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Master Dissertation

Model Identification from Ambulatory Data for Post-Prandial Glucose Control in type 1 Diabetes

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Abstract

Patient characterization is the key for the successful treatment of type 1 diabetes mellitus. This characterization is currently done heuristically by physicians over continuous clinical visits to the patient. Improving diabetes care has been identified as a priority in national and international health programs. In this context, attention has been focused on automated control strategies of plasma glucose -the so called *Artificial Pancreas*-, and significant investment has been done by governments and pharmaceutical companies to its development. Mathematical modeling of the patient is crucial in this aspect, and the parametric characterization of the patient in the mathematical model has proven to be a difficult task to accomplish.

In this thesis, identifiability studies have been performed on several models present in literature. A critical review of the models based on their identifiability has been performed, and a new model has been proposed to overcome the problems found. A clinical protocol has been developed to test this methodology, based on home continuous glucose monitoring of subjects with type 1 diabetes mellitus. Preliminary results of this validation study are shown here.

Contents

Chapter 1

Glucose Control and Diabetes

Glucose is the main source of energy for the metabolism of the cells. In particular, brain metabolism is strictly dependent on glucose supply from the bloodstream. Thus, it is not surprising that regulation of glucose metabolism in the human body implies many different control systems, relating several hormones and organs. Indeed, the hormonal interplay regulates glucose production (basically in the liver and, to a lesser extent, in the kidney) and glucose uptake from tissues, as to maintain blood glucose concentrations in a narrow range.

However, there exist a number of pathologic conditions that affect glucose metabolism, the most famous (and frequent) being Diabetes Mellitus (DM). This chapter exposes the most important cycles and reactions that take place in the organism in order to maintain the glucose homeostasis, and discusses what the disease called Diabetes Mellitus consists in, and how it endangers the glucose regulation.

1.1 Glucose Metabolism

In humans plasma glucose is normally maintained within a narrow range (approximately 65-140 mg/dl), in both the fasting and fed state, due to a tightly linked balance between glucose production (basically from the liver) and utilization (from all the other tissues: the muscle, the adipose tissue and the brain). This is critical in patient's health, as explained by the devastating effects of deregulation of glucose metabolism. Indeed, excessive increase in plasma glucose concentration (diabetes) over years is responsible for a 2-5 fold increase in cardiovascular morbidity and mortality among diabetic people as compared to the general population. On the other hand, maintenance of plasma glucose above the threshold of hypoglycemia is critical for survival of the whole body. This is because glucose oxidation normally provides more than 90% of the energy needed for brain function and since the brain cannot synthesize glucose, and has reserves sufficient for only a few minutes, its function is almost totally dependent upon a continuous supply of glucose from the arterial circulation. Thus, it is not surprising that control mechanisms which maintain plasma glucose homeostasis are complex and that organs which normally release glucose into the circulation, namely liver and kidney, play a key physiological role in supporting brain function. The central nervous system and several hormones (insulin, glucagon, epinephrine, norepinephrine, GH and cortisol) participate into the regulation of glucose metabolism. However, as explained below, insulin is certainly the main actor. For more information about glucose metabolism check Williams and Pickup [105].

1.1.1 Role of Insulin

Insulin is the main regulatory hormone used in the body for reducing the glucose concentration in blood. Its main function is to enable the glucose absorption from blood by muscles and liver, and then convert that glucose

into glycogen. It is also the hormone that controls the absorption of glucose by the adipose tissue, and then stores that glucose as triglycerides. It has also an effect over the metabolism of many nutrients, as carbohydrates and proteins.

Insulin is secreted from the pancreas, in the zones called *Langerhans islets*, and specifically by the β-cells. The Langerhans islets are regions of the pancreas where the hormones related with the glucose homeostasis and metabolism are produced. Four main types of cells can be found: α-cells producing glucagon; β-cells producing insulin and amylin; δ-cells producing somatostatin; PP cells producing pancreatic polypeptide.

In both the fed and fasted states, insulin is foremost among the factors that regulate glucose production and utilization. Under normal circumstances, an increase in plasma glucose concentration such as after carbohydrate ingestion, is accompanied by a prompt increase in insulin secretion. The resultant increase in plasma insulin concentration accelerates glucose utilization and suppresses production. Conversely, a decrease in plasma glucose concentration is accompanied by a decrease in insulin secretion; the resultant decrease in circulating insulin concentration causes a decrease in glucose utilization and an increase in endogenous glucose production.

Hence, plasma insulin levels change according to the metabolic status, ensuring the balance between glucose production (by the liver) and glucose utilization (by the other tissues), and resulting in stability of plasma glucose concentrations. Rates of glucose production and utilization are also influenced by the so called "counterregulatory hormones" glucagon, adrenaline, cortisol and growth hormone independent of changes in insulin concentration. All of these hormones have biological effects that can oppose those of insulin and are involved in physiological responses to prevent/limit hypoglycemia.

Post-absorptive and fasting state

The four-hour to six-hour interval following ingestion of a meal is generally referred to as the post-absorptive state. At this point, plasma glucose concentrations average 80 to 90 mg/dl, and rates of glucose utilization are approximately 2 mg/kg/min. At least 50% of whole body glucose utilization is due to noninsulin-dependent uptake of glucose from the brain. The formed elements of the blood, renal medulla and muscle, metabolize glucose to pyruvate and lactate. These substances can be released into the circulation and serve as substrates for gluconeogenesis. In the postabsorptive state, insulin sensitive tissues such as muscle, adipose tissue, and liver account for less than 30% to 50% of overall glucose utilization. Following meal ingestion, however, liver and muscle take up glucose to replenish their glycogen stores and transiently increase their utilization of glucose.

If fasting is prolonged beyond the post-absorptive period, plasma glucose concentrations decrease over the succeeding 48 to 78 hours to reach a nadir of approximately 45 to 60 mg/dl that can be maintained for several weeks. Plasma free fatty acids and ketone body concentrations increase several-fold, reaching levels of 1 to 2 mmol/l by 72 hours. Glucose utilization decreases during this time to approximately 1 mg/kg/min and remains constant thereafter. These changes are in large part due to decreases in plasma insulin concentration that permits accelerated lipolysis with increased ketone body formation. Muscle and other tissues become progressively more dependent on free fatty acids and ketone bodies. Also, ketone bodies replace glucose as the predominant fuel for neural tissues, thus reducing the obligatory glucose uptake by the brain.

Absorptive state

The increase in plasma insulin concentration that occurs immediately following a meal suppresses endogenous glucose production, an effect also

mediated by the increased plasma glucose concentration. Consequently, hepatic glycogenolysis is suppressed and glycogen deposition stimulated. Approximately 50% of an oral glucose load is taken up by the liver and the remaining by peripheral insulin-sensitive tissues. Three to four hours following meal ingestion, the liver again releases glucose into circulation. Ultimately, the rate of glucose released equals the rate of glucose utilization so that plasma glucose concentrations are maintained stable.

Nearly all tissues, to varying degrees, oxidize glucose to derive energy for metabolic demands. Yet only the liver and kidney release glucose. This release results from the presence in these organs of glucose-6-phosphatase which liberates glucose into the bloodstream. The liver and kidney do not, however, contribute equally to post-absorptive glucose homeostasis. It is generally believed that the liver makes the major quantitative contribution during this state, while the kidney plays a minor role.

1.1.2 Role of Glucagon

In the experiments of Banting and Best that led to the discovery of insulin in 1921 [4], a "contaminant" in pancreatic extracts was reported that caused a transient increase in blood glucose. Nevertheless, the hypoglycemic effect of the extract was sustained and predominated. Insulin was isolated from the extract and went into immediate use for treatment of diabetes. Working in the shadow cast by the discovery of insulin, Murlin and colleagues [42] [58] went on to define the hyperglycemic factor in pancreatic extracts. They wrote in 1923: "There are two substances in these aqueous extracts, one of which lowers the blood sugar and the D:N ratio and raises the R.Q. (insulin), the other raises the blood sugar of both normal and depancreatized animals. ..." Based on their observations, these investigators proposed the existence of a second hormone secreted by the pancreas. They proposed the name glucagon, a contraction of the words "glucose" and "agonist", for this putative hormone.

The full significance of glucagon in physiology and diabetes was not appreciated until the development of the radioimmunoassay, which made plasma glucagon measurement routine. Exercise has been used as a physiological stimulus to challenge the glucoregulatory system in a dog model and to define the roles of glucagon, demonstrating its important role in maintaining blood glucose. It was shown that glucagon has mainly an hepatic effect, being the key to both the glycogenolytic and gluconeogenic responses to exercise [100]. This means that it stimulates glucose production by the liver, allowing for compensation of increased glucose uptake from the muscle during periods of physical activity, therefore preventing plasma glucose fall to hypoglycaemia. Indeed, several studies have demonstrated that glucagon secretion, along with suppression of endogenous insulin production, is the first physiological counterregularoy response to impending hypoglycaemia [56]. Disfunction of this counterregulatory system is responsible for the burden of hypoglycemia in people with diabetes [19].

1.1.3 Role of Epinephrine

Epinephrine, also known as Adrenaline, is a hormone and neurotransmitter secreted by the adrenal glands. Catecholamines (mainly adrenaline) appear to play a key role in counterregulatory response to hypoglycemia. In fact, blockade of their effects causes severe hypoglycemia despite increases in other counterregulatory hormones, particularly glucagon. In contrast to glucagon which exerts its effects exclusively on glucose production, catecholamines exhibit multiorgan effects, including suppression of endogenous insulin secretion, stimulation of hepatic and renal glucose production, inhibition of peripheral glucose utilization, and stimulation of lipolysis. Like glucagon, it is likely that the sustained increase in glucose production is primarily due to stimulated gluconeogenesis ([47]).

1.1.4 Role of slow-acting Hormones

Growth hormone and cortisol are referred to as "slow-acting" hormones because their effects become evident after a few hours of their increase in plasma. Therefore, the counterregulatory role of these hormone is appreciated only after 3 hours of hypoglycemia. Both cortisol and growth hormone are critical to counterregulation because absent response of either one of these two hormones is not compensated by even larger responses of other hormones, including the rapid-acting hormones glucagon and adrenaline.

1.1.5 Effectiveness of Glucose Control

Blood glucose control has two attributes that make it very effective. First, there is redundancy of control due to multiple layers of the glucoregulatory response. Changes in pancreatic islet glucagon and insulin secretion normally prevent hypoglycemia. Should the response of the pancreas be inadequate, other controllers (e.g., catecholamines, cortisol, growth hormone, and glucose autoregulation) are in place to prevent a deeper fall in blood glucose. Second, there is distribution of control that includes nutrition, liver function, and energy metabolism. Glucose delivery is a function of glucose concentration and vascular regulation. The ability of the gut to supply glucose in the postprandial state and the liver to do so in the postabsorptive state maintains blood glucose concentration. By doing so, these organs sustain glucose delivery and exert control over peripheral (mainly muscle) glucose uptake. In fact, in the postabsorptive state the rate that glucose is released from the liver is the most sensitive regulator of muscle glucose uptake. With prolonged exercise or mild hyperinsulinemia, the muscle is highly permeable to glucose but muscle glucose uptake still declines. During prolonged exercise, the glycogen-depleted liver cannot sustain blood glucose.

With iatrogenic hyperinsulinemia (i.e., treatment of diabetes), the release

of glucose from the liver is suppressed, causing a decrease in blood glucose. In short, factors that control the release of glucose from the liver such as insulin, glucagon, and nutritional state are part of distributed control.

1.2 Diabetes Mellitus

For 2,000 years diabetes has been recognized as a devastating and deadly disease. In the first century A.D. a Greek, Aretaeus, described the destructive nature of the affliction which he named "diabetes" from the Greek word for "siphon". Eugene J. Leopold in his text Aretaeus the Cappodacian describes Aretaeus' diagnosis: "...For fluids do not remain in the body, but use the body only as a channel through which they may flow out. Life lasts only for a time, but not very long. For they urinate with pain and painful is the emaciation. For no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine".

Physicians in ancient times, like Aretaeus, recognized the symptoms of diabetes but were powerless to effectively treat it. Aretaeus recommended oil of roses, dates, raw quinces, and gruel. And as late as the 17th century, doctors prescribed "gelly of viper's flesh, broken red coral, sweet almonds, and fresh flowers of blind nettles".

In the 17th century a London physician, Dr. Thomas Willis, determined whether his patients had diabetes or not by sampling their urine. If it had a sweet taste (due to a phenomenon known as glycosuria, which occurs when blood glucose goes up above the threshold of 180 mg/dl) he would diagnose them with diabetes mellitus- "honeyed" diabetes. This method of monitoring urine glucose went largely unchanged until the 20th century.

In the early 20th century, diabetologists such as Dr. Frederick Allen prescribed low calorie diets-as little as 450 calories per day for his diabetic patients. His diet prolonged the life of people with diabetes but kept them

suffering from near starvation. In effect, people with diabetes suffered a painful wasting death. Then in 1921 something truly revolutionary occurred in Ontario, Canada. A young surgeon Frederick Banting, and his assistant Charles Best, kept a severely diabetic dog alive for 70 days by injecting it with a murky concoction of canine pancreas extract. With the help of Dr. Collip and Dr. Macleod, Banting and Best administered a more refined extract of insulin to Leonard Thompson, a young boy dying of diabetes. Within 24 hours, Leonard's dangerously high blood sugars had dropped to near normal levels. Until the discovery of insulin, most children diagnosed with diabetes were expected to live less than a year. In a matter of 24 hours the boy's life had been saved. News of the miracle extract, insulin, spread like wildfire across the world.

Since insulin's discovery, medical breakthroughs continued to prolong and ease the lives of people with diabetes. In 1935 Roger Hinsworth discovered there were two types of diabetes: "insulin sensitive" (type 1) and "insulin insensitive" (type 2). By differentiating between the two types of diabetes, Hinsworth helped open up new avenues of treatment. Indeed, type 1 and type 2 diabetes are characterized by different pathophysiologic processes, resulting in different therapeutical approaches.

In the last decades it has become a major health problem worldwide. Its impact all over the world, and especially in the developed countries, has alarmed the health organizations in many countries, and major efforts are being performed to overcome this threat. Scoping into the future is even more shocking. In figure 1.1 the estimate of diabetes prevalence per country in 2010 can be seen. The increase in population combined with aging of people makes the problem of diabetes to get into epidemic proportions in the next decades, as can be seen in figure 1.2.

Insulin has a major importance in treatment of diabetes. It is usually delivered subcutaneously, which delays the effect of the insulin in the blood as compared with to natural insulin in healthy persons that is secreted directly

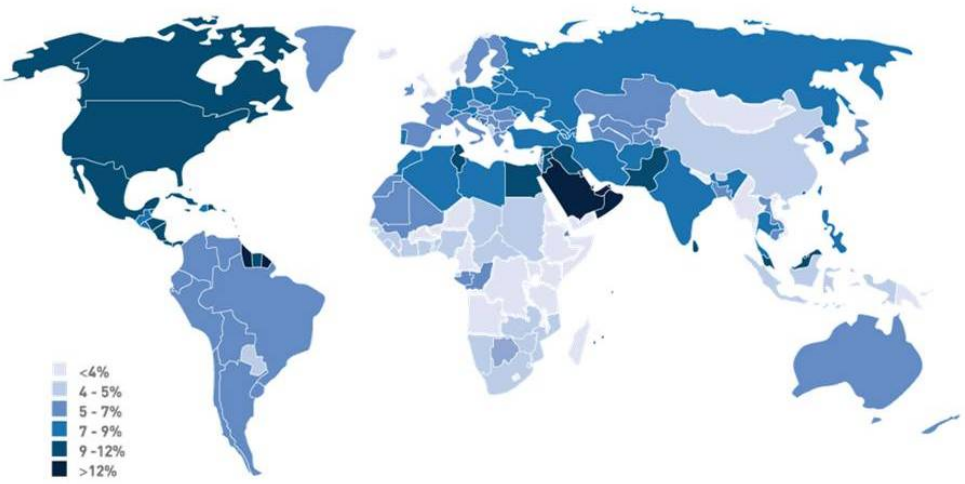

Figure 1.1: Prevalence estimates of diabetes (29-70 years old) in 2010 [39]

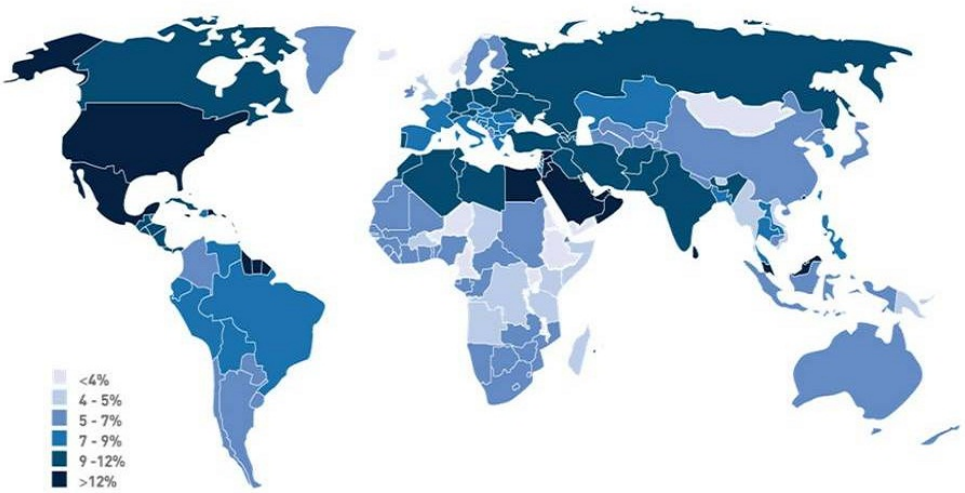

Figure 1.2: Prevalence estimates of diabetes (29-70 years old) in 2030 [39]

into the circulatory system. Human insulin is found in what is called *hexamer* form, in which there are six insulin molecules aggregated by means of a zinc atom. This can be seen in figure 1.3, where every twisted figure is a single *monomer* of insulin, and the six of them and the nucleus form the whole molecule.

Figure 1.3: Structure of insulin in its hexamer form [15]

Subcutaneous absorption of insulin in the hexamer form is really slow, and it usually has to dissociate into monomers to be able to pass through the subcutaneous tissue into the bloodstream. The most stable form of insulin (human insulin) is the hexamer form, and that is the way is stored for Diabetes treatments, but insulin analogs have been developed in recent years, which change their most stable form to monomer or *dimer* (intermediate stage between monomer and hexamer). The fact that their most stable form is monomer form makes these insulin analogs to be much faster absorbed than human insulin, and that has made insulin treatments much more flexible.

There are two main types of diabetes mellitus. Type 1 diabetes is characterized by absolute insulin deficit, due to the autoimmune destruction of the pancreatic beta cells. Hence, the treatment for people with type 1

diabetes is necessarily the replacement of the endogenous insulin secretion by means of the administration of exogenous insulin. On the other hand, type 2 diabetes is the result of two concomitant alterations: 1) insulin resistance (i.e. the liver and the muscle have less than normal sensitivity to the insulin action); 2) impaired beta cell function (i.e. the physiological response of the beta cell to a meal is lost, as well as its ability to compensate for insulin resistance). This results in relative insulin deficit, which can be approached with several non pharmacological (physical exercise) and pharmacological measures. However, the natural history of type 2 diabetes is characterized by progressive lost of the beta cell function overtime, finally leading to a condition of absolute insulin deficit requiring replacement with exogenous insulin.

There are other types of DM, like the pathologies that are induced by infections or endocrinopathies, and they can be of transitional character, like the gestational diabetes occurring in pregnant women, or remain chronic for the patient, but these sorts of DM are not going to be studied in here. Diabetes type 1 and 2 will be explained in detail in chapters 1.2.1 and 1.2.2.

The degree of metabolic control obtained by people with diabetes can be measured by the concentration of *glycated hemoglobin* in blood, also called *HbA1c*. Hemoglobin is the protein used to transport oxygen though the circulatory system. In presence of glucose it undergoes a non-enzymatic reaction, becoming glycated. This transformation is in relation to the average concentration of glucose in blood, due to the half-life of red blood cells, it is representative of mean blood glucose concentrations during the past 8-12 weeks. For the record, a healthy person has a 5.5% of hemoglobin in glycated state, while a diabetic patient is considered to be under control if its HbA1c is under 7%.

1.2.1 Diabetes type 2

Diabetes Mellitus type 2 is the most extended sort of diabetes, and accounts for 85% of cases in developed countries. It is related to various clinical risk factors such as increasing age, obesity, and racial and geographical characteristics. It is the diabetes type 2 the one that threats with epidemic proportions worldwide. Its onset peak is around 50 years and almost 80% of type 2 diabetic subjects are obese.

Two main defects characterize the pathophysiology of T2 DM:

1. Beta cell dysfunction. Usually the deterioration affects initially the prandial insulin secretion. Indeed, the so called first phase of insulin response is lost early on in the natural history of the disease, resulting in post-prandial hyperglycemia. However, Beta cell function deteriorates progressively overtime, leading to an absolute insulin deficit.

2. Insulin resistance. Hepatic insulin resistance causes excessive glucose production, contributing to fasting hyperglycemia. Peripheral (muscle) insulin resistance leads to inefficient glucose utilization. It is related to obesity and physical inactivity, both related to hepatic and intra-muscle lipid accumulation. However, insulin resistance is not able 'per se' to cause diabetes. Indeed, the normal beta cell can compensate for insulin resistance and this is the reason because obese people are not always diabetic.

Diabetes develop when defective beta cell cannot compensate for insulin resistance.

A wide therapeutic armamentarium is available for the treatment of type 2 diabetes mellitus. Unfortunately deterioration of β-cells does not stop with any drugs, and diabetic patients type 2 will become dependent of exogenous insulin, just as type 1 diabetic people are. The treatment related to insulin

administration will be explained in chapter 1.2.2.

1.2.2 Diabetes type 1

Aetiology

This type of diabetes is an autoimmune disease, and as said before, idiopathic, meaning that the disease arises spontaneously, or from an obscure or unknown cause. It is related to a low level of insulin in blood, which causes the blood glucose to be constantly in high levels, which can cause severe symptoms including ketoacidotic coma in some patients. The disease is also suddenly discovered in most patients, who are usually lean people that present recent loss of weight. Patients with Diabetes Mellitus Type 1 presents markers of antibodies denoting the destruction of β-cells. This destruction causes the low insulin levels that lead to the rest of the symptoms, such as constant high blood glucose concentrations and ketoacidotic coma in the extreme cases. The aetiology (chain of events leading to diagnosis) of DM1 is complex and not completely understood, but it is supposed to imply both genetic predisposition and environmental factors, as can be seen in figure 1.4.

Physiopathology

The problem for the patients of DM1 is then that they do not have an endogenous (proceeding from within) insulin secretion system and this insulin has to be given in an exogenous (coming from outside) way.

Normal non-diabetic subjects maintain plasma glucose below 100 mg/dl during fasting state, and below 140 mg/dl in the post-prandial period. During fasting, maintenance of normoglycaemia is possible because of the continuous release of insulin from the pancreas which restrains hepatic glucose production and prevents hyperglycaemia. At meal times, the normal

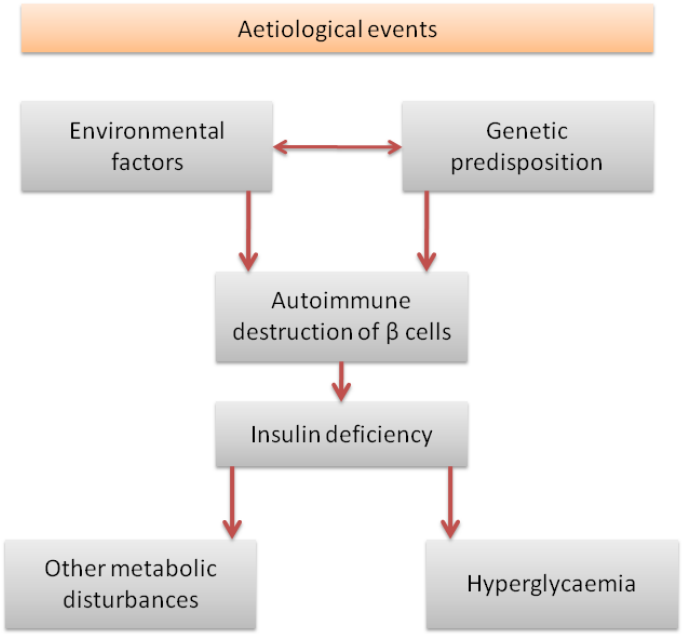

Figure 1.4: Aetiology of type 1 diabetes [105]

pancreas releases insulin very rapidly in response to meal ingestion as indicated by the early and elevated insulin peak appearing in peripheral plasma. It can be estimated that the corresponding "portal" plasma insulin concentrations of the prandial peaks are nearly twice as elevated. This is what is needed in terms of insulin delivery to prevent post-prandial hyperglycaemia.

However, of similar importance is the rapid decrease of plasma insulin 60-90 minutes after meal ingestion, preventing hypoglycaemia in the post-prandial period. Also, the fact that between meal plasma insulin is flat and peakless is a key factor in the prevention of interprandial and fasting hypoglycaemia, particularly at night.

This model of natural insulin dynamics should be imitated whenever insulin has to be replaced. Given that Diabetes Mellitus type 1 is characterized by absolute insulin deficit and therefore the only treatment is its replacement, the logical strategy to palliate the effects of the disease is to mimic the non-existent insulin secretion rate.

Current strategies for insulin replacement

In the early 1980s human insulin was introduced to the market by drug companies substituting animal insulin emphasizing the belief that diabetic people should be treated with "naturally" secreted insulin from the human body. Better glycaemic control was expected in people with diabetes using human compared with animal insulin. This was not the case, since no single advantage could be proven for humans versus animal insulin ([89]).

However, the positive aspect of human insulin was the innovative technology used for its production (DNA-recombinant technique) versus the traditional insulin extraction method from animal pancreata. This new technique helped to develop a number of insulin analogues. Major

efforts were started to modify the human insulin and develop "modified" insulins for administration to diabetic subjects. Slow and rapid acting insulin analogues are available now for the different stages of the treatment of diabetes. Slow acting insulins (up to 24h permanence in blood) can be used for substituting the flat insulin level in the interprandial periods. Fast acting insulin analogues (1-2 hours life cycle) on the contrary, may be used to replicate the postprandial insulin peaks of the (non-existent) insulin secretion.

Regardless of the system of glucose measurement or the way insulin is delivered, the control philosophy for glucose control in DM1 is to replicate the insulin secretion pattern of the non-diabetic person. As already explained, in the fasting and post-absorptive state, insulin secretory rate is regulated in a feedback fashion by plasma glucose levels. This is known as *basal insulin*, which modulates hepatic glucose production to exactly compensate for peripheral glucose utilization maintaining plasma glucose concentrations in a very narrow range. In the post prandial state, beta cells increase insulin secretion to cope with glucose absorption from the gut into the bloodstream. This is called *prandial insulin* secretion, which results in high plasma insulin concentrations that suppress hepatic glucose production (unnecessary since glucose is being absorbed from the gut) and increase glucose disposal into the liver and the muscle, allowing for very small meal-induced fluctuations in plasma glucose concentrations. It should be noted that the feedback mechanisms regulating insulin secretion, probably rely on measurement of glucose concentration in the blood (or in some compartment in fast equilibrium with the blood). Thus, mimicking physiological insulin secretion must translate into replacement of both basal and prandial components, and ideally it should be based on measurements of blood glucose concentrations and on insulin infusion directly into the blood stream.

However, for practical reasons in clinical practice, insulin is usually injected subcutaneously. This introduces a delay between insulin injection and insulin action, which represents the time needed for the absorption

of insulin from the subcutaneous tissue into the blood. This lag time depends on the chemical properties of the insulin injected (which influence its rate of absorption) and is one of the barriers to the development of the artificial pancreas. The insulin molecule has been modified in order to obtain preparations suitable for more accurate insulin replacement ([84]). Indeed, current strategies for insulin administration use a long-acting insulin analogs (the molecule has been modified to ensure a constant 24 hour absorption from the subcutaneous tissue, following injection) for basal replacement and a fast acting insulin analogs (the molecule has been modified to accelerate its absorption from the subcutaneous tissue) for prandial requirements. This therapy is called *basal-bolus* strategy, and it is clearly limited by the pharmacokinetics of insulin, and leaves no possibility of reaction to unexpected events, such us too low absorption rate of glucose, or sudden increase of insulin sensitivity of the patient.

Figure 1.5: Insulin pumps [54]

Subcutaneous insulin pumps (as shown in figure 1.5) traditionally use basal-bolus strategy, but the possibility of adjusting the insulin delivery rate at any time rises scenarios of a closer control. The main advantages of using Continuous Subcutaneous Insulin Infusion (CSII) are:

1. Use of rapid acting analogs both for meal insulin and basal insulin. Indeed, they show better reproducibility of subcutaneous absorption

as compared to long acting insulins resulting in lower variability.

2. Possibility to adjust basal insulin requirements to the subject needs (ex circadian variations in insulin sensitivity). This is not possible with long acting insulins with 'fixed' pharmacokinetics and pharmacodynamics.

These new CSII scenarios require of a more efficient glucose measuring system as well, and the recent subcutaneous real-time glucose monitors, like the guardian real-time glucose monitoring system from Medtronic shown in figure 1.6, provide this continuous monitoring required to close the control loop.

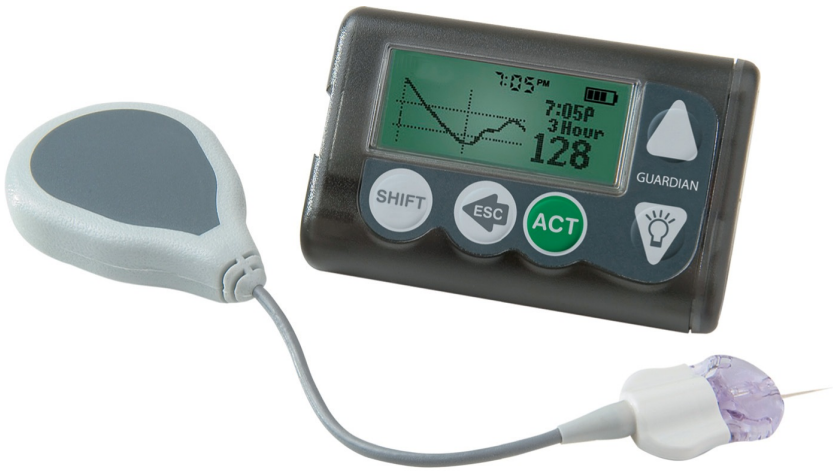

Figure 1.6: Guardian Real-Time Glucose Monitoring System from Medtronic [54]

Given the chance to read glucose in real-time and act over it with (at least) one control action, which is the insulin infusion, it is defined a control system, and there are several control laws that can be applied to create a tighter control of blood glucose than trying to mimic the behavior of the physiological insulin production rate. The "natural" physiological control is impossible to obtain with the subcutaneous infusion of insulin. However, the presence of continuous sensors, even though the uncertainty that present,

opens the possibility of designing new control strategies that will stabilize glycaemia in diabetic patients.

Even though the simplifications performed to the "real" model are strong, a reliable control law can be implemented and tested in real patients. This control problem has been a matter of research for over 40 years, and it is still going on. The product that is edxpected from the design and implementation of the control law that is to replace the damaged β-cells in the pancreas is called *Artificial Pancreas*, and it is the framework of research this thesis is placed in.

1.3 Artificial Pancreas

Over the last 30 years, even with the availability of new insulin preparations with more physiological profiles, continuous administration systems aimed at emulating endogenous insulin secretion, and new education strategies, there is still no universal, efficient and safe system able to normalize the glucose levels of diabetic patients. Progress with enzyme electrodes in the 1970s [104] allowed for the emergence of continuous glucose monitoring (CGM), and for the subsequent development of the first prototypes of glucose-sensor controlled insulin infusion systems, by different groups ([1] and [2]).

The next two decades saw huge progress in the development of continuous glucose sensing. Research focused on the skin as an appropriate candidate for direct glucose measurement. Indeed, the subcutaneous tissue is easily accessible for sensor implantation and measurement of glucose in the interstitial fluid, with fewer problems as compared to the intravascular space. The amperometric glucose-sensing technique was refined and this process culminated, in 1999, with the development and FDA approval of the CGMS®, the first commercial CGM device [53]. Since then, technological progresses have fueled research on closed-loop glucose control systems using

the subcutaneous route (see below), for effective treatment of diabetic subjects.

Preliminary studies using off-the-shelf insulin pumps and subcutaneous continuous glucose monitoring (CGM) sensors have suggested that, in research settings, closed-loop systems that automatically dispense insulin can achieve better control of glucose levels than open-loop systems in which a person makes dosing decisions [92]. Such promising results prompted the Juvenile Diabetes Research Foundation (JDRF) to push the research forward by launching its Artificial Pancreas Project 4 years ago, and the US Food and Drug Administration (FDA) to designate the artificial pancreas as a priority within its Critical Path Initiative. However, so far only a few prototypes have been developed and tested in controlled clinical settings. In fact, several challenges do still exist:

1. Coping with big disturbances affecting the system, such as meals, stress and exercise
2. Robustness face to the great variability of patient's physiological behavior
3. Accuracy and reliability of continuous glucose monitors, that must be improved to a higher degree
4. Safety of insulin pumps and detection of faults
5. Adequate correction for the slow responsiveness of controllers due to delays in the control loop (see below)

Control of post-prandial glycaemic excursions is certainly a key issue in the artificial pancreas. Indeed, meals are one of the major perturbations to counteract and the main challenge found in current clinical validations of the few existing prototypes of closed-loop glycaemic control systems. This thesis focus on this issue, aiming at the development of new feedback strategies for post-prandial glycaemic control.

1.3.1 Current state of development

The first experiment conducted closing the control loop in a patient with diabetes can be traced back to 1964 by Kadish [41]. It was the first trial to control the blood glucose with a continuous glucose monitor, and the control algorithm was just an 'on-off' system with constant supervision of doctors, and the control action (insulin) was delivered in an intravenous way, which minimizes the delays related to insulin transport in tissues.

In 1974 an 'artificial endocrine pancreas' was developed simultaneously by two different researchers, Albisser [1] and Pfeiffer [72], which led to the first commercial device that emulated an artificial pancreas: The Biostator. The device implemented a complex algorithm aiming to prevent postprandial hyperglycaemia, but it was still a bulky machine (figure 1.7) with need of constant supervision and none at all designed for an independent use.

As already said, considerable improvement has been made in the technology of glucose monitors for the past 20 years, and insulin pumps have been developed and proven to be reliable and to improve life quality for diabetic patients, as shown by Pickup [73]. The use of continuous insulin infusion coupled with subcutaneous aims to solve the main problem the Biostator supposed, its low manageability, but it adds new delays to the control loop, which makes the algorithms needed much more complicated.

The classification of closed-loop systems based on the body interface, and thus related to its average delay stays as follows:

- **Intravenous measuring and intravenous insulin delivery.** This option is the most invasive system, and it represents the minimum delay possible from the glucose measuring to its response (about 30 minutes). A revision of the control algorithms used in this paradigm was done by Parker [69]. Its application is unfeasible in clinical practice and might be used, in the near future, only in critical patients and hospital

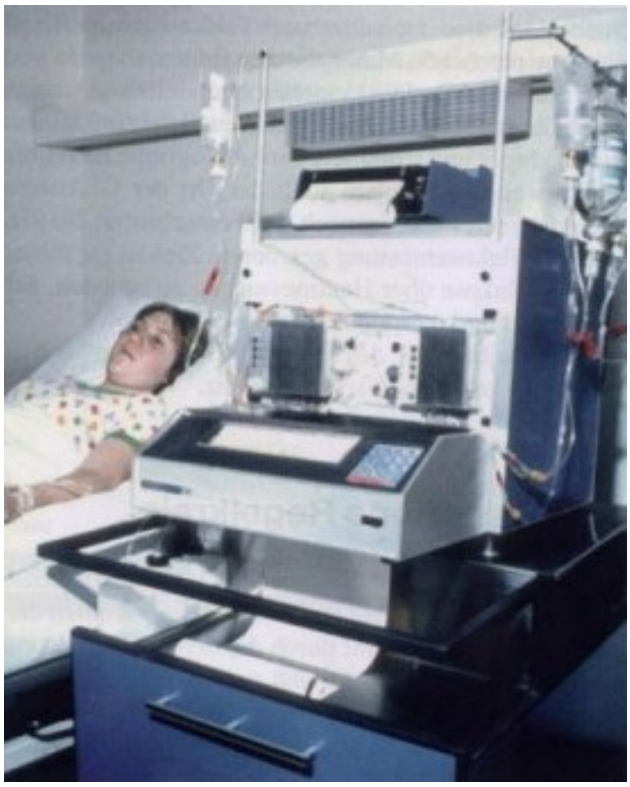

Figure 1.7: Biostator designed by Pfeiffer [72]

treatments (in contexts where invasive techniques do not constitute a barrier to its implementation). The Biostator is the main example for this sort of interface.

- **Intravenous measuring and intraperitoneal insulin delivery.** Implantable insulin pumps have been used for intraperitoneal (into the abdominal cavity) infusion, which has many of the advantages of the full-intravenous interface. However, it still is invasive and adds the delay related to the absorption of the insulin.

- **Subcutaneous measuring and subcutaneous insulin delivery.** It is the less invasive option but also the choice that adds the largest delays to the control loop. This system is the more suited for long time treatments, and is the one that is going to be studied in detail in this thesis.

The increasing delay added by the less invasive interfaces is a present problem anytime designing a controller for blood glucose. Revision of the main drawbacks and advantages for every method was done by Hovorka [33], and the delays present in every sort of control system can be seen in figure 1.8.

Other possible classification for closed-loop control in diabetes will be regarding the control algorithm implemented:

- **PID control.** The classical approach control of Proportional-Integral-Derivative (PID) control is the broadest implemented control algorithm in industrial applications due to its simplicity and the fact that tuning algorithms for the controller have been developed for decades.

$$IIR = K_p(G - G_t) + K_I \int (G - G_t) + K_d \frac{\partial G}{\partial t} \tag{1.1}$$

  Where IIR represents the insulin infusion rate, K_p, K_d and K_i are the parameters of the controller (to be determined), G is the measured glucose, and G_t is the target glucose. Due to its simplicity, many times

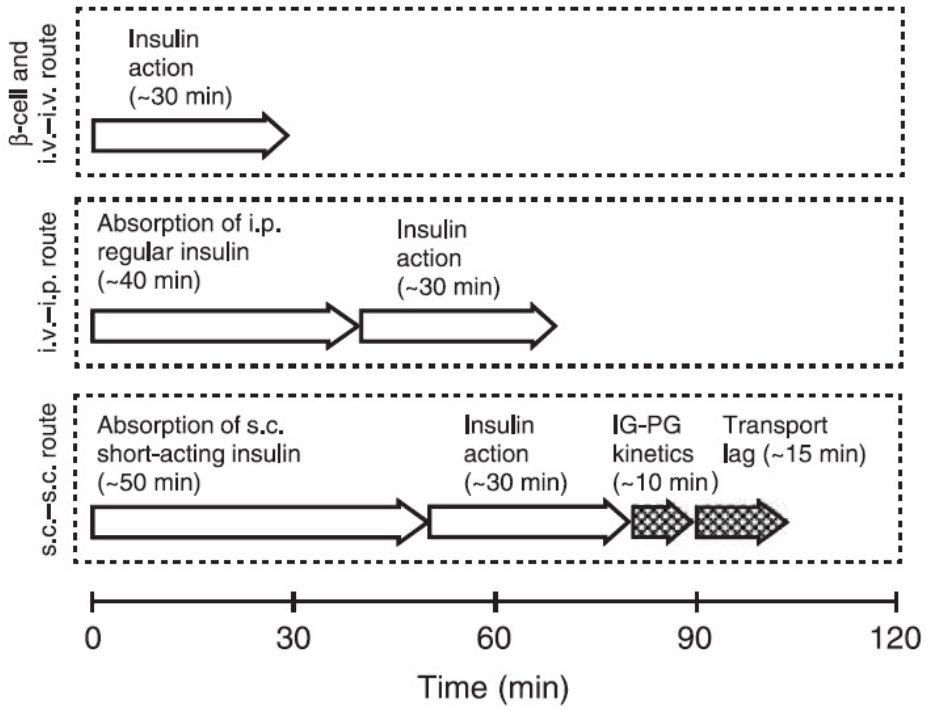

Figure 1.8: Delays related to the interface of the artificial pancreas system as stated by Hovorka [33]. s.c. stands for the subcutaneous route, i.p. stands for the intraperitoneal route and i.v. stands for the intravenous interface.

the PID gives the base structure to the controller, and many heuristic methods make the controller an "expert" controller. Marchetti [52] for example, developed one of these algorithms for type 1 diabetic patients and Chee [16] did it for critically ill patients.

- **State-feedback control.** The so called "Optimum control" methodology has been used to design algorithms as a feedback of the state of the model considered. Palumbo [65], for example, used this approach to design a controller for a Delayed Differential Equation model of the glucose regulation system.

- **Model predictive control (MPC).** MPC is a rather more complex control philosophy, based on optimization methods to find the optimum input that leads the controlled variable to the desired reference in a target time. It is, as well as the PID controller, widely implemented in industries, and the tuning algorithms are very efficient and have been refined for the last decades. A complete overview for the development of the algorithm and its impact on industry was performed by Camacho and Bordons [14]. In the context of artificial pancreas MPC is the most applied method of control, and several controllers have been developed, such as the one of Parker [68], or the one implemented by Hovorka [34], which was tested in its application on critical patients by Plank [74], showing that patients were more often within the glucose target range than with the usual therapy, and that hypoglycemia episodes were avoided completely by using the MPC controller.

About the optimum algorithm to be chosen in order to control a determined patient, the answer is not clear. Despite MPC methodology has been the most used option, it is mathematically proven that if the model is close enough to reality, the feedback of the state is the most robust and fastest control possible. That raises the question of whether the models used are reliable or useful, and how much should we deepen in the matter of modeling, or just use impulse and step models, as many MPC controllers do. The question of modeling is explained in depth in chapter 2.

The last classification of artificial pancreas systems is regarding the situation of the patient during the control, or the population that the system aims to control:

- **Pregnant woman transitional diabetes.** Gestational diabetes has been studied from the point of view of artificial pancreas in several works. Murphy et al. [59] showed the effectiveness of continuous glucose monitoring in pregnant women with diabetes, and Hernando et al. [30] used algorithms based in diabetic models to plan insulin therapy. No specific controllers have been designed for this particular case.

- **Critical patient control.** Critical patients are monitored in detail, not only in glucose, but also in many other important measures of body functions, which are intended to be as controlled as possible. This fact gives the opportunity to test many controllers designed for glucose regulation. The previously mentioned controller of Chee et al. [16] and the one designed by Hovorka's group in Cambridge [74], are examples of controllers used to maintain the glucose homeostasis in intensive care unit patients.

- **Overnight fasting control.** Overnight period is usually related to a natural reduction of the sensibility to insulin, and the lack of consideration of this effect creates an increase in blood glucose that is commonly known as "Dawn effect". Hovorka's group, for example, has achieved great success in controlling this kind of behavior by means of glucose monitoring and MPC controllers both with subcutaneous and intravenous interfaces [86].

- **Postprandial control.** The main disturbance to blood glucose control is the absorption of glucose from the gut. The postprandial blood glucose control aims to soften the abrupt increase of glucose after a meal without risking the patient's health. This thesis will be focused in this kind of control, which will be explained in detail in chapter 1.3.2.

Despite all the work that has been done already, the practical realization of a human pancreas is not yet possible, nor implanted as an artificial organ due to maintenance issues, neither emulated by an external device. The main problem with the external approach, as stated by Hovorka [33], is the low reliability and exactitude of the subcutaneous continuous glucose monitors, assuming the subcutaneous (and more comfortable to the patient) interface. Work has yet to be done in this area principally about characterizing the monitor behavior or designing controllers that manage to overcome measuring inexactitudes.

In addition, artificial pancreas research has been developing slowly during the last years due to ethical restrictions in the experiments, and the fact that some health and drugs agencies only considered allowing closed loop experiments in humans after having successful experiments with animals. Recently, in the Diabetes Technology Meeting of 2008 [91] an Food and Drug Administration (FDA) [24] approval was presented to substitute the stage of experiments on animals with *in silico* trials with the University of Virginia Simulator [44]. Many simulators have been developed lately for research purposes, and most of them come from members of the Juvenile Diabetes Research Foundation (JDRF) [40] closed-loop consortium which is one of the most important funding entity for diabetes research in the international level.

1.3.2 Postprandial control of mixed models

Postprandial response of blood glucose is usually a sudden increase in its concentration, usually resulting in long hyperglycemia situations, which lead to harmful pathologies in diabetic patients. Its control and understanding is one of the objectives of the artificial pancreas project.

Modeling of glucose absorption is the most complicated issue to achieve a good postprandial control, due to the huge variability implied in the composition of meals, the variation between patients, and even within the

same patient, as stated by Steil and Reifman [91]. Many models of the glucose absorption, including different types of nutrients, and variable emptying rate of the stomach have been developed in the last years, and will be shown in the chapter 2.2.2.

The control approaches for postprandial control can be classified in three blocks, depending on the nature of the control loop:

- **Insulin delivery without meal announcement.** This approach is the pure closed loop approach, and there is no feed-forward action given by the patient. Some variations of this approach include *predictors* or *alarms*, that MPC controller, achieving positive results.
- **Insulin delivery and qualitative meal announcement.** In this case, the patient informs the controller if there is going to be a meal event, but there are no further specifications about the event, such as the composition of the meal or the size of it. Few work has been done in this field, and only one full system has been described by Panteleon et al. [66].
- **Insulin delivery and quantitative meal announcement.** In this case, there is an announcement of the meal event, and some information about it is given, such as the amount of carbohydrates of the meal. This situation is the most common, and is also the closest one to the classic approach, in which the insulin bolus quantity is proportional to the size of the meal. Many controllers have been developed for this scenario, and tested *in silico*, and despite that there are some examples of control of the postprandial glucose response in diabetic patients, regulation to perform experiments in real patients has been very restrictive so far, especially regulations by the FDA in the USA. Strategies to improve postprandial response by means of an adaptive therapy have been developed by Cesar Palerm [63] [62] as a way to help doctors with their recommendations to patients, but no closed-loop controllers have been developed for this case in particular.

A different approach has been used by Revert et al. [81] to calculate the best combination of basal and bolus delivery rate for the postprandial control. This work is based on a previous one developed by Bondia et al. [11], parting from interval analysis of different models. The set-inversion methods utilized to infer the best infusion to be delivered use discretization of glucoregulatory models under conditions of uncertainty, which permits finding the bounding regions of all the possible glucose responses considering some uncertainties. Calm et al. [13] already discretized postprandial models considering uncertainty in parameters and meal intake. If only the insulin infusion rate is considered as uncertainty, then restrictions in the blood glucose, such as 'no hypoglycemia' or 'limited time hyperglycemia', describe a set of inputs that will always accomplish with the restrictions.

The set inversion methods for postprandial control are currently being developed by the INSULAID2 research group [12], in which this thesis is placed. This methods, together with those developed by Palerm in Santa Barbara, and the rest of controllers described before, have the same requirement, and that is a model that describes the postprandial response in detail, and that, as has been stated before, is the main problem for this control scenario in diabetes.

Chapter 2

Modeling the glucose-insulin system in type 1 diabetes

One of the main problems for glucose control is the insufficient accuracy of existing mathematical models for describing the physiology of the glucoregulatory system. In this chapter the modeling context for the artificial pancreas will be reviewed, and the state of the art of mathematical models in literature will be described.

2.1 Behavioral and phenomenological models

It is often said that "all models are wrong, but some are useful". So the objective of a model is not to be accurate, or find any truth, but to be useful in the aim that it is intended to be. Walter and Pronzato [99] listed some objectives a model may aim at. Some of them are:

- Analyzing phenomena to deepen understanding. Models for simulation.
- Estimating quantities for which no sensor is available. Estimators of

state.

- Testing hypothesis.
- Controlling processes and testing controllers. Models for control.

Depending on the aim of the model (and this aim must always be clear before starting modeling), the model is radically different. Models for control, for example, tend to simplify the system they are representing much more than models for simulation, which are usually complex, more accurate models.

A model is characterized by its structure, and this is the first choice to be made when deciding which model is appropriate. The main distinction to be made when looking at the model structure is whether it has to be *phenomenological* or *behavioral*. A phenomenological model is a model based on prior knowledge about a physical or, in the case of the artificial pancreas, physiological principles. This kind of processes are often called *knowledge-based* models as opposed to behavioral models, which merely approximate the observed behavior of the output without any prior knowledge of the process. Behavioral models are focused on data reproduction, and not at all in the process behind, while phenomenological models only use the data to adjust the parameters, while the structure is determined by the process itself.

Examples of phenomenological models are:

- Chemical reactions. Biological reactions
- Systems of force equilibrium.
- Models of deposit systems.
- Electromagnetic models. Electrical engines.

Examples of behavioral models are:

- ARX/ARMAX models.
- Polynomial models.
- Random models.

The behavioral models exposed do not have a purpose on imitating any real process, and are "all-purpose" models that have to be adjusted to any particular system, while the phenomenological models shown are specific of the process they represent. Table 2.1 shows a comparison of the differences between both modeling paradigms.

	Phenomenological models	Behavioral models
Parameters	have a concrete meaning	have no concrete meaning
Simulation	long and difficult	quick and easy
Prior information	taken into account	neglected
Validity domain	large (if structure is correct)	restricted

Table 2.1: Phenomenological and behavioral models as seen by Walter and Pronzato [99]

Usually, phenomenological models tend to be complex, and highly nonlinear. Linearizing a phenomenological model changes its aim, and therefore it changes its nature. When a nonlinear phenomenological model is designed, its aim is usually a better understanding of the system through simulation. Reasons for linearizing are usually attempts to control, or design of better controllers, but this transformation neglects the prior information of the system and its complexity, so the model results in a behavioral model, with a restricted validity domain and lost of the meaning of the parameters.

In the context of the artificial pancreas almost every model published is phenomenological, even the simplest ones, due to the vast knowledge of the physiology available from the physicians. There are though some methods that use simplification and linearization of those models to extract some information out of them, but this problem will be explained later in detail.

2.2 Physiological processes (models) of the glucose-insulin system

Modeling of any insulin therapy for type 1 diabetes involve three main subprocesses:

- **Insulin absorption model.** This model represents the way insulin gets into the organism, which involves its pharmacokinetics, diffusion through different tissues and natural insulin degradation. Insulin absorption depends on the type of insulin used for the therapy and the interface used for its delivery. Insulin is injected or infused in the subcutaneous tissue, delaying its appearance in plasma compared to insulin secretion by the pancreas. In case multiple daily injections are used, pharmacokinetics of both rapid-acting and long-acting insulin will have to be modeled. In case of insulin pump (and the artificial pancreas) only rapid-acting insulin is used.

- **Glucose absorption model.** This model is also called the gastrointestinal model, because it involves the process of ingestion, digestion and absorption from the intestine into blood of glucose and other nutrients. The nutritional composition of the meal has influence over the process of digestion, and that may slow down the flow of carbohydrates through the gut.

- **Glucoregulatory model.** The internal regulation of glucose is represented by this model. The transformation of glycogen to glucose by the liver (hepatic glucose production) and glucose uptake by peripheral tissues, the influence of different hormones in blood glucose, insulin independent consumption of glucose, and in summary, every effect that, in the organism, can affect the concentration in glucose. The models representing all these physiological processes and relations tend to be really complex, and it is really common to disregard some of

the influences on the glucose concentration, so that the model becomes simpler and for other purposes than simulation.

The insulin absorption and gastrointestinal models are usually considered as the *input models* for the glucose-insulin system, for they characterize the two main exogenous (that come from outside the body) inputs into blood that have influence on the glucose concentration (figure 2.1). A good review of the physiology and models of the systems described can be found in Amores [3]. Other reviews in literature include Willinska review [103] and Nucci and Cobelli review [61].

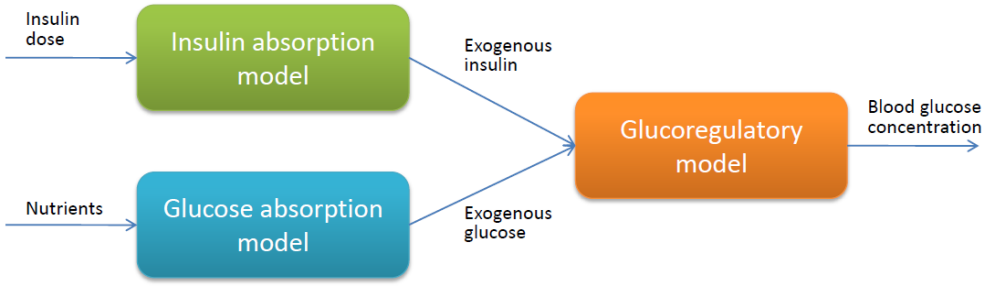

Figure 2.1: Glucose-insulin system and its subprocesses

Subcutaneous insulin injection or pump delivery is the only control action that can be used to counteract the main disturbance considered, meal ingestion. Insulin pharmacokinetics, has been studied for a long time, and the behavior of insulin analogues is well documented in bibliography. Complex glucose absorption models have been developed in the last years with increasing accuracy, but the physiological behavior of the digestive and intestinal absorption processes during a mixed meal ingestion, which is almost every meal a normal person has, is yet to be represented by a gastrointestinal model. The main difficulty in characterization of the gastrointestinal model is that absorption of glucose is only measurable with tracer methods [6], but few studies have been done in this area so far. The only experiments done in this area were not performed using real mixed meals, but instead the patients ate marked jelly with eggs and bacon. The influence of the

nutritional composition is very relevant in the final model output, and it has not been taken in consideration so far.

Several models for the systems described are going to be shown in the next sections, and later a critical review of the usefulness of these models is going to be performed, in order to narrow down the scope of the research, not to forget that the last objective of this thesis is identification of postprandial models for control.

2.2.1 Insulin absorption models

Insulin absorption models are going to be reviewed starting in one compartment model, viewing next models with several compartments and finally to models in partial differential equations. In order to make this chapter easier to read, there are going to be shown only the structure and basic concepts and equations of the model. Some models will be explained in further detail if considered necessary.

Kobayashy et al. [43]

In this model, published in 1983, the subcutaneous absorption of a short-acting insulin is represented by a one compartment model, with another compartment representing the pool of insulin in blood, as seen in Figure 2.2.

The equations related to this model are:

$$\dot{x}_1(t) = -k_a x_1(t) + u(t-\tau) \tag{2.1}$$

$$\dot{i}(t) = -k_e i(t) + \frac{k_a}{V_d} x_1(t) \tag{2.2}$$

The four parameters to be identified are shown in Table 2.2.

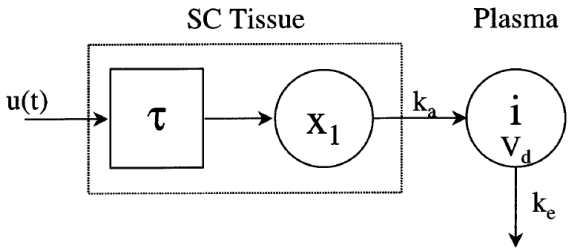

Figure 2.2: Kobayashy model compartments

Parameter	Published value	Units
τ	7	min
k_a	2.7×10^{-2}	min^{-1}
k_e	1.2×10^{-2}	min^{-1}
V_d	1.5×10^{3}	ml kg^{-1}

Table 2.2: Nominal values of the parameters in Kobayashy's model

This was one of the first models for insulin pharmacokinetics published, and it was only designed for *Actrapid* insulin in a concentration of 40 U/ml, which makes the model outdated (current insulin concentration are 100 U/ml).

Kraegen et al. [45]

Kraegen model was published also in 1984, and it removes the delay block from the Kobayashy model to substitute it with a compartment that acts as such delay. It also considers degradation of insulin in every stage of the diffusion of insulin in the interstitial space. The compartment diagram can be seen in Figure 2.3.

The equations related to this model are:

$$\dot{x}_1(t) = -(k_d + k_{21})x_1(t) + u(t) \tag{2.3}$$

$$\dot{x}_2(t) = k_{21}x_1(t) - (k_d + k_{ps})x_2(t) \tag{2.4}$$

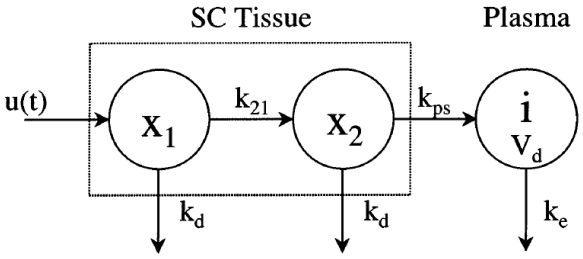

Figure 2.3: Kraegen model compartments

$$\dot{i}(t) = \frac{k_{ps}}{V_d} x_2(t) - k_e i(i) \tag{2.5}$$

The five parameters to be identified are shown in Table 2.3.

Parameter	Published value	Units
k_{21}	2.97×10^{-2}	min^{-1}
k_d	0.0	min^{-1}
K_{ps}	9.67×10^{-3}	min^{-1}
K_e	9×10^{-2}	min^{-1}
V_d	12×10^{3}	ml

Table 2.3: Nominal values of the parameters in the Kraegen model

It must be pointed out that the published value of the k_d parameter is identically zero, which makes the degradation of insulin in the compartments of insulin subcutaneous diffusion non existent. This fact makes the model identifiable, while having that parameter to be identified would make the model globally non identifiable. The issue of identifiability will be discussed in depth in Chapter 3.

Puckett et al. [77]

Puckett model considered the combined action of long-acting and short-acting insulins. Insulin degradation is only considered in the place of the injection as an insulin effectiveness constant.

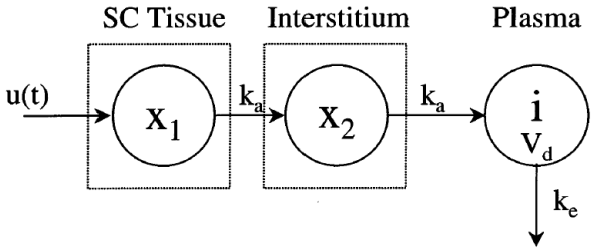

Figure 2.4: Puckett model compartments

The equations related to this model are:

$$\dot{x}_1(t) = -k_a x_1(t) \qquad x_1(0) = \frac{\alpha D}{V_d} \tag{2.6}$$

$$\dot{x}_2(t) = -k_a \left[x_1(t) - x_2(t)\right] \qquad x_2(0) = 0 \tag{2.7}$$

$$\dot{i}(t) = k_a x_2(t) + k_e \left[i_b h(t) - i(t)\right] \qquad i(0) = i_b \tag{2.8}$$

The dose injected is considered to have an effectiveness α, which represents the degradation of insulin, and it is set as the initial condition of the first compartment x_1. i_b is the constant term for the plasma insulin describing the effect of long-acting insulin, and $h(t) = 1$ for the first 24 hours of simulation. This model is non identifiable, so the authors decided to agregate α and V_d parameters in a new parameter $\beta = V_d/\alpha$, which is shown in Table 2.4.

Parameter	Published value	Units
k_a	1.42×10^{-2}	min^{-1}
k_e	6.25×10^{-2}	min^{-1}
β	3.47×10^{-3}	ml
i_b	14.58	ml^{-1}

Table 2.4: Nominal values of the parameters in Puckett model

Shimoda et al. [88]

Shimoda et al. published a model in 1997 valid for two subcutaneously injected insulin preparations: soluble and monomeric insulin analogue. The

model has the same structure for both insulin preparations, and the difference is only in the parameters, which are different for each type of insulin used. The structure of the model is shown in Figure 2.5.

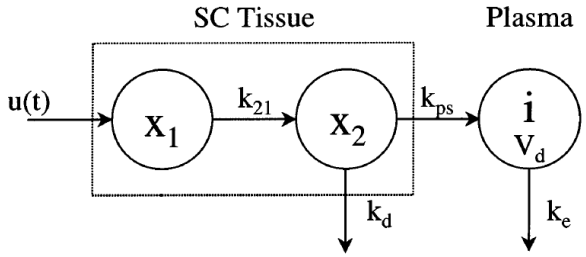

Figure 2.5: Shimoda model compartments

The equations related to this model are:

$$\dot{x}_1(t) = -k_{21}x_1(t) + u(t) \tag{2.9}$$

$$\dot{x}_2(t) = k_{21}x_1(t) - (k_d + k_{ps})x_2(t) \tag{2.10}$$

$$\dot{i}(t) = \frac{k_{ps}}{V_d}x_2(t) - k_e i(t) \tag{2.11}$$

the sets of parameters for each insulin type are shown in Table 2.5.

Parameter	Published value (soluble)	Published value (monomeric)	Units
k_{21}	1.1×10^{-2}	1.7×10^{-2}	min^{-1}
k_{ps}	1.5×10^{-2}	4.8×10^{-2}	min^{-1}
k_d	2.1×10^{-3}	2.9×10^{-3}	min^{-1}
k_e	9.9×10^{-2}	1.33×10^{-1}	min^{-1}
V_d	1.25×10^{-1}	8×10^{-2}	ml kg^{-1}

Table 2.5: Nominal values of the parameters in Shimoda model

Berger et al. [8]

Berger et al. model is a non-compartmental model that allows kinetic description of different insulin preparations, such as *regular*, *NPH*, *lente* and

ultralente insulins. The percent of the insulin absorbed subcutaneously with respect to the amount injected is given by:

$$A_{\%}(t) = 100A(t) = 100 - \frac{100t^s}{T_{50}^s + t^s} \tag{2.12}$$

$$T_{50} = aD + b \tag{2.13}$$

Where s, a and b are parameter depending on the insulin preparation, D is the insulin dose, and T_{50} is the time interval to reach a 50% absorption of the total dose. The insulin input flux to the plasma compartment is easily calculated by multiplying the time derivative of $A(t)$ by D. The single expression for the Berger model, together with equation 2.13 stands:

$$\dot{i}(t) = -k_e i(t) + \frac{\dot{A}(t)D}{V_d} = -k_e i(t) + \frac{t^{s-1} s T_{50}^s D}{V_d (T_{50}^s + t^s)^2} \tag{2.14}$$

Two sets of parameters are shown in Table 2.6, one for regular insulin, and one for NPH insulin.

Parameter	Published value (soluble)	Published value (NPH)	Units
s	2	2	-
a	3	10.8	min U^{-1}
b	102	294	min
k_e	9×10^{-1}	9×10^{-1}	min^{-1}
V_d	12×10^{-3}	12×10^{-3}	ml

Table 2.6: Nominal values of the parameters in Berger model

Cobelli et al. [51]

The model proposed by Cobelli's group has also two compartments for the interstitial space, and it considers that the elimination of insulin takes place entirely after the absorption to plasma. There are two variants of the model, depending on the complexity considered for the model of distribution of insulin. The first and simpler model is the one shown in Figure 2.6.

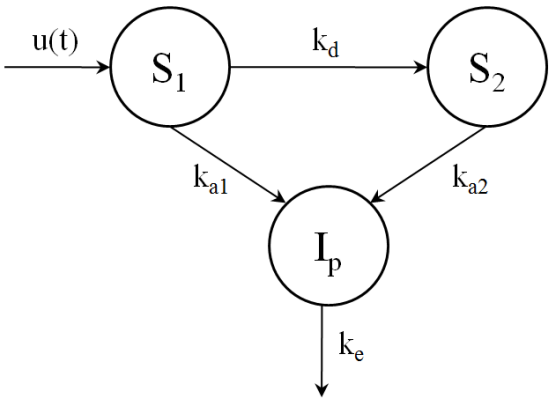

Figure 2.6: Cobelli model with one compartment for the plasma insulin

The absorption takes place from both stages in the subcutaneous route. The equations related to the model are:

$$\dot{S}_1(t) = -(k_{a1} + k_d)S_1(t) + u(t) \tag{2.15}$$

$$\dot{S}_2(t) = k_d S_1(t) - k_{a2} S_2(t) \tag{2.16}$$

$$\dot{I}_p(t) = k_{a1} S_1(t) + k_{a2} S_2(t) - k_e I_p(t) \tag{2.17}$$

But the subcutaneous part is usually considered together with a more complex distribution and elimination model, also proposed by Cobelli's group. The new model is displayed in Figure 2.7.

Now the elimination of insulin takes places both by degradation in the plasma compartment and in the liver, that is considered as another compartment. The corresponding system of equations related is exactly the same as before, but substituting equation 2.17 by the following two differential equations:

$$\dot{I}_l(t) = -(m_1 + m_3)I_l(t) + m_2 I_p(t) \tag{2.18}$$

$$\dot{I}_p(t) = -(m_2 + m_4)I_p(t) + m_1 I_l(t) + k_{a1} S_1(t) + k_{a2} S_2(t) \tag{2.19}$$

No published values of the parameters for T1DM people have been

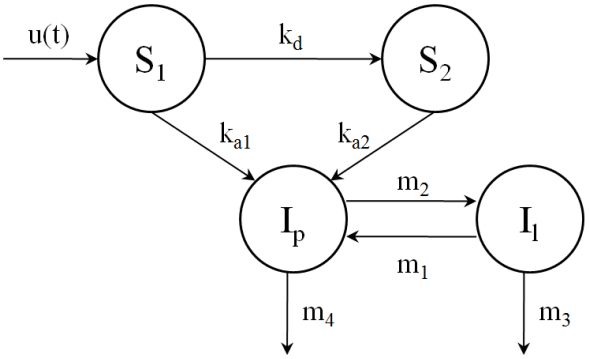

Figure 2.7: Cobelli model considering insulin in the liver and in plasma

published. Insulin pharmacokinetics parameters have not been published either. Published values [21] for healthy and T2DM patients for the distribution and elimination part of the model are shown in Table 2.7. Parameter m_3 is only constant for T1DM patients while for the published cases it has dynamic behavior depending on the endogenous insulin secretion. Nevertheless, this model is implemented in the University of Virginia Simulator [44], and nominal parameters for healthy and diabetic patients are used in the simulations performed with it.

Parameter	Normal value	T2DM value	Units
m_1	0.19	0.379	min^{-1}
m_2	0.484	0.673	min^{-1}
m_4	0.194	0.269	min^{-1}

Table 2.7: Published values of the Cobelli model

Willinska et al. [102]

In 2005 Willinska performed a comparison of subcutaneous models increasing in complexity. Those models where evaluated for treatments of bolus and continuous infusion with insulin pumps with insulin *lispro*, a human insulin analog. The model with a better fit to experimental data is shown in Figure 2.8.

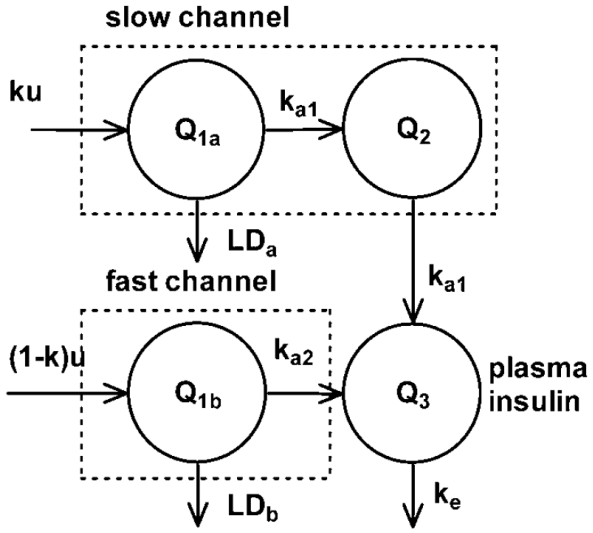

Figure 2.8: Willinska model compartmental structure

It is one of the most complex compartmental models existing. The equations related to the model are:

$$\dot{Q}_{1a}(t) = ku - k_{a1}Q_{1a} - LD_a \tag{2.20}$$

$$\dot{Q}_{1b}(t) = (1-k)u - K_{a2}Q_{1b} - LD_b \tag{2.21}$$

$$\dot{Q}_2(t) = k_{a1}Q_{1a} - k_{a1}Q_2 \tag{2.22}$$

$$\dot{Q}_3(t) = k_{a1}Q_2 + k_{a2}Q_{1b} - k_eQ_3 \tag{2.23}$$

$$i(t) = \frac{Q_3}{V \cdot BW} \tag{2.24}$$

$$LD_a = \frac{V_{MAX,LD}Q_{1a}}{k_{M,LD} + Q_{1a}} \tag{2.25}$$

$$LD_b = \frac{V_{MAX,LD}Q_{1b}}{k_{M,LD} + Q_{1b}} \tag{2.26}$$

$$\tag{2.27}$$

The most significant characteristic of this model is the existence of two channels of insulin, one of slow absorption and a fast absorption insulin channel, both with degradation of insulin governed by a Michaelis-Menten kinetic equation. The insulin concentration is now directly calculated from

the fourth compartment. Published parameters of the model are shown in Table 2.8.

Parameter	Published value	Units
k_{a1}	$1.12 \cdot 10^{-2}$	min^{-1}
k_{a2}	$2.1 \cdot 10^{-2}$	min^{-1}
k_e	$1.89 \cdot 10^{-2}$	min^{-1}
k	0.67	-
V	$56.45 \cdot 10^{-2}$	L kg^{-1}
$V_{MAX,LD}$	1.93	mU min^{-1}
$k_{M,LD}$	62.6	mU

Table 2.8: Nominal values of the parameters in Willinska model

Trajanoski et al. [96]

This model considers diffusion of insulin in the subcutaneous tissue and is described by partial differential equations. This kind of equations make this model much more complicated than all the others, and also computationally heavier. The Trajanoski model [96] was published in 1993 as a simplification of Mosekilde model [57] assuming that at therapeutic concentrations insulin binding to proteins, therefore inactive insulin, in the subcutaneous space is negligible. Under those assumptions, the model equations stand:

$$\frac{\partial h(r,t)}{\partial t} = P\left[Qd^3(r,t) - h(r,t)\right] + D\nabla^2 h(r,t) \tag{2.28}$$

$$\frac{\partial d(r,t)}{\partial t} = P\left[-Qd^3(r,t) + h(r,t)\right] + D\nabla^2 d(r,t) - Bd(r,t) \tag{2.29}$$

$$\frac{\partial i(t)}{\partial t} = \dot{i}(t) = -k_e i(t) + \frac{1}{V_d}\int_{SC}(Bd(r,t))dV_{SC} \tag{2.30}$$

where:

- h is the state representing the insulin concentration in subcutaneous tissue in hexamer state and it is measured in $\frac{U}{ml}$.

- d is the state representing the insulin concentration in subcutaneous tissue in dimer state and it is measured in $\frac{U}{ml}$.
- i is the state representing the insulin concentration in blood, measured in $\frac{U}{ml}$.
- r is the variable representing the radial distance from the point of injection.
- Q is the parameter representing the chemical equilibrium of the transformation of insulin into different states.
- P is the parameter of velocity of the transformation of insulin into other states.
- D is the parameter representing the diffusion rate.
- B is the parameter representing the rate of absorption of insulin.
- k_e is the parameter for the elimination of insulin in blood.
- V_d is the parameter for the distribution volume of insulin in blood.

In this model, a simple, single compartment model has been used for plasma insulin dynamics, just as the Berger model. The absorption is the result of an integral all over the control surface of the concentration of insulin in dimer state, due to the fact that only dimer insulin is transported into blood.

Table 2.9 shows the parameters for this model.

Tarín et al. [93]

The Tarín model was developed in the same research group as this thesis. It is a model based on the Trajanoski model and tries to extend the model for long acting insulin glargine. This is done by considering a new virtual compartment called *bound* state (not to be confound with *binding* state in

Parameter	Published value	Units
Q	1.3×10^{-1}	$\mathrm{ml^2U^{-2}}$
P	5×10^{-1}	$\mathrm{min^{-1}}$
D	9×10^{-5}	$\mathrm{cm^2min^{-1}}$
B	1.3×10^{-2}	$\mathrm{min^{-1}}$
k_e	9×10^{-2}	$\mathrm{min^{-1}}$
V_d	12×10^{-3}	ml

Table 2.9: Nominal values of the parameters in Trajanosky model

Trajanoski model that represents inactive insulin), which is a virtual initial state of this type of insulin when injected. This fact adds a new partial differential equation, and the model equations are:

$$\frac{\partial c_d(r,t)}{\partial t} = P\left[c_h(r,t) - Qc_d^3(r,t)\right] - B_d c_d(r,t) + D\nabla^2 c_d(r,t) \tag{2.31}$$

$$\frac{\partial c_h(r,t)}{\partial t} = -P\left[c_h(r,t) - Qc_d^3(r,t)\right] + \kappa c_b(r,t)\left[c_{h,max} - c_h(r,t)\right] + D\nabla^2 c_h(r,t) \tag{2.32}$$

$$\frac{\partial c_b(r,t)}{\partial t} = -\kappa c_b(r,t)\left[c_{h,max} - c_h(r,t)\right] + d_b D\nabla^2 c_b(r,t) \tag{2.33}$$

$$\frac{\partial i(t)}{\partial t} = \dot{i}(t) = -k_e i(t) + \frac{1}{V_d}\int_{SC}(B_d c_d(r,t))dV_{SC} \tag{2.34}$$

The variables of the model are:

- c_h is the state representing the insulin concentration in subcutaneous tissue in hexamer state and it is measured in $\frac{U}{ml}$.
- c_d is the state representing the insulin concentration in subcutaneous tissue in dimer state and it is measured in $\frac{U}{ml}$.
- c_b is the state representing the insulin concentration in subcutaneous tissue in bound state and it is measured in $\frac{U}{ml}$.

And the parameters are exactly the same as for Trajanoski model, except for the κ parameter, that represents the rate of dissociation of insulin in bound state into hexamers, $c_{h,max}$ that limits the concentration of hexamer insulin

and d_b that reduces the speed of diffusion of the bound insulin. As for the rest parameters, the P parameter is considered to be fixed for every type of insulin and patients, due to its low sensibility. The rest of the parameters are shown in Table 2.10 for the Glargine insulin.

Parameter	Published value (Glargine)	Units
Q	3.04	ml^2U^{-2}
D	8.4×10^{-5}	$\text{cm}^2\text{min}^{-1}$
B_d	1.18×10^{-2}	min^{-1}
κ	0.01	$\text{ml min}^{-1}\text{U}^{-1}$
$c_{h,max}$	15	U ml^{-1}
d_b	0.1	-
k_e	9×10^{-2}	min^{-1}
V_d	12×10^{-3}	ml

Table 2.10: Nominal values of the parameters in Tarin model

An extensive identifiability and identification analysis has been performed by Ana Revert [80] in this model for *lispro* insulin, showing that it is able to mimic with certain fidelity the behavior of different types of insulin, including slow acting insulins, usually used to keep constant basal insulin concentration.

Li-Kuang et al. [49]

Li and Kuang published a model simpler than the previous models able to simulate different types of insulin. This model is based on the Tarin model, but it does not consist of partial differential equations, what makes it much simpler to identify. The model adds a new equation if using slow acting insulins such as the glargine insulin, that simulates a virtual bound state as Tarin model does. The ordinary differential equations that represent each

state of insulin in Li-Kuang model are:

$$\dot{B}(t) = -kB(t)\frac{C_{max}}{1+H(t)} \tag{2.35}$$

$$\dot{H}(t) = -p(H(t) - qD^3(t)) + kB(t)\frac{C_{max}}{1+H(t)} \tag{2.36}$$

$$\dot{D}(t) = p(H(t) - qD^3(t)) - \frac{bD(t)}{1+I(t)} \tag{2.37}$$

$$\dot{I}(t) = \frac{rbD(t)}{1+I(t)} - d_i I(t) \tag{2.38}$$

Every equation represents a compartment, and each compartment is a state in insulin transformation before it can go through the vascular walls in it dimeric form. The states of the model are:

- $B(t)$ represents the insulin in bound state. This state is only present for slow acting insulins, and the input to the model is the initial state of this variable in those cases.
- $H(t)$ is the compartment representing the hexamer form of the insulin. For regular and rapid acting insulins the initial state of this variable is the input of the model.
- $D(t)$ is the dimer insulin compartment.
- $I(t)$ is the mass plasma insulin compartment. Insulin concentration is directly calculated from this variable by dividing by the apparent distribution volume for insulin.

In their paper of 2009 [49], Li and Kuang perform a complete mathematical analysis of the solutions of the model, and they also propose a set of parameters identified and extracted from bibliography. This set of parameters is shown in Table 2.11.

Parameter	Published value (lispro)	Published value (Glargine)	Units
p	0.5	0.5	min^{-1}
q	0.13	3.04	ml^2U^{-2}
r	0.2143	0.2143	-
b	0.0068	0.02	U min^{-1}
d_i	0.081	0.0215	min^{-1}
k	-	2.35×10^{-5}	min^{-1}

Table 2.11: Nominal values of the parameters in Li-Kuang model

Wong et al. [108]

Wong, in 2008, published a new model for diverse insulin types with a compartmental structure. It goes even further, predicting the behavior of insulin kinetics when there are mixed insulin types, or multiple injections, or mixed pump infusion. Its structure is way more complex than any other previous, and it has a different compartment and dynamics for every type of insulin considered, having different pools for the hexamer insulin and dimer/monomer insulin.

The decision of use a compartmental structure for such a complex model is based on the principle of providing a computationally-minimal model, yet consistent, and physiologically united framework for all insulin types. The fact of only using ordinary differential equations speeds up the computations, as the complexity of the structure helps with the consistency of the model. Figure 2.9 is shown to depict the structure of the model, and for more information, the reader is referred to Wong thesis [108] and papers [107] [106].

The Figure shows that every insulin (NPH, Lente, RI, MI, Ultralente and Glargine) has its own sub-model, behaves by its own kinetic, and is one input of the main model. The model of pharmacokinetics itself is not much different than the other ones that have been shown before, and in fact, Wong uses the values of the parameters shown in previous tables as a priori identified values, and then fixes the values of those parameters in order to

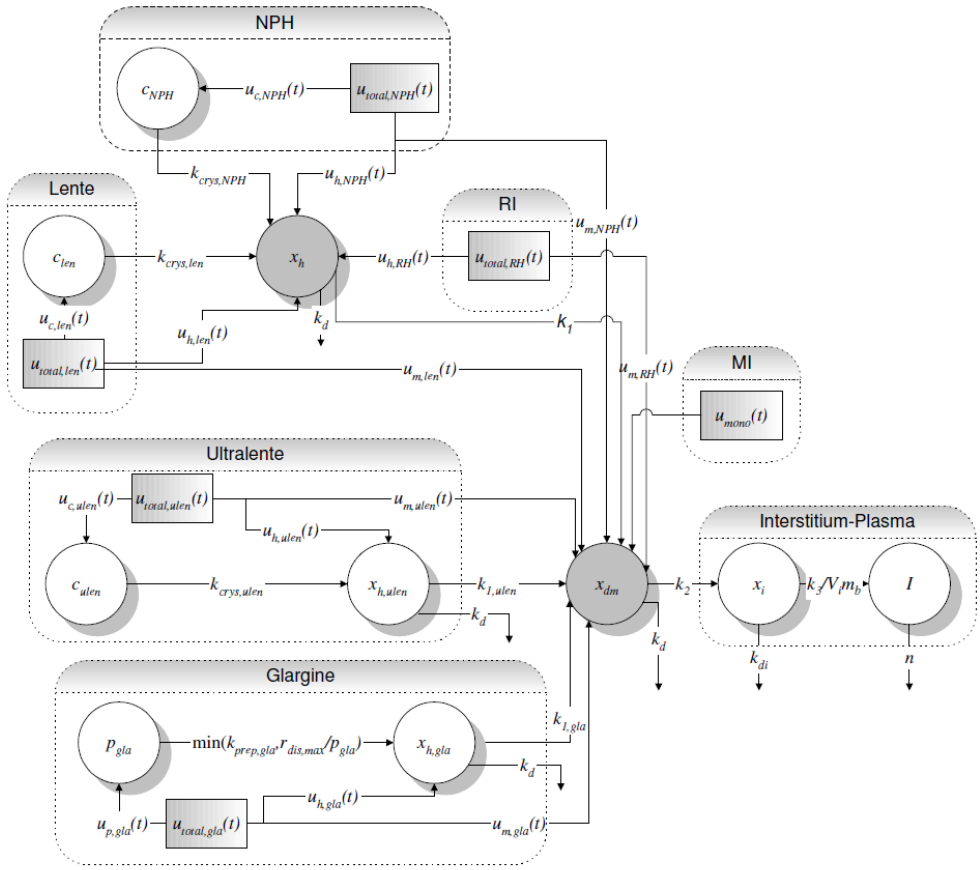

Figure 2.9: Wong model compartmental structure

make easier the identification of each insulin block.

Summary

In Table 2.12 all the models reviewed are displayed, showing the characteristics that make them different, and with which types of insulin have been used or are capable of simulate.

Model	Types of Insulin	Structure
Kobayashy	Actrapid $40U/ml$	input delay, compartmental
Kraegen	-	compartmental
Puckett	-	compartmental
Shimoda	monomeric and soluble	compartmental
Berger	regular, NPH, lente and ultralente	algebraic
Cobelli	-	compartmental
Willinska	lispro (CSII)	compartmental
Trajanosky	NPH and soluble	PDE
Tarín	glargine	PDE
Li-Kuang	lispro, glargine	ODE no compartmental
Wong	NPH, lente, RI, MI, ultralente and glargine	compartmental

Table 2.12: Insulin absorption models. Insulin types in blank are not specified by the authors of the model

2.2.2 Glucose absorption models

The models described in this section aim at characterizing the flux of exogenous glucose absorbed by the intestine under different circumstances. There are different scenarios to be simulated by these models. One of the most common experiments performed in diabetic patients is the so called "Oral Glucose Tolerance Test" (OGTT), and its objective is to observe the response of blood glucose when the patient drinks a solution of glucose. This glucose is rapidly absorbed by the intestine, and that boosts the blood glucose

concentration, forcing the pancreas (if able) to secrete insulin to counteract the rising of glucose. This scenario is broadly used to characterize sensitivity and tolerance parameters to glucose but is of no use when compared to the absorption of a common meal ingestion. The nature of the meal, its size and composition, as well as the speed of ingestion, and patient conditions, have influence on the rate of stomach emptying [55] and the final absorption rate of glucose, which make the mixed meal ingestion very difficult to characterize.

The models shown in here were designed regarding to the scenarios described, some only looking at the OGTT, others having a broader sight. The optimal model would be able to simulate both, the OGTT and a mixed meal ingestion, but unfortunately, there is no such thing as the perfect model.

The structure of the models for glucose absorption have some elements in common. The gastric emptying is one of the critical points in the flow of food through the gastrointestinal tract, due to its dependence on different variables [37]. Figure 2.10 shows the general diagram for glucose absorption models, with the food intake as input (described most of times as amount of carbohydrates), and the exogenous flux of glucose (rate of appearance) G_{ex}, as output.

In the following, literature models are described.

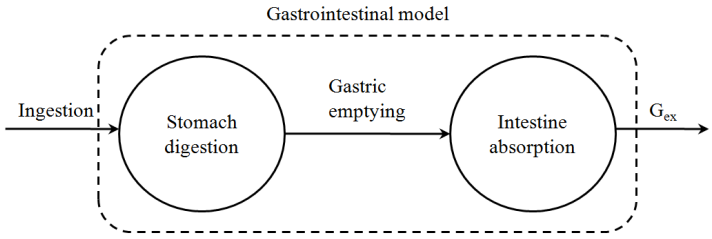

Figure 2.10: Block diagram of the gastrointestinal model

Hunt et al. [38][94]

The model presented here is an extended version of the Hunt model. Hunt et al published a model of gastric emptying in 1975 extended in its intestinal absorption part by Teufel. The combined system is a very complete model that uses a set of algebraic equations to characterize the gastric emptying, and a set of partial differential equations to simulate the transformation of the carbohydrates from their polysaccharide form into the final monosaccharide form, which is the only one that is possible to be absorbed by the intestine walls.

The equations related to the gastric emptying are not ordinary differential equations, but algebraic, and the output is not the flux of glucose due to the gastric emptying, but the volume of glucose remaining in the stomach $V(t)$.

$$V(t) = V_0 e^{-at} + (1 - e^{-at})\frac{q_{basal}}{a} \tag{2.39}$$

$$a = \frac{ln2}{V_{meal}(0.1797 - 0.167e^{-0.2389\kappa})} \tag{2.40}$$

$$\kappa = \frac{1}{V_{meal}}(0.0167m_{ch} + 0.0167m_{prot} + 0.0377m_{lip}) \tag{2.41}$$

The solution to the previous equations will give the remaining volume of carbohydrates in the stomach. Operating with that variable, the output of the stomach as a flux of carbohydrates can be obtained. The parameters and variables involved are:

- V is the stomach volume, measured in ml. V_0 is the value of the variable at time 0.
- V_{meal} is the total volume of the ingested meal.
- a represents the emptying speed of the stomach.
- κ is the weighted influence of the amount of carbohydrates, lipids and proteins in the gastric emptying.

- m_{ch} is the total amount of carbohydrates present in the meal in mg.
- m_{prot} is the total amount of proteins present in the meal in mg.
- m_{lip} is the total amount of lipids present in the meal in mg.

Once determined the rate of emptying of the stomach, the rest of the model consists in a series of partial differential equations for every stage in the dissociation process of the carbohydrates, from polysaccharides to monosaccharides:

$$\frac{\partial}{\partial t}p(z,t) = -\upsilon\frac{\partial}{\partial z}p(z,t) - \frac{Q_p p(z,t)}{K_{mp} + p(z,t)} \tag{2.42}$$

$$\frac{\partial}{\partial t}o(z,t) = -\upsilon\frac{\partial}{\partial z}o(z,t) + \frac{Q_p p(z,t)}{K_{mp} + p(z,t)} - \frac{Q_o o(z,t)}{K_{mo} + o(z,t)} \tag{2.43}$$

$$\frac{\partial}{\partial t}m(z,t) = -\upsilon\frac{\partial}{\partial z}m(z,t) + \frac{Q_o o(z,t)}{K_{mo} + o(z,t)} - \frac{Q_m m(z,t)}{K_{mm} + m(z,t)} \tag{2.44}$$

$$G_{ex}(t) = \int \frac{Q_m m(z,t)}{K_{mm} + m(z,t)}dz \tag{2.45}$$

The gastric emptying will come into the previous equations as a boundary condition in $p(0,t)$, and then carbohydrates will move forward in the linear space z that represents the gut space. The transformation fluxes are defined by a Michaelis-Menten dinamic equation, and the exogenous flux of glucose is calculated considering the monosaccharides present in all the intestine. Each Michaelis-Menten equation adds two new parameters that will have to be identified. The published values of these parameters are shown in Table 2.13 with the rest of the published parameter values.

Hovorka et al. [34]

Hovorka proposed a much simpler model for glucose absorption in his paper of 2004, where the gastrointestinal system is modeled by compartmental model with two identical compartments with the same transfer rate. Later, the

Parameter	Published value	Units
q_{basal}	0.4861	ml min^{-1}
υ	1	min^{-1}
K_{mm}	30	
K_{mo}	100	
K_{mp}	100	
Q_m	60	
Q_o	30	
V_0	50	

Table 2.13: Nominal values of the parameters in Hunt model

model was refined in a new paper [101] considering the transfer rate t_max as a time-varying parameter. The equations of the model are:

$$\dot{G}_1(t) = -\frac{G_1(t)}{t_{max}} + Bio \cdot D(t) \tag{2.46}$$

$$\dot{G}_2(t) = \frac{G_1(t)}{t_{max}} - \frac{G_2(t)}{t_{max}} \tag{2.47}$$

$$G_{ex} = \frac{G_2}{t_{max}} \tag{2.48}$$

where:

- $D(t)$ is the amount of carbohydrates ingested in grams. The meal in this model is considered as a pulse input.
- Bio is the effectiveness of the absorption of the carbohydrates ingested i.e. is the portion of the carbohydrates that have been eaten that will go into the circulatory system.
- t_{max} is the maximum absorption time of the carbohydrates. This parameter regulates the transfer speed between the compartments. It is a bounded parameter following:

$$t_{max} = \begin{cases} t_{max\ ceil} & \text{if } G_{ex} > G_{ex\ ceil} \\ t_{max} & \text{otherwise} \end{cases} \tag{2.49}$$

where $t_{max\ ceil} = \frac{G_2}{G_{ex\ ceil}}$ and $G_{ex\ ceil}$ is the maximum glucose flux from the gut.

The nominal values of the parameters are shown in Table 2.14.

Parameter	Published value	Units
t_{max}	40	min
Bio	0.8	-
$G_{ex\ ceil}$	$[0.02, 0.035]$	mmol kg^{-1} min^{-1}

Table 2.14: Nominal values of the parameters in Hovorka model

This model has the weakness of not considering the different compositions of mixed meals, as most models. That is not the aim of this model though, but to rapidly provide a coherent input for the glucoregulatory system.

Fabietti et al. [23]

Fabietti et al. published a model of the complete glucoregulatory system, with a gastrointestinal part, that is going to be described in the following lines. The model considers three paths of absorbing nutrients, depending on the nature of the meal ingested. The speed of absorption is related to the complexity of the carbohydrates present in the meal. For example, if the meal has a high percentage of glucose in its monosaccharide form, the absorption will be done mainly through the fastest path, and making it slower as the complexity of the carbohydrates increases in the meal (majority of polysaccharides).

The type of input is also different depending on whether we consider the meal as an impulse or a pulse signal (Figures 2.11 and 2.12 respectively).

Once determined the shape of the input the meal is decomposed into monosaccharides and fast/slow absorption polysaccharides, with different dynamics, following the hierarchy shown in Figure 2.13. The parameters

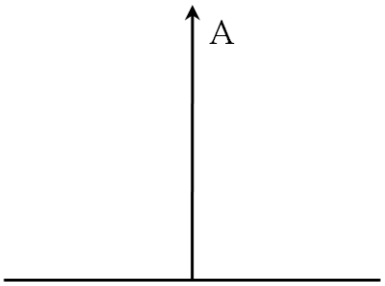

Figure 2.11: An impulse meal input. All the meal is considered to be eaten instantaneously

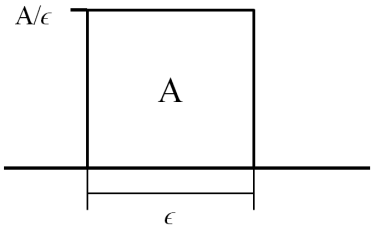

Figure 2.12: A pulse meal input, considered along a period of time

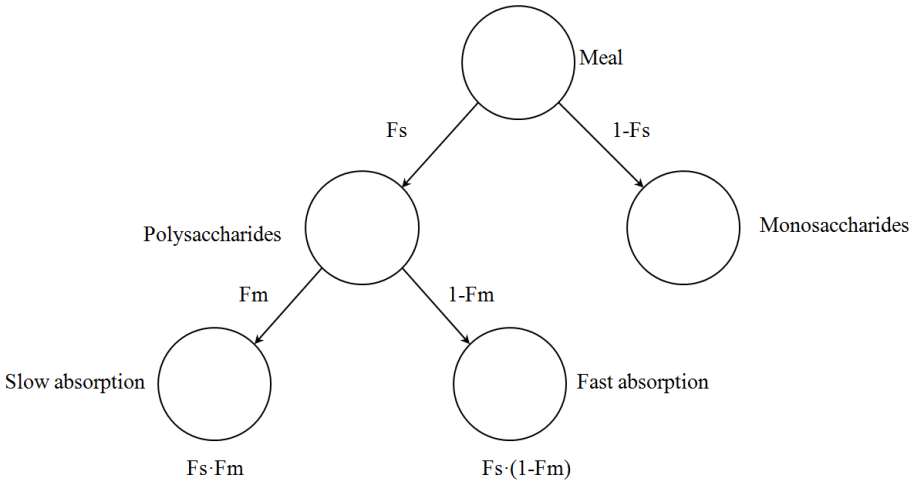

Figure 2.13: The meal is absorbed by a different model in the proportions marked by F_s and F_m

F_s and F_m are parameters dependent on the composition of the meal being ingested. The equations that follow are each one of the models for the channels of absorption. Note that the order of the system decreases with the speed of absorption of the carbohydrates:

$$A_g(s) = (1 - F_s)\frac{16.6}{(s + 1.44)(s + 135)}R_i(s) \tag{2.50}$$

$$A_s(s) = F_s(1 - F_m)\frac{467}{(s + 1.61)(s + 7.20)(s + 7.18)}R_i(s) \tag{2.51}$$

$$A_m(s) = F_s F_m \frac{75.1}{(s + 0.466)(s + 5.54)(s + 5.86)(s + 6.43)}R_i(s) \tag{2.52}$$

$$G_{ex} = A_g + A_s + A_m \tag{2.53}$$

where $R_i = A$ for an impulse meal or $R_i(s) = \frac{1}{s} \cdot \frac{A}{\epsilon} \cdot (1 - e^{-\epsilon s})$ for a pulse meal of duration ϵ.

This is a very stiff model, and its structure only changes with the shape of the input considered and with the composition of the meal. The parameters related to the poles and zeros of the models for every kind of carbohydrates are already given.

Natalucci et al. [60]

The Natalucci model is a very simple set of two equations, in which one describes the evolution of the amount of glucose in the gut, while the other represents the gastric emptying rate. These equations are:

$$R_{ge}(t) = Dk\beta e^{(-kt)^\beta} \tag{2.54}$$

$$\dot{G}_{gut}(t) = R_{ge}(t) - k_{abs}G_{gut}(t) \tag{2.55}$$

where D is the amount of glucose ingested in mg. Once solved the equations shown above, the rate of appearance is easily calculated by:

$$G_{ex}(t) = k_{abs}G_{gut}(t) \tag{2.56}$$

This model only considers the absorption of glucose in a OGTT scenario, and it is of no use when trying to simulate a mixed meal. The parameters identified by Natalucci are shown in Table 2.15.

Parameter	Published value	Units
k_{abs}	2.89	min^{-1}
k	0.014	min^{-1}
β	1.23	-

Table 2.15: Nominal values of the parameters in Natalucci model

Elashoff et al. [32]

The model proposed by Elashoff et al. is quite similar to the proposed by Natalucci, but with a more complex formula for the gastric emptying, and a new parameter f that defines the effectiveness of the absorption of glucose by the gut. The rate of gastric emptying is going to be denoted here as $G_{empt}(t)$ in order to be consistent with the references. The equations related to the model are:

$$G_{empt}(t) = D\beta k^{\beta} t^{\beta-1} e^{(-kt)^{\beta}} \tag{2.57}$$

$$\dot{G}_{gut}(t) = G_{empt}(t) - k_{abs} G_{gut}(t) \tag{2.58}$$

$$G_{ex}(t) = f k_{abs} G_{gut}(t) \tag{2.59}$$

And the published parameters related are those in Table 2.16.

Parameter	Published value	Units
k_{abs}	2.89	min^{-1}
k	0.011	min^{-1}
β	1.23	-
f	1	-

Table 2.16: Nominal values of the parameters in Elashoff model

Lehmann et al. [48]

Lehmann model defines the gastric emptying as a trapezoidal function (Figure 2.14) given by:

$$G_{empt} = \begin{cases} \frac{V_{max}}{T_{up}} \cdot t & \text{if } t < T_{up} \\ V_{max} & \text{if } T_{up} \leq t < T_{up} + T_{max} \\ V_{max} - \frac{V_{max}}{T_{down}} \cdot (t - T_{up} - T_{max}) & \text{if } T_{up} + T_{max} \leq t < T_{up} + T_{max} + T_{down} \\ 0 & \text{otherwise} \end{cases} \tag{2.60}$$

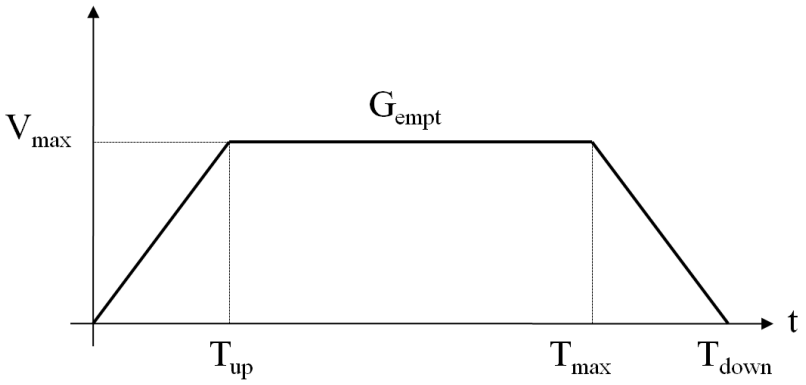

Figure 2.14: The form of the gastric emptying is a trapezoidal function

where parameters characterize the nature and composition of the meal, as well as the patient behavior in front of that particular meal. V_{max} can be directly calculated by considering that the area of the trapezoid is the total amount of glucose ingested (D), as follows:

$$V_{max} = \frac{2D}{T_{up} + 2T_{max} + T_{down}} \tag{2.61}$$

The rest of the parameter values published are shown in Table 2.17.

The intestinal absorption part of the model is defined a a single-compartment model as in the previous models exposed. The equations

Parameter	Published value	Units
T_{up}	9.37	min
T_{max}	6.44	min
T_{down}	27.81	min

Table 2.17: Nominal values of the parameters in Lehmann model

related are:

$$\dot{G}_{gut}(t) = G_{empt}(t) - k_{abs}G_{gut}(t) \tag{2.62}$$

$$G_{ex}(t) = fk_{abs}G_{gut}(t) \tag{2.63}$$

Dalla Man et al. [20]

Chiara Dalla Man published in 2006 a complete gastrointestinal model and a critical review of the existing models in literature. This model considers a two-compartment model for digestion and a simple single-compartmental model for the absorption in the gut. The model follows the structure shown in Figure 2.15.

The two compartments in the stomach part suppose two parts of the digestion of glucose before the gastric emptying. The emptying of the stomach is a non-linear function of the total amount of glucose in the stomach, as will be shown in the model equations later. The compartmental model equations are:

$$\dot{q}_{sto1}(t) = -K_{21}q_{sto1}(t) + D\delta(t) \tag{2.64}$$

$$\dot{q}_{sto2}(t) = -K_{empt}(q_{sto})q_{sto2}(t) + K_{21}q_{sto1}(t) \tag{2.65}$$

$$\dot{q}_{gut}(t) = -K_{abs}q_{gut}(t) + K_{empt}(q_{sto})q_{sto2}(t) \tag{2.66}$$

$$G_{ex}(t) = fK_{abs}G_{gut}(t) \tag{2.67}$$

where $\delta(t)$ is the Dirach delta, simulating an impulse input to the model. The rest of parameters added are flux constants, for the transfer of glucose

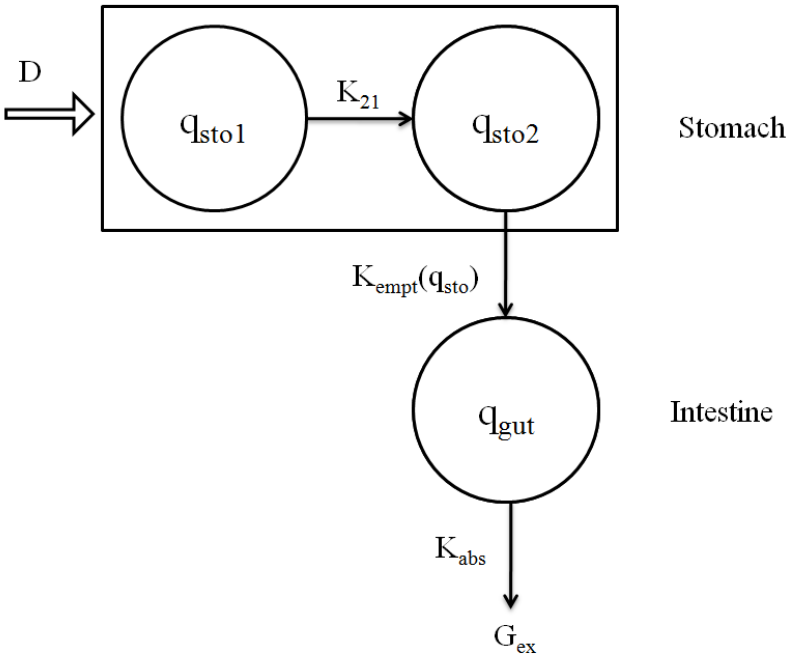

Figure 2.15: A two compartment model represents the stomach and a single compartment the intestine

through the system, except for the K_{empt} parameter, which is time-varying and defines the form of the gastric emptying. The equations describing the transfer rate describing the flow of glucose from the stomach to the intestine are:

$$\begin{aligned} K_{empt}(q_{sto}) &= K_{min} + \tfrac{K_{max}-K_{min}}{2} \cdot \\ &\cdot\{tanh[\alpha(q_{sto} - b \cdot D)] - tanh[\beta(q_{sto} - c \cdot D)] + 2\} \end{aligned} \tag{2.68}$$

$$q_{sto}(t) = q_{sto1}(t) + q_{sto2}(t) \tag{2.69}$$

$$\alpha = \frac{5}{2D(1-b)}; \qquad \beta = \frac{5}{2Dc} \tag{2.70}$$

These equations give the gastric emptying a very characteristic shape. In Figure 2.16 the K_{empt} is plotted against the amount of glucose remaining in the stomach q_{sto}.

The parameters have been identified both for an Oral Glucose Tolerance Test (OGTT) and a mixed meal. Parameter K_{21} is forced to be equal to K_{max} for identifiability issues. The published values are shown in Table 2.18.

Parameter	Published value (OGTT)	Published value (meal)	Units
K_{abs}	0.205	0.071	min^{-1}
K_{21}	0.045	0.054	min^{-1}
K_{max}	0.045	0.054	min^{-1}
K_{min}	0.013	0.006	min^{-1}
b	0.85	0.69	-
c	0.25	0.17	-

Table 2.18: Nominal values of the parameters in Dalla Man model

Some work has been done within this research group on identifiability of mixed meals with the Dalla Man model [5], showing a dependence of the identification results on the size of the meal considered. A library of identified meals has also been developed by Pau Herrero in 2008 [31]. Dalla Man model will be also studied in this thesis and used to design optimal

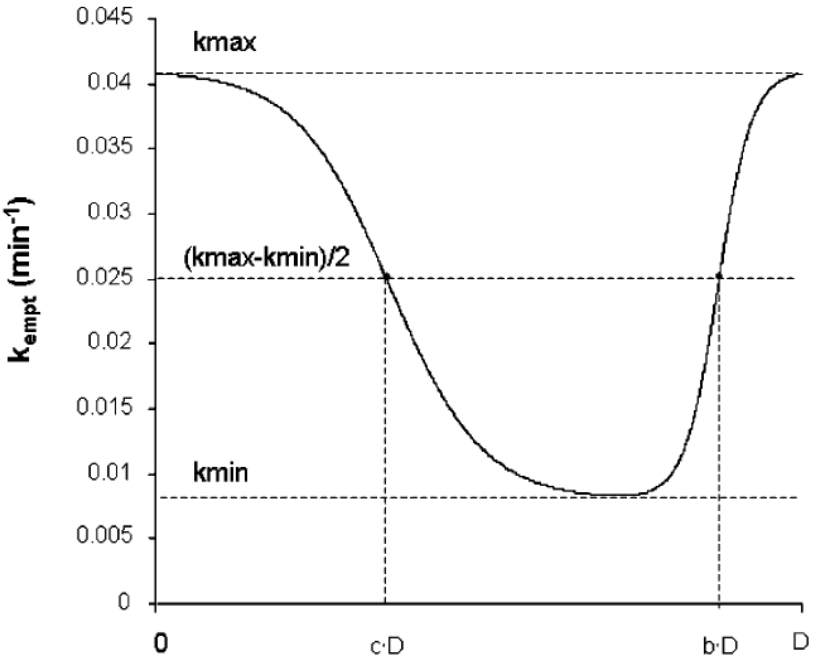

Figure 2.16: Gastric emptying rate versus glucose remaining in the stomach [20]

clinical experiments.

Summary

In Table 2.19 all the gastrointestinal models reviewed are displayed, showing their structures for the stomach and intestine parts, and the gastric emptying process.

Model	Stomach	Intestine	Gastric emptying
Hunt	algebraic	PDE	direct
Hovorka	-	2 compartments	-
Fabietti	-	3 transfer functions	-
Natalucci	1 compartment	1 compartment	algebraic
Elashoff	1 compartment	1 compartment	algebraic
Lehman	-	1 compartment	trapezoidal
Dalla Man	2 compartments	1 compartment	depends on mass of CHO in the stomach

Table 2.19: Glucose absorption models

2.2.3 Endogenous models

Glucoregulatory models for type 1 diabetic patients are going to be described in the following lines. The endogenous model is the part of the glucose-insulin model that describes the different regulatory pathways of blood glucose concentration. Given that this thesis is focusing in the control and identification of T1DM people, the authors decided that the dynamics and equations describing the secretion of insulin were no relevant to be shown for those models that describe it.

Usually the endogenous model has two sub-models, one for the insulin distribution and elimination system (if not considered in the insulin absorption model), and the other for the glucose metabolism, transformation and elimination. This second sub-model has to consider the influence of the

liver and the kidneys on the blood glucose, as well as the peripheral intake by muscles and adipose tissue, and any other influences that may affect glucose concentration. The complexity of the model will be increasing as more effects are considered in the modeling of the metabolic phenomena present in this system.

Bergman et al. [9]

The first model to be reviewed is going to be the (probably) most used and best known among all the models used in diabetes. It is called the Bergman minimal model because it only describes the influence of insulin on blood glucose concentration, and it does not consider many other phenomena, or it considers them in a very simplified way. The justification for this simplicity is that the objective of this model was, initially, to simulate the response of the IntraVenous Glucose Tolerance Test (IVGTT), which has a very simple behavior.

Bergman minimal model considers that insulin actions on glucose are delayed, and that delay is represented by a new compartment of *remote* insulin. The scheme of the model is shown in Figure 2.17.

The equations related to the model are:

$$\dot{I}(t) = -nI(t) + p_4 u_1(t) \qquad I(0) = I_b = \frac{p_4}{n} u_{1b} \quad (2.71)$$

$$\dot{X}(t) = -p_2 X(t) + p_3[I(t) - I_b] \qquad X(0) = 0 \quad (2.72)$$

$$\dot{G}(t) = -p_1 G(t) - X(t)G(t) + p_1 G_b + \frac{u_2(t)}{Vol g_G} \qquad G(0) = G_b \quad (2.73)$$

Depending on the model of insulin absorption used, equation 2.71 can be substituted by the corresponding equation of the model chosen. $X(t)$ is the remote insulin compartment, $G(t)$ is the blood glucose concentration, $u_1(t)$ is the insulin flow coming from the insulin system, $u_2(t)$ is the exogenous flow of glucose coming either intravenously or from the gastrointestinal system.

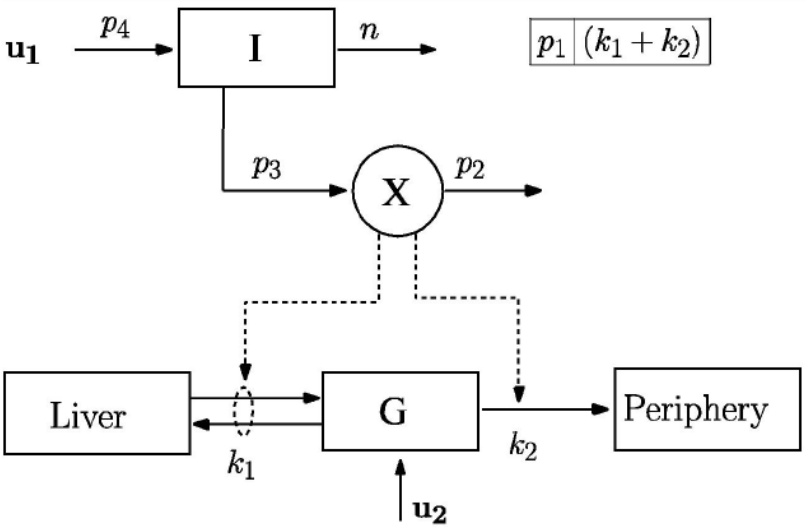

Figure 2.17: Bergman minimal model of insulin and glucose dynamics, adapted from Bergman and colleagues [9]

Published values for the model parameters are shown in Table 2.20.

Parameter	Published value	Units
p_1	0.035	min^{-1}
p_2	0.05	min^{-1}
p_3	0.000028	$\text{ml}/\mu U \cdot \text{min}^2$
p_4	0.098	ml^{-1}
n	0.142	min^{-1}
Vol_G	117	dl

Table 2.20: Nominal values of the parameters in Bergman model [85]

Bergman model has been used for more than 20 years in diabetes research due to its identifiability and controllability properties, but it is far of being the perfect model. There have been many critics to this model, both from the medical and control point of view [79], and later on this thesis, Bergman model will be analyzed in detail. In fact, this is one of the models tested and used for experimental design in this work.

Panunzi et al. [67]

Simona Panunzi and the group of biomathematics in Rome published a study in 2007 comparing some of the characteristics of Bergman model and new features of a proposed model for the IVGTT scenario, with a delayed insulin secretion rate. The new model proposed surpassed the rest in simulated experiments and in identifiability properties, but it was only tested in healthy patients. The equations of the model are:

$$\dot{G}(t) = -K_{xgl} I(t) G(t) + \frac{T_{gh}}{V_g} \tag{2.74}$$

$$\dot{I}(t) = -K_{xi} I(t) + \frac{T_{ig\ max}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma}{1 + \left(\frac{G(t-\tau_g)}{G^*}\right)^\gamma} \tag{2.75}$$

This model includes delayed differential equations for the insulin production sub-model, but when simulating type 1 diabetic patients, whom do not have endogenous insulin secretion, the model becomes much more simple. The parameters involved in the previous model are:

- G_b is the basal glucose concentration.
- I_b is the basal plasma insulin.
- K_{xgl} is the insulin sensitivity. It represents the insulin-dependent glucose uptake by tissues per unit of insulin concentration.
- T_{gh} represents the balance between the hepatic outtake of glucose and the insulin-independent glucose intake, including the one of the liver.
- V_g is the apparent glucose distribution volume.
- K_{xi} is the disappearance rate of insulin.
- G^* is the glycemia at which the insulin secretion rate is half of its maximum.

- $T_{ig\ max}$ is the maximum rate of insulin release.
- V_i is the apparent insulin distribution volume.
- τ_g represents the apparent delay with which the pancreas changes insulin release in response to a variation in blood glucose.
- γ is the progressivity with which the pancreas reacts to circulating glucose concentrations.

The values published for these parameters, only for healthy patients, are shown in Table 2.21.

Parameter	Published value	Units
V_g	0.152	L kg^{-1}
τ_g	19.271	min
K_{xgl}	1.43×10^{-4}	min^{-1} pM^{-1}
K_{xi}	0.101	min^{-1}
γ	2.464	-

Table 2.21: Nominal values of the parameters in Panunzi model

Panunzi model is also considered for the study performed in this thesis because of its simplicity, but some variations were made due to the focus of this model on healthy patients and the IVGTT scenario.

Vicini et al. [98]

Vicini et al. published a simulation (non-minimal) model in 1999. The compartmental structure of the model for a healthy person is shown in Figure 2.18.

The model for diabetic patients is slightly different than the one shown for healthy patients. A type 1 diabetic patient will not have insulin secretion $S(t)$ and so, compartment $q_4(t)$ disappears, and every insulin input will go directly from the subcutaneous insulin model, into the $q_3(t)$ compartment,

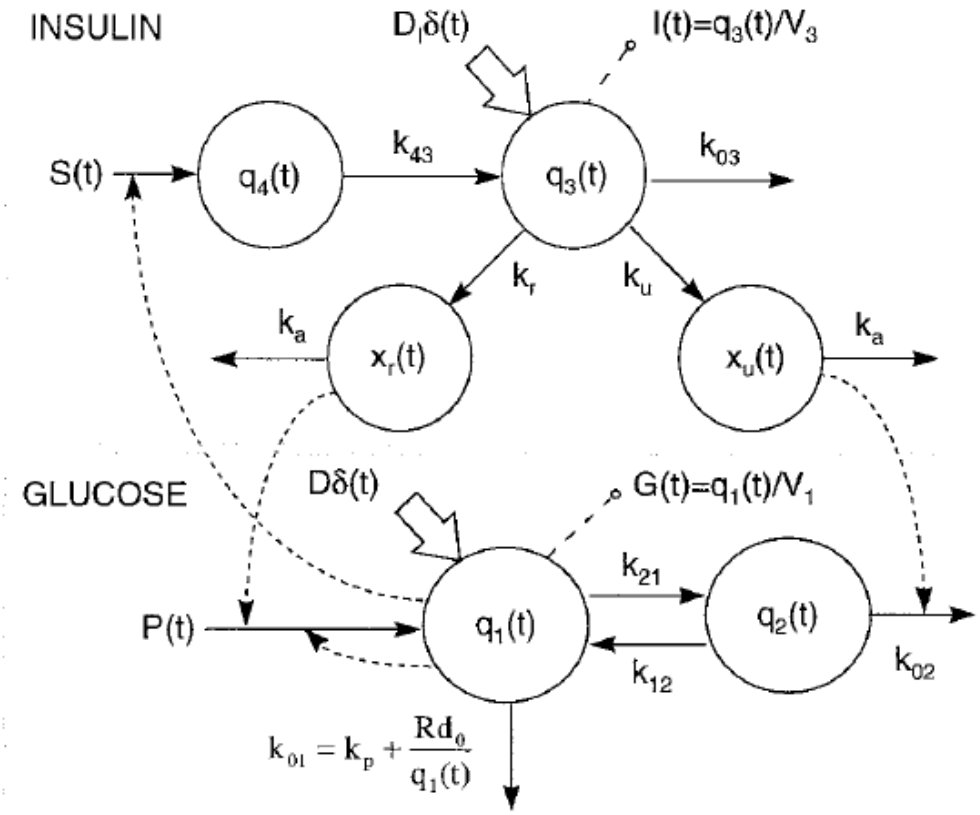

Figure 2.18: Vicini model compartmental structure for a healthy person. It consists of two compartments for glucose, two for insulin and two virtual insulin actions [98]

which is the plasma insulin compartment. The variables related to the model are:

- $q_1(t)$ is the compartment representing the blood glucose mass.
- $q_2(t)$ represents the mass of glucose in the interstitial fluid.
- $q_3(t)$ is the plasma insulin mass compartment.
- $x_r(t)$ is the remote insulin action on the glucose production.
- $x_u(t)$ is the remote insulin action on glucose utilization.
- D_i is the insulin input. In this model, insulin is considered to be an intravenous bolus (impulse).
- D is the glucose input. In Figure 2.18 it is considered as an intravenous impulse input, but again, if instead of the Dirach delta $\delta(t)$ there is a digestive model, the input is the output of the gastrointestinal model.
- $P(t)$ Is the endogenous glucose production.

The equations of the model are:

$$\dot{q}_1(t) = -[k_p + \frac{R_{d,0}}{q_1(t)} + k_{21}]q_1(t) + k_{12}q_2(t) + P(t) + D\delta(t) \tag{2.76}$$

$$\dot{q}_2(t) = -[k_{02} + k_{12} + x_u(t)]q_2(t) + k_{21}q_1(t) \tag{2.77}$$

$$\dot{q}_3(t) = -k_{03}q_3(t) + D_I\delta(t) \tag{2.78}$$

$$\dot{x}_u(t) = -k_a x_u(t) + k_u[I(t) - I_b] \tag{2.79}$$

$$\dot{x}_r(t) = -k_a x_r(t) + k_r[I(t) - I_b] \tag{2.80}$$

$$P(t) = P_b - k_l[q_1(t) - q_{1b}] - x_r(t)q_1(t) \tag{2.81}$$

$$I(t) = \frac{q_3(t)}{V_3} \tag{2.82}$$

$$G(t) = \frac{q_1(t)}{V_1} \tag{2.83}$$

Finally, the parameter values published by the authors are shown in Table 2.22.

Parameter	Published value	Units
V_1	1.58	dl kg^{-1}
V_3	65.36	ml kg^{-1}
k_{21}	0.043	min^{-1}
k_{12}	0.059	min^{-1}
k_{02}	0.006	min^{-1}
k_p	0.0049	min^{-1}
k_l	0.0044	min^{-1}
k_{03}	0.2114	min^{-1}
k_a	0.045	min^{-1}
k_u	6.48×10^{-6}	μIU ml^{-1} min^{-2}
k_r	3.76×10^{-5}	μIU ml^{-1} min^{-2}
$R_{d,0}$	1	-
P_b	4	mg kg^{-1} min^{-1}

Table 2.22: Nominal values of the parameters in Vicini model

Cobelli et al. [21]

Cobelli model is one of the most important models in diabetes research. It is a very complex model almost exclusively based in physiological knowledge of the glucose metabolism. It is usually combined with the Dalla Man gastrointestinal model and the insulin pharmacokinetics model of the same group (in fact all the models were developed together) in a large mathematical model of the glucose metabolism. Magni et al. [51] used the complete Cobelli model to control an *in silico* diabetic patient. It is also the model implemented in the UVa (University of Virginia) simulator [44], accepted by the FDA as substitute of animal trials in the context of a protocol application of University of Virginia and Padova for a controller validation clinical trial. The core structure is pretty simple, as shown in Figure 2.19:

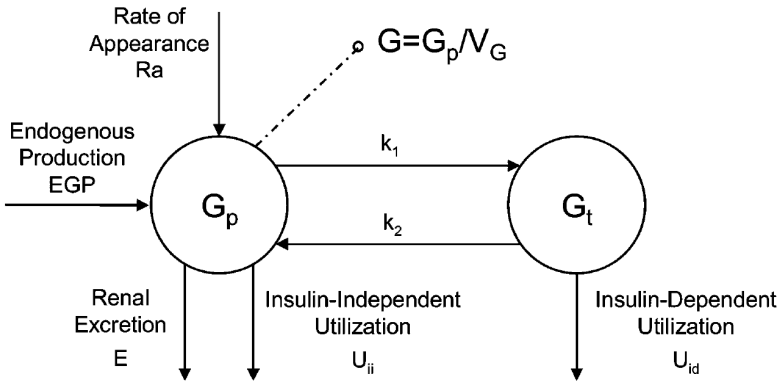

Figure 2.19: Cobelli model core is composed of two compartments of glucose, one for blood and one for the tissues interstitial fluid

The model equations are:

$$\dot{G}_p(t) = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 G_p(t) + k_2 G_t(t) \tag{2.84}$$

$$\dot{G}_t(t) = -U_{id}(t) + k_1 G_p(t) - k_2 G_t(t) \tag{2.85}$$

$$G(t) = G_p(t)/V_G \tag{2.86}$$

In the previous equations there are many inputs and outputs to the glucose compartments that have to be described. It must be noted that so far there is no insulin related equations; insulin will have influence in the flow of glucose coming in or out of the different compartments. The meaning of these variables will be explained now:

- Ra is the exogenous flux of glucose coming from the gut.
- U_{ii} is the utilization of glucose that is non dependent on insulin. It is usually considered constant and equal to F_{cns}.
- U_{id} is the utilization that depends on the insulin concentration, and it

follows the following set of equations:

$$\dot{X}(t) = -p_{2U}X(t) + p_{2U}[I(t) - I_b] \tag{2.87}$$

$$V_m(t) = V_{m0} + V_{mx}X(t) \tag{2.88}$$

$$U_{id}(t) = \frac{V_m(t)G_t(t)}{K_m + G_t(t)} \tag{2.89}$$

where $X(t)$ is the remote insulin, $I(t)$ is the plasma insulin, I_b is the basal insulin and $V_m(t)$ is the transfer rate for the Michaelis-Menten equation shown in equation 2.89.

- $E(t)$ represents the renal excretion, which occurs if plasma glucose exceeds a certain threshold. Is modeled as follows:

$$E(t) = \begin{cases} k_{e1}[G_p(t) - k_{e2}] & \text{if } G_p(t) > k_{e2} \\ 0 & \text{otherwise} \end{cases} \tag{2.90}$$

where k_{e1} is the glomerular filtration rate and k_{e2} is the renal threshold of glucose.

- $EGP(t)$ is the Endogenous Glucose Production, and it depends on a delayed insulin signal as follows:

$$\dot{I}_1(t) = -k_i[I_1(t) - I(t)] \tag{2.91}$$

$$\dot{I}_d(t) = -k_i[I_d(t) - I_1(t)] \tag{2.92}$$

$$EGP(t) = max\{0, k_{p1} - k_{p2}G_p(t) - k_{p3}I_d(t)\} \tag{2.93}$$

where $I(t)$ is the insulin concentration in plasma.

The published parameters for healthy and type 2 diabetic (no type 1 diabetic parameters have been published) patients are those in Table 2.23. Even though the parameters shown are those of a healthy and T2DM patients, no endogenous production of glucose has been described in here fot this model, which is the case of a T1DM person.

Parameter	Healthy	Type 2 diabetes	Units
V_G	1.88	1.49	dL kg^{-1}
k_1	0.065	0.042	min^{-1}
k_2	0.079	0.071	min^{-1}
k_{p1}	2.70	3.09	mg kg^{-1} min^{-1}
k_{p2}	0.0021	0.0007	min^{-1}
k_{p3}	0.009	0.005	mg kg^{-1} min^{-1} per pmol L^{-1}
k_i	0.0079	0.0066	min^{-1}
F_{cns}	1	1	mg kg^{-1} min^{-1}
V_{m0}	2.5	4.65	mg kg^{-1} min^{-1}
V_{mx}	0.047	0.034	mg kg^{-1} min^{-1} per pmol L^{-1}
K_{m0}	225.59	466.21	mg kg^{-1}
p_{2U}	0.0331	0.0840	min^{-1}
k_{e1}	0.0005	0.0007	min^{-1}
k_{e2}	339	269	mg kg^{-1}

Table 2.23: Nominal values of the parameters in Cobelli model

Hovorka et al. [36]

Roman Hovorka endogenous model regards separately at each action of insulin on different phenomena with its final effect on blood glucose. The model adds a new compartment for every action of insulin, and there are three considered events:

- Insulin increases the flow of glucose from blood to the tissues.
- Insulin increases the glucose uptake by muscles and adipose tissue.
- Insulin inhibits production of glucose of glucose in the liver.

These three influences are reflected in the model as virtual compartments. The relation between actual insulin in plasma, every virtual compartment representing insulin actions and the two compartments for glucose is shown in Figure 2.20. x_1, x_2 and x_3 represent the insulin actions, Q_1 is the glucose mass in the accessible compartment, and Q_2 is the glucose present in the non-accessible compartment.

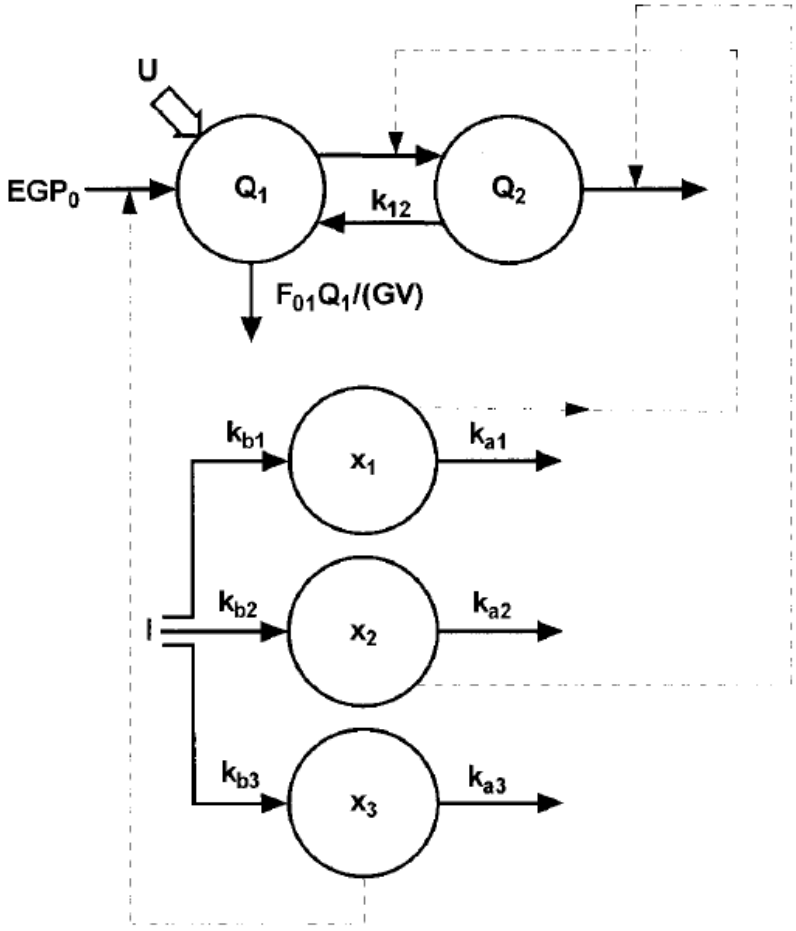

Figure 2.20: Hovorka endogenous model structure arranged in compartments

The equations that represent this model are:

$$\dot{x}_1(t) = -k_{a1}x_1(t) + k_{b1}I(t) \qquad x_1(0) = 0 \tag{2.94}$$

$$\dot{x}_2(t) = -k_{a2}x_2(t) + k_{b2}I(t) \qquad x_2(0) = 0 \tag{2.95}$$

$$\dot{x}_3(t) = -k_{a3}x_3(t) + k_{b3}I(t) \qquad x_3(0) = 0 \tag{2.96}$$

$$\dot{Q}_1(t) = -\left[\frac{F_{01}^c}{V_G G(t)} + x_1(t)\right] Q_1(t) + k_{12}Q_2(t) - F_R + EGP + G_{ex}(t) \quad Q_1(0) = Q_{1,0} \tag{2.97}$$

$$\dot{Q}_2(t) = x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t) \qquad Q_2(0) = Q_{2,0} \tag{2.98}$$

$$G(t) = Q_1(t)/V_G \tag{2.99}$$

Equation 2.97 has several terms that have to be defined:

- EGP stands for Endogenous Glucose Production, which is the flux of glucose coming from the liver. It is defined as:

$$EGP = \begin{cases} EGP_0[1 + x_3(t)] & \text{if } EGP \geq 0 \\ 0 & \text{otherwise} \end{cases} \tag{2.100}$$

- F_{01}^c is the insulin-independent glucose flux, and it is defined as:

$$F_{01}^c = \frac{F_{01}^s G}{G + 1.0} \text{ where } F_{01}^s = \frac{F_{01}}{0.85} \tag{2.101}$$

- F_R is the renal glucose clearance above the glucose threshold of R_thr, and it is defined as:

$$F_R = \begin{cases} R\_cl(G - R\_thr)V_G & \text{if } G \geq R\_thr \\ 0 & \text{otherwise} \end{cases} \tag{2.102}$$

  Where R_cl is the renal clearance.

The model has many parameters to be identified, specially in the part of insulin actions, where there are two parameters for each action corresponding to the input and output flows of the compartment. Usually these parameters are reformulated into what are called *insulin sensitivities*, due to their physiological meaning since they correspond to the glucose decrement per unit of insulin given. The reformulation is then:

- $S_{IT} = \frac{k_{b1}}{k_{a1}}$ where S_{IT} is the insulin sensitivity to the transport of glucose.
- $S_{ID} = \frac{k_{b2}}{k_{a2}}$ where S_{ID} is the insulin sensitivity to the distribution of glucose.
- $S_{IE} = \frac{k_{b3}}{k_{a3}}$ where S_{IE} is the insulin sensitivity to the endogenous glucose production.

After this transformation, equations (2.94), (2.95) and (2.96) result in:

$$\dot{x}_1(t) = -k_{a1}x_1(t) + S_{IT}k_{a1}I(t) \qquad x_1(0) = 0 \qquad (2.103)$$

$$\dot{x}_2(t) = -k_{a2}x_2(t) + S_{ID}k_{a2}I(t) \qquad x_2(0) = 0 \qquad (2.104)$$

$$\dot{x}_3(t) = -k_{a3}x_3(t) + S_{IE}k_{a3}I(t) \qquad x_3(0) = 0 \qquad (2.105)$$

The published values of all the parameters are those in Table 2.24. The parameters shown in here are mean values of the several sets of parameters published.

Hovorka model hss been used both for simulation and control purposes, in many different scenarios, from critical patients [35] to overnight experiments [34] with successful results, and recently it has been implemented in a complete mathematical patients simulator [101], like the UVa simulator.

Parameter	Published value	Units
k_{12}	0.066	min^{-1}
V_G	0.16	L kg^{-1}
EGP_0	0.0161	mmol kg^{-1} min^{-1}
F_{01}	0.0097	mmol kg^{-1} min^{-1}
k_e	0.138	min^{-1}
V_i	0.12	L kg^{-1}
k_{a1}	0.006	min^{-1}
k_{a2}	0.06	min^{-1}
k_{a3}	0.03	min^{-1}
S_{IT}	51.2×10^{-4}	mU L^{-1} min^{-1}
S_{ID}	8.2×10^{-4}	mU L^{-1} min^{-1}
S_{IE}	520×10^{-4}	mU L^{-1} min^{-1}

Table 2.24: Nominal values of the parameters in Hovorka model

Summary

In Table 2.25 all the gastrointestinal models reviewed are displayed, showing their structures for the stomach and intestine parts, and the gastric emptying process.

Model	**Purpose**	**Implemented in**
Bergman	control (minimal)	-
Panunzi	control (minimal)	-
Vicini	simulation	-
Cobelli	simulation	UVa simulator
Hovorka	simulation	Hovorka simulator

Table 2.25: Glucose absorption models

Chapter 3

Identification techniques and procedures

The identification of the parameters of a model is an inverse problem. An inverse problem consists in finding the conditions and inputs to a system given the outputs of the system. In the glucose-insulin model identification, the inverse problem is to find parameters and model that characterize a patient given the glucose behavior of that patient.

Identification can be solved by means of optimization algorithms that try to optimize an index of the fit of the model's output to the available data. That index can be formulated, for example, as a quadratic error depending on a set of parameters p that has to be minimized:

$$J(p) = \sum_{i=1}^{N} (y_i(p) - \tilde{y}_i)^T Q_i (y_i(p) - \tilde{y}_i) \tag{3.1}$$

where $y_i(p)$ are the model predictions and $\tilde{y}_i$ are the experimental measurements, therefore, the data that has to be fitted. Q_i is the data weighting matrix, which permits to fit more accurately some data in

detriment to other data samples. Q_i is usually chosen as a diagonal matrix, due to the assumption that data samples are independently correlated to each other. The choice of the diagonal values in the matrix are usually referred to as "weights" of the data samples.

A usual compromise choice for the ponderation matrix is to make the relative errors of each data sample weight the same in the cost index. This is achieved by forcing the diagonal of Q_i to be equal to $1/\tilde{y}_i^2$. This ponderation matrix has the disadvantage of giving less importance to big errors in big values of the output of the model than in small values. Usually it is desired that all errors are normalized in the optimization index, and this is achieved with other Q_i, like for example all the elements of the diagonal to be equal to $1/max(\tilde{y}_i)^2$. This way the contribution of every data sample is standardized and the errors are not weighted in any way.

Countless strategies and softwares have been developed for every specific type of optimization problem. There are several methods focused in parametric identification and a couple of them will be explained in the last part of the chapter.

In order to analyze the structural properties of the model, it is necessary some kind of study to try to forecast if the problem is going to be solvable and in which terms. This is what is called identifiability study.

3.1 Identifiability a priori

Considering now the case of a given model and given parameters, the identifiability of the system can be studied at two different levels. By one side, there is the identifiability of the parameters given the structure and under ideal conditions, and by the other side there is the identifiability of the parameters given the parameter values, and considering measurement noise. The first case is called identifiability *a priori* and the second is the

identifiability *a posteriori*.

There are many methods for testing models for structural identifiability and the one that will be shown next is completely valid for non-linear models. That method is the Taylor series approach for identifiability *a priori*.

Taylor series approach

Considering then an state-space, non-linear, time invariant model:

$$\frac{d}{dt}X(t) = f[X(t), u(t), t, P] \qquad x(0) = x_0(p) \tag{3.2}$$

$$y(t, P) = h[X(t), P] \tag{3.3}$$

here $X(t)$ is the state vector, $y(t, P)$ is the output of the model, $u(t)$ is the input, P is the vector of parameters, and $f(\cdot)$ and $h(\cdot)$ are non-linear functions. In this case, defining the derivative order k of the output as:

$$a_k(P) = \lim_{t \to 0+} \frac{d^k}{dt^k} y(t, P) \tag{3.4}$$

then, based on Pohjanpalo's paper [75], if $a_k(\hat{P}) = a_k(P^*)$ yields $\hat{P} = P^*$, then the model is structurally identifiable, which means that only one set of parameters can simulate a determined output. Notation has been chosen to be coherent with [99], and $\hat{P}$ represents the model parameters, while P^* represents the system's hypothetical real parameters. Examples, further explanations and more methods can be found in [99] and [82].

3.2 Identifiability a posteriori

Now, the fact that a model is structurally identifiable does not mean that identifications performed to that model are going to be successful. There is another type of identifiability that has to be tested that will determine if a given set of parameters can be estimated from the outputs they give. Obviously, if there is no *a priori* identifiability, i.e. there is more than one set of parameters that can produce the same output, it will be impossible to identify the model. But the information contained by a realization of the model may be insufficient to induce which parameters produced it, and that information analysis is what *a posteriori* identifiability consists in.

Again, there are several methods to quantify the identifiability of a model, but only one will be shown in detail in the following, the Fisher Information Matrix (FIM) approach.

The Fisher information matrix approach

Analyzing with detail the Fisher Information Matrix (FIM from now on), all information about identifiability of the model can be extracted, but only in local basis, due to the fact that this method's application implies linearization of the model.

To understand the method, let's take the index defined in equation 3.1. The statistical estimation of the index for a set of parameters slightly different of the optimal is given by:

$$E[J(p+\delta p)] \cong \delta p^T \left[\sum_{i=1}^{N} (\frac{\partial z}{\partial p}(t_i))^T Q_i (\frac{\partial z}{\partial p}(t_i)) \right] \delta p + \sum_{i=1}^{N} tr(V_i Q_i) \qquad (3.5)$$

where V_i represents the covariance matrix of the measurement errors (Q_i is typically chosen as V_i^{-1}), z is the model output and N is the number of data samples. The term between brackets is what is known as the Fisher Information Matrix and it expresses the quantity of information contained in the experimental data, as explained in detail by Ljung [50]:

$$FIM = \sum_{i=1}^{N} \left(\frac{\partial z}{\partial p}(t_i) \right)^T Q_i \left(\frac{\partial z}{\partial p}(t_i) \right). \tag{3.6}$$

The terms $\partial z/\partial p$ are the sensitivity functions and they are of great importance for the evaluation of the practical identifiability. The FIM is a square matrix with dimension equal to the number of parameters that are to be identified. The inverse of the FIM is also an approximation of the covariance matrix of the estimation error of the model parameters:

$$C = FIM^{-1} = \left[\sum_{i=1}^{N} (\frac{\partial z}{\partial p}(t_i))^T Q_i (\frac{\partial z}{\partial p}(t_i)) \right]^{-1} \tag{3.7}$$

The diagonal of C contains the information of the confidence interval in the estimation of every parameter. The maximum lower bound of this confidence interval is called Cramer-Rao Bound. Cramer-Rao also defined the inverse of the FIM evaluated in the real parameters as the lower bound of the covariance matrix of the parameters (in the real system). The bound of the coefficient of variation for the parameter p_i being identified is calculated as:

$$CV_i = \frac{\sqrt{C_{ii}}}{p_i} \tag{3.8}$$

The interpretation of the Cramer-Rao limit is simple. If, for example, a parameter p_i has a CV of 0.4 it means that, for the measurement error

which variance was considered in the calculation of Q_i, successive parameter estimations will have a deviance of 40% of the parameter value. As such, coefficient of variation is a relative measure of the parameter standard deviation given the error variance considered in $Q_i = V_i^{-1}$, being V_i the the error variance. There is more useful information to be drawn off the FIM, like the correlation matrix. This matrix, the elements of which are the approximated coeficients of correlation between the i^{th} and the j^{th} parameters, is defined as:

$$R_{ij} = \frac{C_{ij}}{\sqrt{C_{ii}C_{jj}}} \tag{3.9}$$

Analyzing the correlation matrix gives and idea of the compensation effect of the changes in the values of the parameters over the model output. If two parameters, p_i and p_j, are highly correlated, a change in the output due to a change in parameter p_i can be hidden by the appropriate change in p_j.

In practical terms, the identifiability analysis must be done applying some simplifications. The sensitivities of the parameters have to be calculated by approximating the derivatives of the output with first order approximations. In general, application of the analytic expression of the derivative function is the correct way of performing the FIM calculation. With the models exposed before though, the analytical expression of the derivative with respect to the parameters of the outputs of those equations is not feasible, and it has not been done in here.

Usually, the sensitivity function is calculated applying the linearization of the model around the nominal parameter, and obtaining the symmetric first order difference. In practice, two simulations of the model are calculated, one with a positive variation of the selected parameter, and the other with a negative variation, as seen in Figure 3.1. The sensitivity function is calculated with equation (3.10).

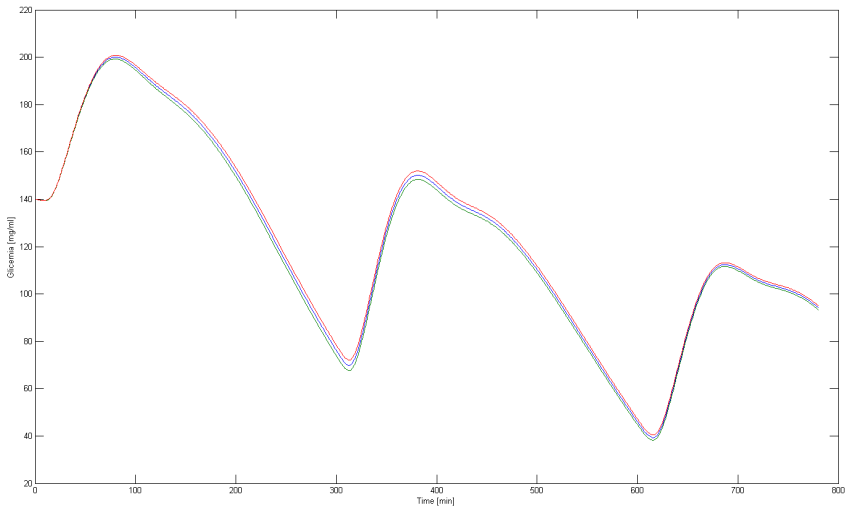

Figure 3.1: A three meals simulation with perturbation in one parameter is shown. The blue line represents the nominal parameter's simulation, while the red and green lines are the simulations variating the selected parameter

$$S_p = \frac{z(p + \Delta p) - z(p - \Delta p)}{2 \cdot \Delta p} \tag{3.10}$$

Also, if the FIM results to be singular it can not be inverted, and that is a sign of non-identifiability. In fact, it is a sign of *a priori* non-identifiability, so that analysis is being carried out with this method as well. Usually, when working with noisy measurements, it is really difficult to get that the FIM is completely singular, and yet it will be difficult to identify any parameter because the FIM is bad-conditioned. The condition number has to be analyzed then, and checked if it is large enough to permit inversion of the matrix and identifiability.

When ill-conditioning happens the solution is usually to fix some parameter to a determined value. The decision of which parameter to fix is taken from the singular value decomposition analysis of the sensitivity matrix. Defining the sensitivity matrix as a matrix with as many columns

as parameters being analyzed, and rows as data samples, decomposition can be applied and interesting properties arise. Singular Value Decomposition (SVD) is defined as:

$$M = U\Sigma V^* \tag{3.11}$$

where M is the matrix being decomposed in three other matrices. Matrix U is a unitary square matrix, Σ is a diagonal matrix with non-negative values of the same dimensions as M, and V^* is the conjugate transpose of V, which is another unitary square matrix. For further information about the singular value decomposition check the classic reference of Golub [28].

Applying that decomposition, the values of the diagonal matrix Σ quantify the sensitivities of the singular directions in the parameter space in decreasing order. The last value of the diagonal is then the less sensitive direction of the parameter space. In order to find what parameter has the bigger influence in that direction (and then, which is the less influential parameter), one have to look at the V matrix of the singular value decomposition. The columns of V are the eigenvectors of the sensitivity matrix and the last column expresses the influence of the parameters in the less sensitive direction of the parameter space. The bigger entry in the last eigenvector defines the parameter to be fixed in the identifiability analysis.

In summary, there are two ways of increasing the identifiability of a model: (1) Changing the experiment paradigm. (2) Not to try to identify some of the parameters, the decisions of which parameter to fix being taken based on the identifiability analysis results, for example, depending on the sensitivity matrix properties or with the correlations between parameters.

3.3 Practical Identifiability

So far theoretical background on identifiability analysis has been explained and some broadly used methods for the calculation of identifiability estimators has been given. In the following lines there is a depiction of the steps taken to quantify identifiability in this thesis, as well as some hints for calculation of the FIM and its estimators.

Given a model and a set of parameters, the sensibility analysis has to be performed at first. Variations on the number of parameters will have to be done until there is a model found identifiable, but identifiability has to be quantified. In the case of this thesis, a model is identifiable when all the parameters of the model analyzed have coefficients of variation of less than 0.3 and there are no correlations between the parameters greater than 0.98. For non-invertible matrices, the singular value decomposition explained in the previous section can be carried out in order to determine which parameter to fix. The steps to follow in order to determine which set of parameters are identifiable can be seen in Figure 3.2.

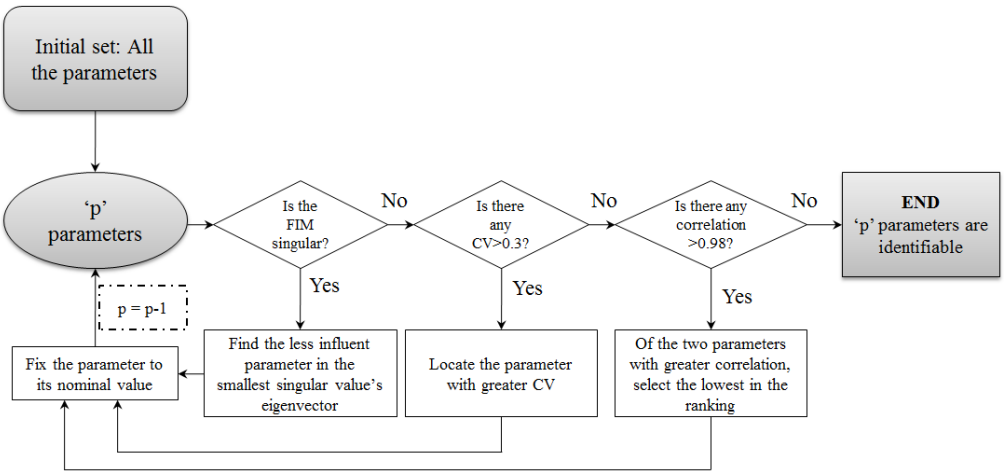

Figure 3.2: The model starts with all of its parameters, but they fall off the identification as prove themselves not sensible enough or too related to another parameter

Following that flow chart, the sensitivity analysis starts with all the parameters of the model i.e. 'p' parameters. The sensitivities of all the parameters are calculated, and the FIM is evaluated. If the FIM is singular, it means that it is not invertible, and thus, no confidence intervals for the estimation of parameters are calculable. Non-invertibility is always related to a small condition number of the matrix, and that is why the most efficient way to estimate the invertibility of the matrix is calculate its condition number. A condition number of 10 times the maximum float precision, i.e. $2.2 \cdot 10^{-16}$ is considered small enough to label the matrix as non-invertible [82]. When this happens, the most influent parameter in the smallest singular value's eigenvector is fixed to it's nominal value, and it is not used anymore in sensitivity analysis. The analysis considers now 'p-1' parameters, and the FIM is now a matrix of dimensions (p-1)×(p-1).

Once the FIM has an inverse matrix, the objective of the analysis is to reduce coefficients of variation (CVs) of the rest of the parameters. The Cramer-Rao bound has to be calculated for every parameter, and the one with the highest value is then fixed, reducing the number of parameters of the analysis by one. After several iterations, when all the parameter CVs are to be under a prefixed value, let's say under 0.3 (as it says in Figure 3.2). A value of 0.3 will guarantee that at least the sign of the value will be captured. The decision of which parameter to fix in this case is up to the user. Of the two parameter correlated, one has to be fixed, and it can be either the one with the highest CV, or the one that is lower in the influence ranking (that may differ of the highest CV parameter due to the correlations not considered in the ranking).

Once the appropriate set of parameters is selected, there is still the question of whether or not the model is truly identifiable. Identifiability has been calculated and it has resulted theoretically satisfactory, but many simplifications and assumptions were made in the way, so a real attempt of identification may not be successful. In other words, the sensitivity analysis has to be *validated*. In order to do so a *virtual identification* can be performed.

Virtual identification is an identification in which the "experimental" data is obtained from simulation, and error is added to the signal, so it emulates possible measurement or modeling errors in the real identification. With the noise addition trick multiple data sets can be obtained, and so statistics of the identification, referring to every data set as a sample, can be calculated. These statistics can be comparable to the outputs of the sensibility analysis, being then able to validate it's success or to disprove it. The flow chart summarizing the steps to perform a virtual identification can be seen in Figure 3.3.

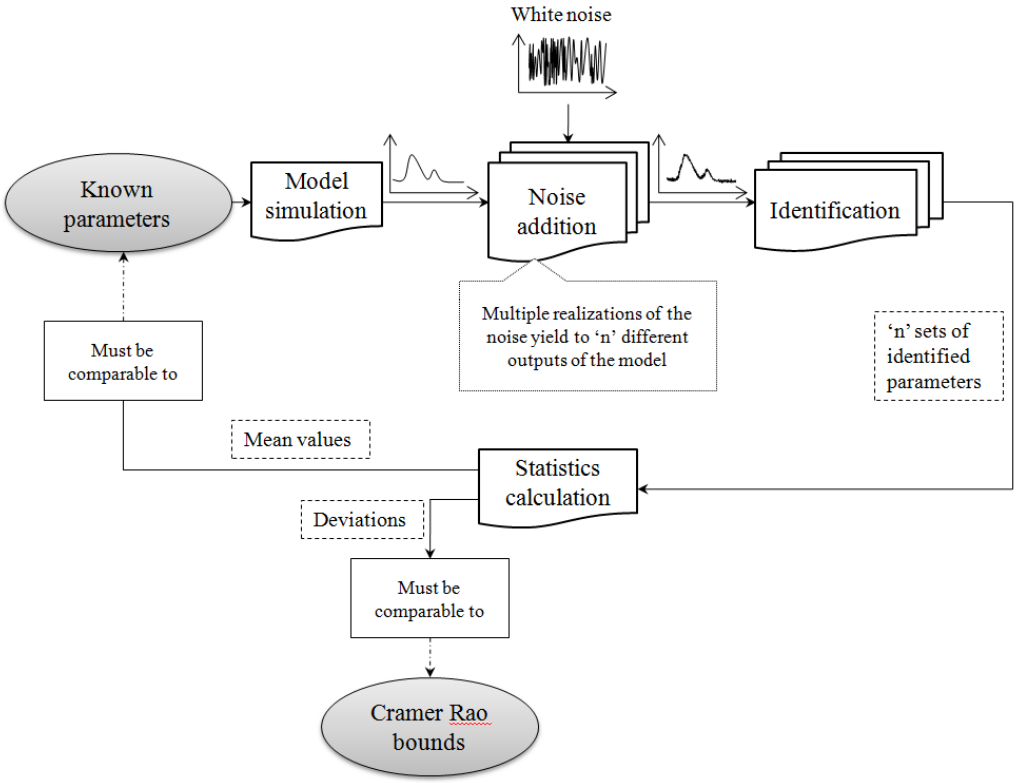

Figure 3.3: The final objective of the virtual identification is to find similar results as the sensitivity analysis, under the same conditions

Following the flow chart, we start from a set of known parameters (nominal parameters), and the sensitivity analysis has already been performed. The model simulation is performed, obtaining "perfect" data, without noise or variation in the parameters. By adding different realizations

of a white noise (mean 0 and uncorrelated), several "noisy" data, that can be considered as different outputs of the model, are obtained. Identification is then carried out to all of the noisy sets of data, obtaining multiple sets of parameters identified. Statistics can be calculated for every parameter, because from the different identifications the same parameter has been identified many times. The mean values of every parameter has to be comparable to the initial (nominal) parameter. The deviations of the identifications for each parameter must be contained in the confidence intervals obtained by the sensitivity analysis, following the same probability distribution.

If sensibility analysis and virtual identification statistics are (roughly) similar, then the model is proven to be identifiable, as long as the nominal parameters considered are correct. This does not mean that the model is correct. The aim of identification is to find a model that imitates the behavior of a system, if the data sets given by the system are not at all like the model output, the identification may still be unsuccessful.

3.4 Optimization and software

Once the identifiability analysis shows that the model is identifiable, identification still has to be done. As was said before, identification is a problem that can be formulated as an optimization (minimization) of an index measuring the error between the model output and the measurements. A good example of an index to be minimized was shown in equation 3.1. There are several algorithms that can be used to execute that minimization. A quick review and classification of optimization algorithms will be now done.

The first classification to be done is about local and global optimization. The local approach assumes solution is in a region near to the starting point, and that there is only one solution in that region that has to be found. The

global approach does not consider regions, and assumes that there can be several optimal points in there respective regions, but only one is the global optima. Local algorithms are usually deterministic searchers, and are efficient solving linear problems or adjusting linear models to experimental data.

In the case of the models seen in this thesis, global optimizers have to be used because of the non-linearities and discontinuities the models present. This kind of optimization problems needs of global optimizers, that usually involve using stochastic sampling methods or multiple starting points using deterministic algorithms. Also, the problem of identification is always bound because the parameters cannot take any values imaginable. There are non-negativity boundaries and theoretical stability limits in the values of certain parameters (some values of certain parameters may make the model unstable. This fact is very important in the choice of an algorithm to identify, for the boundaries are usually treated as non-linearities, and thus non-linear algorithms tend to be more prepared to deal with this kind of problems.

3.4.1 Nonlinear programming

The first algorithm to be used for identification was a non-linear local solver that fits into the group of solvers denominated as "Nonlinear programming solvers", or "Constrained nonlinear optimizers". This sort of algorithms are deterministic solvers that use first and second derivatives of the objective function, along with some heuristics to cope with the various problems that deterministic local searchers have. Abundant information about this kind of algorithms can be found in Coleman and Li paper of 1996 [18], Powell's conference in 1978 [76], or for a more general reference see Bazaraa's book [7].

The suite used is part of Matlab's Optimization Toolbox, which is composed of many different searchers to solve any optimization problem in the Matlab environment. The function used in the identification of

postprandial models is the main nonlinear programming function in the toolbox, the "fmincon" function. The use of this function has a major drawback, due to its local scope. It usually gets stuck in local minima instead of searching for the global optimum.

3.4.2 Scatter search for Matlab

Scatter search for Matlab (SSM from now on) is a global optimizer based on statistical principles that has already been used in the artificial pancreas project, with the objective of patient identification, by Cesar Palerm in Santa Barbara [64].

SSM optimizer is a project of the CSIC (Centro Superior de Investigaciones Cientificas) and the university of Vigo. It is a global optimizer, and as such it is easily comparable with genetic algorithms [27]. Scatter search does not use codification of the population as genetic algorithms do, but it does work generating new generations (offspring) of the function optima by combining the properties of the previous (parents) population. Plus, it does not generate random "mutation" on the population, but it does renew the existing individuals by adding new random samples to the new generations of optimal solutions. The details of the inner algorithms are not going to be exposed in here. For the better understanding of the searcher check out Julio Banga's group papers in 2006 [83] and 2007 [22].

This optimizer has the advantage of using local solvers to refine the search when it seems to have found some optimum solution. The local solver to be used can be chosen from a list available in the SSM's documentation. *fmincon* is one of the many solvers available, so the use of SSM incorporates the use of the other solver described before.

Chapter 4

The Challenge of Model Identification in Diabetes

Identification of a model in the artificial pancreas context consists on the characterization of a patient with a series of parameters. Those parameters can be constant, time-varying, yes/no parameters, periodic, etcetera. Parameterization of the patient is of common practice in diabetes treatment heuristically estimated woth parameters such as:

- **Insulin sensitivity.** It is the decrease of glucose related to a certain amount of insulin. It is one of the principal parameters for the characterization of a diabetic patient, and it is subject to circadian and long term variations. It determines rate of basal insulin to be administered to a diabetic patient.
- **Insulin to carbohydrate ratio.** It is the amount of insulin required to counteract a certain amount of ingested carbohydrates (CHO). It is also subject to circadian and long term variations.

These parameters can be heuristically determined by simple observation of the patient, but there are other parameters in a diabetic mathematical model that are representative of internal physiological processes, and their quantification is not straightforward. Some of those parameters are:

- Endogenous glucose production.
- Glucose uptake by tissues.
- Glucose absorption rate.
- Insulin absorption rate.
- Insulin degradation rate.

These parameters are very difficult to characterize because their dynamics are usually related to several hormone concentrations, and those relations are usually subject to circadian and long-term variations. Furthermore, those dynamics are not completely well understood, and proposed models are not accurate. The difference with the observable parameters described before is that the quantification of the variations (especially the circadian) is very difficult, and usually including complicated dynamics in the mathematical models yields to non-identifiable models.

One of the most complex models describing the physiology of diabetes is the model seen in section 2.2.3, and its published simulator. That model represent in a detailed manner physiological processes, describing the dynamics with a set of equations, and reducing the patients characterization to a set of constant parameters, shown in Table 2.23.

This model and the simulator developed by the University of Virginia has been accepted by the FDA for controller testing in the context of a clinical trial at Padova and Virginia. The FDA acceptance was not due to the models capabilities on characterizing individual patients behavior but

due to the set of virtual patients included, characterizing variability found in a real population. The simulator is distributed with a non-disclosed set of parameters that is able to simulate over 300 patients (100 children, 100 adolescent and 100 adults).

In this chapter, the ability of the model to test controllers is not discussed, but the identifiability of this model and its practicality when trying to characterize a real patient.

A set of experimental data from several T1DM patients was available for the use of the INSULAID2 project, which has already been used for real time glucose estimation in continuous monitoring [46]. That data will be used for model fitting in order to prove Cobelli's model feasibility to adjust to experimental data. The study included 18 patients with type 1 diabetes following the protocol approved by the Dr. Josep Trueta University Hospital of Girona's Ethics Committee. Patients were monitored for three days (one day at the hospital and two days at home) using the CGMS Gold (MiniMed CGMS). The CGMS Gold was applied to the subcutaneous abdominal region of each patient and was used continuously for a period of 72 h. After the third day, the monitor data were downloaded to a computer using the CGMS Gold algorithm (Solutions Software 3.0). The CGMS Gold was calibrated with capillary glucose measurements using conventional self-measurement of blood glucose. During the first day, plasma glucose was simultaneously measured with a Beckman Glucose Analyzer every 15 minutes during 2 hours after a meal and every 30 minutes otherwise. Plasma insulin was also measured.

4.1 Cobelli's model identifiability

Prior to the experimental identification of the patients from the Josep Trueta Hospital, the model's identifiability is going to be analyzed. Previous work on identifiability of the insulin model was done by Ana Revert [80], given that

plasma insulin data was also available in this study. The insulin submodel was then considered known for several patients in which the identification was successful, and the plasma insulin was considered as an input to the model.

In this identification study, initial states were also considered as parameters of the model to be identified. This was done in order to consider the identification as a broader general case. Only the initial states of the compartments of the glucose model were considered to be different to its basal values, the rest of the initial conditions were considered equal to the basal parameters (EGP, insulin delays, ...) due to the fact that at the beginning of the day there are no previous insulin bolus or meals. The two new parameter added are:

- G_{p0} - Initial state for mass of plasma glucose.
- G_{t0} - Initial state for glucose in the tissues.

Another variation has been included in the model in order to improve identifiability and to simulate patients with more accurate physiologic conditions. The "dawn effect" is a well known rising in blood glucose in diabetic patients after the night period [10] [71]. This phenomenon is known to be caused by a decrease in insulin sensitivity during the night. Insulin sensitivity is known to have circadian variations of different intensity depending on the patient. A 24 hours periodic variation of insulin sensitivity has been included into Cobelli's model, as shown in Figure 4.1, and two new parameters have been added to adapt the variation depending on the patient:

- *modsens* - sensitivity variation's modulation. It amplifies the variation of insulin sensitivity.
- *sensdelay* - sensitivity variation's delay. It shifts the variation of insulin sensitivity in time, advancing or delaying the peaks or the valleys of insulin sensitivity depending on the patient.

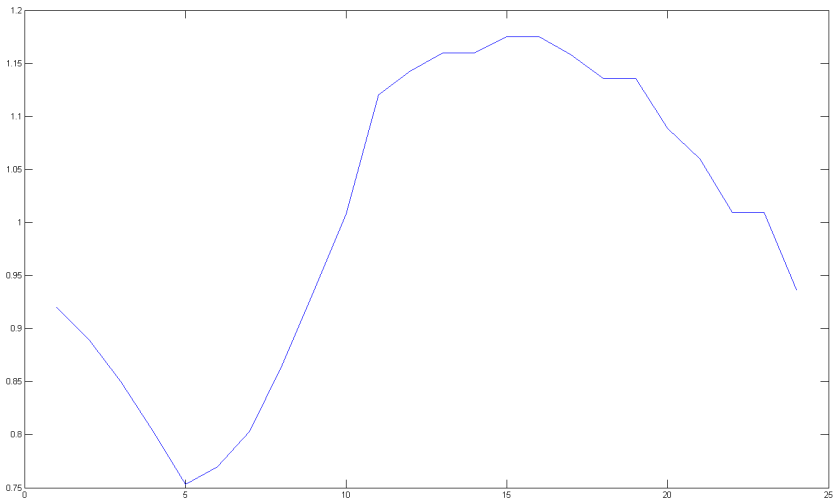

Figure 4.1: Circadian variation over 24 hours in an average diabetic patient. It multiplies insulin sensitivity. Extracted from [87]

Identifiability analysis has been applied to this model for a three meals scenario. The analysis was done following the scheme shown in Figure 3.2, and results are shown in Table 4.1.

The table shows the evolution of each parameter coefficient of variation at each iteration of the sensitivity analysis. The first iteration shown is the first one in which the FIM is not singular. The parameters in which no CV is shown are the parameters that made the FIM singular. As can be seen, all the confidence intervals decrease as more and more parameters are fixed to their nominal values. Always the highest CV determines the parameter to be fixed.

At iteration 11, all the parameter CVs are under 0.3, which is the threshold decided for identifiability. The next iteration was performed due to the correlation of two parameters. The correlation matrix for the parameters left in the 11th column of Table 4.1 is that shown in Table 4.2. As can be seen in that table, of the two parameters with a correlation bigger than 98%,

Number	Parameter	1	2	3	4	5	6	7	8	9	10	11	12
1	K_{abs}	-	-	-	-	-	-	-	-	-	-	-	-
2	K_{max}	0,84	0,47	0,46	0,41	0,37	0,23	0,23	0,22	0,09	0,05	0,05	0,04
3	K_{min}	4,79	4,77	-	-	-	-	-	-	-	-	-	-
4	b	1,63	1,24	0,55	0,46	0,41	0,13	0,12	0,12	0,10	0,08	0,08	0,08
5	c	1,78	1,70	0,74	0,68	0,66	0,36	0,36	0,36	0,18	0,12	0,12	0,11
6	EGP_b	0,56	0,38	0,37	0,37	0,35	0,25	0,21	0,17	0,13	0,07	0,05	0,04
7	G_b	-	-	-	-	-	-	-	-	-	-	-	-
8	V_g	1,73	1,40	1,37	1,20	1,06	0,74	0,73	0,70	0,16	0,08	0,07	0,05
9	V_{mx}	4,51	1,03	1,03	1,02	0,90	0,75	0,53	0,53	0,53	-	-	-
10	K_{m0}	3,13	3,12	3,10	2,74	-	-	-	-	-	-	-	-
11	k_2	9,17	-	-	-	-	-	-	-	-	-	-	-
12	k_1	3,68	2,24	2,22	1,87	1,26	0,90	0,86	0,77	-	-	-	-
13	p_{2U}	2,97	2,72	2,72	2,17	1,61	-	-	-	-	-	-	-
14	k_i	1,87	1,57	1,57	1,29	1,27	0,85	0,76	0,41	0,40	0,39	-	-
15	k_{p2}	4,89	4,17	4,17	-	-	-	-	-	-	-	-	-
16	k_{p3}	2,58	1,69	1,69	1,51	0,94	0,93	0,91	0,49	0,40	0,26	0,16	-
17	$modsens$	1,46	1,08	1,08	1,06	0,59	0,48	0,38	0,30	0,30	0,09	0,06	0,01
18	$sensdelay$	1,48	1,40	1,40	1,27	1,12	1,03	0,99	-	-	-	-	-
19	G_{p0}	2,15	1,90	1,87	1,72	1,34	0,98	0,69	0,67	0,31	0,11	0,11	0,10
20	G_{t0}	5,44	2,44	2,44	2,30	1,28	1,17	-	-	-	-	-	-

Table 4.1: Cobelli's model parameter confidence intervals (CV) for a three meals identification. Each row represents an iteration in the sensitivity analysis, and parameters that don't have CV are fixed due to non-identifiability

parameters 16 and 17, the one that is lower in the ranking is parameter 16, which results to be the one with the biggest CV as well. The decision taken was then, fixing parameter 16.

	2	4	5	6	8	16	17	19	Ranking
2	1,00	0,02	-0,07	-0,16	0,88	0,60	-0,54	0,70	95,50
4	0,02	1,00	0,72	-0,12	-0,20	-0,25	0,26	-0,13	35,64
5	-0,07	0,72	1,00	-0,44	-0,04	-0,37	0,39	0,13	24,43
6	-0,16	-0,12	-0,44	1,00	-0,07	0,60	-0,69	-0,33	131,10
8	0,88	-0,20	-0,04	-0,07	1,00	0,71	-0,66	0,83	92,69
16	0,60	-0,25	-0,37	0,60	0,71	1,00	-0,98	0,41	48,62
17	-0,54	0,26	0,39	-0,69	-0,66	-0,98	1,00	-0,33	217,62
19	0,70	-0,13	0,13	-0,33	0,83	0,41	-0,33	1,00	22,97

Table 4.2: Parameter's correlations for the last iteration of the sensitivity analysis. The last column is not part of the correlation analysis but the ranking of the parameters in the most influent eigenvalue of the FIM.

Starting from a model in which 20 parameters were characterizing a diabetic patient, only 7 parameters remain identifiable at the end of the analysis. Identification of two real patients is going to be performed with blood glucose for a whole day, and validation will be done by comparing the results of simulating the two following days to the identification, and comparing it to CGMS home data (no blood glucose data is available).

Cost ponderation for the fitting is decided to be a diagonal matrix where all the entries of the diagonal are equal to the maximum of the experimental data, as explained in Chapter 3.

4.2 Experimental Data Fitting

In this chapter some examples of data fitting are going to be shown and discussed. The number of available patients was initially 22, but few of those patients were possible to be identified in their insulin sub-model due to anomalous absorption or high variability. Out of the patients that were

successfully identified in their insulin sub-model, few of them were possible to fit accurately to the Cobelli's model. Many experimental identifications were performed, and only two of those data fitting were satisfactory. The fitting of those two patients is shown in Figures 4.2 and 4.3.

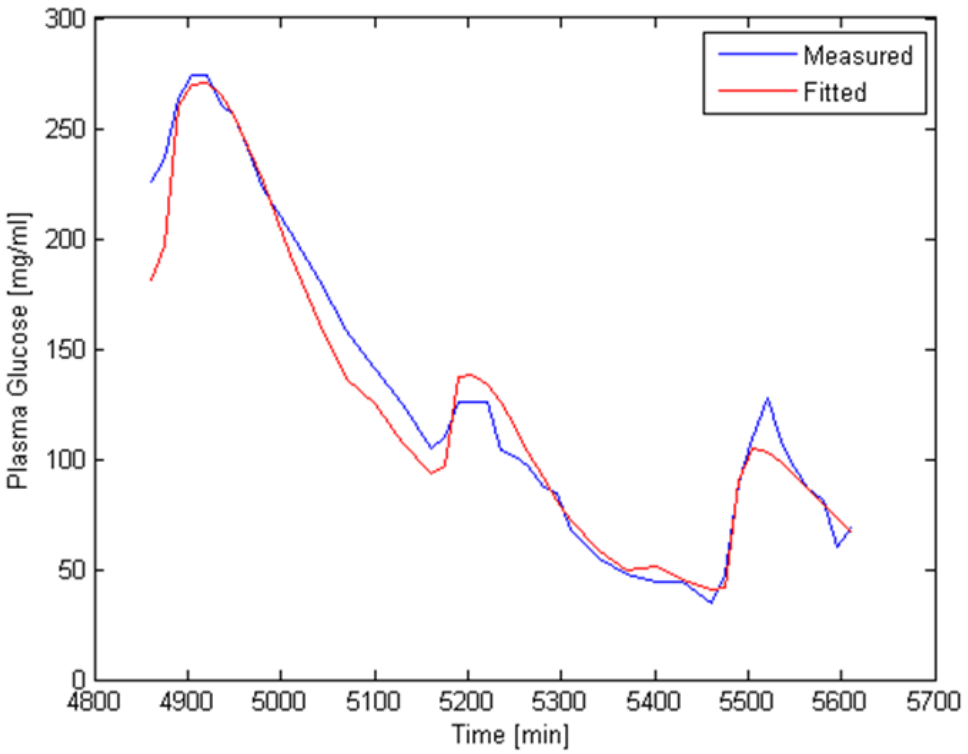

Figure 4.2: Data fitting of Cobelli's model to blood glucose experimental data

In those figures the blue line represents the blood glucose data, and the red line is the model prediction. In the first identification, all three meals are very well simulated by the identified model, as well as the general descendant tendency of the day. In the second identification, the first meal is not very well fitted, but the descendant tendency in the following hours is very well captured. Both cases are successful in terms of similarity of the response and repeatability of the optimizer. Several runnings of the optimizer were done in order to prove a single solution. Other patients data were discarded due

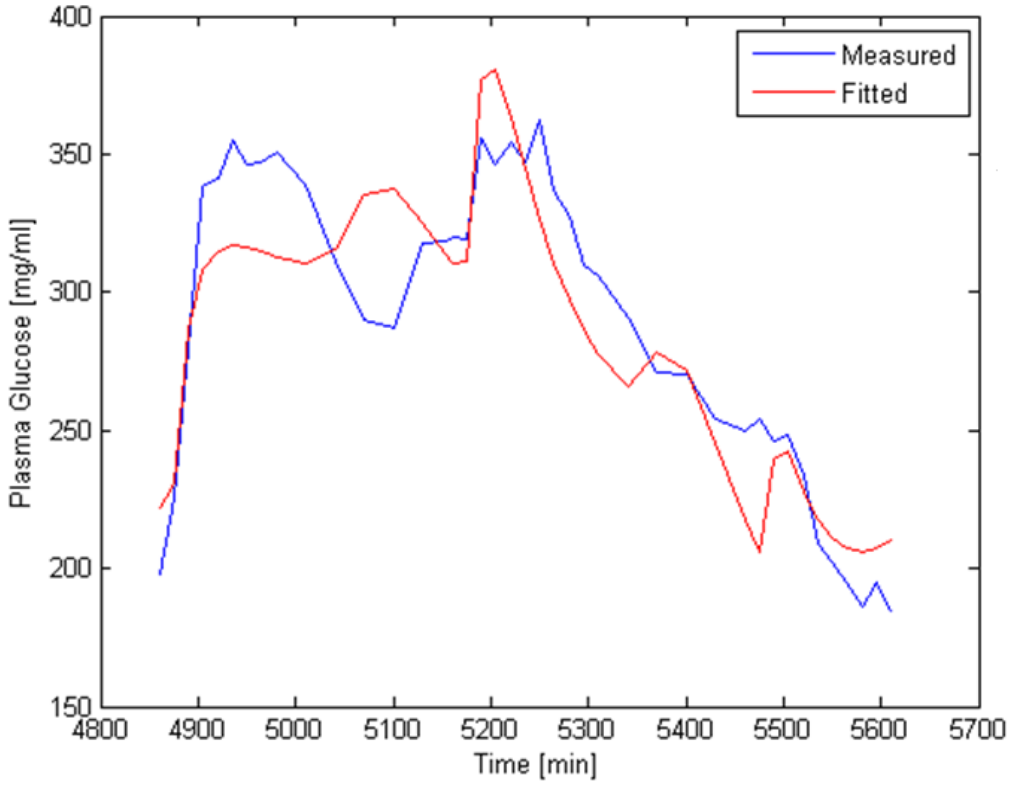

Figure 4.3: Data fitting of Cobelli's model to blood glucose experimental data

to this problem.

Although data fitting was successful for two data sets, this does not mean the model is useful. Model identification has to be validated with some data different than the utilized for the identification. In the case of the data available for this experiment, the Josep Trueta monitoring, the validation data that was used was the CGMS data acquired at home in the two following days to the hospital monitoring. The results of that validation are shown in Figures 4.4 and 4.5.

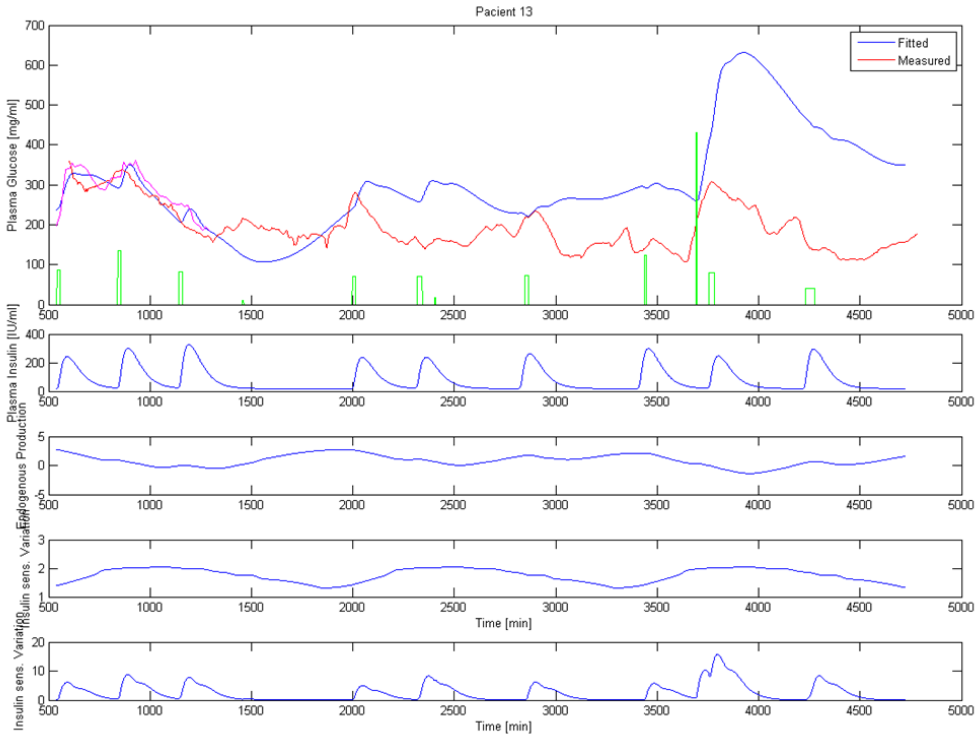

Figure 4.4: Identification of a three days real monitoring. The first day was used for identification while the two last days were used for validation of the identified model

In these figures several signals that are considered interesting for the understanding of the model's behavior are plotted. The top graph is the patient's glucose, now the red line being the CGMS signal, the blue line being the identified model prediction, the pink line in the first day being the

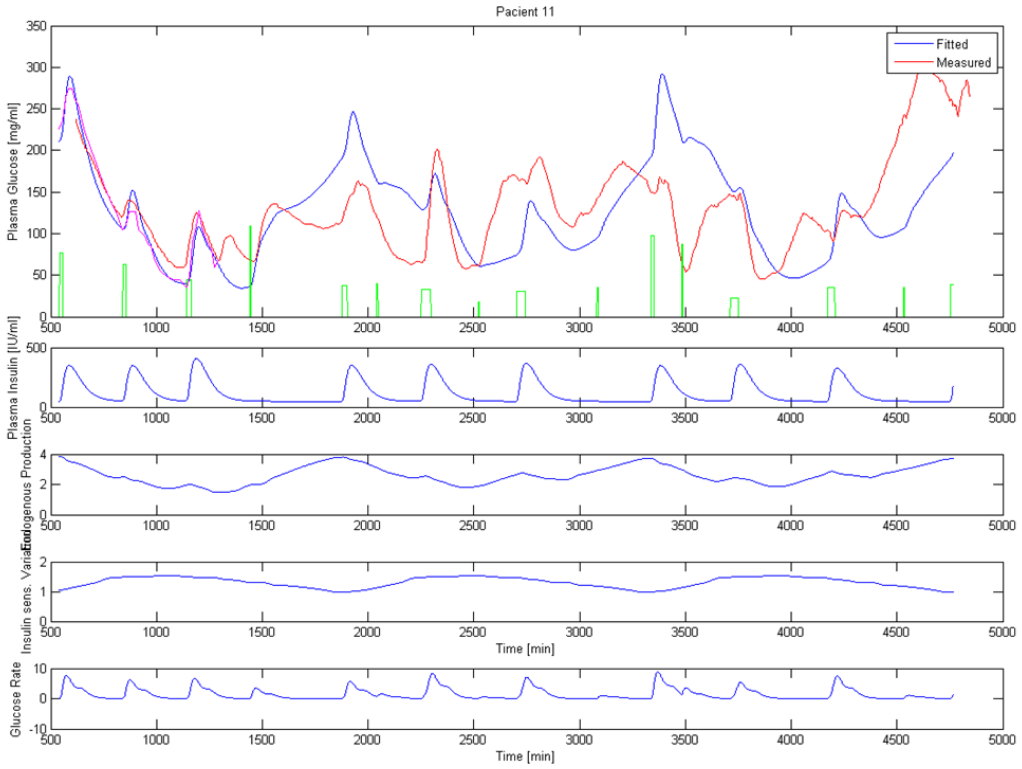

Figure 4.5: Identification of a three days real monitoring. The first day was used for identification while the two last days were used for validation of the identified model

blood glucose data (already shown in previous figures), and the green spikes being the meal ingest periods. The second graph (from the top) that is shown in the figures is the plasma insulin profile from the model. It can clearly be seen the times of the bolus infusions, and how the level of plasma insulin increases drastically during meal times. There is also a basal level of insulin assumed constant. The third graph is the endogenous glucose production, which is an internal state of Cobelli's model and that is dependent on the plasma insulin. The forth graph is the insulin sensitivity variation along the three days of monitoring, as described before. The bottom graph is the rate of appearance of glucose in blood as delivered by Dalla Man's model.

As it is clearly seen by Cobelli's model validations, even though the model fits perfectly the identification data, it does not reproduce the validation days, which is its main purpose. This is not an unexpected result, and the validity of this model was questioned at every step. Anyway, a prediction horizon of 2 days, as was considered in the previous identification, is unrealistic, but given that this work with Cobelli's model is a preliminary contact with modeling in diabetes, it is a useful result. No model for diabetes has been proven good for predictions of more than a two hours horizon, and only predictions of populations, not single individuals. Following work on this field will be focused on the postprandial stage and it's prediction, with prediction horizons of no more than 5 hours.

Cobelli's case study and its identifiability study proves that the model is too complex, even without attempting to identify the insulin subsystem. Simpler models are going to be analyzed in the following, and Cobelli's endogenous model will not be used anymore, except maybe in future work, using the simulator for testing controllers.

Simple postprandial identification trials with Bergman's model were also performed on the Josep Trueta's data with similar results. Bergman's model identifiability will be discussed in chapter 6.1. In this case, the insulin submodel was also being identified, but the philosophy of identification was

different. In order to avoid variations in the gastric emptying, and thus in the gastric submodel parameters, the meals identified are the three breakfasts of one patient, whom repeated the same breakfast for three days, even in quantity of CHO. The fact of being the breakfast the meal identified was also good due to the fasting state in which patients arrived to the beginning of the meal, which is the most similar state to a steady state in a diabetic patient. This time, two days were used for fitting of the model, and one was used for validation, as can be seen in Figure 4.6. All the data was extracted from a CGMS in this case, in order to minimize the difference between identification data

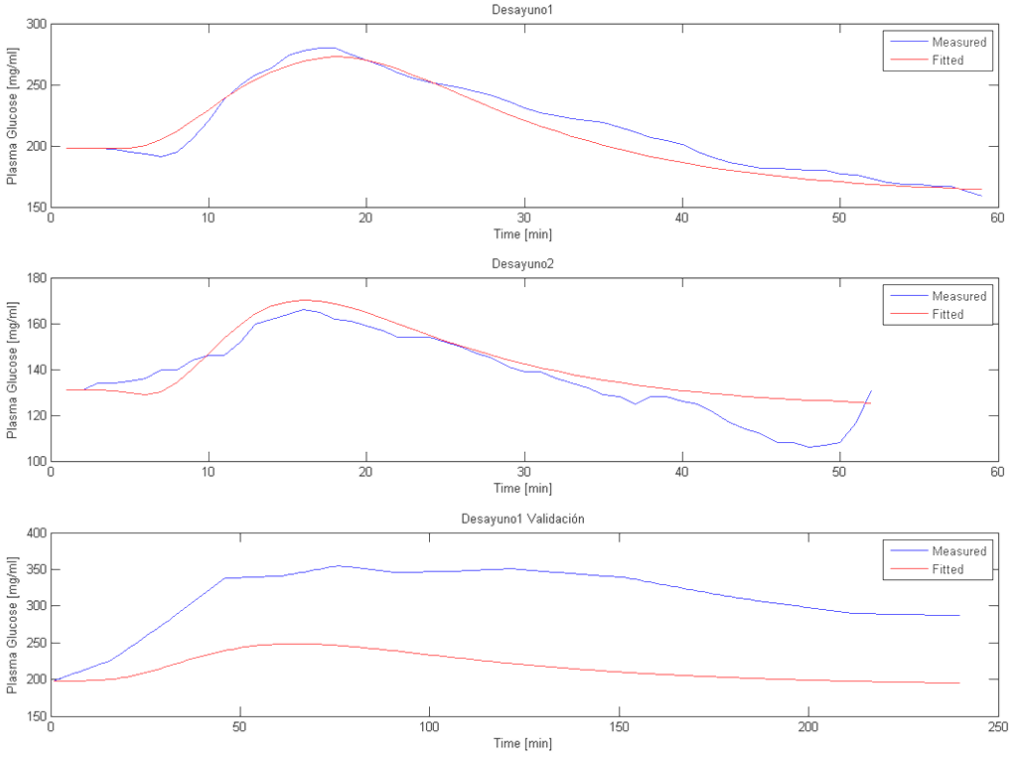

Figure 4.6: Identification of a three meals real monitoring. The two first meals were used for identification, while the third was used for validation. All the date was extracted from a continuous glucose monitor

In that figure, the blue lines represent the CGMS data, and the red lines are the identified model response. The two graphs in the top of the figure are the postprandial responses of the patient and the model to the breakfast.

The same model is being fitted to both breakfasts. The graph in the bottom is the validation breakfast.

As can be seen, even with simpler models the validation of model identification is tricky in diabetes. The reasons for this lack of repeatability are many. The metabolic state of a person in terms of diabetic physiology is not completely understood. Trying to reproduce consecutive days (meals) with the same model, considering the models that are now published in literature, may not be possible. Many parameters that are considered constant in the endogenous models are variable with time, and not only in a circadian manner.

Data provided may be not appropriate for identification, and that is the reason why the Josep Trueta's data will not be used anymore in this thesis. Instead, new sources of data will be used. Taking advantage of a new collaborative way with the "Hospital Clinic Universitari de Valencia", possibility of new data acquisition arises. Plus, new models will be studied and analyzed.

4.3 Critical selection of models

The identification problem in diabetes has been proven really difficult even for the simplest models, like in the study of Ana Revert [80], or the pure control approach of Stål [90] in Lund. The problem of the identification is not about adjusting the data existing to the models provided. That task is usually performed with success. But when using the model identified for further simulations, models prove themselves mainly useless.

Of course, the main solution to this problem is to develop new, more efficient models for the glucoregulatory system, but that is not the main objective of this thesis. Instead, a critical review of the most used models is going to be quickly done in the following lines.

The fact that the set of Cobelli's group models is now accepted by the FDA as a simulator of diabetes makes those models to look like the correct choose to be used in research works like this thesis. Also Dalla Man describes the gastric emptying of the stomach as a function of the fraction of glucose in the stomach, being the only model implementing this feature, so this was the model chosen to be the exogenous glucose model in this research. While working on this thesis, there was a parallel research being done by INSULAID2 (the research project in which this thesis is involved) with the Willinska model, showing much better identifiability results than with previous work done with other models [80], and so this model was used for the identifiability and optimal experiment analysis.

When trying to choose an endogenous model the question is much trickier. Following the same logic as before, reason dictates Cobelli's model has to be chosen because of it's FDA acceptance. Willinska published a review of the identifiability of models for simulation [103], stating that Cobelli's model has the problem of having too many parameters to be identified from clinical data, what makes the identifiability of the model to drop.

Minimal models (not used for simulation) such Bergman's or Panunzi's model skip the problem of overpopulation of parameters, but obviously describe with less accuracy glucose behavior. Bergman's model has been strongly criticized in late years because of it's simplicity and the fact that it does not fit correct glucose behavior against insulin. Quon et al [78] proved in 1994 with a series of experiments involving the Biostator device that Bergman model underestimates insulin action on glucose removal from blood, and it overrates the effect of glucose concentration in its own disappearance (*glucose effectiveness*).

In 1999, Regittnig et al. [79] confirmed the overestimation of *glucose effectiveness*. They also proved that all minimal models are inevitably wrong if they consist of one single compartment for glucose, without considering the interstitial dynamics or other situations. Considering that a minimal

model has to stay simple, let us take a closer look to the equations related to the glucose compartment in minimal models, like the Bergman model. Considering that there is no exogenous input of glucose, equation (2.73) stands:

$$\dot{G}(t) = -p_1 G(t) - X(t)G(t) + p_1 G_b \tag{4.1}$$

The part of the equation $-p_1 G(t)$ is the term of the Bergman model that represents the glucose effectiveness, and it depends directly on the parameter p_1, that has to be identified. The term $p_1 G_b$ sets the equilibrium point of the model to the basal glucose if insulin is at basal level and there is no glucose input. The term $X(t)G(t)$ is the insulin related term, applying insulin with a delayed compartment. Looking at the equation of the glucose compartment of another minimal model, the Panunzi model:

$$\dot{G}(t) = -K_{xgl} I(t) G(t) + \frac{T_{gh}}{V_g} \tag{4.2}$$

The term related to glucose effectiveness does not exist. The term related to insulin input, $-K_{xgl} I(t)G(t)$, is applied without a delay because Panunzi's model was designed for healthy patients and the delay is considered in the endogenous secretion of insulin. The term $\frac{T_{gh}}{V_g}$ is similar to the equilibrium point term in equation 4.1, both are constant terms that define the equilibrium point of the equation, but they are considered in different ways. In the Bergman model, the basal level is stated explicitly, while in the Panunzi model it is seen as a hepatic balance of glucose. Both approaches are true and useful, and the identification is done in the same way in both examples.

In this thesis, experiments will be performed with the Bergman model because it is considered in diabetes research as a sort of "benchmark" model to test any methodology, but every result will be compared with a variation of Panunzi's model that will be explained in the following lines.

Bergman model has an odd behavior when simulating a diabetic patient to whom basal insulin infusion is removed. The correct behavior to a empty

insulin compartment in a diabetic patient is blood glucose to increase without measure. In Figure 4.7 a simulation with Bergman's model is shown, with a warming period of 10 hours in which the insulin infusion is stopped; then, at minute 600, insulin infusion is restored, a 75 grams of a mixed meal ingested (simulated by Dalla Man's model) simultaneously to a 7.5 units of insulin injected as a bolus.

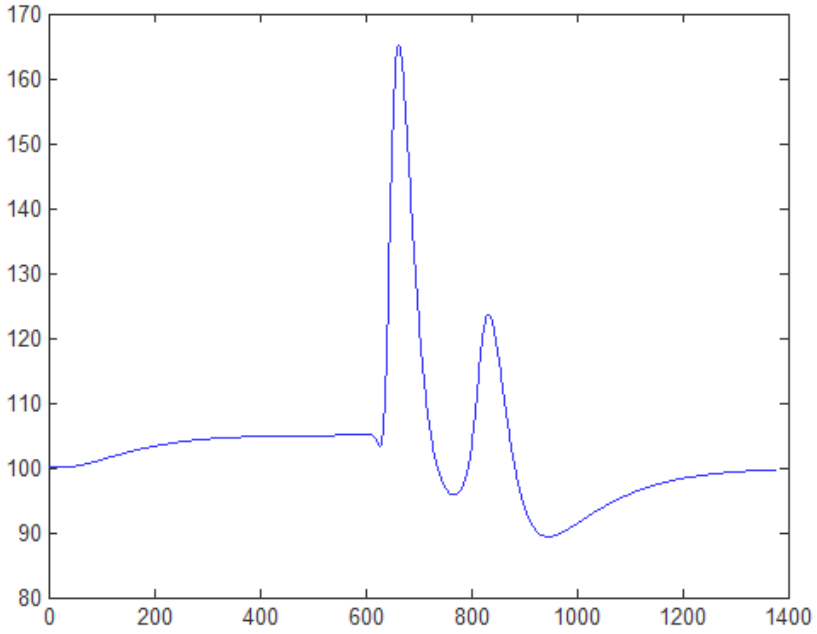

Figure 4.7: Bergman simulation of a change in basal level and nominal values of glucose effectiveness

If there is an stop in basal insulin infusion with a smaller glucose effectiveness, the results are shown in Figure 4.8.

The behavior observed in the warming period of the previous figures is unrealistic. A diabetic patient whose insulin infusion is removed should become an unstable process, not just change its equilibrium point. Panunzi's model, in its equation (4.2) becomes a pure integrator if insulin is removed, making the system unstably increasing. Panunzi's model seems more suited to the physiology of glucose in this case, but it also has its disadvantages. As it was said before, the Panunzi model represents the delay of insulin action

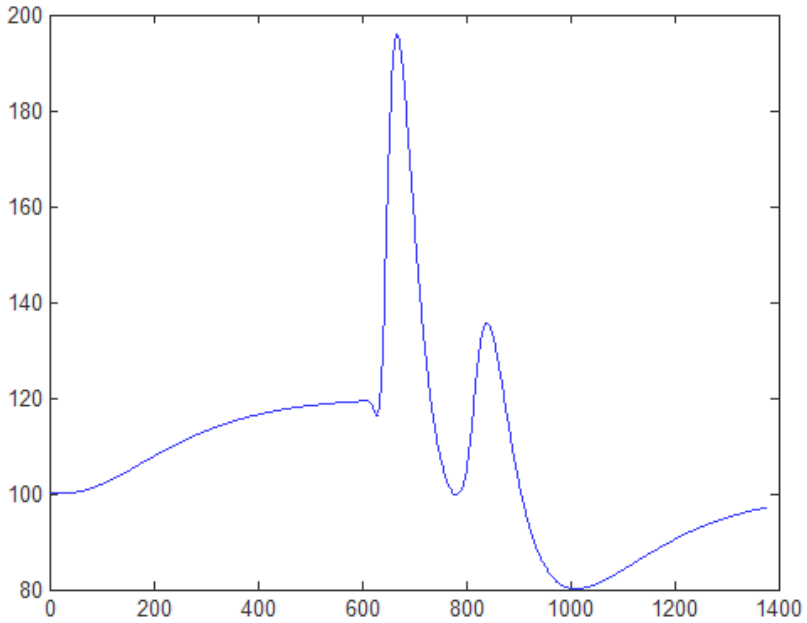

Figure 4.8: Bergman simulation of a change in basal level and 50% reduced glucose effectiveness

in the equation of secretion, but that equation (2.75) is eliminated when simulating diabetic patients, so the delay effect is removed. This results in a faster acting of the bolus insulin in front of the simultaneous meal ingestion, making blood glucose to drop inmediately after the injection, as can be seen in Figure 4.9.

This phenomenon can be easily avoided by adding a delay equation (4.4) to Panunzi's model, resulting in the next model:

$$\dot{G}(t) = -K_{xgl}X(t)G(t) + \frac{T_{gh}}{V_g} \tag{4.3}$$

$$\dot{X}(t) = -k_i[X(t) - I(t)] \tag{4.4}$$

With the addition of a new parameter to the model. This new parameter has to be set to a new nominal value, and it is going to be done by bibliography review. In [29] Helms quantifies the insulin action delay with a 20 minutes settling time, which makes the parameter k_i to be approximately equal to

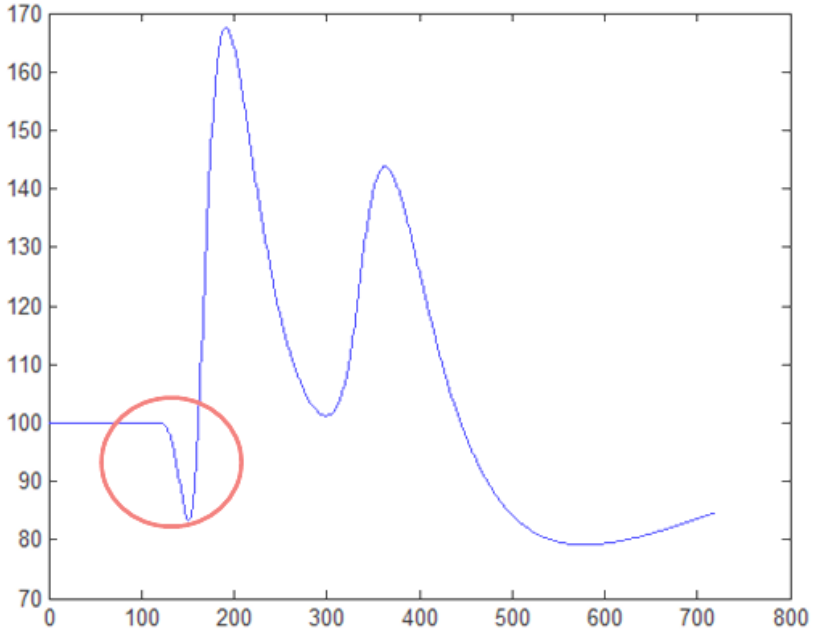

Figure 4.9: Panunzi's simulation of a meal at minute 120

0.08 min^{-1}. The response to a meal and a bolus in that case is shown in Figure 4.10, where the dropping of glucose just after the bolus time is almost non present.

The shown model is completely satisfactory for identification purposes and control. There is one last check to be done to the model to prove its reliability. In their paper of 1994 [95], Torlone et al. showed a series of experiments in which insulin bolus is injected some minutes prior to a intravenous glucose infusion. This experiment shows clearly the effect of insulin, and how it makes glucose to drop an impulse response behavior. In Figure 4.11 this behavior is shown for almost one hour before the glucose infusion starts.

In the previous figure it can be seen that there is no change in blood glucose until 15 minutes after bolus injection, and then glucose drops for 30 minutes until approximately 70 mg/dl (approximately 3 $mmol/l$). In the case of simulation with the Panunzi model with delayed insulin action, the

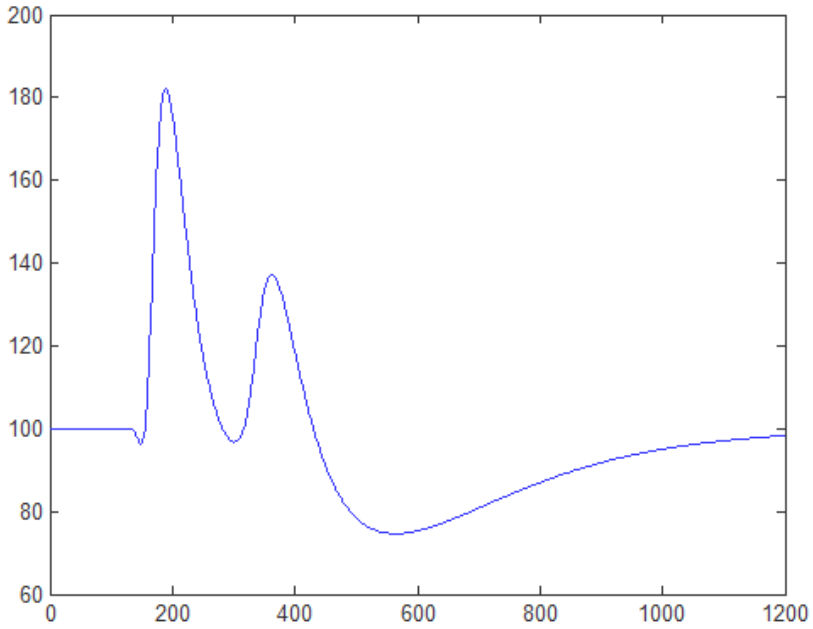

Figure 4.10: Variation of Panunzi's model simulation of a meal at minute 120

results are shown in Figure 4.12, in which no intravenous glucose infusion was simulated.

In simulation, the response is exactly as expected: no significant change in blood glucose in the first 15 minutes, and in the next half hour, glucose level drops to almost 70 mg/dl. This makes the new model much more reliable than Bergman or Panunzi's models, and as such it will be used in this thesis.

Another simple feature was included in the modified Panunzi model. Endogenous hepatic glucose production is one of the parameters of the model, T_{gh}, and it is considered constant. This is actually not true, for endogenous hepatic production is suppressed by insulin. A simple variation of the model was introduced, considering the T_{gh} parameter to be reduced when plasma insulin surpassed a defined threshold:

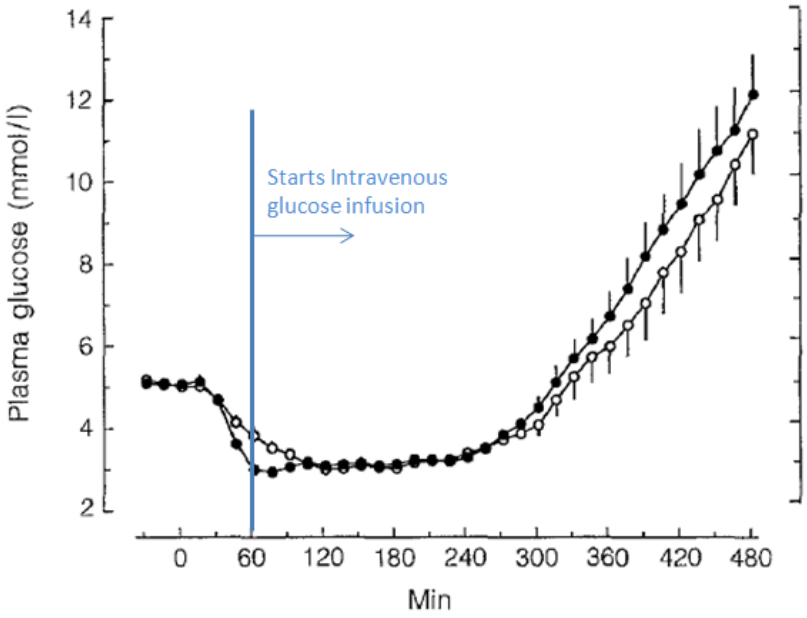

Figure 4.11: Insulin impulse response of glucose after bolus and counteraction with intravenous glucose infusion [95]. Black dots are the blood glucose measurements for monomeric insulin analog, and the white dots for human insulin

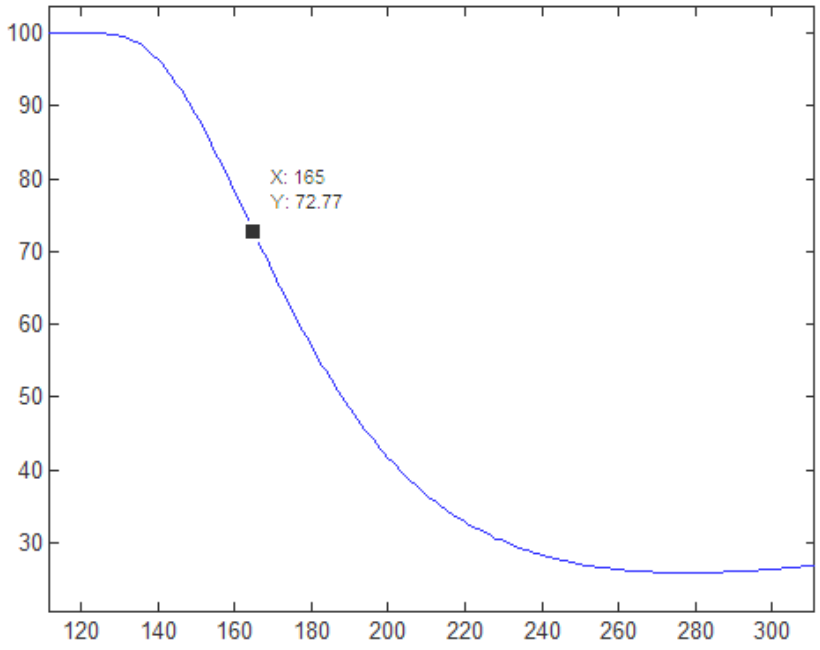

Figure 4.12: Variation of blood glucose (mg/dl) in Panunzi's model simulating a fall of glucose after insulin injection. Insulin is given in minute 120

$$T_{gh} = \begin{cases} T_{gh} & \text{if } I_p < 30\ mIU/l \\ 0.1 * T_{gh} & \text{otherwise} \end{cases} \tag{4.5}$$

In summary, one model was chosen for simulating purposes between the so called models for simulation. That is Cobelli's model, which is the one accepted by the FDA as a valid simulator, as seen in Chapter 4.1. Out of the minimal models, two were chosen: Bergman's model, because it is probably the most used model in diabetes research for the las 20 years, and it has been studied and compared thoroughly, and also a variation of Panunzi's model was chosen, because of its simplicity and its properties.

Chapter 5

Optimal experiment design

In the diabetes research scenario, the fact of performing experiments is a high-cost, time consuming task that has to be thoroughly planned in order to obtain the biggest benefit out of it. In the case that is being reviewed in here, the objective of that planning is to get the models to be easier to identify. There are some methods that will help the researcher to obtain the best identifiability of a given model, choosing from a constrained set of possible experiments.

An experiment of data recollection in diabetes initially has infinite number of variables that can change under different circumstances. The models chosen is the first choice to be made, and it is not an obvious one. In this thesis case the models have already been chosen, but for the optimal experiment design only the two minimal models will be used. The reason of that decision is simply of computational effort. The experiment design implies solving optimization problems whose computation times depends on the complexity of the models, and those times are usually very long.

The design of an optimal experiment usually consists of the following steps:

1. Define an optimality criterion related to the final purpose of the modeling, in this case optimal identifiability, *via* a scalar cost function.
2. Take into account all constraints on feasible experiments.
3. Optimize the chosen cost function with respect to the experimental variables available to the experimenter.

The experiment design will usually result in a non-linear constrained optimization problem and thus, global optimization solvers will be needed in order to find the solution. In this chapter there will be a justification of the optimal experiment design in diabetes, followed by the formulation necessary to define the criterion of optimality for identification. Finally results of optimal designs will be shown.

5.1 The need of optimal design

There is a classical example seen in [99] that explains very clearly the need of optimal design for almost every experiment to be performed. That example will be reproduced in the following lines, showing that usually the intuitive approach for experimentation is not optimal.

Example.-

There are three objects called O_1, O_2 *and* O_3 *with respective weights* w_1^*, w_2^* *and* w_3^* *to be estimated. The spring balance used for this purpose produces a biased random measurement error, defined by a Gaussian distribution* $\mathcal{N}(0, \sigma^2)$ *and the measurement bias* w_0^*. *Only four measurements can be done in this experiment.*

Intuition dictates to do the first of the measurements $y(0)$ *without any*

object on the balance, in order to characterize the bias, and then have the other three resting measurements for each of the objects. In that case the estimates of the weight for each object is $\hat{w}_i = y(i) - y(0),\ i = 1,\ 2,\ 3$. *The estimates in this case are unbiased (which is very good), and have variances* $var(\hat{w}_i) = 2\sigma^2$ *and covariances* $cov(\hat{w}_i, \hat{w}_j) = \sigma^2,\ i \neq j$.

Another case has to be considered now. If the first measurement is now taken with all the objects in the balance, being then $y(0) = w_0^* + w_1^* + w_2^* + w_3^*$, *the estimates of the weights for the objects are:*

$$\hat{w}_i = \frac{y(0) + y(i) - y(j) - y(k)}{2},\ i = 1,\ 2,\ 3,\ i \neq j,\ i \neq k,\ j \neq k \qquad (5.1)$$

In this case, the variances of the estimators, which is a good approximation of the identification performance, are $var(\hat{w}_i) = \sigma^2$ *and its covariances* $cov(\hat{w}_i, \hat{w}_j) = 0,\ i \neq j$. *Compared to the first intuitive approach, this second approach yields to a more accurate estimation and independent estimates, plus the estimation is also unbiased.*

In the context of the artificial pancreas there are few published examples of experiment design, and even fewer of them are based on the optimality of the experiment in terms of identifiability. One of the earliest attempt to improve the identification in an endogenous model was carried out Cobelli in 1986 [17]. The approach is based in the FIM methodology that will be explained in Section 5.2, and it is the same method that will be used in the work done in this thesis. Cobelli though, used a simplified version of experimental design evaluating only the identifiability of single parameters instead of evaluating the identifiability of the model as a block, combining the identifiability of different parameters.

There are several examples of modified standard protocols to perform better identifications, like the work of Percival et al. [70] where it is proven that simply by separating the instants of insulin bolus injection and the beginning of the meal the identification of a model is improved. However, no theoretical study is presented with this regard.

Only in the last years publications have appeared with complete identifiability studies and optimal design for the identification in diabetes. Galvanin [26] published a study of optimal experiments based on Hovorka's model, checking identifiability involving meal ingestion or oral glucose intake, yielding in quite complex insulin infusion rates like the one shown in Figure 5.1.

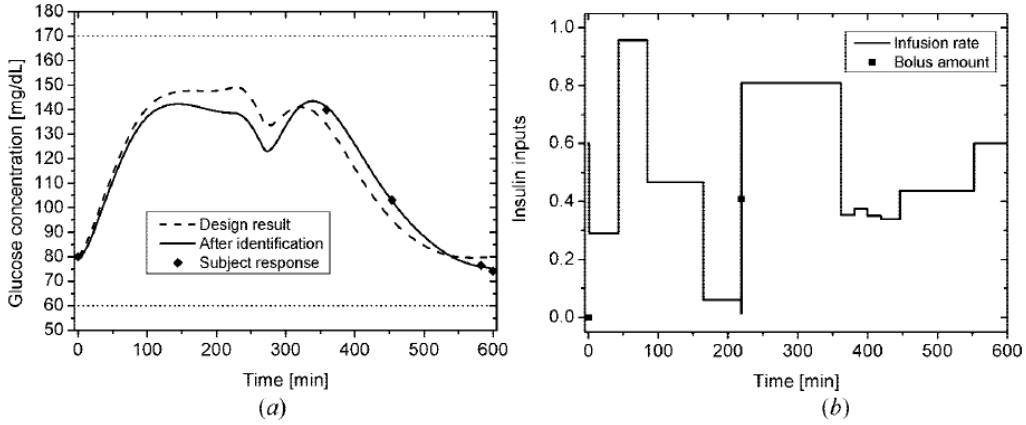

Figure 5.1: (a) Glucose concentration profiles predicted by Hovorka's model (dashed line) and after identification (solid line). (b) Insulin infusion rate designed for the identification. Extracted from [26]

Given the huge problem that identification of models supposes in the artificial pancreas environment, it seems logical to ease the problem as much as possible. In this thesis work several approaches to optimal experiment design based on different models using the FIM methods will be carried out as stated in Section 6.

5.2 Methods based on the FIM

The aim and need of the experiment design is now clear, and the question of how to perform that design arises. So far, identifiability has been analyzed as a property of a parameter, quantified as the confidence interval in the

estimation of each parameter. That information is obtained from the Fisher Information Matrix (or better said from its inverse), which summarizes the information of all the parameters of the model for a given experiment. The problem of optimal design can be expressed then as an optimization problem of finding the minimum value of a certain scalar function of the FIM. That function is called optimality criteria, and its general expression is:

$$j(\boldsymbol{\Xi}) = \phi[F(\mathbf{p}, \boldsymbol{\Xi})] \tag{5.2}$$

where ϕ is a scalar function. The evaluation of the Fisher Information Matrix is a function F of $\mathbf{p}$, the parameters vector, and $\boldsymbol{\Xi}$, the experiment conditions to be optimized.

There are several criteria that can be used in this case, as seen in [25]:

- D-optimality, in which the scalar function chosen is the determinant of the FIM. The three following equations are equivalent, and all of them define the D-optimality criterion and whether it has to be maximized or minimized in order to improve identifiability:

$$\boldsymbol{\Xi} = argmin_{\boldsymbol{\Xi}}\ j_D(\boldsymbol{\Xi}) = argmin_{\boldsymbol{\Xi}}\ det(F^{-1}(\mathbf{p}, \boldsymbol{\Xi})) \tag{5.3}$$

$$\boldsymbol{\Xi} = argmax_{\boldsymbol{\Xi}}\ j_D(\boldsymbol{\Xi}) = argmax_{\boldsymbol{\Xi}}\ det(F(\mathbf{p}, \boldsymbol{\Xi})) \tag{5.4}$$

$$\boldsymbol{\Xi} = argmax_{\boldsymbol{\Xi}}\ j_D(\boldsymbol{\Xi}) = argmax_{\boldsymbol{\Xi}}\ ln(det(F(\mathbf{p}, \boldsymbol{\Xi})) \tag{5.5}$$

- E-optimality, in which the function is the smallest eigenvalue of the information matrix, and it has to be maximized.
- A-optimality, in which the problem is solved by maximizing the trace of the information matrix.

In order to better understand the meaning of each one of these criteria, spatial analogy is needed. If every parameter is placed in an axis of the space, then the region defined by the confidence intervals of each one of the

parameters defines an ellipsoid the axis of which are given by the eigenvalues of the inverse of the information matrix. Given that the objective of the optimization is to minimize all the regions of confidence, every axis of the ellipsoid have to be minimized, or equivalently, the volume of the ellipsoid has to be minimized, and that volume is exactly the determinant of the inverse of the FIM. The rest of the criteria have similar meanings that are summarized in Figure 5.2.

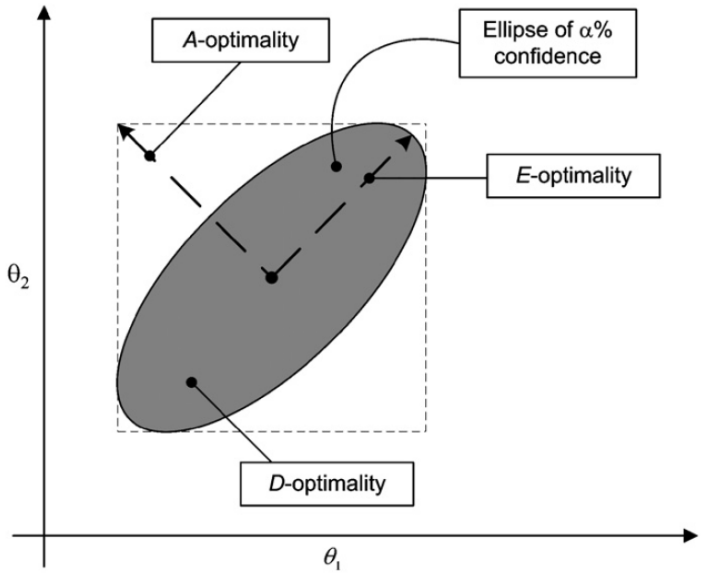

Figure 5.2: Each criterion reduces the confidences intervals attempting to minimize one singular scalar value [25]

The question of which criteria to be used arises now. The D-optimal is the most used of the three standard criteria cited above. This is due to some exclusive appealing properties of the criterion [25]:

- Easy geometrical interpretation, as seen in Figure 5.2.
- Invariance with respect to non-degenerated transformation applied to the model parameters, such as rescaling. This property is applied in

equation (5.5) in order to work, during the optimization process, with smaller quantities.

- Yielding to optimal experiments which correspond to replications of a small number of different experimental conditions.
- Optimal experiment design yields to non-singular FIM.

The main drawback this criterion has is that it gives too much importance to the parameter to which the model is most sensitive. Geometrically, this problem is equivalent to the idea of trying to minimize the volume of the ellipsoid by reducing mostly its bigger axis.

There are other criteria available for different purposes, like the modified E-optimality, that tries to maximize the FIM condition number, aiming to make the confidence ellipsoid as spherical as possible [97]. The correct application of this criterion would be in a case of strong parameter correlations, and the design will yield to a decoupled identification in parameters.

That is not the case in this thesis though. D-optimality will be the one used for the experiments designed for diabetic patients, and for every model tested.

Chapter 6

Optimal Design Results

The first task to be done when designing an experiment is to determine what parameters is the experiment going to be based on. The model for the experiment design is excited by its inputs. These inputs are the variables that can be adjusted in the experiment. For obtaining an optimal experiment, the best combination of the inputs have to be found, regarding at the identifiability of the model.

Another variable usually considered in the optimization of the inputs is the sampling period of the measurements. In the experiments to be performed in here, the measurements are taken with the Continuous Glucose Monitoring System (CGMS), so the measurements are taken with the sampling period of the monitor, and its number increases with the experiment. The problem is then about how long the experiment should last. Usually, identifiability of the model increases as the samples do, so the boundary of the experiment time is not of identifiability issues but of the patient's comfort. It was decided that the time of the experiment was to be fixed at five hours after a meal.

The inputs of a complete glucoregulatory model are two, the meals and the insulin infusion (supposing insulin pump treatment). The complexity of

the meal absorption and the absence of satisfactory models has historically made meals to be considered as a disturbance, but in this work it is treated as an input to be designed. Insulin is considered as an input as well. Both inputs can be parameterized as:

- Parameterization of the meal.
    1. Meal size
    2. Meal composition
- Parameterization of the insulin.
    1. Insulin bolus size
    2. Insulin bolus time (relative to meal time)
    3. Basal infusion rate

In order to parametrize the meals that patients have to eat there are two variations that can be done. One is the size of the meal, and the other is the composition. In the digestive model being analyzed in here, the Dalla Man model, the set of parameters published were identified under specific conditions listed below:

- Caloric input: 10 kcal/kg
- Carbohydrate: 45%
- Protein: 15%
- Fat: 40%
- Glucose: 90±5 g

The grams of glucose represent the size of the meal. The rest of the parameters are supposed to determine the gastric emptying profile, and

the identification performed in [20] transform the composition of the meal in the parameter values shown in Table 2.18. Unfortunately, no further identifications have been performed on this model. Therefore, if one looks for better identifiability of the model, the experiments should be performed with similar composition as shown. The size of the meal is going to be one of the parameters for the experiment design.

Considering the insulin input, it is much more complex than the meal ingestion, which is only considered as an impulse. The insulin pump treatment can have any shape imaginable respecting the pump limitations. Designing an absolutely free insulin profile, i.e. a non-parametric input, would be too expensive in computational terms (for more information see [99]), so a parametric input is chosen. The usual profile of basal-bolus infusion is preserved in this experiment design for simplification purposes and to increase the patient's compliance in the experiment design.

Once decided that a traditional treatment is going to be followed, the only parameters to be chosen are the amount of insulin to be given in the bolus, the basal insulin level, and the instant the bolus is administered. Basal variations during meal time were considered at first, but the importance of it in the postprandial response is negligible. The experiment conditions chosen to be optimized are, thus:

- τ - Delay of the insulin bolus with respect the meal time, in minutes. A positive delay means that the insulin dose will be given after the meal and vice versa. The boundaries for the optimization problem are set to -60 and 300 minutes. Maximum advancement of the insulin bolus is defined so as to prevent hypoglycemic events.

- Meal - The size of the meal in grams of carbohydrates. The boundaries for the optimization problem are 0 and 100 grams of carbohydrates.

- Bolus - The amount of bolus insulin units to be given. The boundaries for the optimization problem are 0 and 10 insulin units. These

boundaries were chosen using an insulin-to-carbohydrate ratio of 1:10 as population mean.

Only one meal per day is considered due to the circadian variation of insulin sensitivity. The vector Ξ is then a vector of size $3n_d$, where n_d is the number of days of monitoring. This vector is the output of the experiment design.

Given that the problem is highly non-linear (due to non-linearities of the index and the model) SSM global optimizer is used to obtain the solutions. The constraints for the optimization problem are the restrictions of the blood glucose in order to keep the patient under safe health conditions. The simulation was forced to start from equilibrium in a blood glucose level of 100 mg/dl. The maximum level of glucose (hyperglycemic bound) was set to 250 mg/dl and the minimum level (hypoglycemic bound) was set to 70 mg/dl. These boundaries have to be respected at all times during the experiment design.

Next, several results for experiment design in diabetes for different models are shown. Despite the fact that Bergman's model has been proven unreliable for simulating some glucose dynamics, it is desirable to try the experiment design varying the models used in order to make the experiments as less model-dependent as possible. That is why the first experiment design shown is calculated for this model. After that, two experiments designed for the modified Panunzi model are explained.

6.1 Bergman's model identifiability

Initially, Bergman's endogenous model has only three parameters to be identified, but two more are going to be added to the study, the distribution volume and the basal glucose. Bergman's endogenous model combined with Dalla Man's glucose absorption model and Willinska's insulin subcutaneous

model sums up a total of 17 parameters, described in Table 6.1.

Model	Number	Parameter	Meaning
Endogenous	1	p_1	Glucose efficiency
	2	p_2	Insulin action rate of disappearance
	3	p_3	Insulin action rate of appearance
	4	Vol_g	Distribution volume of glucose
	5	G_b	Basal glucose
Gastric	6	K_{abs}	Glucose absorption rate in the gut
	7	K_{max}	Maximum gastric emptying
	8	K_{min}	Minimum gastric emptying
	9	b	Involved in the gastric emptying
	10	d	Involved in the gastric emptying
Insulin	11	V_i	Distribution volume of insulin
	12	k	Proportion of insulin in the slow channel
	13	k_{a1}	Transfer rate in the slow channel
	14	k_{a2}	Transfer rate in the fast channel
	15	k_e	Insulin elimination
	16	$V_{MAX,LD}$	Michaelis-Menten parameter
	17	$k_{M,LD}$	Michaelis-Menten parameter

Table 6.1: Parameters to be identified in Bergman's model

Considering only blood glucose as the measurable output of the system, and a three days experiment as the identification period for the reasons explained before, all the parameters are not identifiable (as expected). Sensitivity analysis previous to the experiment design was performed, and the results are shown in Table 6.2.

As the results of the sensitivity analysis show, many of the parameters of the model are not identifiable. The parameters that are fixed in the initial iteration of the sensitivity analysis are parameters that present *a priori* non-identifiability, therefore, parameters that make the FIM non invertible. That is the reason for the absence of CVs of the rest of parameters, for those coefficients of variation are calculated from the inverse of the FIM.

Once the FIM was made invertible, only two more parameters had to be fixed to make the model identifiable. The final number of parameters

Number	Parameter			
1	p_1	-	-	-
2	p_2	-	-	-
3	p_3	-	-	-
4	Vol_g	0,25	0,14	0,13
5	G_b	0,12	0,08	0,07
6	K_{abs}	-	-	-
7	K_{max}	0,25	0,24	0,23
8	K_{min}	0,42	-	-
9	b	0,16	0,12	0,04
10	d	0,20	0,18	0,09
11	V_i	-	-	-
12	k	0,34	0,33	-
13	k_{a1}	0,31	0,22	0,09
14	k_{a2}	-	-	-
15	k_e	0,22	0,14	0,12
16	$V_{MAX,LD}$	-	-	-
17	$k_{M,LD}$	-	-	-

Table 6.2: Bergman's model parameter coefficient of variation (CV) for a three meals identification. Each column represents an iteration in the sensitivity analysis, and parameters that don't have CV are fixed due to non-identifiability

identifiable, out of the initial 17, is 7. Only two of those parameters are part of the endogenous model, while three of them characterize the gastrointestinal model, and the other two are part of the insulin model, as can be seen in Figure 6.1

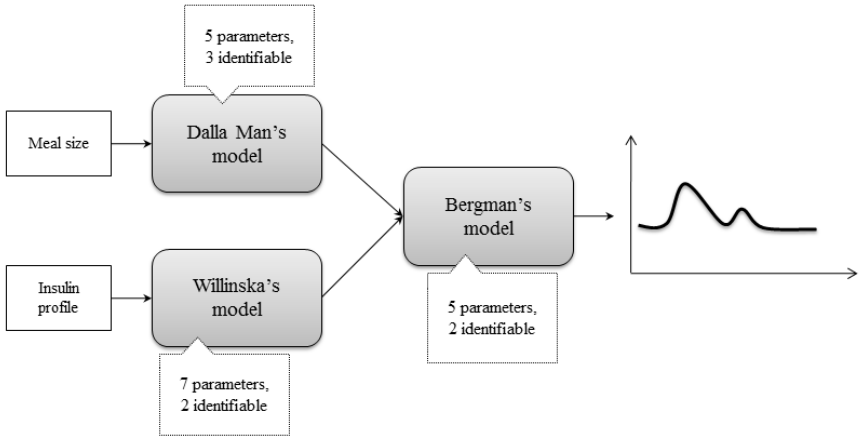

Figure 6.1: Total number of parameters identifiable in Bergman's model

Those 7 parameters are the ones used to calculate model's identifiability in the experiment, thus the only ones involved in the calculation of the cost index for optimal design.

6.2 Experiments designed with Bergman's model

Experiments with Bergman's model were designed considering only the set of parameters decided optimum by the sensitivity analysis, and for a range of experiment days from 1 to 4 days. At the end of the experiment design for all the models under study, the best option was chosen from within of all the experiments designed, including the different options of parameter sets, models, and length of the experiments.

The results of an experiment designed for only one day of monitoring consisting on the five following hours to a meal is shown in Table 6.3.

Experiment	Units	Day 1
τ	minutes	-31,59
Meal	gr CHO	100
Bolus	IU	10

Table 6.3: Experiment designed for Bergman's model considering one day of monitoring

As it can be seen, in the case of only being able of monitoring one day, the optimum experiment to be followed by the diabetic patient is to advance the bolus approximately half hour, and then eat 100 grams of carbohydrates. It is worth remembering that 100 grams of carbohydrates is the top value given to the optimizer for the experiment design. Also, 10 is the top boundary for the bolus variable in the optimization, and it is the corresponding value of insulin for an standard treatment of insulin boluses for a 100 grams of carbohydrates meal. This means that, in addition to maximizing identifiability of the model, the experiment design keeps the patient under good glycaemic control.

The Bergman's model response for the experiment described can be seen in Figure 6.2.

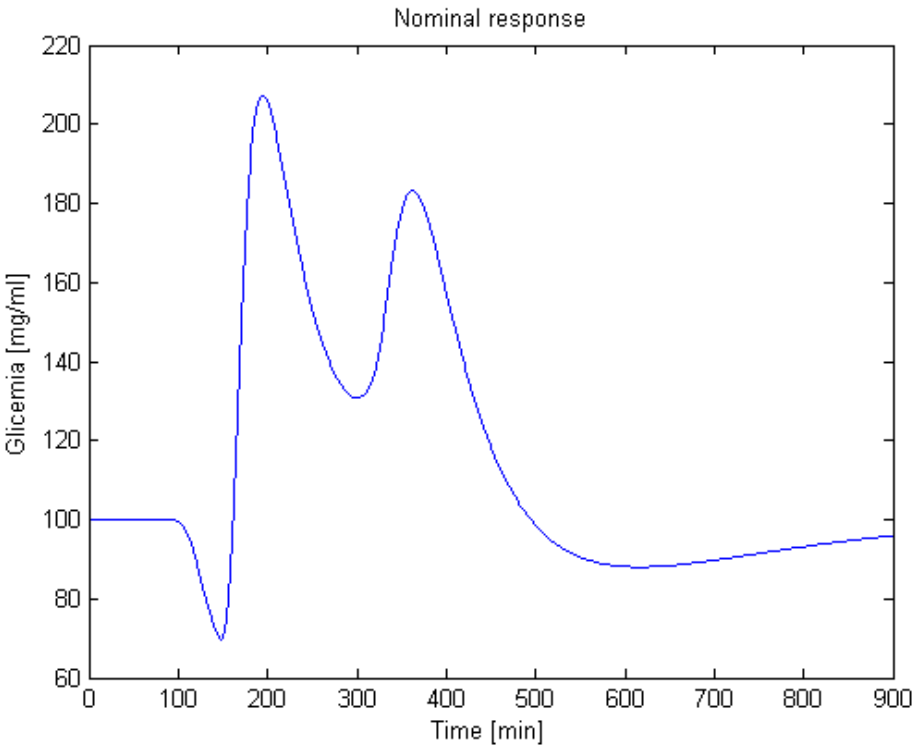

Figure 6.2: Bergman's model response to the proposed experiment for 1 day

The model's response shows a very quick response of the blood glucose to the advanced insulin bolus, falling quickly to a level of approximately 70 mg/dl. This level is the safety threshold indicated to the optimizer to keep the patient under safe conditions. That means that the optimizer is moving the signal utilized for identification to the limits, and then rising it up to the highest level it can, but always keeping the (virtual) person in safe levels.

The results of the experiment designed for two days monitoring are shown in Table 6.4.

Experiment	Units	Day 1	Day 2
τ	minutes	25,23	-29,58
Meal	gr CHO	86,81	100
Bolus	IU	10	10

Table 6.4: Experiment designed for Bergman's model considering two days of monitoring

In this new experiment two different therapies are applied to the patient. The second day is the same case as in a single day experiment. In the first day of identification, a bolus of 10 insulin units is delayed approximately 25 minutes, for a meal of 86.81 grams of carbohydrates. Now the proportion of insulin units to grams of carbohydrates is not maintained. Now the proportion of insulin units to grams of carbohydrates is not maintained, and thus, not a good glycaemic control os performed on the patient (including the effect of the delay).

The model response for the designed two days experiment is shown in Figure 6.3.

Observing the first day response of the model to the proposed experiment, the fact of non-proportionality of insulin to carbohydrates makes more sense. The model moves from 250 mg/dl down to 70 mg/dl, which are the top and bottom thresholds in the experiment design. The optimizer is trying to move the identification variable (blood glucose) in all the range that is possible, so

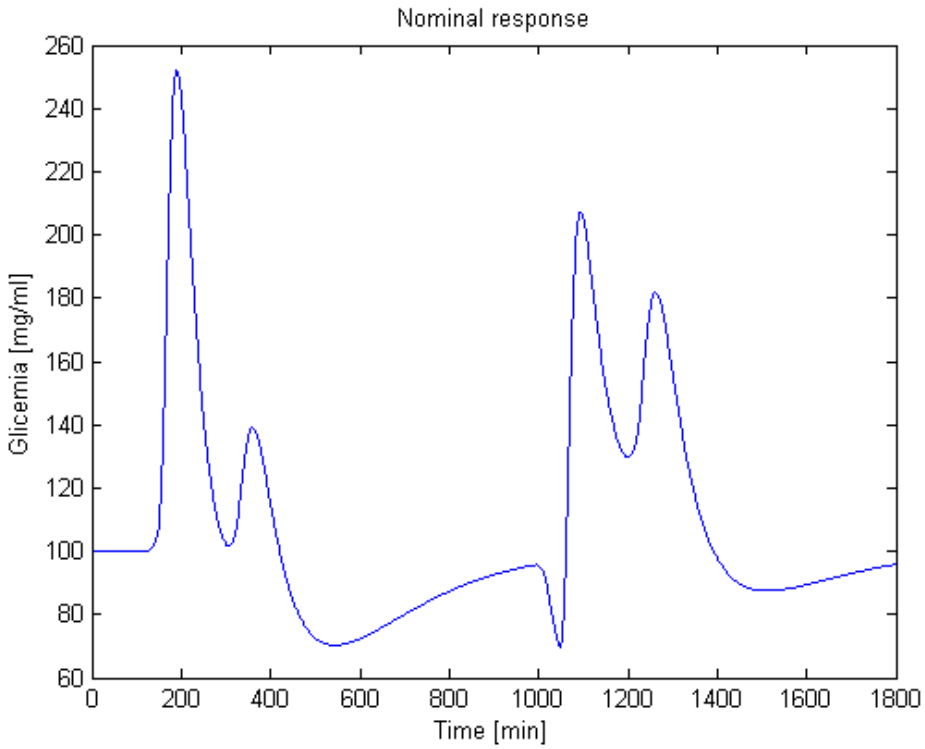

Figure 6.3: Bergman's model response to the proposed experiment for 2 days

to maximize identifiability. Given that in the first day, due to the delay of the insulin bolus, there is no falling of the blood glucose to the lowest level, it has to drop to that level after the meal, that is why the insulin bolus is still relatively big with respect to the size of the meal. Given those values, the maximum amount of carbohydrates for that meal is 86.81.

It is interesting to understand why the two days differ in the time in which the bolus is administered. In the first day, no insulin variation is given for approximately 30 minutes, and so, all the information extracted from that period is only increasing identifiability for the other input model, the Dalla Man model. In the other day, the opposite situation is happening. Only the insulin subcutaneous model is experimenting variations, so information is being created for the parameters of that model. The strongest the variation of the states of the model in that period, the greater the identifiability will be.

The experiment designed for the case of a three days monitoring is shown in Table 6.5.

Experiment	Units	Day 1	Day 2	Day 3
τ	minutes	26,43	-30,44	-30,71
Meal	gr CHO	85,60	100	100
Bolus	IU	10	10	10

Table 6.5: Experiment designed for Bergman's model considering three days of monitoring

In this case, the advancing of the bolus is repeated two days. Given that the meals does not have to be consecutive, or that one day does not have any relation to the others, the order of the experiment days is not important for the result of the experiment.

Model's response to the experiment proposed is shown in Figure 6.4.

The second and third days are virtually the same, and the first one is again

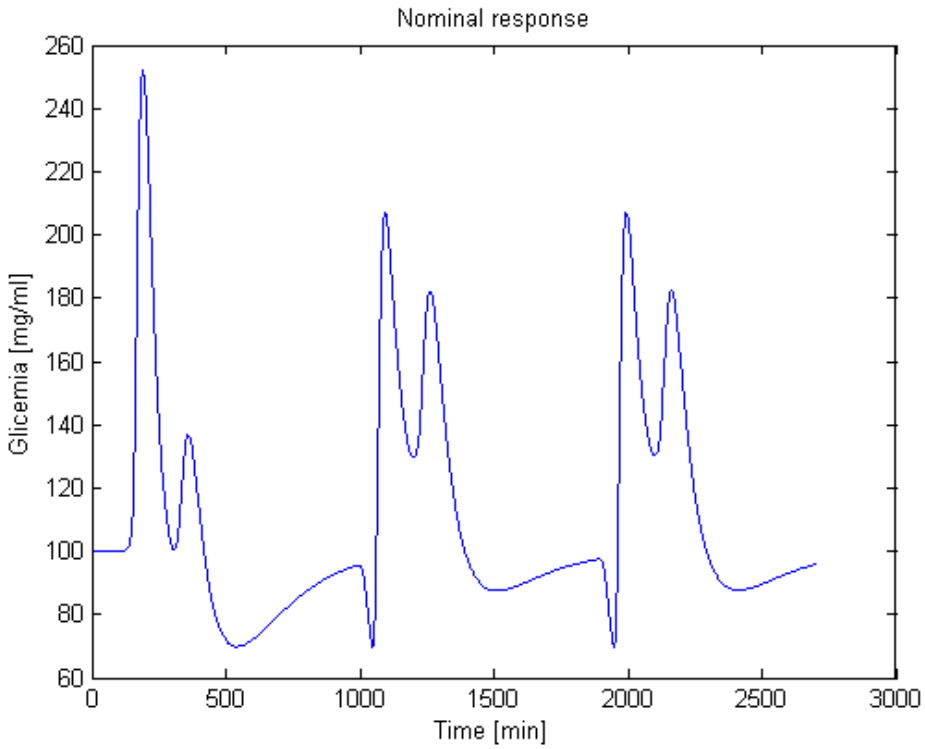

Figure 6.4: Bergman's model response to the proposed experiment for 3 days

rising and falling to both boundaries. It is again clearly seen the separation of dynamics.

The four days experiment results are shown in Table 6.6.

Experiment	Units	Day 1	Day 2	Day 3	Day 4
τ	minutes	25,44	14,36	-29,92	-30,88
Meal	gr CHO	86,81	99,64	100	100
Bolus	IU	10	10	10	10

Table 6.6: Experiment designed for Bergman's model considering four days of monitoring

In this case the last days are repeated again with the advance of the insulin bolus, and a new delayed bolus profile appears, but in this case with a big meal. The delay on the bolus is smaller so that the meal can be bigger, improving this way the identifiability of the Dalla Man model.

The response of the model for the four days experiment is shown in Figure 6.5.

As it can be observed, there is not much difference in the first two days of identification because the difference in the meal size is relatively small.

The most relevant observation of this experiment design with the Bergman model is that separating dynamics is the key to improve the identification. It is better for model's general identifiability to advance the bolus rather than having it delayed, but the best situation is to have both situations in an experiment of 2 days minimum.

The number of days of the experiment has to be selected paying attention to both identifiability and conditions of the experiment. It has been stated that a minimum of two days for monitoring seems reasonable for identification purposes due to the two different profiles of experiment. In Figure 6.6 and 6.7 evolution of identifiability of each parameter of Bergman's model can be observed for all the cases exposed.

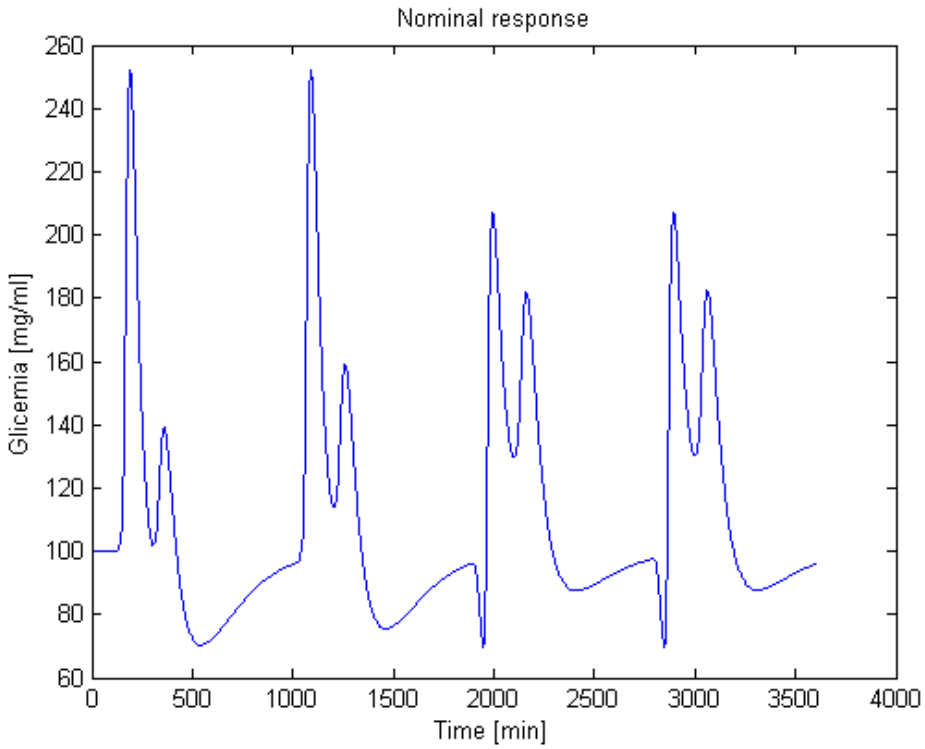

Figure 6.5: Bergman's model response to the proposed experiment for 4 days

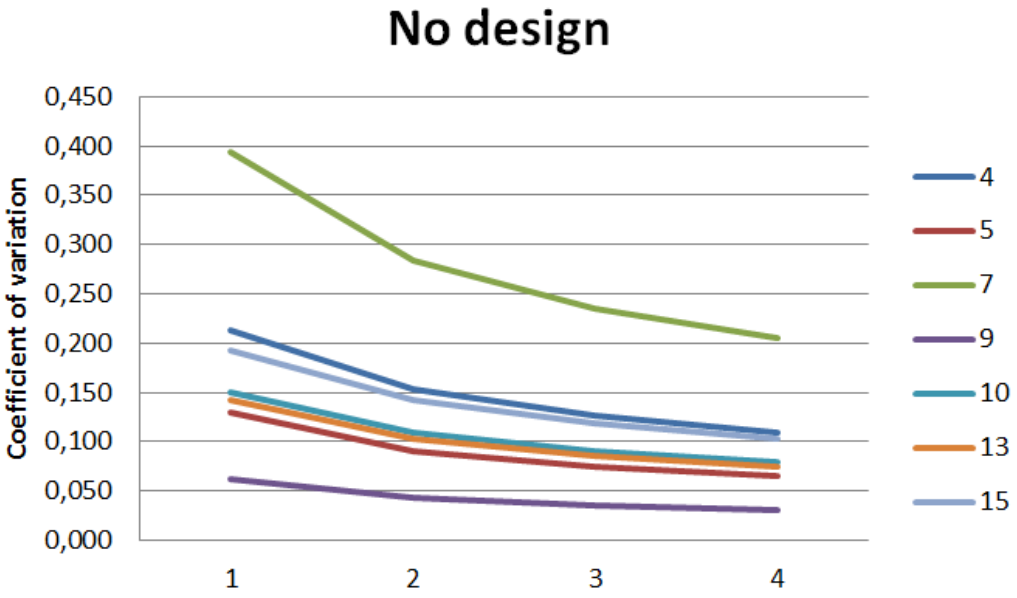

Figure 6.6: Bergman's identification parameters and its coefficients of variation as they get smaller with the number of monitoring days

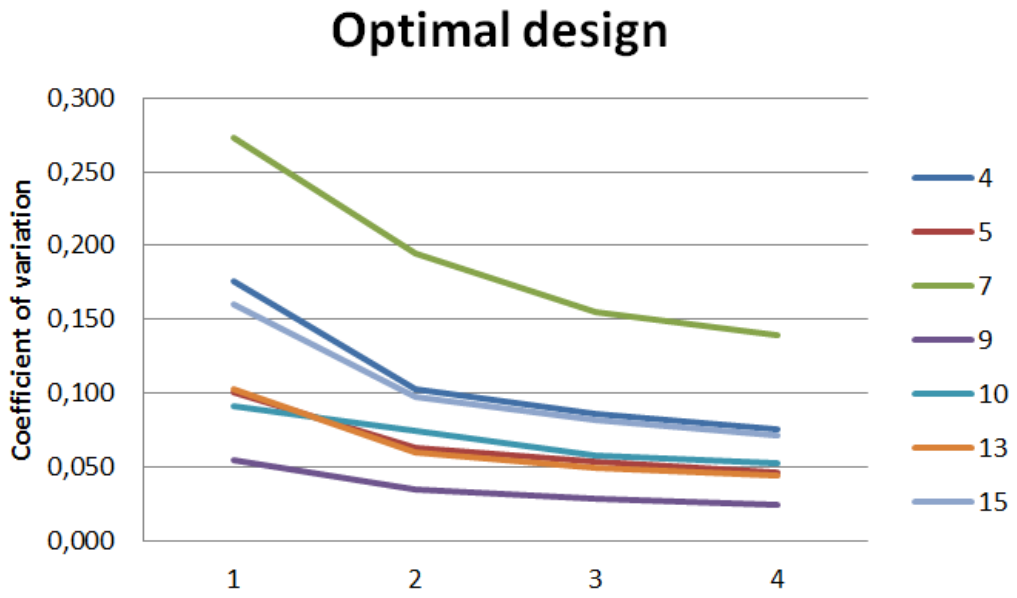

Figure 6.7: coefficients of variation of Bergman's parameters for the experiments designed as they get smaller with the number of monitoring days

It can be clearly seen that a sudden falling of the coefficient of variation happens when the monitoring days increases from one to two. After that, identifiability of all the parameters keeps increasing, but more slowly. Similar tendencies are observed for the identifiabilities of the parameters in the case of applying the experiment design, but the levels of the coefficients of variation of the same parameters are much lower. The comparison of coefficients of variation before and after optimal design is shown in Figure 6.8.

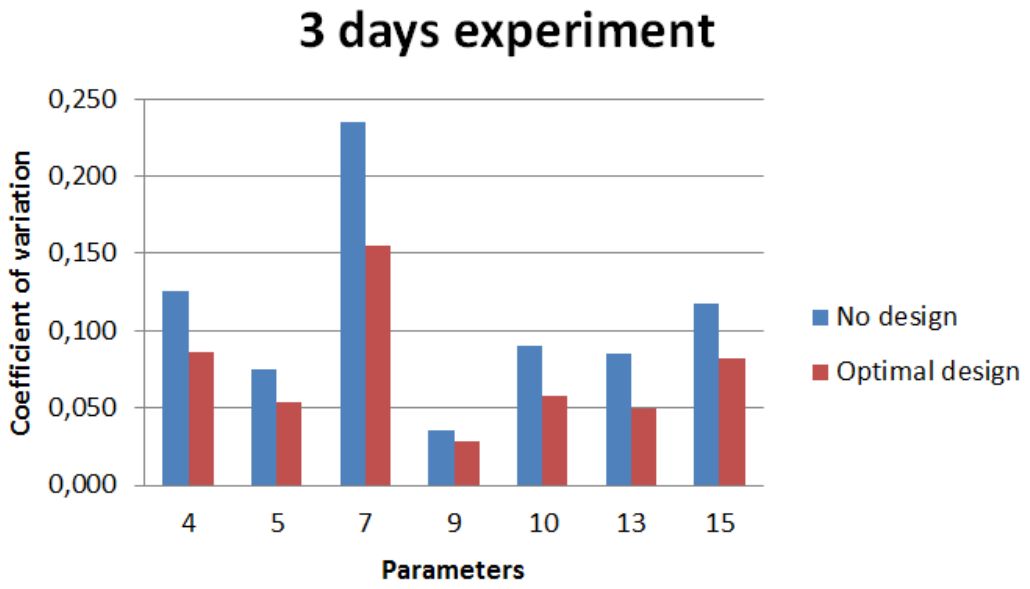

Figure 6.8: A comparison of identifiability for each parameter with and without the experiment design for the case of a three meals monitoring

A remarkable fall in the coefficient of variation is observed for all the parameters, although to a different extent.

A three-day experiment was chosen thinking on clinical implementation of the experiment design. It is desired to have as many identification days as validation days, which makes the real monitoring period twice as long as the experiment designed. Given that the average life period of a continuous glucose monitor is around one week, the three days experiment was chosen (in this case) as monitoring duration, for maximizing the identifiability. Results have to be compared with other models experiment design to make the

experiments as less model-dependent as possible.

6.3 Modified Panunzi's model identifiability

The modified version of Panunzi's endogenous model described in Section 4.3 is going to be tested, starting with its identifiability. In this case the parameters of the model to be identified are 16, including the 4 corresponding to the endogenous model. The 16 parameters are described in Table 6.7.

Model	Number	Parameter	Meaning
Endogenous	1	K_{xgl}	Insulin sensitivity
	2	V_g	Distribution volume of glucose
	3	T_{gh}	Hepatic balance
	4	k_i	Insulin action delay
Gastric	5	K_{abs}	Glucose absorption rate in the gut
	6	K_{max}	Maximum gastric emptying rate
	7	K_{min}	Minimum gastric emptying rate
	8	b	Involved in the gastric emptying
	9	c	Involved in the gastric emptying
Insulin	10	V_i	Distribution volume of insulin
	11	k	Proportion of insulin in the slow channel
	12	k_{a1}	Transfer rate in the slow channel
	13	k_{a2}	Transfer rate in the fast channel
	14	k_e	Insulin elimination
	15	$V_{MAX,LD}$	Michaelis-Menten parameter
	16	$k_{M,LD}$	Michaelis-Menten parameter

Table 6.7: Parameters to be identified in Modified Panunzi's model

Many of the parameters involved in the sensitivity analysis for Bergman's endogenous model, in particular those of the insulin and intestinal submodels, are repeated in this model, but the numeration is different due to the different number of parameters in the endogenous model. The results of the identifiability study are shown in Table 6.8.

Number	Parameter						
1	K_{xgl}	2,95	1,14	0,98	0,55	0,53	0,31
2	V_g	0,70	0,46	0,43	0,26	0,24	0,23
3	T_{gh}	0,55	0,51	0,18	0,18	0,18	0,06
4	k_i	4,93	4,91	-	-	-	-
5	K_{abs}	2,00	1,60	1,12	0,67	-	-
6	K_{max}	0,95	0,78	0,66	0,53	0,24	0,24
7	K_{min}	1,27	0,87	0,68	0,33	0,33	0,30
8	b	0,43	0,41	0,20	0,18	0,17	0,13
9	c	0,87	0,66	0,51	0,34	0,20	0,18
10	V	6,47	-	-	-	-	-
11	k	1,16	0,91	0,81	0,36	0,29	0,27
12	k_{a1}	0,74	0,45	0,43	0,26	0,25	0,20
13	k_{a2}	6,17	3,77	2,57	-	-	-
14	k_e	3,36	0,88	0,71	0,49	0,49	0,30
15	$V_{MAX,LD}$	1,96	1,92	0,92	0,66	0,62	-
16	$k_{M,LD}$	-	-	-	-	-	-

Table 6.8: Modified Panunzi's model parameter coefficients of variation (CV) for a three meals identification

In this case, only two parameters were not identifiable because of FIM singularity, parameters 10 and 16 which have their respective rows in the previously mentioned table in blank. Parameter 16 is discarded because its low sensitivity, and parameter 10 is fixed to its nominal value due to a very strong correlation (actually, it has a proportional relation) to parameter 1.

Even though the threshold for identifiability was fixed at 30% of variation, the set of 10 parameters on the last column of Table 6.8 is considered the optimum set of parameters for the modified Panunzi's model proposed. There are three parameters that are in the limit of the proposed identifiability: K_{xgl}, K_{min} and k_e. Of those three, the most critical one (greater variation), which is the insulin sensitivity K_{xgl} is very important to be identified since it is a physiological parameter that suffers huge variations between patients, and it is key in patient's treatment. The other two parameters are in the limit of their own identifiability, so it was decided to treat them as identifiable parameters. The summary of identifiable parameters is explained in Figure

6.9.

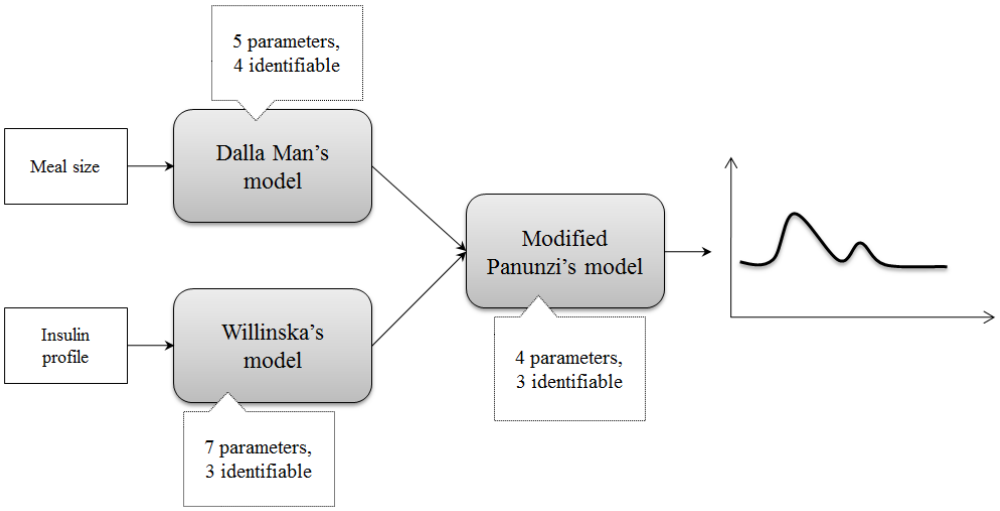

Figure 6.9: Total number of parameters to be identified in the modified Panunzi's model

These 10 parameters will be used in the experiment design for the calculation of the index of total identifiability of the model.

6.4 Experiments designed with modified Panunzi's model

Two different sets of parameters are considered in the experiment design of this model. The first set of parameters is the one concluded as optimum for the model's identifiability, as shown in the previous section. In that set the parameter K_{abs}, key for the intestinal absorption characterization, was not included. The other set of parameters includes the parameter K_{abs} in the identification, which is the constant rate of absorption of glucose from the gut to the blood. This parameter has a great physiological importance in the understanding of how different meals can be absorbed by the gastrointestinal tract, and it is supposed to be related to the composition of the meal. Due

to its importance, it is decided that K_{abs} is forced to be identified, creating a new set of parameters called *suboptimal* set of parameters, as shown in Figure 6.10.

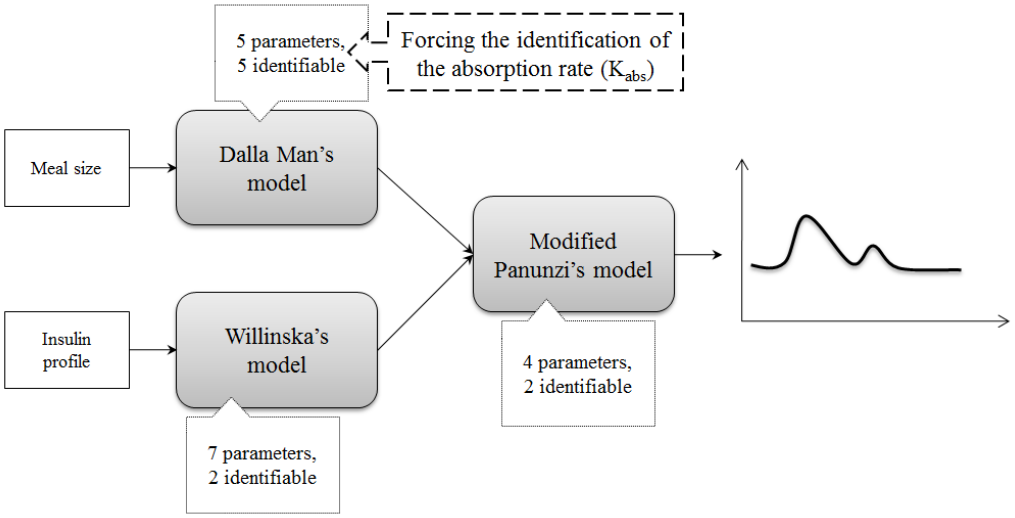

Figure 6.10: *Suboptimal* set of parameters to be identified in the modified Panunzi's model

Two parameters are not being considered in the suboptimal set that were being identified for the optimal set, those are V_g and k_e. These parameters and their identifiabilities before the design are shown in Table 6.9.

Number	Parameter	CV
1	K_{xgl}	0,028
3	T_{gh}	0,048
5	K_{abs}	0,580
6	K_{max}	0,496
7	K_{min}	0,227
8	b	0,135
9	c	0,263
11	k	0,290
12	k_{a1}	0,199

Table 6.9: Panunzi's model suboptimal parameters coefficients of variation (CV) for a three meals identification

Anyway, the first set of parameters that is going to be considered for the

experiment design is the optimal one, described in Section 6.3. The results for the experiment designed for one day is show in Table 6.10.

Experiment	Units	Day 1
τ	minutes	-17,959
Meal	IU	10
Bolus	gr CHO	100

Table 6.10: Experiment designed for Panunzi's model considering one day of monitoring and the optimal set of parameters

The same profile as in the Bergman's model experiment design is observed in this case. The advance in the insulin bolus is a little smaller, but the meal and bolus size is again maximum. The response of the new model to the experiment designed is shown in Figure 6.11.

Comparing modified Panunzi's model response in a single day experiment with the Bergman's model response, the glucose profile is virtually identical. That somehow, proves the independence of the results of the experiment design from the model used to calculate them. Of course the parameters being identified are not the same in one or other model, but the signal from where information is being extracted is the same, and thinking about that signal from an theoretical point of view, an optimal signal in terms of information for one model, must contain big amounts of information for any other model too. That is why it is expected of optimal experiment results to be similar for the new model to the results for the other experiments already designed.

The experiment design results for a two days experiment can be seen in Table 6.11.

The second day in this experiment is the same as the single day experiment, in which the bolus is administered in advance to the meal time, thus only the insulin system is being identified in that case. In the first day, a new situation is proposed, similar to the case of Bergman's design in which

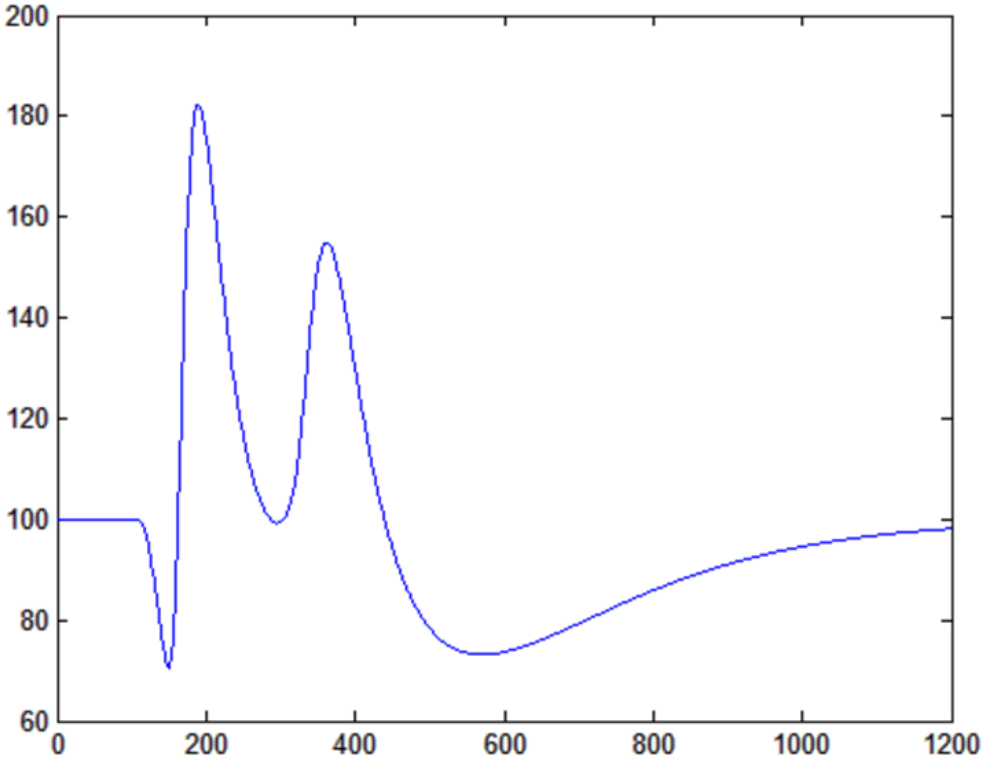

Figure 6.11: Modified Panunzi's model response to the proposed experiment, with its optimal set of parameters, for 1 day

Experiment	Units	Day 1	Day 2
τ	minutes	157,80	-17,92
Meal	gr CHO	44,25	100
Bolus	IU	3,07	9,99

Table 6.11: Experiment designed for modified Panunzi's model considering two days of monitoring and the optimal set of parameters

the bolus was delayed, but in this case, the delay is much bigger. However, delaying the insulin bolus up to two hours and a half can be quite dangerous for the patient because of risks of hyperglycemia.

In Figure 6.12 the response of the model to the experiment proposed can be observed.

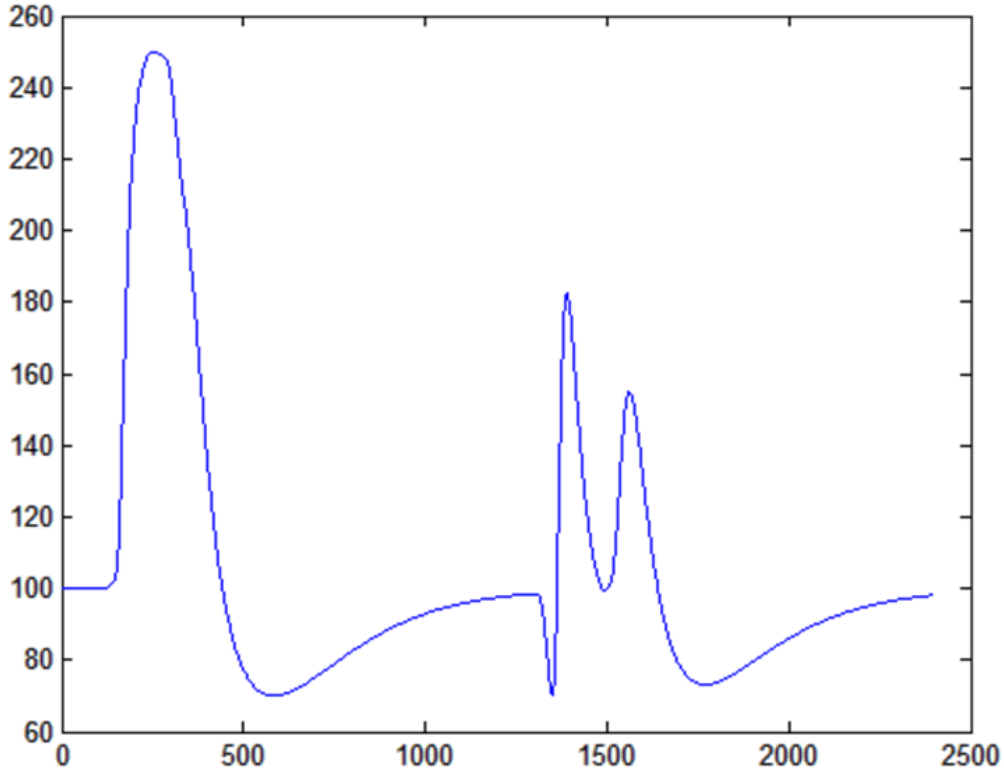

Figure 6.12: Modified Panunzi's model response to the proposed experiment, with its optimal set of parameters, for 2 days

In the case of the first day can be observed that the small amount of carbohydrates given to the patient (44,25 grams) have the objective of rising the blood glucose up to the superior limit of safety of the patient. The insulin bolus is given when the blood glucose gets to the maximum established, and the amount of insulin given is so that will make the blood glucose to fall to the inferior limit of safety. Again, the experiment design is moving the signal used for identification from one boundary to the other, in order to maximize

the amount of information.

Bergman's model was probably not able rise so fast up to the limit of hyperglycemia due to the so called term of glucose efficiency (as explained in Section 4.3) that makes glucose to fall automatically when it rises above the stability point.

The results of the three days experiment can be seen in Table 6.12.

Experiment	Units	Day 1	Day 2	Day 3
τ	minutes	-17,83	-18,42	165,74
Meal	gr CHO	100	100	44,38
Bolus	IU	10	10	3,01

Table 6.12: Experiment designed for modified Panunzi's model considering three days of monitoring and the optimal set of parameters

In this case the advanced bolus administration is given in two out of the three days of the experiment, while the other day a small meal is given, with the insulin bolus delayed 2,5 hours, just like in the two days experiment.

The response of the model is shown in Figure 6.13.

This is a very good example of how the different experiments designed for each independent day are not dependent on the order of those days. Sometimes the case of the small meal and delayed bolus is in the first day, some others at the end, and it can also be in the middle of the 3 days.

The final case of the experiment design with 4 days and the optimal set of parameters, is shown in Table 6.13.

The last day is a little bit different than the previous ones, but it hardly defines a new type of therapy for a day of identification. It is a variation of the profile with a small meal and delayed insulin bolus, only that the delay is smaller so that the insulin bolus has not only a role of correction of the level of blood glucose, but also tries to counteract the rise of blood glucose that

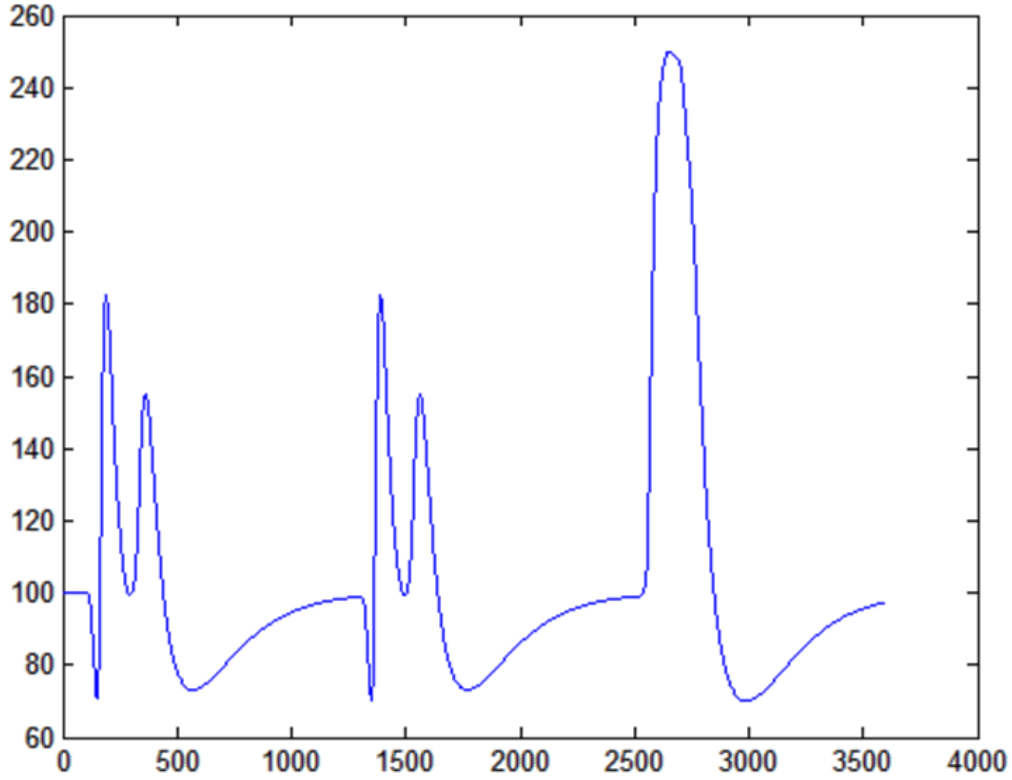

Figure 6.13: Modified Panunzi's model response to the proposed experiment, with its optimal set of parameters, for 3 days

Experiment	Units	Day 1	Day 2	Day 3	Day 4
τ	minutes	167,06	-17,22	-18,41	86,19
Meal	gr CHO	44,25	100	100	47,07
Bolus	IU	3	10	10	4,13

Table 6.13: Experiment designed for modified Panunzi's model considering four days of monitoring and the optimal set of parameters

is still coming from the gut. That is observed in Figure 6.14, where the time of administration of the bolus does not wait for the blood glucose to stop rising and get stabilized, and instead, it forces it down before the absorption is over.

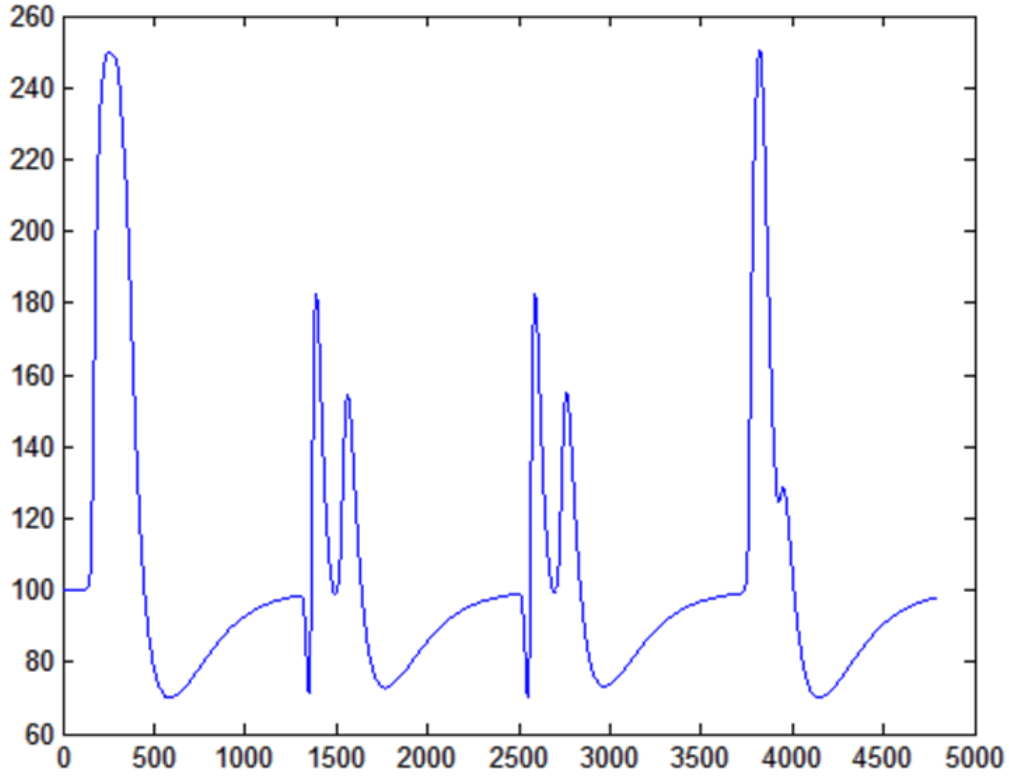

Figure 6.14: Modified Panunzi's model response to the proposed experiment, with its optimal set of parameters, for 4 days

As a summary, with the optimal set of parameters of the modified Panunzi's model, two different profiles of glucose are determinant for the good identification of the model.

- The first therapy has already been seen in Bergman's model experiment design, and it consists of an advance of the bolus of insulin to the meal time, improving this way the identifiability of the insulin subsystem.
- The second therapy is a big delay (2-3 hours) in the administration of

the bolus, while giving a small amount of carbohydrates (40-50 grams) to avoid excessive hyperglycemia. In this way, separation of insulin and glucose dynamic from the meal is obtained, while maintaining plasma glucose in a safe range.

In Figures 6.15 and 6.16 the evolution with the number of days of the parameters identifiability is shown for the optimal set of parameters.

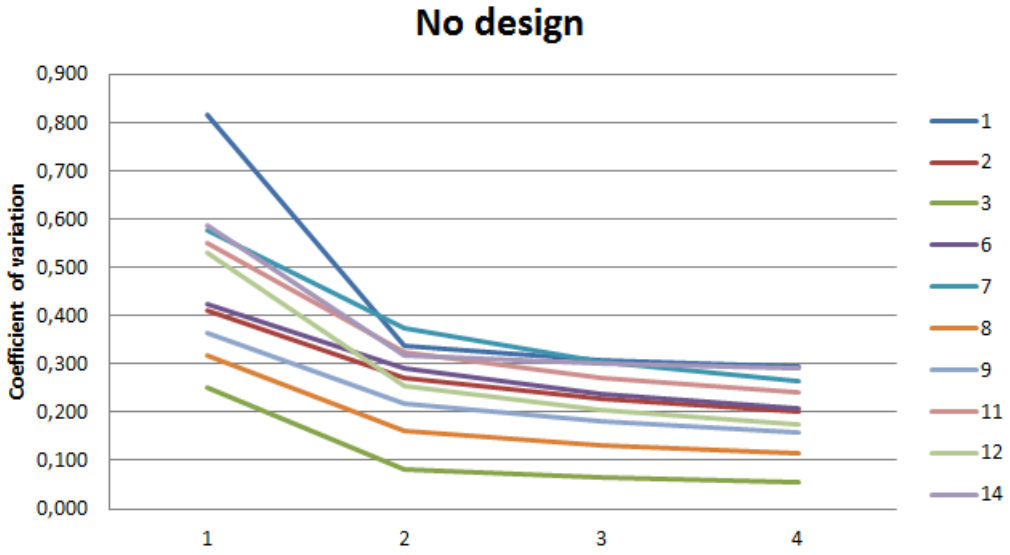

Figure 6.15: Modified Panunzi's optimal set of parameters and their coefficients of variation as they get smaller with the number of monitoring days

The graphs are very similar to those seen in the analysis of Bergman's model. The influence of the number of days, especially when it goes from one to two is very important, and no negligible, both in the case of experiment and no experiment design.

The influence of the experiment design in the identifiability of the model can clearly be seen in Figure 6.17, where it is shown that experiment design improves identifiability dramatically. In this case, it can be observed that identifiability of almost all the parameters rises enormously, getting their

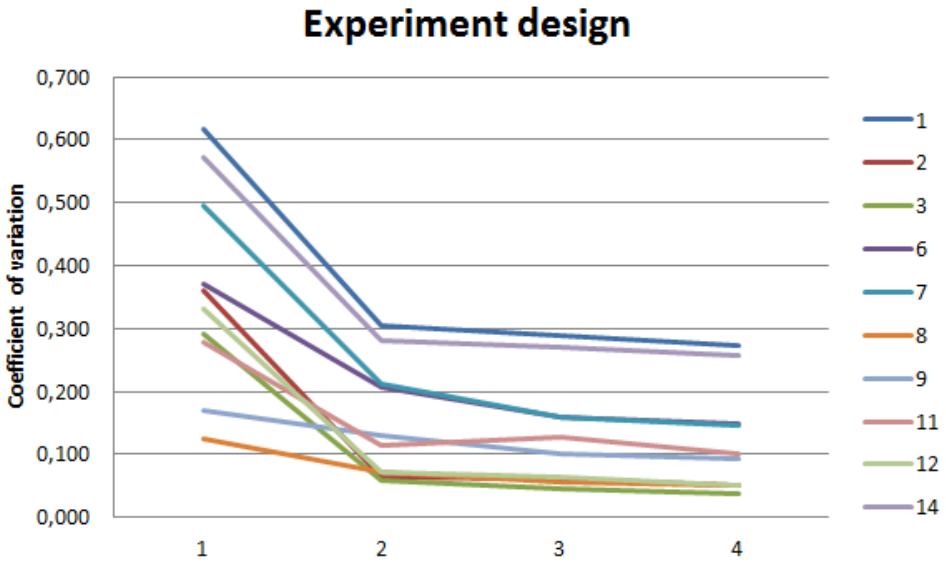

Figure 6.16: coefficients of variation of modified Panunzi's optimal parameters for the experiments designed as they get smaller with the number of monitoring days

coefficients of variation divided by two or three. Special cases are the parameters 1 and 14, whose identifiability rises to a smaller extent. This strange behavior might be explained by the strong correlation between these two parameters since both of them are very related to the plasma insulin and its influence in blood glucose (parameter 1,K_{xgl}, is the insulin sensitivity and parameter 14, k_e, is the plasma insulin elimination).

These results have yet to be compared to the experiment design results with the suboptimal set of parameters of modified Panunzi's model. For this new set of parameters, another experiment design was performed. This set of parameters was the one that was going to be identified in ambulatory conditions, because it was physiologically interesting for the reasons stated before. It is expected that the results are not radically different to anything already seen, and this experiment design is going to be considered as a whole new design as it was a completely new model.

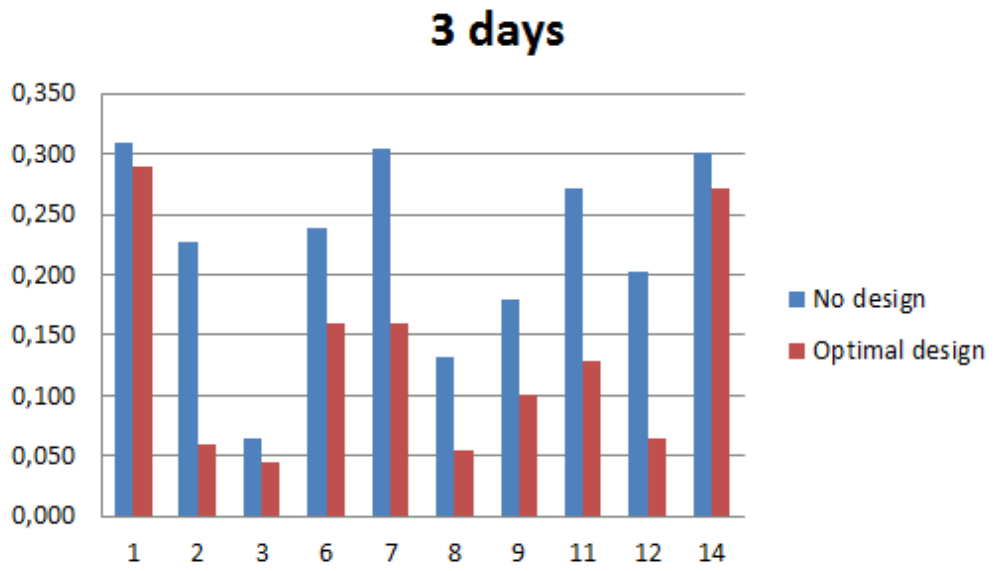

Figure 6.17: Identifiability of the optimal set of parameters of modified Panunzi's model before and after the experiment design for the case of a three meals monitoring

The results of the experiment design for the case of a single day of monitoring are shown in Table 6.14.

Experiment	Units	Day 1
τ	minutes	-18,41
Meal	gr CHO	100
Bolus	IU	10

Table 6.14: Experiment designed for modified Panunzi's model considering one day of monitoring and the suboptimal set of parameters

It shows again the administration of the bolus in advance to the meal time. This sort of therapy seems to be the most efficient way to extract information for the model, regardless the model being identified.

The response of the model to that therapy is show in Figure 6.18, which is actually exactly the same figure as the model's result with the

optimal parameters' set. The same model and the same input must give the same output. The small differences that can be found are related to small differences on the convergence of the optimizer, that are translated to small differences in the input of the model.

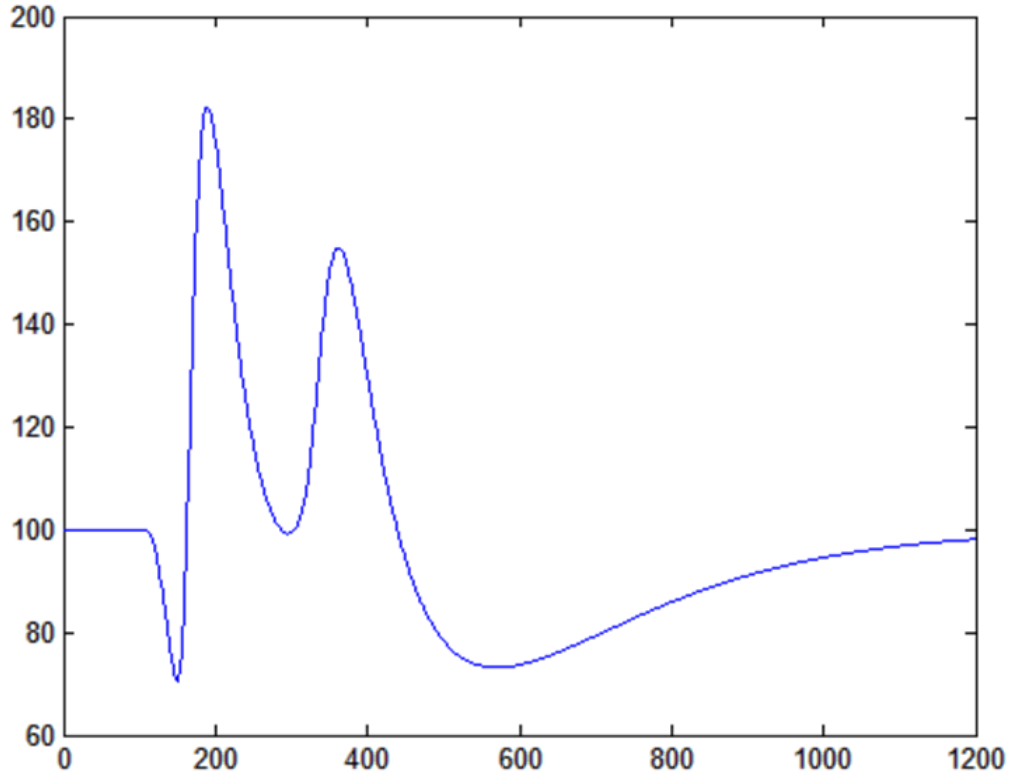

Figure 6.18: Modified Panunzi's model response to the proposed experiment, with the suboptimal set of parameters, for 1 day

The results for the two days experiment are shown in Table 6.15.

A new type of experiment is designed in the first day. There is the delay again in the insulin dose, but now the meal is as big as it gets, and the insulin is not exactly proportional to the meal size. This can be a problem, because the insulin control may not be accurate.

The model response can be seen in Figure 6.19.

Experiment	Units	Day 1	Day 2
τ	minutes	19,49	-17,50
Meal	gr CHO	100	100
Bolus	IU	8,16	10

Table 6.15: Experiment designed for modified Panunzi's model considering two days of monitoring and the suboptimal set of parameters

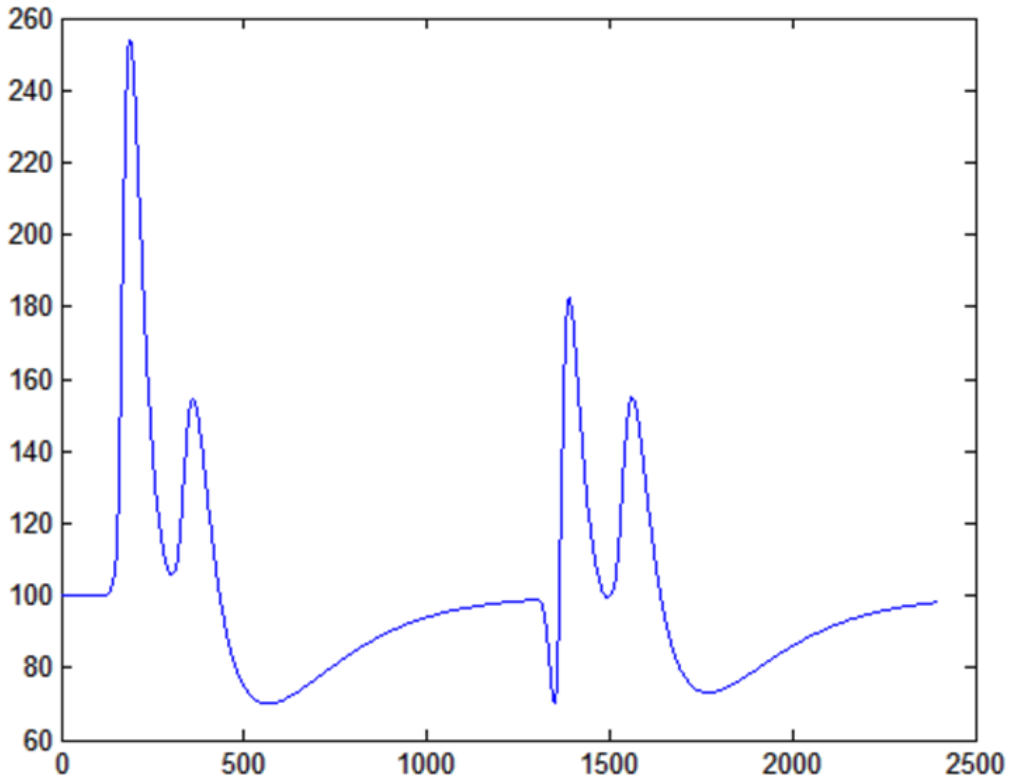

Figure 6.19: Modified Panunzi's model response to the proposed experiment, with the suboptimal set of parameters, for 2 days

It can be observed in the first day of simulation how the delay in the insulin administration and the big size of the meal make the blood glucose to rise up to the limit of safety, and then drop down to the lower limit. Probably, a bigger insulin dose would lead to hypoglycemia, and lower meal sizes will not make the Dalla Man model's identifiability large enough. It is worth remembering that the whole gastrointestinal model is being identified in this case.

The experiment results for a three days experiment are shown in Table 6.16, and the model's results are drawn in Figure 6.20.

Experiment	Units	Day 1	Day 2	Day 3
τ	minutes	-18,26	18,77	-17,96
Meal	gr CHO	99,62	99,56	99,18
Bolus	IU	9,98	8,10	9,91

Table 6.16: Experiment designed for modified Panunzi's model considering three days of monitoring and the suboptimal set of parameters

Again, the advance of the insulin bolus is repeated, as it is the most efficient way of getting information from the signal. The day in the middle is the delayed insulin profile as described in the previous experiment. It can be observed again that the order of the days does not matter, and having the delayed insulin therapy in the first, the second, or the third day, will have the same result.

The last experiment designed, the one for four days of monitoring, is shown in Table 6.17, and the simulation is in Figure 6.21.

Experiment	Units	Day 1	Day 2	Day 3	Day 4
τ	minutes	19,42	-17,77	-17,54	-17,69
Meal	gr CHO	100	100	100	100
Bolus	IU	8,16	10	10	10

Table 6.17: Experiment designed for modified Panunzi's model considering four days of monitoring and the suboptimal set of parameters

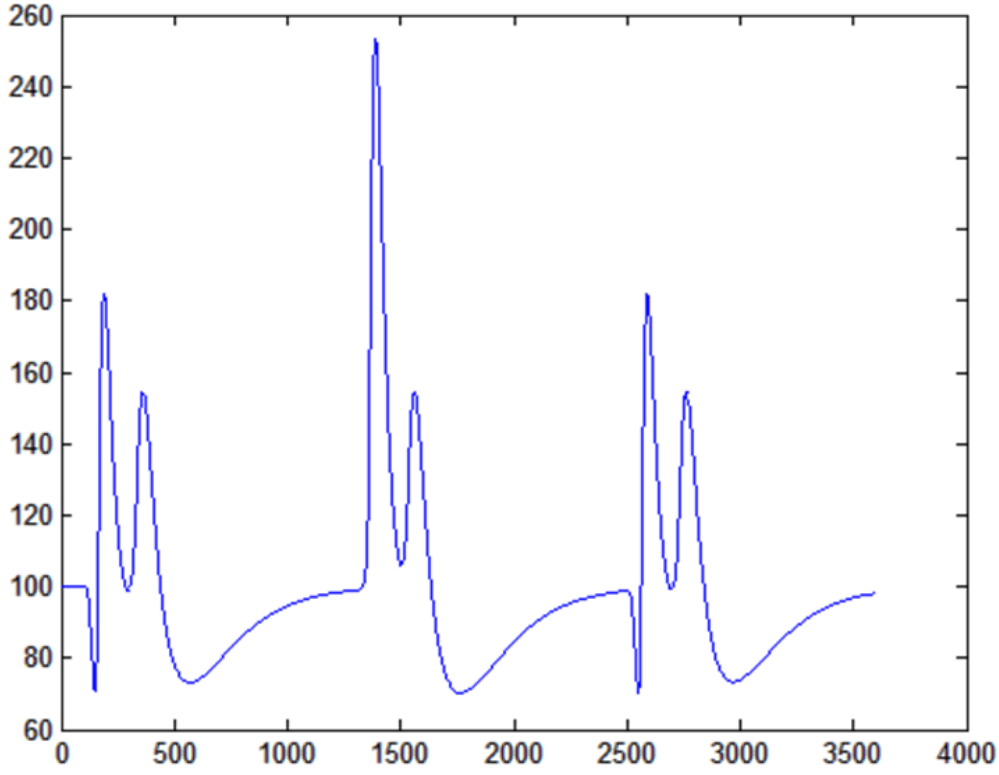

Figure 6.20: Modified Panunzi's model response to the proposed experiment, with the suboptimal set of parameters, for 3 days

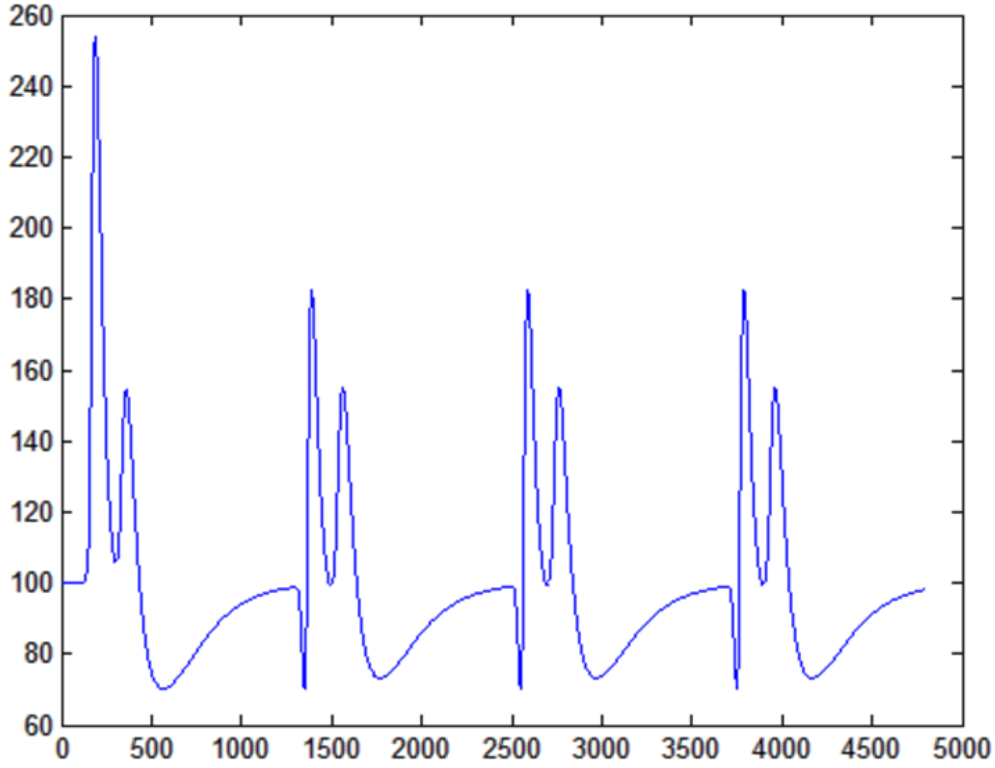

Figure 6.21: Modified Panunzi's model response to the proposed experiment, with the suboptimal set of parameters, for 4 days

In this last experiment, the administration of the insulin dose is advanced three times, while the delay is applied only once. Given that with this set of parameters, Dalla Man's model is being completely identified, and that it is assumed that the delays on insulin bolus are associated with the better identifiability of the gastrointestinal system, on can only assume that the importance of identifiability of Dalla Man's model to the total identifiability of the model gets to a relative minimum with only one day of insulin delayed.

As a summary, the identifiability of the models, increase with longer periods of monitoring (Figures 6.22 and 6.23), regardless of the experiment design.

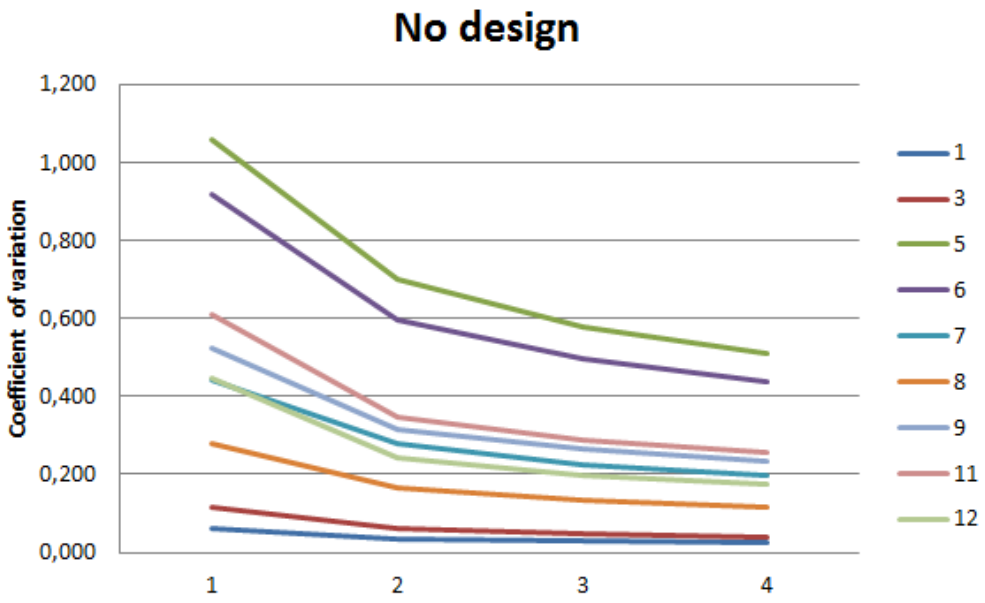

Figure 6.22: Modified Panunzi's suboptimal parameters and their coefficients of variation as they get smaller with the number of monitoring days

The only difference (they look mostly the same) in this figures is the level in where the coefficients of variation move. The comparison between the cases of before and after the experiment design can be observed in Figure 6.24 for the 3 days case.

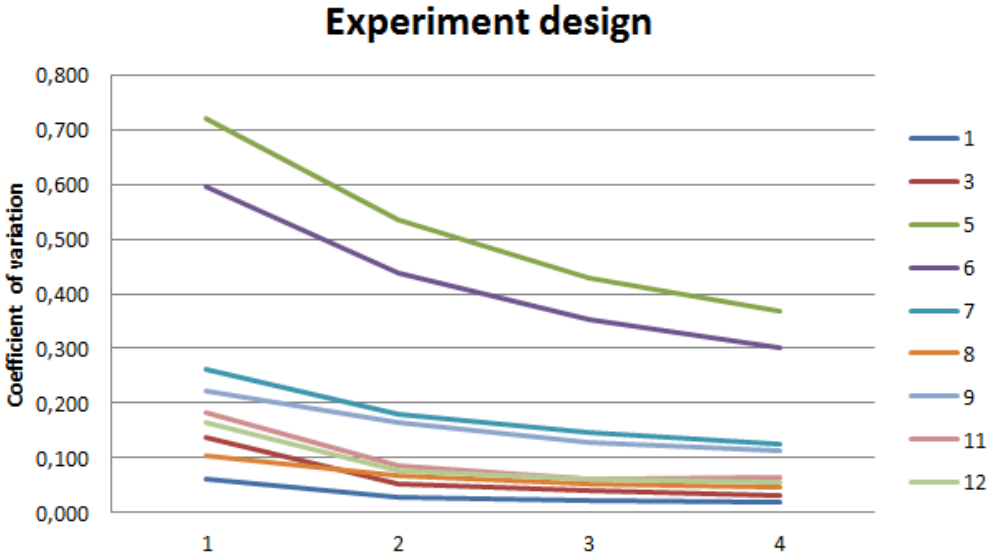

Figure 6.23: coefficients of variation of modified Panunzi's suboptimal parameters for the experiments designed as they get smaller with the number of monitoring days

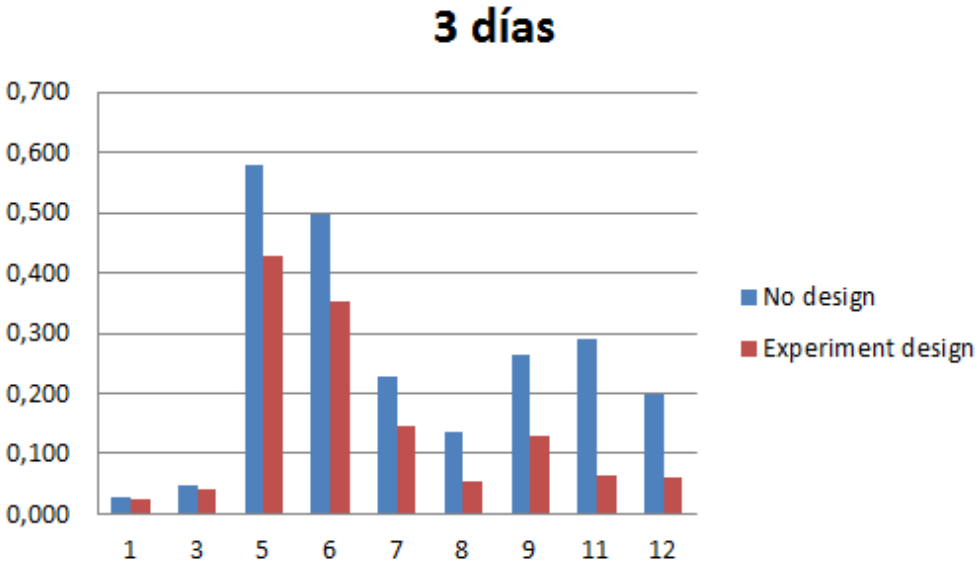

Figure 6.24: Identifiability of the suboptimal set of parameters of modified Panunzi's model before and after the experiment design in a three meals monitoring

As can be observed, the experiment design increases the overall identifiability of the model with the experiment design, except for two Dalla Man's model parameters, the 5th and 6th. Those parameters are K_{abs} and K_{max}, and both of them express flow rates of glucose in the gastrointestinal tract. It is likely that they are very correlated. The rest of the coefficients of variation are maintained relatively high probably due to the overlapping of the dynamics derived from those two parameters. This phenomenon would explain the fact that only one day of the experiment (even in a 4 days monitoring) is utilized for individually identify the gastrointestinal model delaying the insulin bolus.

6.5 Discussion and clinical protocol

The results of the experiment design do not have to be taken literally in practice. The assumptions made when using each model and the nominal parameters of it have great importance on the results of the experiment design. However, from a practical point of view, experimenting with several different models allows us to draw some general qualitative conclusions. That is why the design has been repeated several times in this thesis. Qualitative and common characteristics of the experiments designed are going to be extracted in the next lines, trying to get the most important features needed in a monitoring for the good posterior identification of a patient, regardless of the model used.

There are two different single day experiments. The experiment design aims to separate the dynamics of the sub-models for a better identification. In one case insulin dose is given without meal perturbation, limited by the hypoglycemia constraint, in order to obtain information of the subcutaneous insulin model. The other situation is exactly the opposite; a meal is given while the insulin dose is delayed limited by the hyperglycemia constraint. During this time, the intestinal absorption model is the only one acting on

the output signal. Optimal experiment design forces the model to move in all the range of operation set in order to preserve patient's safety, thus extracting more information out of the data.

The application of the designed experiment in ambulatory conditions is not straightforward. In the optimal experiment design the patient (virtual) is supposed to be stabilized and in situation of normal glucose. In the real life, even in the fasting state, patients may not be under steady state conditions, with glucose values in any glycemic range. Under these circumstances, application of the optimal experiment design to the clinical setting requires some cautions. Indeed, if the patient is hyperglycemic at the beginning of the experiment, delaying more than two hours the insulin dose can be dangerous for the patient's health, with extremely high glucose values. On the other hand, if the patient is hypoglycemic, administrating an insulin dose without carbohydrates ingestion can lead to severe hypoglycemia.

Therefore, an adaptation of the optimal experiment design to the initial metabolic state of the patient is proposed. If the patient has a blood glucose level over 150 mg/dl or in the 100-150 mg/dl range with an increasing trend (hyperglycemic risk), the insulin bolus is given followed 30 minutes later by a 100 grams meal. If the glucose level is below 100 mg/dl or in the 100-150 mg/dl range with a decreasing trend (hypoglycemic risk), a 40 or 60 (patient's choice) grams meal is given and the insulin dose administration is delayed 120 minutes. In both situations the dose to be administered is the one recommended to the patient, depending on the size of the meal and his/her usual insulin-to-carbohydrate ratio. The patient can choose among three menus with the same relative nutritional composition. With this protocol the separation of dynamics is achieved, while minimizing risks for the patients.

The protocol has been approved by the Ethical Committee of the Clinic University Hospital of Valencia and clinical trials are currently being performed for validation of the identification procedure. Patients are currently being monitored during two weeks, with a wash-up week in between,

and instructed to follow the protocol defined by the experiment design. In a week, three days are used for identification and three for validation, as it was scheduled due to restriction of the lifetime of the sensor utilized.

Some preliminary results of monitoring, identification and validation considering uncertainty on the parameters identified will be shown in the following chapter.

Chapter 7

Identification with ambulatory data: Preliminary results

Clinical validation of experiment design with modified Panunzi's model started in the Clinical University Hospital of Valencia the 20th of January, 2010, with the first week of monitoring of a diabetic patient.

Every week of monitoring is organized in the following way:

- Day 1 - Insertion of the continuous sensor. Warm-up period to ensure stabilization of the sensor signal.
- Days 2, 3 and 4 - Identification period. At the patient's usual lunch time, the patient is instructed to follow the experimental protocol described in the previous chapter. In particular, they are advised to avoid any snack or additional insulin administration during the five hours period following the meal, unless some harmful event would occur to the patient, such as an hypoglycemic event.
- Days 5, 6 and 7 - Validation period. The patient follows her/his usual treatment without any shift of insulin administration, for validation

purposes. The menus from which the patients can choose are the same of the identification period, reducing variability related to the meal composition.

The results that are shown next are only preliminary results, and only are reviewed qualitatively for identification purposes. The complications related to experimental data acquisition in diabetic patients are highlighted in every case. So far 5 patients have been monitored, some of them several weeks, and others only 1 week. The maximum number of weeks monitored in the same person is 4.

The results shown next consist of two graphs for each week of monitoring: the first one are the three meals of the identification period; the second graph is the data corresponding to the validation period, considering uncertainty. The response of the model considering uncertainty is calculated by means of interval analysis of the models explained before, and only 2 "parameters" are being considered uncertain:

- Meal size is considered with a 10% of uncertainty. Meal size is not a parameter of the model, but the estimation of the amount of carbohydrates is usually done by the patient, incurring in severe approximations of the right size of the meal being ingested.
- K_{xgl}, or insulin sensitivity, is considered to vary in a 20% from its identified value. Indeed, in daily life of people with diabetes insulin sensitivity can change significantly depending on many factors such as the intensity of physical activity, health conditions, emotional stress, and so on.

If the uncertainty considered are to be different in any case, it will be explicitly stated. Based on each patient home glucose monitoring diary, if high variability in the meal size is observed, or if unexpected/unplanned

events potentially influential for K_{xgl} are reported, then greater variability has been considered to obtain more robust predictions.

Considering uncertainty for validation purposes is one of the main outcomes of this thesis. In the diabetes context, great variability of the parameters identified is expected. The ambulatory conditions on which the monitoring of patients happen, makes the data to be extremely noisy, with unplanned events and errors in the treatments proposed. The combination of these sources of error invalidates identifications performed almost immediately.

There exist several ways to overcome the lack of fidelity of the identification to the real process. In the continuous (real-time) control of diabetes, adaptive algorithms for control seem to be necessary in order to follow the patient parameters variations. Consecutive model identifications may be performed every day improving data fitting and prediction capabilities of the model. In an off-line study of several days like the one of this thesis, only one identification may be performed, considering the limitations exposed before (same meal composition, same meal time...). The variations of the patients in this case cannot be copped with successive identifications or adaptive algorithms, but robust controllers have to be developed. Robust control needs of a quantification of the error expected on the model, and this can be done by considering uncertainty on the parameters identified.

Each one of the following sections corresponds to a different patient and his/her number of weeks of monitoring. The patients are designated anonymously with their initials.

7.1 Monitored Data from Patients

7.1.1 Patient HMJ

HMJ was monitored during 4 weeks (not consecutive), following the protocol described explicitly. First week's identification period is shown in Figure 7.1. Each day's postprandial period of 5 hours is separated by vertical dashed lines.

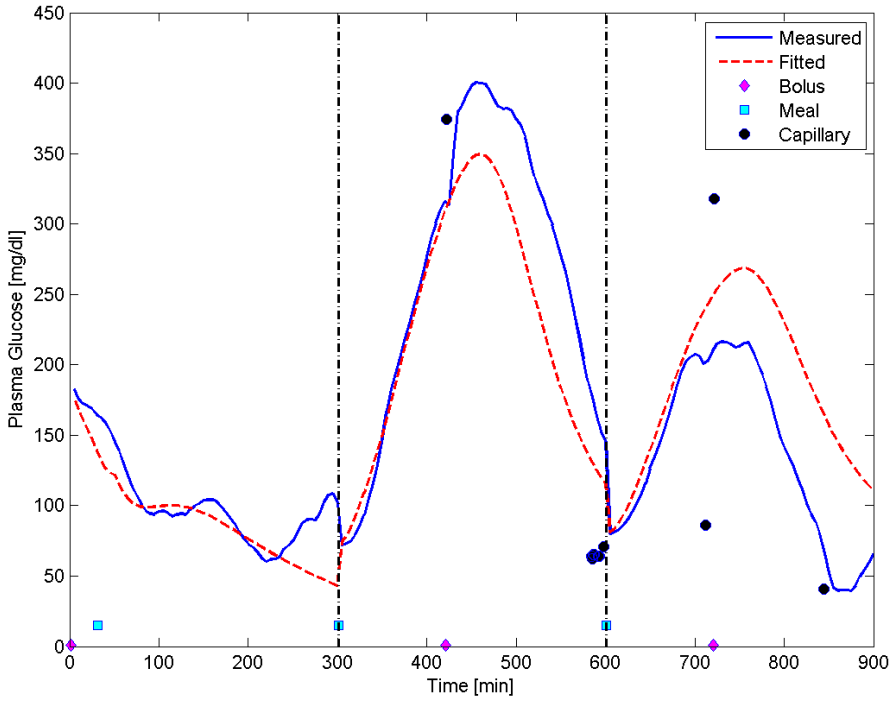

Figure 7.1: HMJ's first week's identification period

The first day's meal the patient ate the meal configuration 1. In this configuration, the insulin bolus was given 30 minutes before the meal time (as shown in the figure), and the meal size was 100 grams. The second and third days the patient ate the meal configuration 2. In this second configuration the insulin bolus is delayed 120 minutes and the patient is given to choose

from a 40 or 60 grams meal. It's worth remembering that regardless the meal size, the meal composition remains constant. The same meal configuration is used for all the patients.

There is a clear difference between the dynamics of the second and third days, and the first one, as the experiment design predicted. The rising of glucose after the meal is though completely faded by the insulin dose. The last day shows an illustrating example of the problems that can be found durign experimental data acquisition. The black dots shown in the graph are the capillary measures of glucose performed by the patient and introduced in the CGMS as calibration points. In the middle of the third day, the patient consecutively introduced two very separated calibration points in the sensor, misleading the signal of the sensor, and consequently, polluting the source of the identification. Despite the human errors related to the monitoring, the identification can be considered successful. First week's validation period is shown in Figure 7.2.

The ideal situation would be to have the continuous line of the monitor completely covered by the band of prediction of the model. In practice this would almost never happen. In the case of the first week of validation for HMJ, the CGMS was very noisy (specially the third day), and the validation was not satisfactory. The lack of similarity in the first day can be attributed to a even bigger (than 20%) variation of insulin sensitivity, making the patient more resistant to insulin, and making blood glucose to be higher at any time. The second day presents a delay of 100 minutes in the glucose absorption, which is not possible to simulate with the model. The third day noise makes the data unreadable.

The second week's identification period is shown in Figure 7.3.

The data has been fitted with great success in this case. The first and second days correspond to meal configuration 2, and the third day meal configuration 1 was eaten. The second day of identification shows an error in the calibration data of the sensor. There is a point of capillary glucose of 119

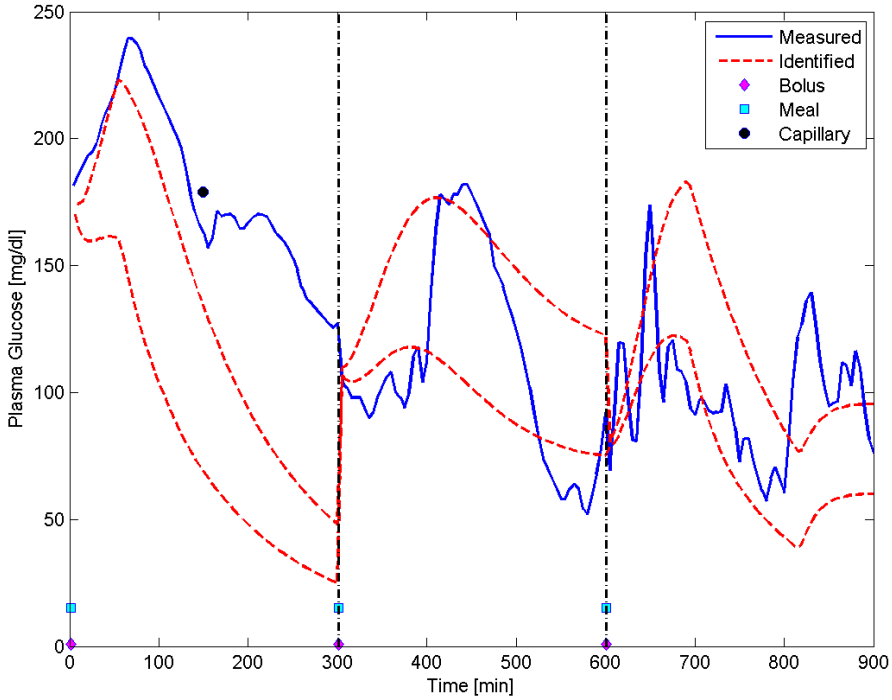

Figure 7.2: HMJ's first week's validation period

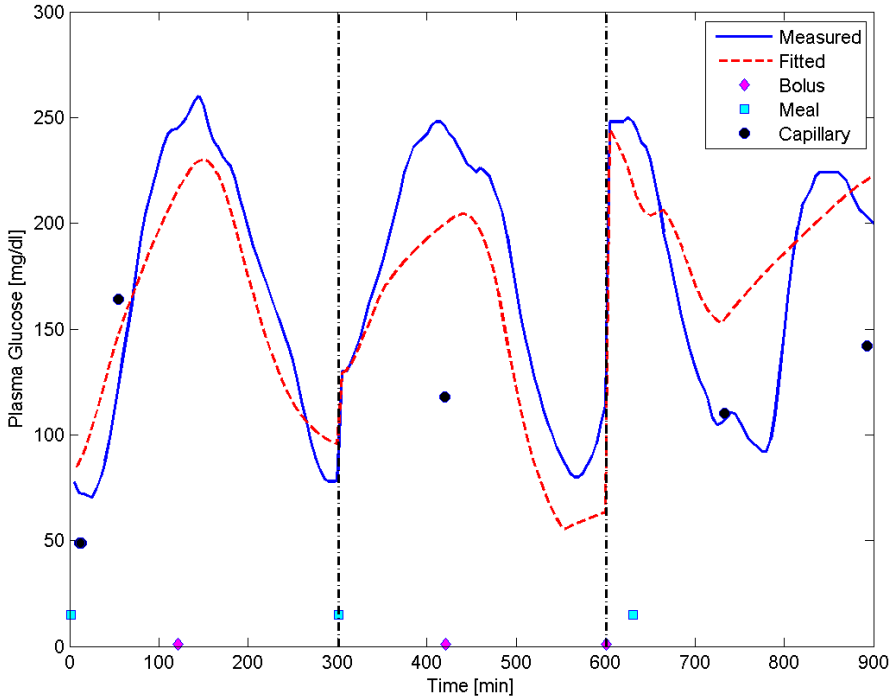

Figure 7.3: HMJ's second week's identification period

mg/dl, while the sensor is more than 100 mg/dl above that level. Given that no correction was done by the CGMS of the signal of the estimation of the blood glucose, it was assumed that the monitor discarded that calibration point. Other outlying calibration point occurs in the third day, but in this case the error is smaller (50 mg/dl).

The validation days for that week are shown in Figure 7.4.

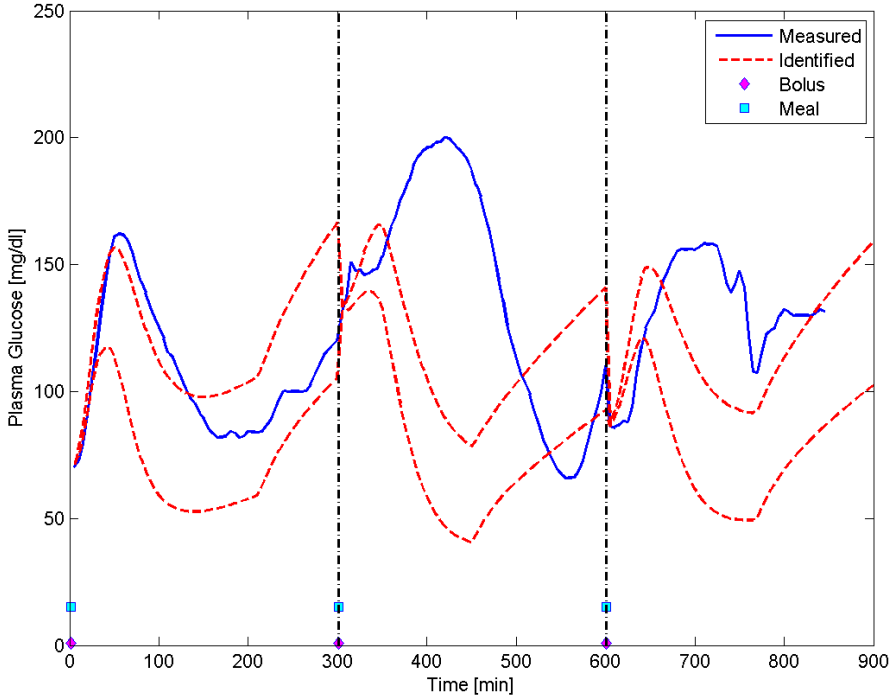

Figure 7.4: HMJ's second week's validation period

The first day of validation is wonderfully fitted, but the other two days show longer absorption profiles than expected, and the patient has higher blood glucose concentrations than the predicted by the model, despite the fact that the five hours prediction was within boundaries in all the cases.

The third week's identification period of monitoring can be seen in Figure 7.5.

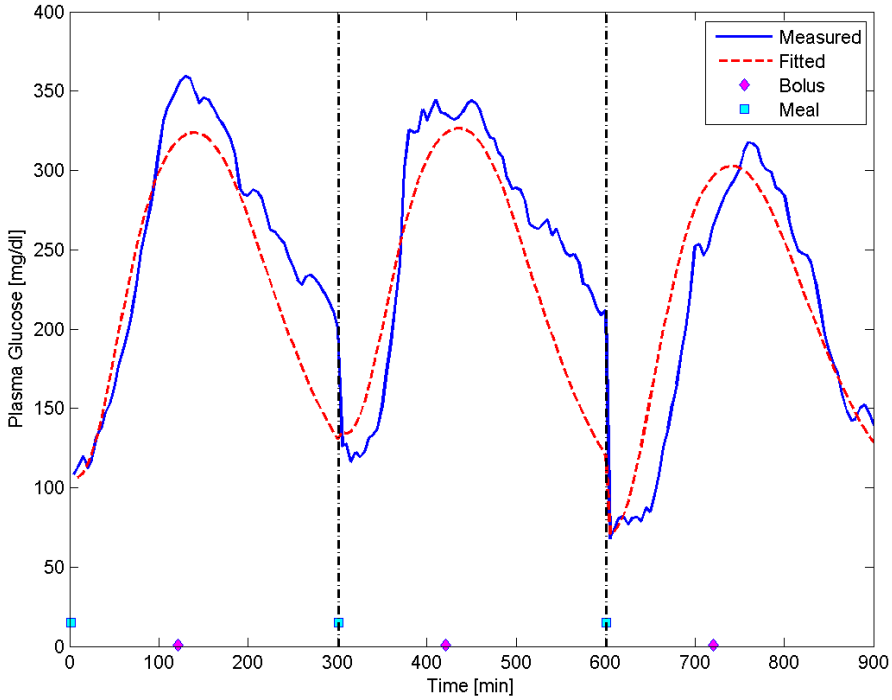

Figure 7.5: HMJ's third week's identification period

In this case the three meals eaten were those of configuration 2. The fitting is quite satisfactory, but it tends to predict hypoglycemias in a five hours time that usually do not happen. The third day fitting is perfect. The case of a three repeated meals with the same configuration does not follow the experiment design findings, and as such, not very good identification is expected, and the validation period should not be very well predicted.

The validation meals and their postprandial periods can be seen in Figure 7.6.

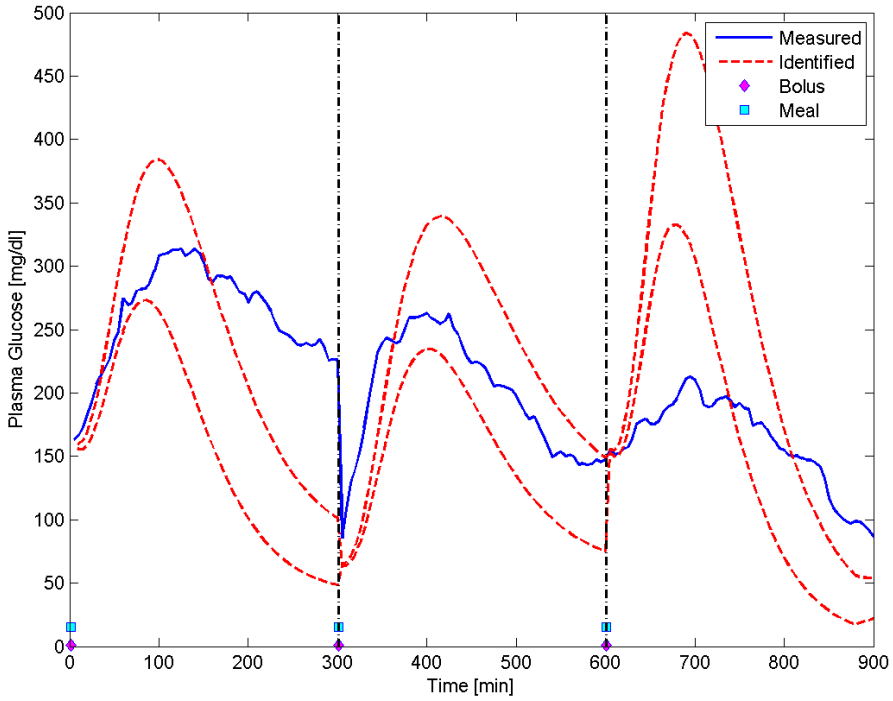

Figure 7.6: HMJ's third week's validation period

The Second day is very well predicted, the first one only in the first two hours, and the third day prediction is not good. The first and third days predictions end in fictional hypoglycemia, while the patient is actually in the safe area. This fact makes the model to predict hypoglycemias in the fourth or fifth hours of the postprandial period. This is an error introduced

by the lack of configuration 1 meals in the identification period, and should be avoided.

The fourth day's identification meals are shown in Figure 7.7.

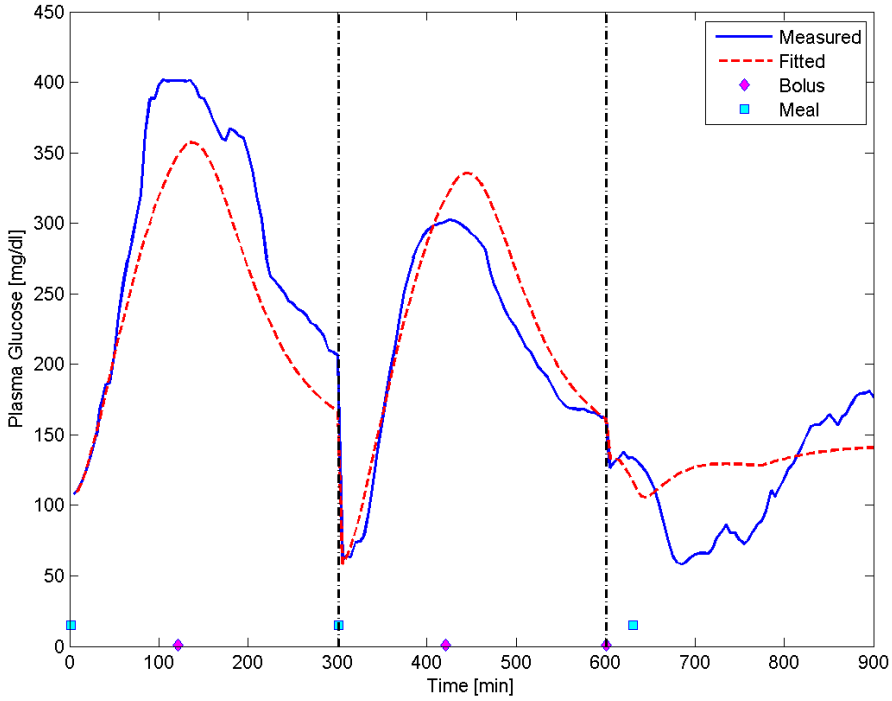

Figure 7.7: HMJ's fourth week's identification period

The first and the second days correspond to configuration 2 meals, and the third day a configuration 1 meal was eaten. The patient ate the same the first and second days, and a clear difference in the monitor's prediction can be seen. Model's fitting is quite good for both days, and a little worse for the third day, but yet satisfactory.

The validation days can be seen in Figure 7.8.

The first day of validation is very well predicted. The second day, the CGMS had a strange behavior, not caused by any erroneous calibration

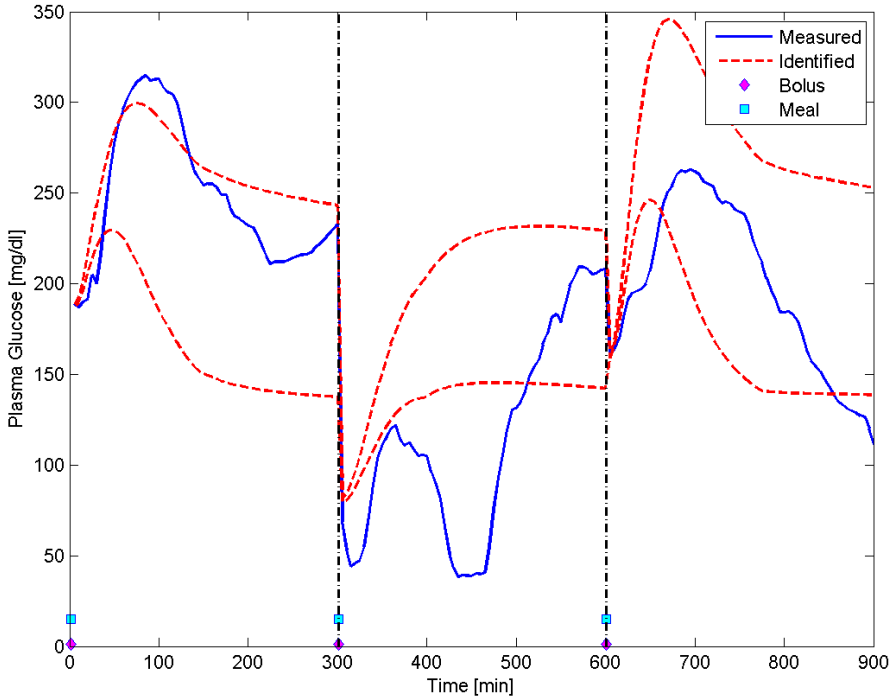

Figure 7.8: HMJ's fourth week's validation period

points as before, but maybe because of external cause related to the patient. The third day's prediction is quite good, despite the fact that the prediction in a 5 hours horizon is overestimating blood glucose.

7.1.2 Patient ACN

This patient was the second one to be monitored, and the last of the patients that were subjected to 4 weeks of monitoring. The first week's identification meals are shown in Figure 7.9.

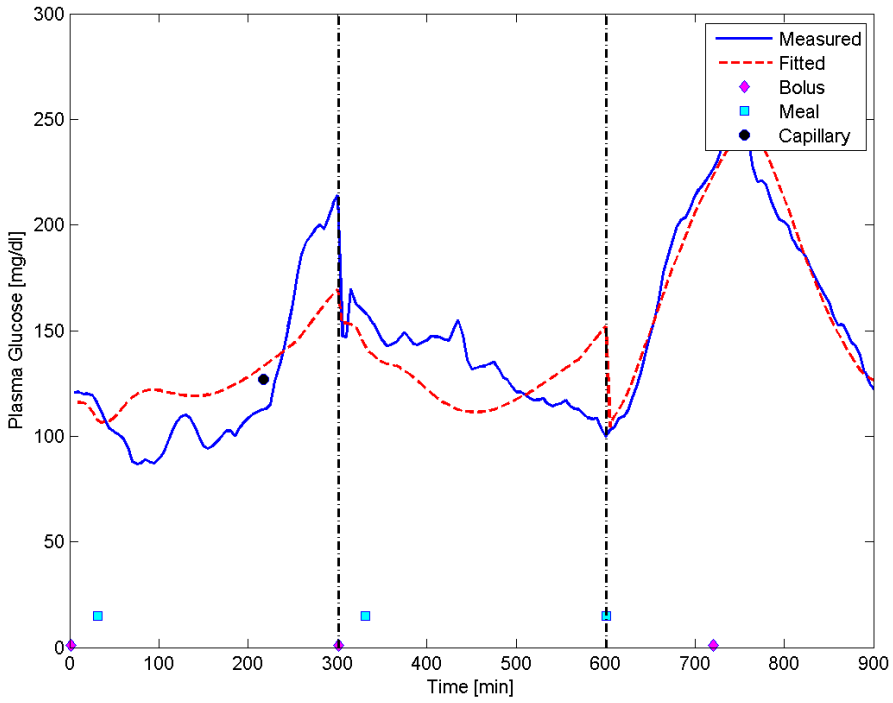

Figure 7.9: ACN's first week's identification period

The two first meals are of configuration 1, and the third day lunch was a configuration 2 meal. The dynamics observed describe very well the difference on the configuration of the meal. In the case of configuration 1, blood glucose does not rise after the meal time as it does in configuration 2 meal. This

happens because, in configuration 1 meals, the peak of insulin concentration in plasma occurs at the same time that the meal starts being absorbed (45-75 minutes), which causes the blood glucose to be constant at any time. Actually, a tighter control of blood glucose is observed in configuration 1 meals than in standard treatments, or in configuration 2 meals, where there is a period of 2 hours without any control at all.

A clear difference in the dynamics of blood glucose can be see by comparing the two first days. The rising tendency in 5 hours after the meal in the first day is completely the opposite than it is in the second day, where the tendency is to drop down. This difference can occur due to variations in the insulin sensitivity of the patient or in other physiologic parameters (metabolic condition of the patient), or maybe due to a sensor dysfunction. Indeed, the first day a calibration point was introduced in the post-prandial period, whereas in the second no calibration was performed. This may have affected the sensor's tendency.

The validation period is shown in Figure 7.10.

Validation is very satisfactory. In the last day, prediction is good up to the fourth hour, where the tendency of the blood glucose is the opposite to the predicted by the model. This corresponds to the same situation observed during the identification days, even with the presence of a calibration point at the end of the third day. The causes can again be various, such as a the effect of that calibration point, or maybe some different conditions of the patient.

The second week's identification period is shown in Figure 7.11.

In this second week of monitoring, the patient ate two configuration 1 meals in the first two days, and a configuration 2 meal in the last day. The fitting is very satisfactory, specially in the first and third days.

The validation period is shown in Figure 7.12.

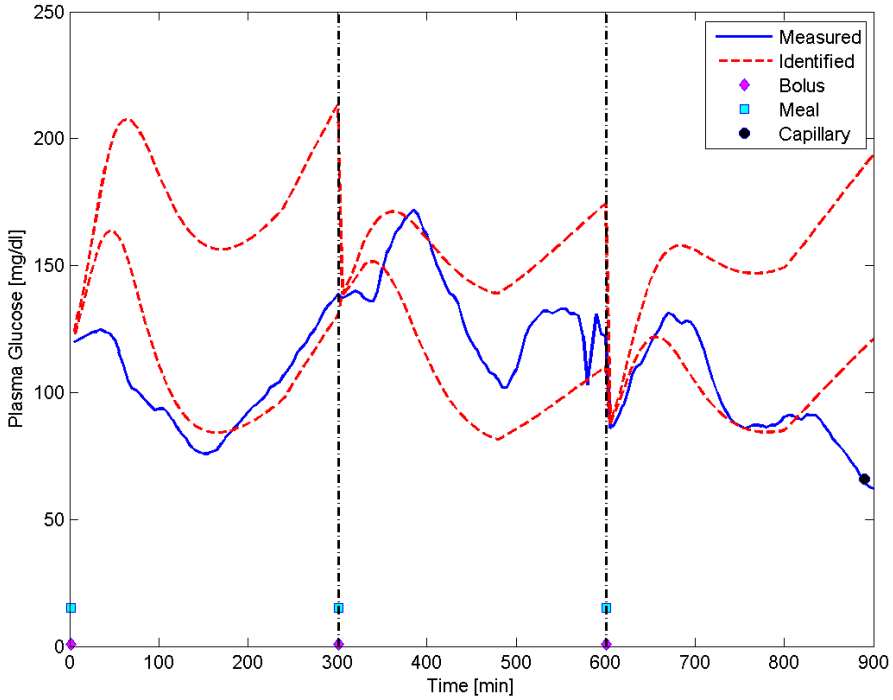

Figure 7.10: ACN's first week's validation period

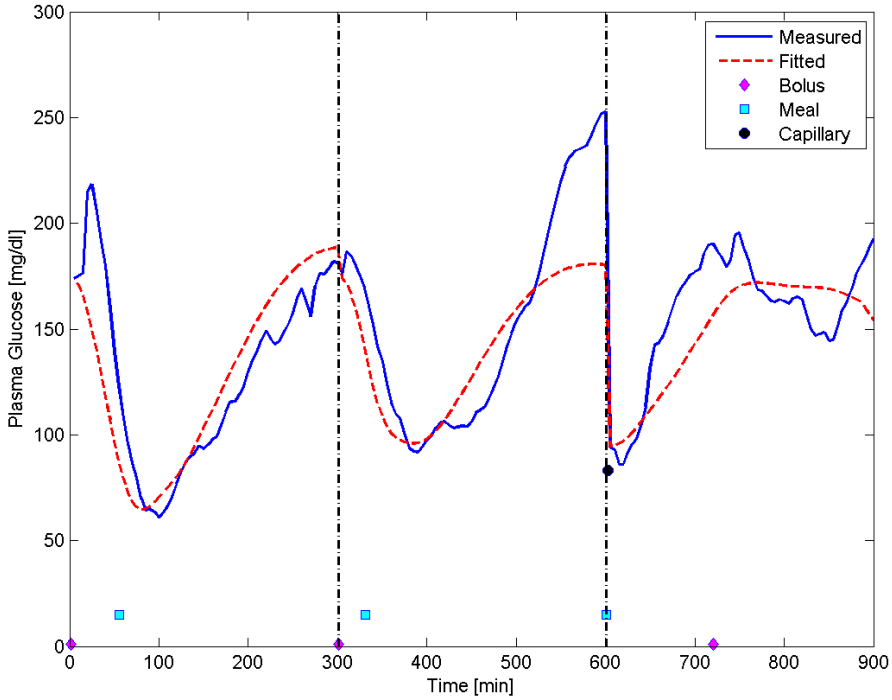

Figure 7.11: ACN's second week's identification period

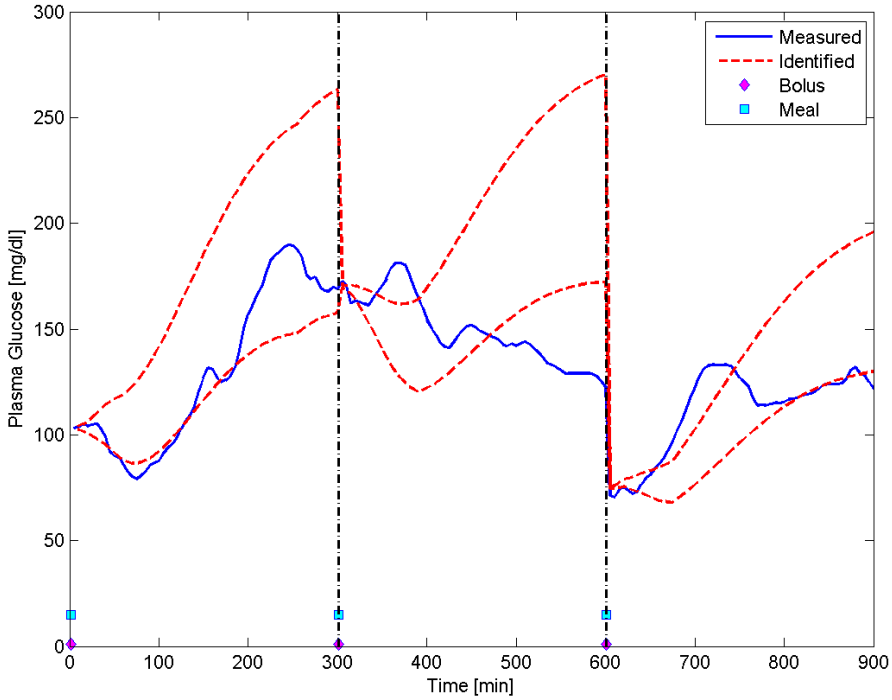

Figure 7.12: ACN's second week's validation period

The model seems prone to predict hyperglycemias in a five hours time lapse, but it is usually correct in its prediction. The exception is the second day of validation, in which the tendency is completely different to the other days.

The third week's monitoring results and fitting are shown in Figure 7.13.

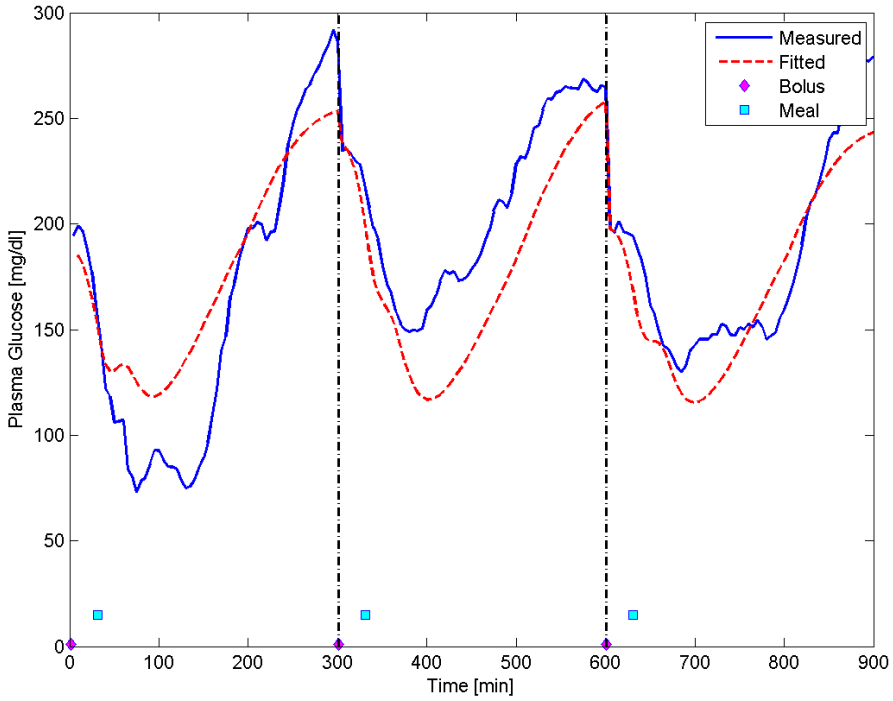

Figure 7.13: ACN's third week's identification period

The patient repeated three times the configuration 1 meal in this case. This is detrimental to the model identification shown by the experiment design, but still, the fitting is very good. It is very interesting to see that, despite the three meals were identical in composition, the absorption of glucose in the first day is much smaller (or slower) than in the other two days, causing a lower fall in the blood glucose.

The validation period for this third week is shown in Figure 7.14.

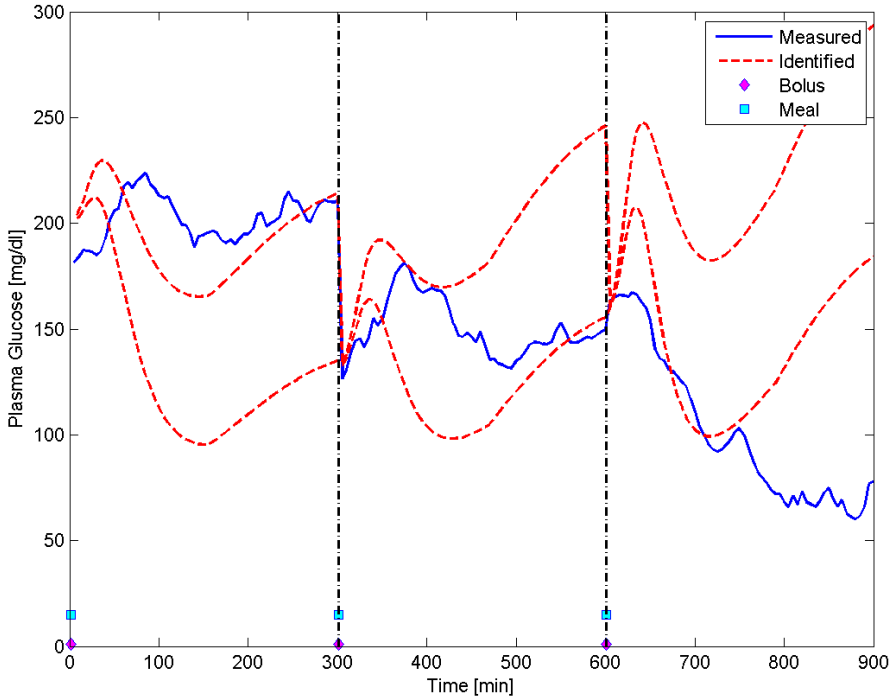

Figure 7.14: ACN's third week's validation period

Validation is not very good in this case. Only the second day is included in the band of the simulation of the model. The other two days describe dynamics very different to the predictions of the model. These problems in the validation may be caused by the fact that only configuration 1 meals are identified in the identification period. This can cause problems in identifiability of the model, as it has been proven in simulation, but also, it the three meals of the identification period follow similar dynamics, the identification of the postprandial model will give a model that mimics that dynamic, and no other. This is overfitting the data of the experiment. For example in the present case, all the days of identification have the tendency of rising the blood glucose at the end of the postprandial period. The model imitates this behavior, even in the case of normal treatments, which is obviously not a physiological behavior of the patient.

The fourth week of identification is shown in Figure 7.15.

The first day the patient ate a meal of configuration 1, and two configuration 2 meals the second and third days. Data fitting is very good for the first and third days, but deficient in mimicking the dynamic and the 5 hours prediction of the second day.

The validation is shown in Figure 7.16. This validation was done increasing the uncertainty of the meal to a 20% of the original value, and a 30% in the insulin sensitivity, as explained before.

The bigger uncertainty in the parameters creates broader bands in the model simulation. The validation of the second and third days is successful, but the first day's tendency is completely different. Also, there is a fictional peak in the first day monitoring, caused by an error in the sensor.

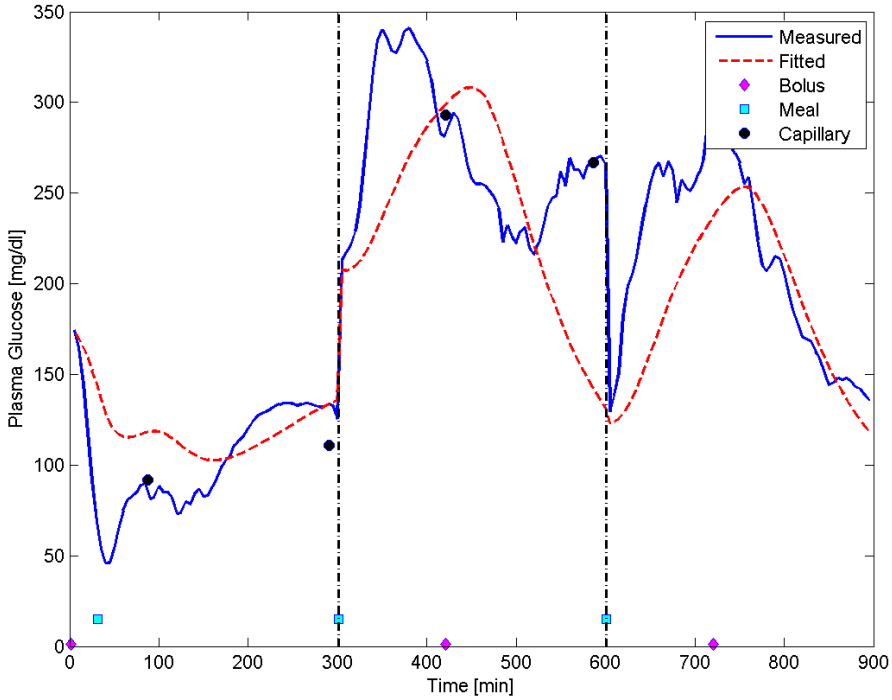

Figure 7.15: ACN's fourth week's identification period

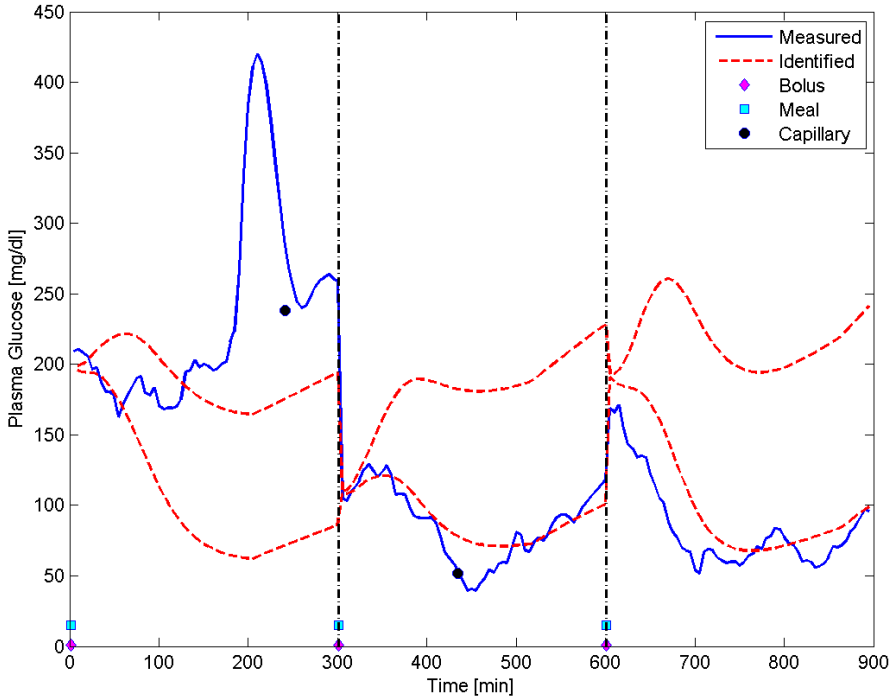

Figure 7.16: ACN's fourth week's validation period

7.1.3 Patient VMD

The third patient monitored, VMD, has been only monitored for one week, and is still being monitored. The only week of monitoring, and it's identification period is shown in Figure 7.17.

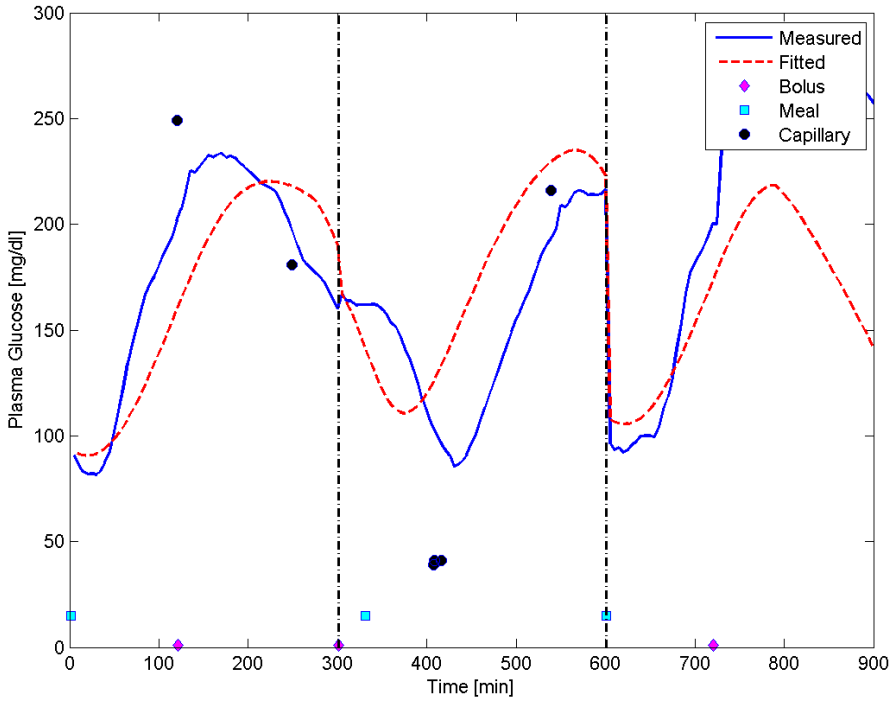

Figure 7.17: VMD's first and only week's identification period

The patient ate a configuration 1 meal the second day, and two configuration 2 meals the other days. The data fitting is pretty good for the first two days, and the dynamics are well identified, even though in the third day the peak of glucose is much higher in the monitor than in the prediction of the model.

The patient overcharged the sensor with calibration points, like in the second day, in which there are 3 consecutive capillary measurements, causing corrections in the signal, and disturbing the dynamics of the sensor

algorithms. But despite that, the results are satisfactory.

The validation period is shown in Figure 7.18.

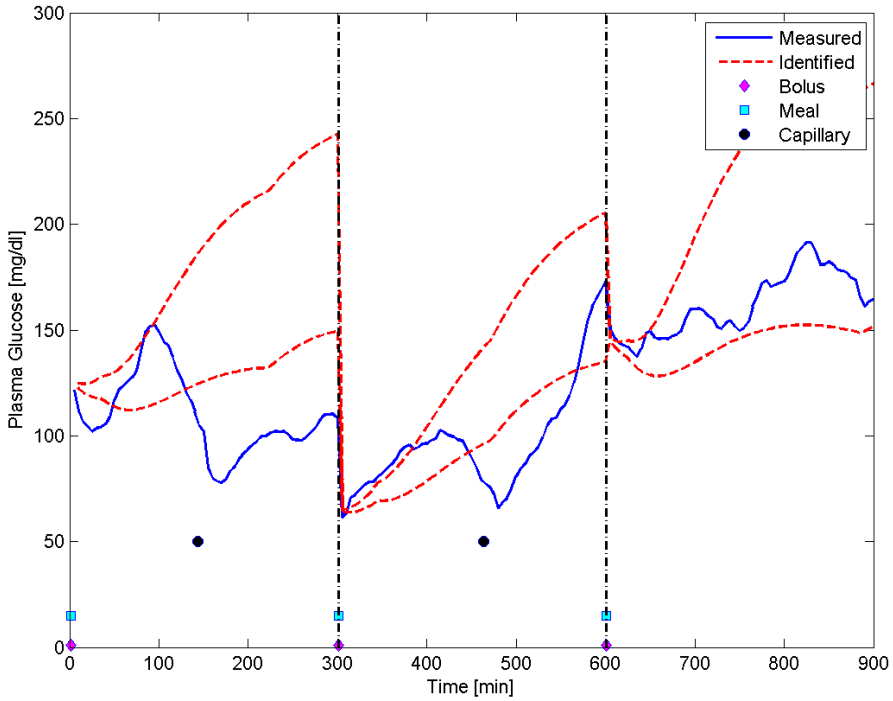

Figure 7.18: VMD's first and only week's validation period

Hyperglycemia is predicted by the model at a five hours time in all the cases. The second and the third days are fitted quite well, and the first one, in the first two hours, is well predicted too. The influence of unexpected calibration points is clearly seen in the first and the second days. The tendency of the signal is clearly modified at the time of the calibration measurement in order to adjust to that data point, and that makes the signal of the sensor to get out of the band predicted by the model.

7.1.4 Patient SAR

Patient SAR was the fourth patient to be monitored, and only one week has been monitored so far. More monitoring week are scheduled in the following months. The identification period is shown in Figure 7.19.

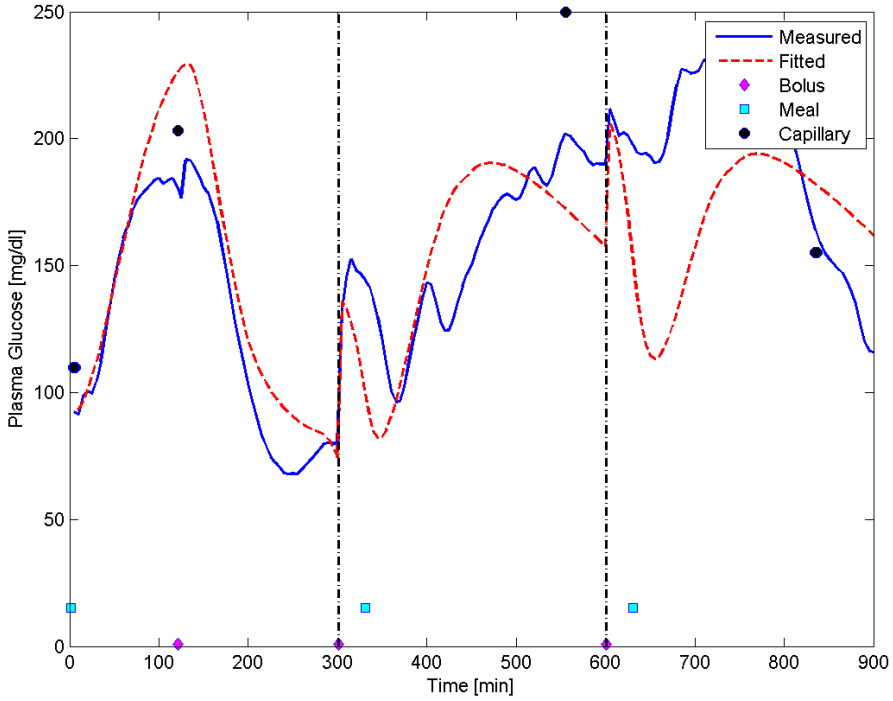

Figure 7.19: SAR's first and only week's identification period

The fitting of the model is very unsatisfying. It is expected the validation to be worse. The causes can be various, such as invalid calibration points, extreme noise influence, or bad use of the monitor from the patient. Especially bad is the last day of fitting, predicting a drop of the blood glucose down to 100 mg/dl, and the patient being actually in a level of 200 mg/dl.

The validation is shown in Figure 7.20.

The first day the patient's glucose rises up to 350 mg/dl, even with the

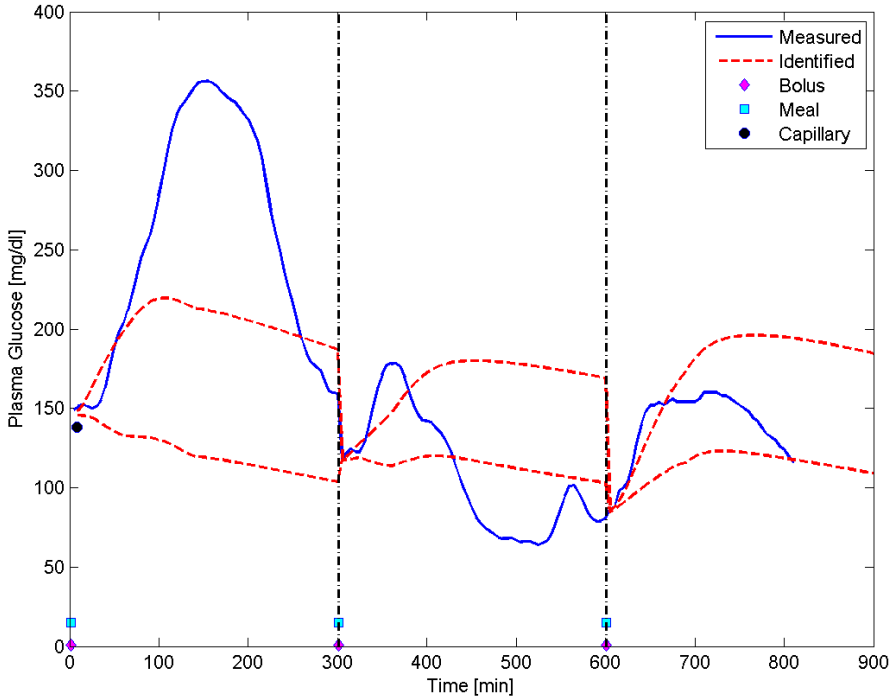

Figure 7.20: SAR's first and only week's validation period

traditional treatment, and the model is not able to predict that behavior. The other two days of validation are poorly validated. The last day the patient stopped the monitor in the fourth hour of the postprandial period, leaving the last day of validation without all the data required.

7.1.5 Patient PGV

Last patient in the study so far was PGV, being monitored only for one week. The results of the monitoring are shown, for the identification period, in Figure 7.21.

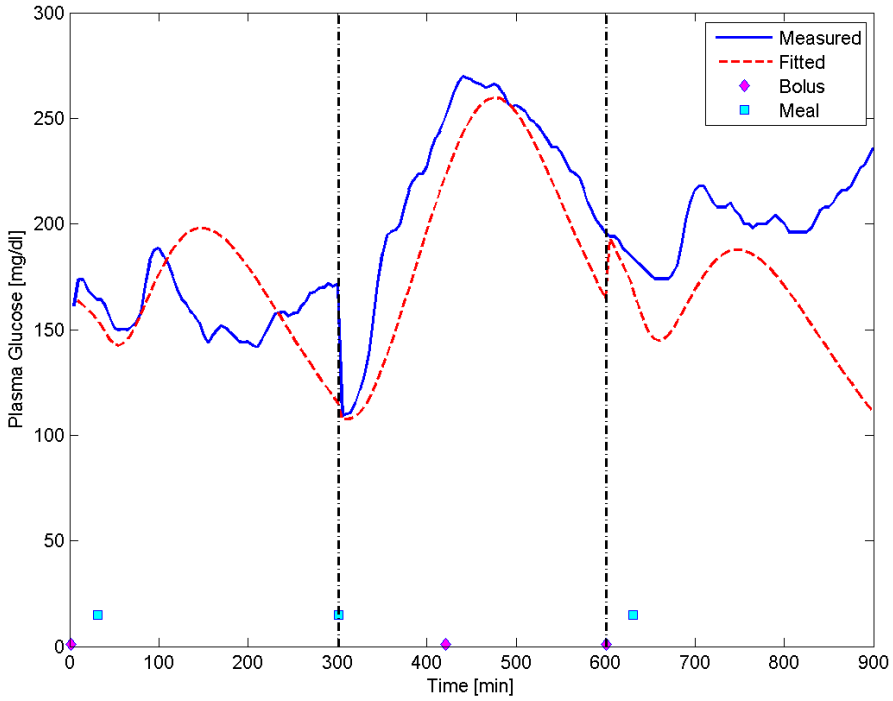

Figure 7.21: PGV's first and only week's identification period

The patient ate two configuration 1 meals, the first and the third days of the identification period, and a configuration 2 meal the second day. The

fitting of the second day is very good, but the tendencies in the first and the third days in the last hour of the postprandial period are not well imitated.

The validation period can be seen in Figure 7.22.

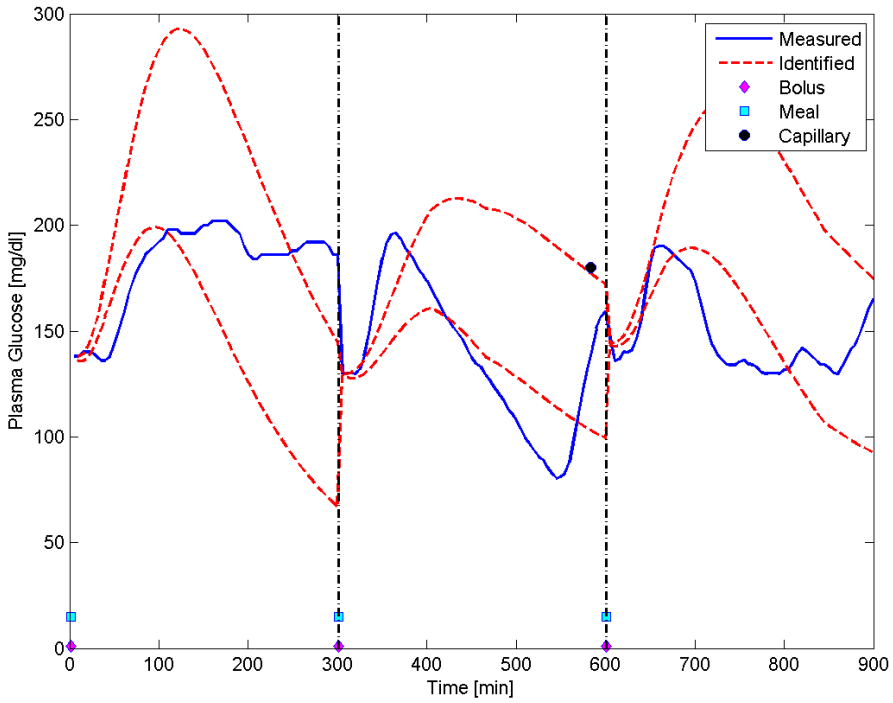

Figure 7.22: PGV's first and only week's validation period

Validation, despite having broad bands for the simulations, is quite poor. The second day the calibration point seems to affect the sensor signal once again. Also, the behavior of the patient in the last hour, in which the glucose seems to start rising, is not reproduced by the model. In the fourth or fifth hour, the digestive process is likely to be finished, and as such, no income of glucose from the intestine is happening. Plus, the insulin bolus is supposed to be totally absorbed at that time. That tendency of increasing glucose seen in almost every day of monitoring have to be then caused by a lack of basal insulin in the patient in the postprandial period. This does not excuse, though, the bad identification of this patient in particular, but it

shows how comparing the results of an identified model can be beneficial for understanding the metabolic state of the patient and his/her treatments.

7.2 Discussion

The first conclusion drawn out of the first weeks of monitoring is that the experimental factor is the most relevant issue, moreover when speaking of real patients. The importance of following the experimental design should be clearly explained to the patients, who may be also advised to report any deviation from the protocol. This is clearly shown in the patients with more than 1 week of monitoring. In the first week, many errors are committed by the patient, such as wrong calibration points, stopping the insulin pump at the wrong moment, or administering the next insulin bolus before the postprandial monitoring ends. Those problems are less frequent when the patient feels familiar with the device and also due to the identification and elimination of the most common errors (by instruction to the patients) by the clinical staff.

Experimental design and identification from real data really helps understanding the model used for simulating patients. Very complex models were discarded from the beginning of the experiment for practical reasons in the implementation and lack of identifiability. However, there are different behaviors that the simpler models can not mimic. Independently identify the dynamics of those behaviors, and reflecting them into the equations of the model is the aim of modeling. It is not possible to do it without the experimental experience of observing the monitoring and identification of the postprandial responses of the patients.

The identification process has remained unchanged for all the patients analyzed. The identification process might be improved by adapting it to each case independently. Also, it is possible by varying the matrix

of weighting Q_i, as seen in equation 3.1 to adjust the model to better conditioned periods of time. This way, the noisy data periods can be avoided to be fitted, or maybe the data can be fitted better in the early hours of the postprandial period rather than the last hours. It makes sense to fit better the periods in where only one sub-model is being perturbed, like for example, in the case of advancing 30 minutes the insulin bolus, adjusting better those 30 minutes.

As a final remark, the identification is satisfactory. Data fitting is usually excellent. The validation period is trickier to simulate for the current models in literature. Nevertheless, in many cases, two out of three postprandial periods were described by the identified model of the same patient, and in almost all the cases, at least one day was well described by adding uncertainty to parameters.

Chapter 8

Conclusions

Much work has already been done in identification and modeling for diabetes. This thesis deepens in the understanding of the models and their capacity of reproducing the physiology of a diabetic patient. Several models where analyzed, a new version of an existing model was proposed and model identification was performed following a protocol designed for maximizing the information to be extracted. In this chapter, the achievements of this thesis will be reviewed, and a list of future items of pending work will be discussed.

8.1 Analysis of the results

The work performed in this thesis was exposed in detail in chronological order. The work performed first was exposed first, and the latest work in the last chapters. For the final analysis of the results, a different point of view may help to summarize the findings of the thesis.

From the point of view of the models analyzed, there were three of them tested:

1. Cobelli's model - The first model tested for identifiability in experimental data was the model accepted by the FDA to simulate diabetic patients. The model was tested in a whole day of monitoring, and validated in the next two following days. The results with the model and the data used were very bad. Out of 22 patients, only 2 were fitted successfully for a whole day of monitoring, and no validation was successful. The model was discarded of use due to identifiability issues.

2. Bergman's model - The same data with which Cobelli's model was tested was used to test the Bergman model. The scenario was different, and a postprandial approach was used, trying to identify only using the 5 hours of monitor data after the meal intake. The data fitting was successful for only one patient, and the validation with other meals failed. The set of data used for identification was discarded as a consequence of that failure raising the need of an optimal experiment design. Bergman's model was also used for designing experiments in order to obtained better quality data.

3. Panunzi's (modified) model - A critical review to Bergman's model dynamics proved it unable to simulate some physiological features of real diabetic patients, leading the author of this thesis to modify a third model (Panunzi's model), to adapt to those dynamics. This third and definitive model was used for designing experiments, and also for identification of the patients monitored in those experiments, with better results than the identifications performed Cobelli's model.

Cobelli's model was proven to be unreliable to fit a whole day in a diabetic patient's life. The computational cost of the solvers when working with this model was another cause to discard using it. Plus, the model was not identifiable in most of its parameters. The rest of the models used are very light in computational terms. The same solver, working on Bergman's equations instead of Cobelli's was twice as fast.

Computational cost is an issue that has hardly been mentioned on this

thesis, but in practice it is one of the biggest drawbacks for the efficiency and implementation of the algorithms. Global optimization methods take thousands of callings to the function being optimized to get to a solution. If the function being optimized is the glucose model, like in the case of a model identification, and if the model evaluation takes around 100 miliseconds, an average identification of the model will take about 1 hour. That is quite a heavy computational cost, but it can get worse. In the case of the experiment design, the cost function is not the glucose model, but the determinant of the FIM. The evaluation of the information matrix involves algebraic calculations and evaluations of the actual glucose model; depending on the number of parameters being varied it can make from 10 to 25 evaluations of the model. Being the objective function much more complex than the glucose model the optimization required for the experiment design uses many evaluations of the cost function, from one hundred thousand up to a million function evaluations. Considering the same model evaluation cost as before, the average experiment design will take 9 days to be finished.

Many implementation problems were not described in the thesis report. The computational cost was a constant problem, and many different implementations of the algorithms were tested. Starting with conceptual Matlab's Simulink diagrams for the glucose models, the programs were later implemented in Matlab code, and then in C programming language, speeding up the function evaluation many times.

The outcomes of the thesis are various:

1. A complete review of the models in literature was done. Identifiability studies on the most relevant models were performed.

2. A new model of endogenous glucose was proposed to better mimic the observed behavior in experimental data

3. Experiments were designed to achieve a better identifiability for diabetes models. A clinical protocol was defined to adapt the results

of the experimental design to the clinic.

4. Experiments of continuous home postprandial monitoring were conducted following the directions set by the experiment design.

5. Validation of the identifications were performed considering intra-patient variability.

Of special importance are the currently ongoing experiments being performed with real patients. Apart from the current experiments, the work described in this thesis has led to many open projects, or lines of research. In the next section the future work (currently being developed), and further ideas for the situations explained in this thesis will be explained.

8.2 Future work

A list of key points in the future work related to this thesis is now shown as the final contribution of this thesis:

1. **Analysis of the results.** Most of the results shown in this thesis are only studied qualitatively. Deep data analysis of these results still has to be done. Some tasks to be performed about this matter are:

    - *Statistical validation:* The experiment design still has to be statistically validated. Preliminary results of the application of the experiment design have been shown in this thesis, but more monitoring weeks have to be added to the work already done, and statistical results of the identifications have to be shown. The identifiability of the model being identified have to be calculated, and compared with its identifiability without the application of the experiment design, expecting better confidence intervals for those parameters identified. Parameters CVs will not be comparable to

those already shown in this thesis because those are calculated based on the nominal values of the parameters, and the validation have to be made based in the parameters already identified.

- *Repeatability:* The monitoring periods identified have to be tested for repeatability in the same period. The same patient in two consecutive weeks can have very different behavior, and this have to be reflected in the model's parameters. The variations between those parameters will give an idea of how much the model can fit the person instead of fitting the situation.
- *Comparison of models:* Every tested model have to be tested as a predictor of the glucose state. The prediction horizon of each identified model have to be tested to see if physiological models have prediction advantages over other sorts of models.

2. **Identification improvement.** Identification of the proposed model has to be improved. Identifiability has been deeply studied, but the process of identification has not been extensively reviewed. Some feasible improvements to the identification process are:

   - *Improvement of data:* Treatment of the data to be fitted is critical for the success of the identification. Currently, the model output is being fit to monitor data, but much more data is available in other formats, that may be relevant for the model identification. The calibration points, which are blood glucose direct measurements, should be perfectly fitted, and may enter cost function of the optimization in the future. The problem of adding those points in the identification to be fitted is that they are an input that the patient have to register in the monitor's log, and patients make lots of errors. That is why along with the calibration points, there has to be some fail detection system, to discard outliers in the capillary measurements or in the monitor signal.
   - *Weight matrix:* More options for improving the identification may involve to vary the matrix of data weighting Q_i, as explained

earlier in the thesis. One may try to better fits some sequences of data than others, or maybe to forget about fitting some particularly noisy data periods.

- *Faster optimization algorithms:* More efficient global optimizers may help to speed up the identifications, helping with one of the biggest problems of these identifications, the computational time.
- *Interval identification:* In this thesis, the process of identification was done prior the interval analysis of the model to be used in validation. These to processes can be mixed into interval identification. This process identifies boundaries of parameters instead of the actual parameters, including the information of the patient in the model (just as regular identification does), as well as quantifying the uncertainty of those parameters identified. This methodology will avoid the heuristic quantification of the uncertainty that has been used in this thesis.

3. **Modeling:** The motivation for the experiment design was to improve the identification of models, due to the low identifiability found up to that point. Other option to improve the fitting is to change the model. It remains as a "to-do" task to continue improving the model proposed in this thesis.

4. **Open-loop control:** In the validation days of the preliminary results, model intervals were shown for considering uncertainty. Heavy mathematical interval theory is behind these interval model simulations which has not been shown in this thesis. Work on Interval Analysis (IA) and Set Inversion Via Interval Analysis (SIVIA) has been done in parallel to this thesis, and all the models used where "intervalized", as explained by Calm et al.[13], for using them with uncertainty.

   The set inversion algorithms permit the robust calculation of therapies basal-bolus for tighter postprandial control, as Revert et al. shown [81] *in silico*. This approach requires of an identified model of the patient to make a good therapy proposal, which relates this thesis' research to

the work done by Revert et al. The validation of these robust methods and therapies in a clinical experiment is something never done before.

Some of the identifications shown in this thesis will be used for the *in vivo* validation of the SIVIA therapy proposals, which will be done in the Hospital Clinic Universitari of Valencia. The patients will be monitored, the model identified and used for the calculation of therapies that happens to be called "ibolus" therapies. Then the patients will be treated one day with the therapy proposed by the algorithm, and other day with the traditional bolus treatment, being monitored their blood glucose both directly and via a monitor. This experiment has been called the "ibolus" experiment, and it is a very related project to this thesis work. Improved treatments by means of SIVIA will have to be analyzed and improved in the future

5. **Closed-loop control:** It must not be forgotten that the final objective for these models and identifications is the control of the blood glucose in a diabetic patient (artificial pancreas). The foundations of this work have been placed, but there still a lot of work to do. Designing the controllers will be one of the last steps of this project, and probably one of the most critical ones.

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