)} \tag{4.15}$$

where $v(t)$ is a new (outer input), yields the following linear equation

$$\dot{z}(t)=Az(t)+Bv(t) \tag{4.16}$$

With A and B a Brunowski pair, given as follows:

$$A=\begin{pmatrix}0&1&0&0\\0&0&1&0\\0&0&0&1\\0&0&0&0\end{pmatrix},B=\begin{pmatrix}0\\0\\0\\1\end{pmatrix} \tag{4.17}$$

Finally, by choosing the new input $v(t)$ as the (outer) feedback

$$v(t)=Cz(t) \tag{4.18}$$

with C a suitable row vector in $\mathbb{R}^4$, the following equation is obtained,

$$\dot{z}(t)=(A+BC)z(t) \tag{4.19}$$

Thus by designing C, such that $A+BC$ is Hurwitz (this is possible since A, B is a controllable pair), we get that $z(t)$ goes to zero exponentially, which returns the glucose to converge to the desired reference signal exponentially.From a mathematical point of view, the control law defined in equations((4.15),(4.18)) can always be computed, since the variable G(t)(at the denominator of equation(4.15) never vanishes: indeed, as it is required from basic assumptions on the qualitative behavior of the solutions, the glucose

dynamics is strictly positive whatever are the chosen initial conditions on the positive orthant (see [4]).It follows that, from a mathematical point of view, the control law defined in equations((4.15),(4.18)) can be used with any physically meaningful initial conditions.As well, equation(4.19) holds with any physically meaningful initial conditions.
Our control law (4.15) is a function of $G(t), I(t), G(t-\tau_g), S_2(t), S_1(t)$. Nevertheless, insulin measurements are slower, more cumbersome to obtain, more expensive , and also less accurate than glucose measurements. A need exists, therefore, to construct a control law avoiding the measurements of insulin in the plasma and in the subcutaneous depot. Since our system is observable, this is not a big problem as it is possible to reconstruct the system's state from its output measurements using a state observer.Next we will consider a state observer for equation(4.5) that will help estimates the plasma and subcutaneous insulin concentration and design a feedback control law base on only glucose measurements.

4.3 State Observer for Our Model

Since our model belongs the class of DDE systems considered in [2], we will use the neutral delay differential observer proposed in [2] for such systems.

$$\begin{pmatrix} \frac{d\hat{G}(t)}{dt} \\ \frac{d\hat{I}(t)}{dt} \\ \frac{d\hat{S}_2(t)}{dt} \\ \frac{d\hat{S}_1(t)}{dt} \end{pmatrix} = \begin{pmatrix} -K_{xgi}\hat{G}(t)\hat{I}(t) + \frac{T_{gh}}{V_G} \\ -K_{xi}\hat{I}(t) + \frac{T_{iGmax}}{V_I} f(G(t-\tau_g)), \\ \frac{1}{t_{max,I}}\hat{S}_1(t) - \frac{1}{t_{max,I}}\hat{S}_2(t) \\ -\frac{1}{t_{max,I}}\hat{S}_1(t) + u(t) \end{pmatrix} + w(t), t \geq 0$$

$$w(t) = Q^{-1}(\hat{G}(t), \hat{I}(t), \hat{G}(t-\tau_g), \hat{I}(t-\tau_g), \hat{S}_2(t), \hat{S}_1(t)).$$
$$\Big(K(G(t) - \hat{G}(t)) - Q_1(\hat{G}(t), \hat{I}(t), \hat{G}(t-\tau_g), \hat{I}(t-\tau_g), \hat{S}_2(t), \hat{S}_1(t))w(t-\tau_g)\Big) \tag{4.20}$$

With initial conditions

$$\begin{pmatrix} \hat{G}(\tau) \\ \hat{I}(\tau) \\ \hat{S}_2(\tau) \\ \hat{S}_1(\tau) \end{pmatrix} = \begin{pmatrix} \hat{G}^0(\tau) \\ \hat{I}^0(\tau) \\ \hat{S}_2^0(\tau) \\ \hat{S}_1^0(\tau) \end{pmatrix} = \xi(\tau), \xi \in C^1([-2\tau_g, 0]; \mathbb{R}^4)$$

$$w(\tau) = \begin{pmatrix} \frac{d\hat{G}^0(\tau)}{d\tau} \\ \frac{d\hat{I}^0(\tau)}{d\tau} \\ \frac{d\hat{S}_2^0(\tau)}{d\tau} \\ \frac{d\hat{S}_1^0(\tau)}{d\tau} \end{pmatrix} - \begin{pmatrix} -K_{xgi}\hat{G}^0(\tau)\hat{I}^0(\tau) + \frac{T_{gh}}{V_G} \\ -K_{xi}\hat{I}^0(\tau) + \frac{T_{iGmax}}{V_I} f(\hat{G}^0(t-\tau_g)), \\ \frac{1}{t_{max,I}}\hat{S}_1^0(\tau) - \frac{1}{t_{max,I}}\hat{S}_2^0(\tau) \\ -\frac{1}{t_{max,I}}\hat{S}_1(\tau) + \tilde{u}(\tau) \end{pmatrix}, \tau \in [-2\tau_g, 0] \tag{4.21}$$

Where:

- $Q^{-1} \in \mathbb{R}^{4x4}$ is the inverse matrix of the jacobian of the observability map ϕ defined in equation(4.9) (see [2, 10, 11] for details), here given by

$$Q(\hat{x}(t), \hat{x}(t-\tau_g)) = \frac{\partial \phi(\hat{x}(t), \hat{x}(t-\tau_g))}{\partial \hat{x}(t)}, where$$
$$\hat{x}(t) = \begin{pmatrix} \hat{x}_1(t) \\ \hat{x}_2(t) \\ \hat{x}_3(t) \\ \hat{x}_4(t) \end{pmatrix} = \begin{pmatrix} \hat{G}(t) \\ \hat{I}(t) \\ \hat{S}_2(t) \\ \hat{S}_1(t) \end{pmatrix} \tag{4.22}$$

- $$Q_1(\hat{x}(t), \hat{x}(t-\tau_g)) = \frac{\partial \phi(\hat{x}(t), \hat{x}(t-\tau_g))}{\partial \hat{x}(t-\tau_g)}$$

- the gain matrix $K \in \mathbb{R}^{4x1}$ is chosen in order to assign suitable eigenvalues to the matrix A-KB (see [2]).

- $\tilde{u}(\tau)$ in $[-\tau_g, 0]$ is any bounded extension of the function $u(t)$ for negative times.

- the function ξ that initializes the observer, represents the a priori knowledge on the system's state.

A nice property of our observer is that, by assuming physically meaningful input signals, a matrix K can be designed such that, if the estimation error at zero is sufficiently small, the estimation error converges exponentially to zero (see [2]).Moreover, the decay rate can be arbitrarily fixed by the choice of K.
Indeed, in order to close the loop from the observed state, we consider the feedback control law:

$$u(t) = \frac{-\alpha(*) + v(t)}{-\frac{K_x gi}{V_I t^2_{max,I}} \hat{G}(t)} \tag{4.23}$$

where $\alpha(*)$, is defined same as in (4.2) with $G(t), I(t), G(t-\tau_g), S_2(t), S_1(t)$,
$\left.\frac{d^i G(\theta)}{d\theta^i}\right|_{\theta=t-\tau_g} \quad i = 1, 2$
replaced respectively by $\hat{G}(t), \hat{I}(t), \hat{G}(t-\tau_g), \hat{S}_2(t), \hat{S}_1(t)$,
$\left.\frac{d^i \hat{G}(\theta)}{d\theta^i}\right|_{\theta=t-\tau_g} \quad i = 1, 2$
Notice that our new control law (4.23) unlike the one in equation(4.15) those not make use of insulin measurements.It uses the glucose and insulin estimates provided by the observer, on the basis of only glucose measurements.

Chapter 5

Simulations, Conclusion and Proposal for Further Studies

5.1 Simulations

We carried out simulations on a virtual patient. The parameters for our model were estimated from the data gotten from an IVGTT experiment done in the department of metabolic disease of the Catholic University of Rome, on a person with Body Mass Index (BMI) $\approx$ 50 (Obese Patient) (see [22]). Below the estimated values are reported interms of their original scale (they refer to the glucose-insulin regulatory system): $G_b = 5.611, I_b = 93.669, T_{gh} = K_{xgi}I_bG_bV_g = 0.003, T_{iGmax} = K_{xi}I_bV_If(G_b) = 1.573, \gamma = 3.205, V_G = 0.187, K_xi = 1.211x10^{-2}, G^\star = 9, \tau_g = 24, V_I = 0.25, K_{xgi} = 3.11x10^{-5}, t_{max,I} = 55$. (The value of $t_{max,I}$ is taken from [40]).
The parameters indicate high normal glycemia and a substantial degree of insulin resistance ($K_{xgi} << 10^{-4}$. Because of the moderate hyperglycemia, obesity and insulin resistance, it is certain that the patient is a prediabetes patient. He is expected to develop type 2 diabetes mellitus sooner than later.
With the zeal to have the estimate of our model parameters for adiabetic patient, we took our virtual diabetic patient to be the Obese patient above, one or two years after after the above estimates were made, assuming that he hasn't carry on any effective therapy. Within this peroid, in this case, the natural progression of the disease will determine the failure of pancreatic insulin secretion and , in the face of insulin resistance, a dropping insulin concerntration, thus giving rise to the emergence of severe hyperglycemia and the establishment of a state of frank type 2 Diabetes Mellitus. Hence the T_{igmax} of the person will be bound to reduce to 15% of its " normal" value. There by pushing I_b and G_b to take new values.
We used the following estimates in our simulation: $T_{iGmax} = 0.236, G_b = 10.66, I_b = 49.29, T_{gh} = 0.003, \gamma = 3.205, V_G = 0.187, K_xi = 1.211x10^{-2}, G^\star = 9, \tau_g = 24, V_I = 0.25, K_{xgi} = 3.11x10^{-5}, t_{max,I} = 55$
The reference signal was chosen such that the plasma glucose decreases exponentially from 10.66 to a steady value of 5.
We made use of the following assumptions:

- Firstly, we assumed that the subject was at rest before the start of the experiment
- Secondly we assummed no malfunction of the insulin infusion device
- Lastly, We assumed not to have complete knowledge of the virtual patient and hence have to rely on the observer for certain measurements.

In addition to the estimates above the following inputs were used:

5.1.1 Inputs:

- eigen values of Observer: $: -0.5 \times 10^{-9} \begin{pmatrix} 4 \\ 1 \\ 2 \\ 3 \end{pmatrix}$
- eigen values of Controller: $: \begin{pmatrix} -0.0027 \\ -0.028 \\ -0.029 \\ -0.030 \end{pmatrix}$
- System's History: $: X(\tau_g) = \begin{pmatrix} 10.66 \\ 49.29 \\ 0 \\ 0 \end{pmatrix}$ and $\hat{X}(\tau_g) = \begin{pmatrix} 20 \\ 61 \\ 10.5 \\ 10.5 \end{pmatrix}$ for $\tau \in [-\tau_g, 0]$ where $X(\tau) = \begin{pmatrix} G(\tau) \\ I(\tau) \\ S_2(\tau) \\ S_1(\tau) \end{pmatrix}$ and $\hat{X}(\tau) = \begin{pmatrix} \hat{G}(\tau) \\ \hat{I}(\tau) \\ \hat{S}_2(\tau) \\ \hat{S}_1(\tau) \end{pmatrix}$

The Observer and Controller gain matrice were calculate using the Ackerman formula.

5.1.2 Results

From 5.1.2 above it can be seeen that our control law works perfectly well as a reasonable plasma glycemia is reached within the first 500 minutes of the simulation.**??** shows that our observer is capable of estimating all the state variables using the plasma glycemia. The simulation is done such that if the designed control law happens to be negative, a zero control input is given to the system.

5.2 Conclusion and Proposal for Further Studies

In this thesis, we formulated a time- delay observer model-based feedback control law, to track a desired plasma glucose evolution. The designed controller gives local assymptotic convergence the tracking error, according to the theory of feedback linearization with

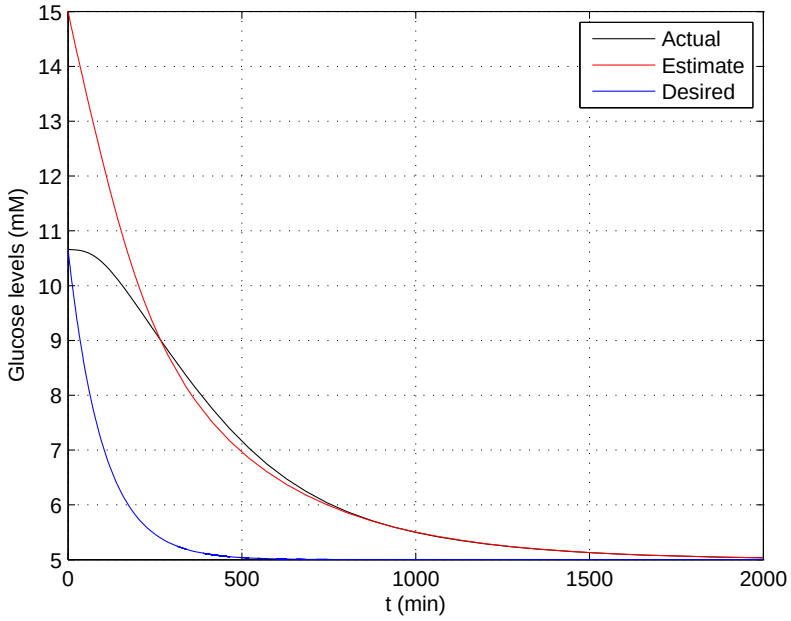


Figure 5.1: Actual, and Observed plasma Glycemia, compared with the desired glucose reference

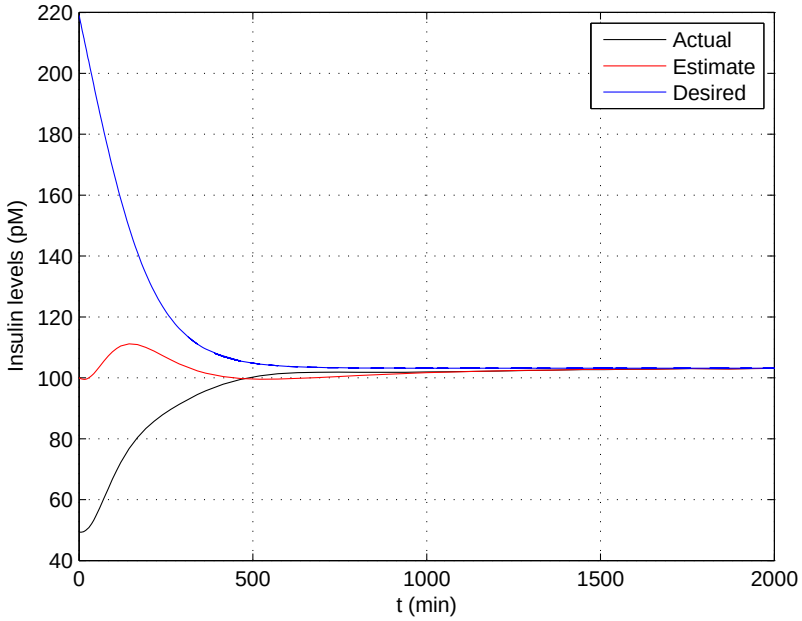


Figure 5.2: Actual, and Observed plasma Insulinemia, compared with the desired insulin reference

delay cancellations. We assumed having knowledge of only glycemis measurements.

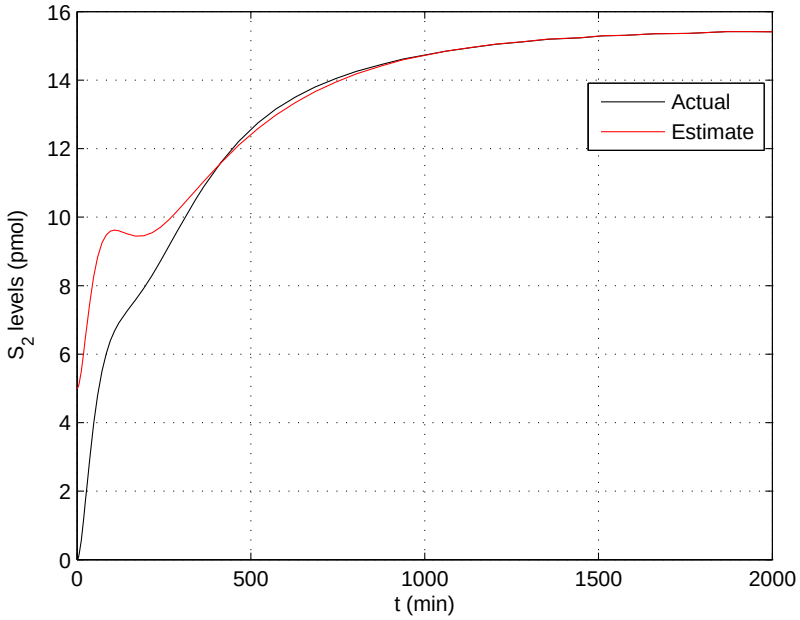


Figure 5.3: The dynamics of the actual, and Observed quantity of insulin in the inaccessible insulin depot

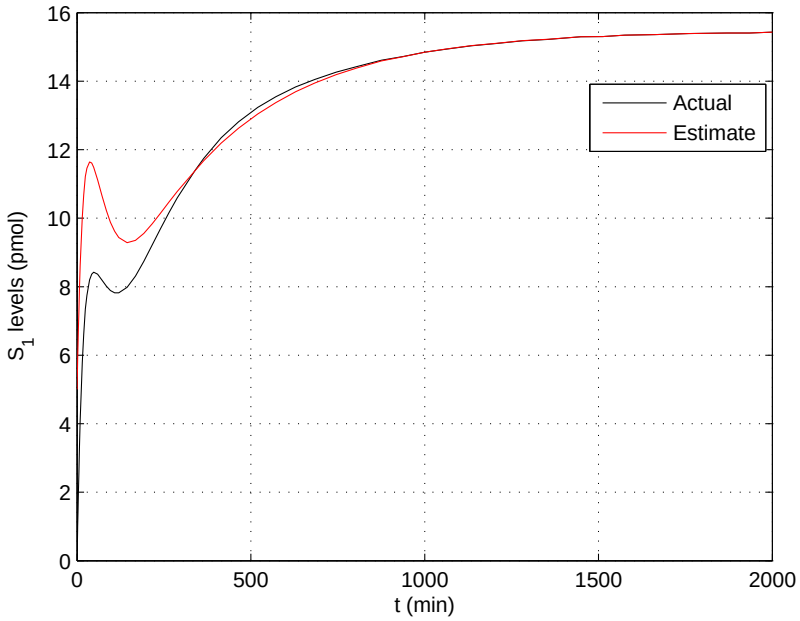


Figure 5.4: The dynamics of the actual, and Observed quantity of insulin in the inaccessible insulin depot

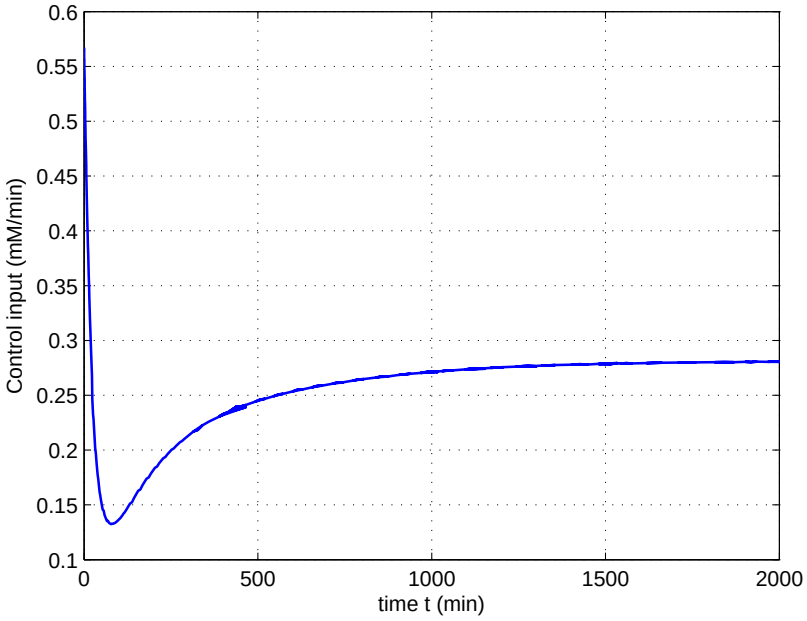


Figure 5.5: Insulin infusion

Thus our feed back control law is based on the use of a non linear observer for discrete-delay systems, in order to prevent the need for insulin measurements. Simulations have been performed on a virtual patient, and reported. The simulations shows high performance of the proposed control law and observer.
Our model has not taken into account exogenous glucose intake. The next thing to do, which my supervisor and I are already looking at, is to include exogenous glucose intake in our model, perform simulations to see how our designed controller reacts to a sudden intake of glucose after the high glycemia of our virtual have been brought to steady state value.In the future, we equally intend to test our control law on heterogenous virtual patients.

Bibliography

[1] Palumbo P., Pepe P., Panunzi S., De Gaetano A.(2012): *Glucose Control by Subcutaneous Insulin Administration: A DDE Modelling Approach*, .

[2] Germani A., Manes C., Pepe P.(2001): *An Asymptotic State Observer for a Class of Nonlinear Delay Systems*, Kybernetika, Volume 37 (2001), Number 4, Pages 459-478.

[3] Palumbo P., Pepe P., Panunzi S., De Gaetano A.(2012): *Time-Delay Model-Based Control of the Glucose-Insulin System, by Means of a State Observer*,

[4] Palumbo P., Panunzi S., De Gaetano A.(2007): *Qualitative behavior of a family of delay- differential models of the glucose-insulin system Discrete Contin. Dyn. Syst.*, Ser. B, 399424.

[5] Palumbo P., Pepe P., Panunzi S., De Gaetano A.(2009): *Observer- Based closed-loop Control of Plasma Glycemia*,in Proc. 48th IEEE Conf. on Denis. and Control, Shanghai, China, 3507-3512, .

[6] Nucci, G., Cobelli, C. (2000): *Models of Subcutaneous Insulin Kinetics.A Critical Review*, Comp. and Programs in Biomed., 62249-257.

[7] Puckett, W.R., and Lightfoot, E.N. (1995),: *A Model for Multiple Subcutaneus Insulin Injections developed from Individual Diabetic Patient Data*,Am. J. Physiol, 269, E1115-E1124

[8] Palumbo P., Panunzi S., De Gaetano A.(2007): *A discrete single delay model for intra-venous Glucose Tolerance test*, Theoretical Biology and Medical Modelling, 4(35), 1-16.

[9] Ciccarella, G., Dalla Mora, M., Germani, A.(1993),*Asymtotic Linearization and Stabilization for a Class of Nonlinear Systems*, Journal of Optimization Theory and Applications, 84, 495-507.

[10] Ciccarella, G., Dalla Mora, M., Germani, A.(1993),*A Luenberger-Like Observer for Nonlinear System*, International Journal of Control, 57, 537-556.

[11] Dalla Mora, M., Germani, A., Manes, C. (1997), *A state Obeserver for nonlinear dynamical sysytems*, Nonlinear analysis, Theory, Methods and Applications, 30(7), 4485-4496

[12] A. Makroglou, J. Li, Y. Kuang (2006), *Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview*, Applied Numerical Mathematics, 56

[13] J. Sturis, K. S. Polonsky, E. Mosekilde, E. Van Cauter ,(1991)*Computer-model for mechanisms underlying ultradian oscillations of insulin and glucose* Am. J. of Physiol. Endocrinol. Metab., 260, E801E809.

[14] Y. H. Chew, Y. L. Shia, C. T. Lee, F. A. A. Majid, L. S. Chua, M. R. Sarmidi, R. A. Aziz,(2009) *Modeling of oscillatory bursting activity of pancreatic beta-cells under regulated glucose stim- ulation, Molecular and Cellular Endocrinology*, 307 , 5767.

[15] J. Li and Y. Kuang(2007), *Analysis of a model of the glucose-insulin regulatory system with two delays*, SIAM J. Appl. Math., 67 , 757776.

[16] I. M. Tolić E. Mosekilde and J. Sturis (2000), *Modeling the insulin-glucose feedback system: the significance of pulsatile insulin secretion*, J. Theor. Biol., 207 , 361375.

[17] A. Drozdov, H. Khanina (1995), *A model for ultradian oscillations of insulin and glucose*, Mathl. Comput. Modelling, 22 , 2338

[18] Li, Y. Kuang and C. C. Mason (2006), *Modeling the glucose-insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays*, J. Theor. Biol., 242 , 722735.

[19] C. L. Chen, H.-W. Tsai (2010), *Modeling the physiological glucose-insulin system on normal and diabetic subjects*, Computer Methods and Programs in Biomedicine,97, 130-140 . (SCI, EI)

[20] R. N. Bergman, Y. Z. Ider, C. R. Bowden, C. Cobelli (1979), *Quantitative estimation of insulin sen- sitivity*, Am. J. Physiol., 236

[21] D.V. Giang, Y. Lenbury, A. De Gaetano, P. Palumbo(2008),*Delay model of glucose-insulin systems: global stability and oscillated solutions conditional on delays*, J. Mathematical Analysis and Applications, 343 , 9961006.

[22] Panunzi, S., De Gaetano, A., Mingrone, G.(2010), *Advantages of a single delay model for the assessment of insulin sensitivity from the intravenous glucose tolerance test*,Theoritical Biology and Medical Modelling 4(35), 1-16 .

[23] A. De Gaetano, O. Arino (2000a), *Mathematical modelling of the intravenous glucose tolerance test*, J. Math. Biol., 40 , 136168.

[24] Palumbo P., Pepe P., Panunzi S., De Gaetano A.(2009): *Robust closed-loop Control of Plasma Glycemia: a Discrete-Delay Model Approach*, Discrete and Continuous Dynamical Systems Series B, 12, 455-468.

[25] Wilinska, L. J. Chassin, H.C. Schaller, L. Schaupp, T.R. Pieber, R. Hovorka,(2005): *Insulin Kinetics in Type-1 Diabetes: Continuous and Bolus delivery of Rapid Acting I Insulin*,IEEE trans. Biom. Eng., 52, 3-12

[26] Shalitin, S. and Phillip M.(2006) *the loop: combining insulin pumps and glucose sensors in children with type 1 diabetes mellitus*, Pediatr Diabetes 7(Suppl 4): 45-49

[27] Hovorka R, Wilinska ME, Chassin LJ, et al(2006), *Roadmap to the artificial pancreas*, Diabetes Res Clin Practise;74: S178-82.

[28] Hovorka, R. (2006),*Artificial Pancreas*, In: Encyclopedia of Medical Devices and Instrumentation, 2nd ed., vol. 5, Webster JG (ed). John Wiley and Sons: Hoboken NJ,pp. 224-32.

[29] Hovorka R, Wilinska ME, Chassin LJ, et al (2007),*The artificial pancreas: Making head- way*, Practical Diabetes Int , 24: 56-58.

[30] Hovorka, R(2008), *The future of continuous glucose monitoring: Closed-loop*, Curr Diabetes Rev 4: 269-79.

[31] Kumareswaran, K., Evans, M. and Hovorka, R. (2009). *Artificial pancreas: an emerging approach to treat type 1 diabetes*, Expert Reviews of Medical Devices 6(4): 401410.

[32] Klonoff, D. (2005).*Continuous glucose monitoring, roadmap for 21st century diabetes therapy*, Diabetes Care 28(5): 12311239.

[33] Bellazzi, R., Nucci, G., and Cobelli, C. (2001), *The subcutaneous route to insulin dependent diabetes therapy*, IEEE Engineering in Medicine and Biology, 20, 5464.

[34] Steil, G.M., Panteleon, A.E., and Rebrin, K. (2004), *Closed-loop insulin delivery the path to physiological glucose control*, Advanced Drug Delivery Reviews, 56, 125144.

[35] Gopakumaran, B., Duman, H.M., Overholser, D.P., Federiuk, I.F., Quinn, M.J., Wood, M.D., and Ward, W.K. (2005), *A novel insulin delivery algorithm in rats with type 1 diabetes: the fading memory proportional-derivative method*, Artificial Organs, 29, 599607.

[36] Marchetti, G., Barolo, M., Jovanovic, L., Zisser, H., and Seborg, D.E. (2008), *An improved PID switching control strategy for type 1 diabetes*, IEEE Trans. Biomed. Eng., 55, 857865.

[37] Toffolo, G., Bergman, R.N., Finegood, D.T., Bowden, C.R., and Cobelli, C. (1980),*Quantitative estimation of beta cell sensitivity to glucose in the intact organism: a minimal model of insulin kinetics in the dog*, Diabetes, 29, 979990.

[38] Cobelli, C., Federspil, G., Pacini, G., Salvan, A., and Scandellari, C. (1982), *An integrated mathematical model of the dynamics of blood glucose and its hormonal control*, Math. Biosci., 58, 2760.

[39] Sorensen, J.T., Colton, C.K., Hillman, R.S., and Soeldner, J.S. (1982), *Use of a physiologic pharmacokinetic model of glucose homeostasis for assesment of performance re- quirements for improved insulin therapies*, Diabetes Care, 5, 148157.

[40] Parker, R.S., Doyle III, F.J., Ward, J.H., and Peppas, N.A. (2000),*Robust H glucose control in diabetes using a physiological model*, AIChE Journal, 46, 25372549.

[41] Dua, P., Doyle, F.J., and Pistikopoulos, E.N. (2006), *Model-based blood glucose control for Type 1 diabetes via parametric programming*, IEEE Transactions on Biomedical Engineering, 53, 14781491.

[42] Trajanoski, Z., and Wach, P. (1998),*Neural predictive control for insulin delivery using the subcutaneous route*, IEEE Trans. on Biomedical Engineering, 45, 11221134

[43] Chee, F., Savkin, A.V., Fernando, T.L., and Nahavandi, S. (2005), *Optimal H_∞ insulin injection control for blood glucose regulation in diabetic patients*, IEEE Trans. on Biomedical Engineering, 52, 16251631

[44] Ruiz-Velázquez, E., Femat, R., and CamposDelgado, D.U. (2004), "Blood glucose con- trol for type I diabetes mellitus: a robust H_∞ tracking problem" Control Engineering Practice, 12, 11791195.

[45] Chee, F., and, Fernando, T. (2007), *Closed-loop control of blood glucose*, Berlin Heidel- berg, Springer-Verlag.

[46] Germani, A., Manes, C., Pepe, P. (2003), *Input-Output Linearization with Delay Cancel- lation for Nonlinear Delay Systems: the Problem of the Internal Stability* International Journal of Robust and Nonlinear Control, 13(9), 909937.

[47] Germani, A., Pepe, P. (2005), *A State Observer for a Class of Nonlinear Systems with Multiple Discrete and Distributed Time Delays*, European Journal of Control, 11(3), 196205.

[48] Chassin, L.J., Wilinska, M.E., Hovorka, R. (2004),*Evaluation of glucose controllers in virtual environment: methodology and sample application*, Artificial Intelligence in Medicine, 32, 171181.

[49] Sename, O. (2007), *Is a mixed design of observer-controllers for time-delay systems interesting?*, Asian J. of Control, 2, 180189.

[50] Farza, M., Sboui, A., Cherrier, E., M'Saad, M. (2010), *High-gain observer for a class of time-delay nonlinear systems* , International J. of Control, 83, 27328

[51] Maitra A, Abbas AK (2005). Chapter 24 - *The Endocrine System. In: Robbins and Cotran Pathologic Basis of Disease*, 7th ed.; Kumar V, Abbas AK, Fausto N (eds). Elsevier Saunders: Philadelphia, pp.1204-05.

[52] Rea, C. (2007).*Blood Glucose Levels: Testing*. WebMD, Diabetes Health Centre.

[53] Emerging Technologies in Diabetes Research: JDRF Artificial Pancreas Project Fact Sheet, 2007. Juvenile Diabetes Research Foundation International, 1-3.

[54] Juvenile Diabetic Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008; 359: 1464-76.

[55] Hovorka, R., Canonico, V., Chassin, L.J., Haueter, U., Massi-Benedetti, M., Federici, M.O., Pieber, T.R., Schaller, H.C., Schaupp, L., Vering, T., and Wilinska, M.E. (2004),*Nonlinear model predictive control of glucose concenjation in subjects with type I diabetes* , Physiological Measurements, 25, 905920.

[56] Chee, F., Fernando, T.L., Savkin, A.V., and van Heeden, V. (2003), *Expert PID control system for blood glucose control in critically ill patients*, IEEE Trans. Inf. Tech. in Biomedicine, 7, 419425.