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Modelling, Optimisation and Model Predictive Control of Insulin Delivery Systems in Type 1 Diabetes Mellitus

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Declaration

I herewith certify that all material in this dissertation which is not my own work has been properly acknowledged.

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Abstract

Type 1 Diabetes Mellitus is a metabolic disease requiring lifelong treatment with exogenous insulin which significantly affects patient's lifestyle. Therefore, it is of paramount importance to develop novel drug delivery techniques that achieve therapeutic efficacy and ensure patient safety with a minimum impact on their quality of life. Motivated by the challenge to improve the living standard of a diabetic patient, the idea of an artificial pancreas that mimics the endocrine function of a healthy pancreas has been developed in the scientific society. Towards this direction, model predictive control has been established as a very promising control strategy for blood glucose regulation in a system that is dominated by high intra- and inter-patient variability, long time delays, and presence of unknown disturbances such as diet, physical activity and stress levels.

This thesis presents a framework for blood glucose regulation with optimal insulin infusion which consists of the following steps: 1. Development of a novel physiologically based compartmental model analysed up to organ level that describes glucose-insulin interactions in type 1 diabetes, 2. Derivation of an approximate model suitable for control applications, 3. Design of an appropriate control strategy and 4. In-silico validation of the closed loop control performance. The developed model's accuracy and prediction ability is evaluated with data obtained from the literature and the UVa/Padova Simulator model, the model parameters are individually estimated and their effect on the model's measured output, the blood glucose concentration, is identified. The model is then linearised and reduced to derive low-order linear approximations of the underlying system suitable for control applications.

The proposed control design aims towards an individualised optimal insulin delivery that consists of a patient-specific model predictive controller, a state estimator, a personalised scheduling level and an open loop optimisation problem subjected to patient specific process model and constraints. This control design is modifiable to address the case of limited patient data availability resulting in an "approximation" control strategy. Both designs are validated in-silico in the presence of predefined, measured and unknown meal disturbances using both the proposed model and the UVa/Padova Simulator model as a virtual patient. The robustness of the control performance is evaluated in several conditions such as skipped meals, variability in the meal content, time and metabolic uncertainty.

The simulation results of the closed loop validation studies indicate that the proposed control strategies can achieve promising glycaemic control as demonstrated by the study data.

However, further prospective validation of the closed loop control strategy with real patient data is required.

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Notation

Modelling, Model Analysis & Optimisation

List of Acronyms

ADA	American Diabetes Association
AP	Artificial Pancreas
ATP	Adenosine triphosphate
CF	Correction Factor
CGMs	Continuous Glucose Monitoring systems
CHO	Carbohydrates
CID	Correction Insulin Dose
CL	Closed Loop
CR	Carb Factor
CSII	Continuous Subcutaneous Insulin Infusion
FDA	Food and Drug Administration
GSA	Global Sensitivity Analysis
HDMR	High dimensional model representation
IDDM	Insulin-dependent diabetes mellitus
IVGTT	Intravenous glucose tolerance test
JDRF	Juvenile Diabetes Research Foundation
M1,M2,M3	Model 1, Model 2, Model 3 (Insulin kinetics)
LADA	Latent autoimmune diabetes in adults
NIDDM	Non-insulin-dependent diabetes mellitus
OGTT	Oral glucose tolerance test
OL	Open Loop
RS-HDMR	Random sampling - high dimensional model representation
T1DM	Type 1 diabetes mellitus
TBV	Total Blood Volume
TDD	Total Daily Dose
WM	Wilinska Model (Insulin kinetics)

List of Variables

Symbol	Definition	Units
Q_i	Blood Flow	dL/min
Q_{CO}	Cardiac Output	mL/min
C_i	Glucose Concentration	mg/dl
$V_{g,i}$	Accessible glucose volume of compartment *i*	dL
u_i	Glucose uptake	mg/min
$r_{u,i}$	Ratio of glucose uptake	-
$r_{CO,i}$	Ratio of cardiac output	-
E	Excretion rate	mg/min
EGP	Endogenous Glucose Production	mg/min
Ra	Rate of glucose appearance	mg/min
p	Rate constant defined as the rate of loss of solute from blood to tissue	dL/min
PS	Permeability surface area product	dL/min
λo	Rate of glucose uptake	dL/min
I_p	Plasma insulin	pmol/L
I_d	Delayed insulin signal	pmol/L
M_L	Liver glucose mass	mg/kg
S_1, S_2	Insulin mass in the subcutaneous compartments	mU
I	Insulin mass in the plasma compartment	mU
u	Continuous insulin infusion	U/min

List of Parameters

Insulin Kinetics		
k_{sub}	Intercompartmental transfer rate constant	min^{-1}
V_{dist}	Insulin distribution volume	L/Kg
k_{elim}	Elimination rate constant	min^{-1}
Glucose Diffusion in the Periphery		
k_1	Rate parameter of insulin dependent glucose uptake	dL^2 per $pmol \cdot min^2$
k_2	Rate parameter of glucose uptake	min^{-1}
k_{2_PS}	Rate constant of permeability surface are product	min^{-1}
k_{1_PS}	Rate constant describing the effect of insulin on permeability surface are product	dL^2 per $pmol \cdot min^2$
Endogenous Glucose Production		
k_{p1}	Extrapolated EGP at zero glucose and insulin	mg/kg/min
k_{p2}	Liver glucose effectiveness	min^{-1}
k_{p3}	Lnsulin action on the liver	mg/kg/min per pmol/L
k_i	Rate parameters for the delay between insulin signal and action	min^{-1}
BW	Body Weight	kg
Rate of Glucose appearance		
k_{max}	Max gastric emptying	min^{-1}
k_{min}	Min gastric emptying	min^{-1}
k_{abs}	Rate constant of intestinal absorption	min^{-1}
k_{gri}	Rate constant of grinding	min^{-1}
k_{empt}	Rate of gastric emptying	min^{-1}
b	Percentage of dose for which *kempt* decreases at *(kmax-kmin)/2*	-
d	Percentage of dose for which *kempt* is back to *(kmax-kmin)/2*	-
f	Fraction of intestinal absorption	-
Glucose Excretion		
CL_{renal}	Renal glucose clearance	dl/min

Variable subscript denotation

Subscript	Denotation	Subscript	Denotation
i	Organ-Compartment	H	Heart
B	Brain	P	Periphery
K	Kidney	P_t	Periphery tissue
L	Liver	P,ISF	Interstitial Periphery
G	Gut		

List of Acronyms

CD	Control design
MPC	Model predictive control
QP	Quadratic Programming
CVGA	Control Variability Grid Analysis

List of Variables

Symbol	**Denotation**
A	State matrix
B	Input matrix
B_d	Input disturbance matrix
C	Output matrix
Cd	Output disturbance matrix
d_i	disturbance
M	Prediction Horizon
N	Control Horizon
Q	Weight Matrix for the states
Q_{KF}	Process noise covariance matrix of Kalman Filter
QR	Weight Matrix for the output
R	Weight Matrix for the input
R_{KF}	Measurement noise covariance matrix of Kalman Filter
R1	Weight Matrix for the change in the control input
ts	Sampling time
u	Control input
Δu	Step change in control input
υ	Measurement noise
w	Process noise
x	System states
y	System output
y^R	Reference point

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1. Introduction & Motivation

1.1 Introduction

Diabetes type 1 is one of the most prevalent severe chronic diseases of childhood. According to Diabetes UK, it is estimated that in the UK 2.6 million people have been diagnosed with diabetes in 2009, 15% of which have type 1 diabetes mellitus (T1DM) and according to (Patterson *et al.*, 2009) the incidence of T1DM is increasing worldwide reaching epidemic proportion (yearly incidence 15 cases per 100.000 people younger than 18 years old, in the United States). T1DM is a metabolic disorder that is characterised by insufficient or absent insulin circulation, elevated levels of glucose in the plasma and beta cells inability to respond to metabolic stimulus. It results from autoimmune destruction of beta cells in the pancreas which is responsible for secretion of insulin, the hormone that contributes to glucose distribution in the human cells. T1DM can cause serious complications in the major organs of the body such as heart, kidneys, eyes and nerves which develop gradually over the years.

Hence, it is important to define effective management strategies of treating T1DM. Patients with T1DM rely on exogenous insulin administration to maintain their blood glucose concentration within a normal range (80-140mg/dl). Insulin is administered either with daily subcutaneous insulin injections or with an insulin pump. Due to the nature of the treatment the controlled T1DM is reformulated from preventing hyperglycaemia to preventing hypoglycaemia. Hypoglycaemia is a life threatening condition that results from inadequate supply of glucose to the brain and causes 4-5% of deaths in T1DM. In order to overcome these complications improved glycaemic control is required. This can only be achieved when the patient continuously adjusts their insulin dose according to their blood glucose measurements. However, this manual control method is subject to several limitations, such as the requirement for patient's appropriate education and adherence to a specific lifestyle and increased risk of poor glycaemic control leading to hyper or hypoglycaemia. Inevitably patient lifestyle and quality of life are significantly affected by the treatment. Motivated by the challenge to improve the living conditions of a diabetic patient and actually to adapt the insulin treatment to patient's life rather than the opposite, the idea of an artificial pancreas that would mimic the endocrine function of a healthy pancreas has been well established in the scientific society.

1.2 The Artificial Pancreas

Currently the most advanced insulin therapy for diabetic patients is the use of an insulin pump. The insulin pump delivers a basal dose of rapid acting insulin and several bolus doses according to the meal plan of the patient. Good glycaemic control requires 4-6 measurements of blood glucose per day. These measurements, taken either by standalone fingersticks meters or by continuous glucose monitoring systems (CGMs), are entered into the pump usually by the user or by wireless connection. These measurements are an indicator whether insulin administration needs adjustment. A wireless connection of the pump data with a personal computer offers a good programming of the pump settings (Medronic, 2008).

The appropriate basal dose for a specific patient is set by the physician and can be modified to several profiles (week days, weekends). The bolus doses are set by the patient themselves, depending on the meal content, and indicated by the blood glucose levels.

The automation of this therapy constitutes the concept of the artificial pancreas. Essentially, the artificial pancreas is a device composed of a continuous glucose sensor, which reports blood glucose concentration approximately every 5 minutes; a controller implemented on smartphone, tablet or pc, which computes the appropriate insulin delivery rate according to the provided data from the sensor and signals the insulin pump to carry out the appropriate delivery of insulin. The insulin pump, the controller and the CGMs are wirelessly connected. This representation of an artificial pancreas is presented in Figure 1.1.

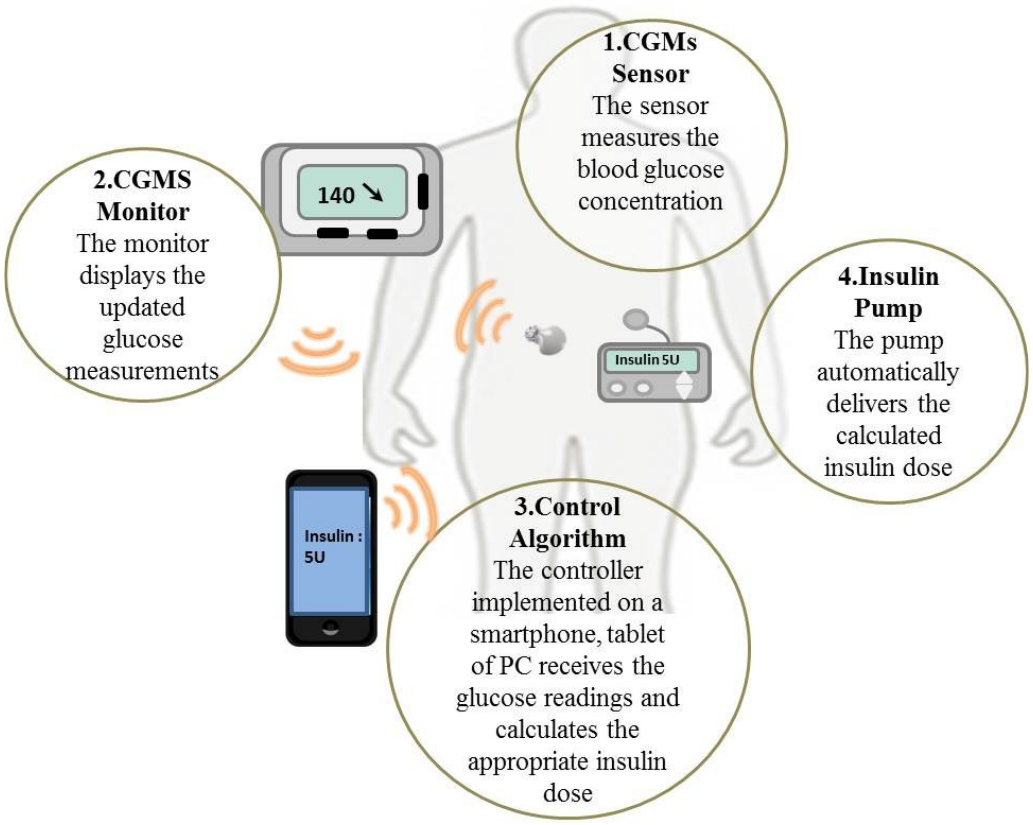


Figure 1.1: Schematic representation of an Artificial Pancreas

Many research groups worldwide have believed in this idea and the research society has directed their focus on the development of the key components for the production of the artificial pancreas. Pump and CGMs manufactures, as well as FDA (Food and Drug Administration) and several organisations for Diabetes, such as JDRF (Juvenile Diabetes Research Foundation) are involved in projects, by encouraging collaborations and solving practical issues in order to accelerate the design of the artificial pancreas. The challenges lie in the improvement of the control algorithms, the development of reliable platforms that incorporate the three features (controller, pump, CGMs) and resolving issues related mainly to the sensor technology.

1.2 Project deliverables

Towards the development of an artificial pancreas, this thesis focuses on two levels. The first level is the development of a detailed mathematical model that describes in depth the complexity of the glucoregulatory system in T1DM, presents adaptability to patient variability and demonstrates adequate capture of the dynamic response of the patient to various clinical conditions (normoglycaemia, hyperglycaemia, hypoglycaemia). The second level is the development of reliable model-based controllers that ensure safe and tight glucose

regulation. The closed loop insulin delivery system is formulated as a model predictive control problem, aiming to reach the desired target of blood glucose concentration subject to safety and operational constraints.

The general framework used for the control design to regulate the blood glucose concentration is presented in Figure 1.2 as modified by (Pistikopoulos, 2012) It involves the development of a high fidelity model that predicts the glucose-insulin dynamics in T1DM, the simplification of the original model with linearisation and model order reduction techniques to derive a reliable approximation of the system dynamics and finally the design of the appropriate control strategy. The involved steps are described analytically in the chapters mentioned in Figure 1.2.

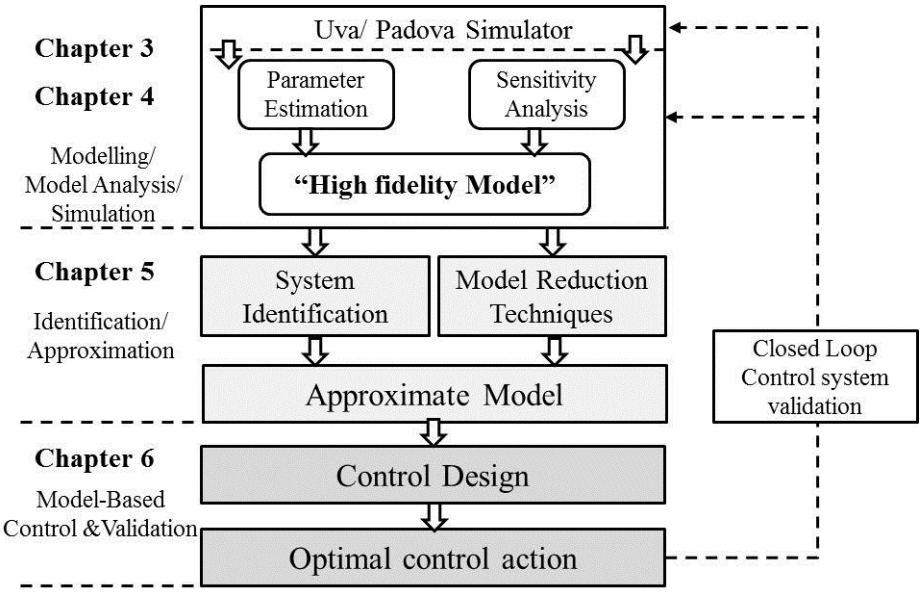


Figure 1.2: Framework for MPC controllers design adapted from (Pistikopoulos 2012)

Mathematical models are used to explain a system, analyse the effect of different components and predict future behaviours of the investigated system. In this context, an informative mathematical model of glucose-insulin interactions in T1DM is developed to understand the system physiology, investigate the effect of insulin and meal disturbances on glucose dynamics and use it as a predictive tool for optimisation and control studies. The proposed physiologically based model combines actual anatomical compartments to describe glucose metabolism and simple compartmental representation to describe insulin administration through the subcutaneous route. The reason why this approach was selected is to increase the level of understanding of the system's physiology using individualised parameterisation obtained from fundamental biomedical properties without the need for complex experimental evidence. Simultaneously, the limitation of experimental data to describe the involved

mechanisms of insulin diffusion, dissociation and absorption induced the use of simpler models that produce the desired output. Global sensitivity analysis is performed to investigate the influence of the parameters on the prediction ability of the model. The model parameters are estimated using data obtained from the UVa/Padova Simulator (B. P. Kovatchev, M. Breton, *et al.*, 2009) which are treated as real patient data. The UVa/Padova T1DMS has been accepted by the FDA for preclinical closed-loop control experiments by substituting animal trials as well as for clinical trials of closed-loop control based entirely on silico tests. Both the proposed model and the UVa/Padova model are simulated and programmed in gPROMS (PSE, 2011b). Issues of model identifiability are analysed and the parameter correlations are quantified in order to evaluate the robustness and validity of the proposed model. This process provides an indication whether the proposed equations require reformulation or re-parameterisation. The model describing individual dynamic responses can be used as a virtual patient for closed loop control validation studies.

Optimisation of insulin dosing minimises the risk of possible hypoglycaemia (over-dosing) and avoids hyperglycaemia (under-dosing). Rigorous optimisation studies are performed in gPROMS (PSE, 2011a) for 10 patients with T1DM on an insulin pump, using both the proposed model as well as the T1DMS model as the process model. The insulin bolus, given to compensate for food consumption, is optimised in terms of time to maximum effect. These results are compared with conventional insulin dosing and finally the insulin regimen that normalises the glucose curve more effectively – maintain blood glucose concentration within the normal range – is determined. Additionally, an alternative to bolus insulin dosing is evaluated and the two dosing types are compared in terms of their effect on glucose concentration. This study intends to identify the most effective dosing strategy to be further used as a background guideline in closed loop studies.

The original proposed model has 16 states. The model is simplified to a linear state-space model suitable for MPC and the control design is developed and evaluated in closed loop validation studies for different scenarios against firstly the original model and secondly the UVa/Padova T1DMS. Model based control design is a suitable control method for the studied system since it can handle constraints, which is the most crucial aspect of glucose regulation and it is able to control time delayed systems and disturbances. Therefore, there has been a wide use of MPC in the context of glucose regulation and many MPC strategies have been clinically evaluated (Hovorka *et al.*, 2014), (B. P. Kovatchev *et al.*, 2013), (Russell *et al.*, 2012), (Breton *et al.*, 2012), (Dassau *et al.*, 2013). The promising results indicate that MPC can be a potential strategy towards the artificial pancreas, and therefore the research on this

field has been intensified. The inherent complications of the system such as the occurrence of disturbances that have a major impact on the system's dynamics, the large time delays and the patient variability make the use of a simple controller insufficient for the optimal solution of the closed loop. Therefore, advanced control techniques are required to safely regulate the system. A generalised control framework is proposed which involves four parts, an MPC a state estimator, an optimiser/or a second MPC and a scheduler. Depending on the nature of the imposed disturbances different parts are activated. Two approaches are investigated i) a systematic approach which aims towards an individualised closed loop insulin delivery and ii) an "approximation" approach which aims towards a generalised applicability of the closed loop system.

1.3 Structure of the thesis

The rest of the thesis is organised as follows: Chapter 2 presents an introduction to the physiology of glucose regulation, the pathophysiology of T1DM and the current treatment approaches. An introduction to modelling of a biomedical system is presented, providing the theoretical background of pharmacokinetic and pharmacodynamic modelling. Finally, a literature review of the specific system of glucose-insulin interactions is presented. Chapter 3 involves the mathematical development of the proposed model for glucose metabolism and four alternative models of insulin kinetics. In Chapter 4 the most suitable model of insulin kinetics is selected by performing a series of model analysis tests. Additionally, a global sensitivity analysis of the entire model is performed to investigate the influence of the model parameters on the uncertainty of the model's prediction ability. The model parameters are estimated using data obtained from the UVa/Padova Simulator and the analytical results for all patients are presented in Appendix B1. Moreover, Chapter 4 presents open loop optimisation studies that on one hand deepen the understanding of the involved time delays of the system and on the other hand can be deemed as an alternative to model validation studies. Chapter 5 describes the available control methods evaluated in the literature as well as a brief introduction to MPC and Kalman Filter. Details about MPC can be found in Appendix B2. The derivation of the approximate model is presented in Chapter 5. Chapter 6 describes the proposed control strategies and the evaluation of the closed loop control performance. The conclusions of this thesis are presented in Chapter 7. Appendix A presents the model of UVa/Padova simulator and the control framework and studies performed using exclusively this model. Appendix B presents tabulations of the model parameters values for the studied patients. Finally, Appendix C describes an example of mpMPC in the context of closed loop

insulin delivery and Appendix D presents the MPC control specifications used in the proposed control strategies.

2. Modelling the T1DM System - An Overview

2.1 Introduction to Diabetes Mellitus

Diabetes Mellitus is a group of metabolic diseases characterised by elevated blood glucose levels. The pathogenesis of diabetes involves a defect in insulin secretion, action or both. Insulin is a hormone which is released from the pancreas and is responsible for glucose transportation in the body cells. Diabetes is a chronic medical condition, meaning that although it can be controlled, it lasts for a lifetime.

Classification

There are two main types of diabetes. Type 1, or previously known as Insulin-dependent diabetes mellitus (IDDM), and type 2 or as formally called non-insulin-dependent diabetes mellitus (NIDDM). The terms IDDM and NIDDM are no longer used because, according to the revised classification of the World Health Organization (World Health Organization, 1999) and the ADA (American Diabetes Association, 2008), these terms have been confusing since they categorised the patients based on the treatment rather than the pathogenesis. Hence, according to the revised classification T1DM, which results from autoimmune mediated destruction of the beta cells of the pancreas, is called Type 1A. It is usually diagnosed in children and young adults, which is why it was previously known as juvenile diabetes. The rate of beta cell destruction is quite variable. In children and adolescents it is very rapid, while there is a form of slow deterioration of metabolic control that may occur later in life called latent autoimmune diabetes in adults (LADA). Additionally, there are some forms of T1DM that have no known aetiology. Clinical conditions such as permanent insulinopenia and proneness to ketoacidosis may appear, but no evidence of autoimmunity is observed, especially among individuals of African and Asian origin. This form is called either Type 1B diabetes or idiopathic type 1 Diabetes.

Type 2 diabetes is the most common form of diabetes. Its key pathognomonic feature is relative (rather than absolute) deficiency of insulin. It is more prevalent in people aged over 40, but nowadays it is becoming more common in children and young people of all ethnicities. The aetiology of type 2 diabetes is still not fully understood but several predisposing factors have been identified, such as obesity, sedentary lifestyle etc. This type

of diabetes frequently remains undiagnosed for many years, because its symptoms are not severe enough to provoke noticeable evidence of the disease.

Another common type of diabetes is gestational diabetes, which can occur transiently during pregnancy. This type of diabetes includes cases in which glucose intolerance is first recognised during pregnancy and also cases that glucose intolerance may precede pregnancy but has not been previously recognised. In most cases, gestational diabetes resolves after delivery but these patients are high risk for developing diabetes type 2 later in life.

Other specific types of diabetes have also been recognised and attributed to different causes such as genetic, exocrine pancreatic, endocrine and drug- or chemically- induced.

Prevalence and incidence of T1DM

Prevalence of a disease in a statistical population is the proportion of people in the population who have the disease at a given time. It is a factor that represents how common a condition is within a population. According to American Diabetes Association, 1 in 400-600 children and adolescents in the USA have T1DM. Internationally, Scandinavia has the highest prevalence rates for T1DM (20% of the total number of people with DM), while China and Japan have the lowest prevalence rates, with less than 1% of all people with diabetes (Khardori, 2014).

Incidence is the rate at which new cases of the disease appear in a population (usually 100.000 persons) within a specified time period (i.e. per annual). According to (Onkamo *et al.*, 1999) and (Patterson *et al.*, 2009) the incidence is increasing worldwide and not only in the populations with high incidence such as Finland (2010: 50/100000 a year) but also in low incidence populations (30/100000 a year).

The incidence of T1DM is dependent on the geographic location, ethnicity, gender and age (Steck and Rewers, 2004). The incidence presents wide variability in geographic location, with higher incidence in the Northern hemisphere exceeding 15/100000. There is also an additional within-country variability, for example in the US, non-Hispanic Whites are 1.5 times as likely to develop T1DM as African Americans or Hispanics (Steck and Rewers, 2004) which indicates that T1DM is related to racial composition of the population. But a study showing that migrants presented adaptability to the incidence of the country in which they are living reflects an impact of environmental factors on the disease aetiology. According to “The Diamond Group Project” (The DIAMOND Project Group, 2006) there is no significant difference in the risk of developing T1DM among males and females, but there is a difference in incidence rate between age groups, with a peak occurring at puberty.

The following figure shows the incidence of T1DM worldwide, for the years 1990-1999, data were obtained from (The DIAMOND Project Group, 2006)

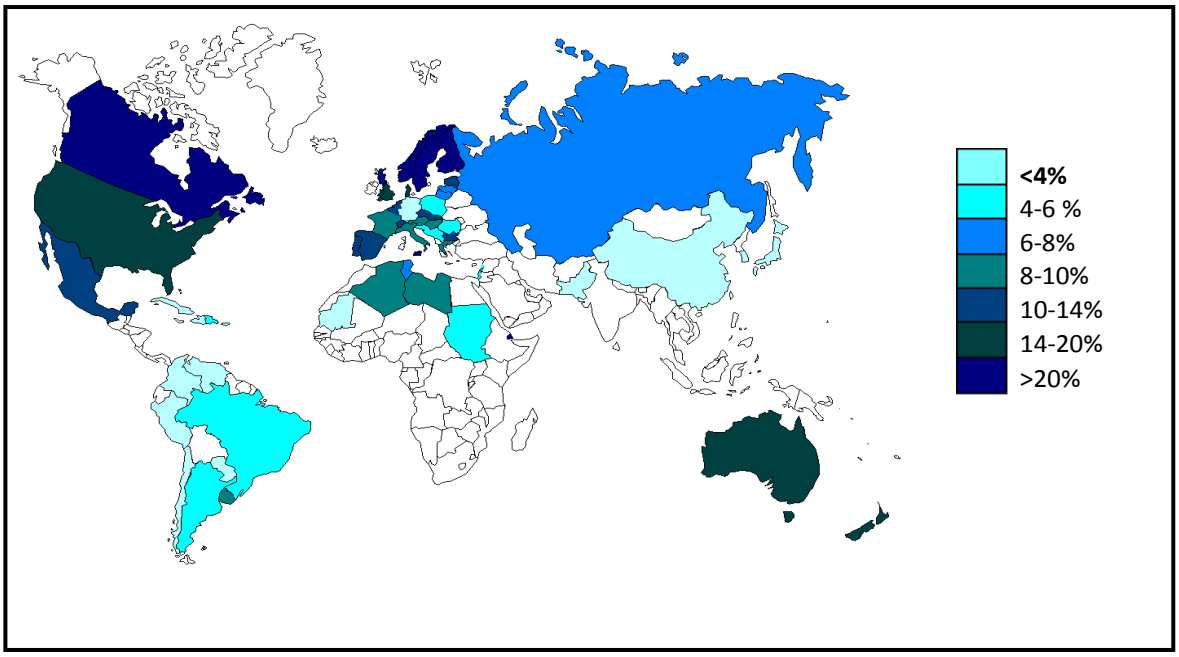


Figure 2.1: Incidence of T1DM worldwide, data from (Onkamo *et al.*, 1999)

2.1.1 Physiology

The body cells require continuous supply of glucose to perform their normal metabolic activities, since glucose is the major source of cellular energy. Blood glucose concentration should be maintained within a very narrow range in order to meet the metabolic requirements of vital organs such as the brain. The regulation of blood glucose is achieved with the contribution of many hormones, with the most crucial being insulin and glucagon. The following section focuses on: (i) glucose sources and role, (ii) pancreas contribution to glucose regulation with insulin and glucagon secretion and finally (iii) the hepatic function in metabolism.

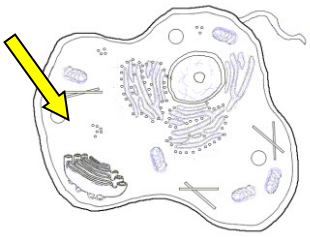
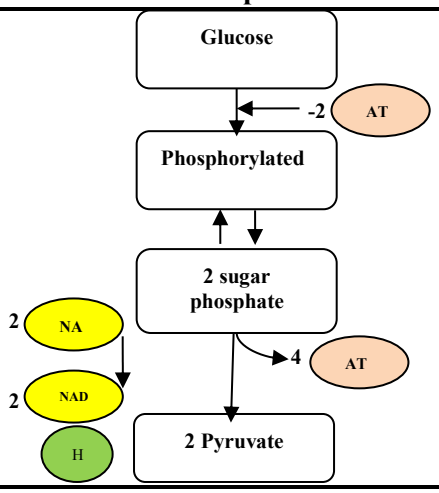
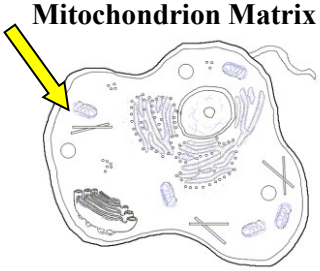
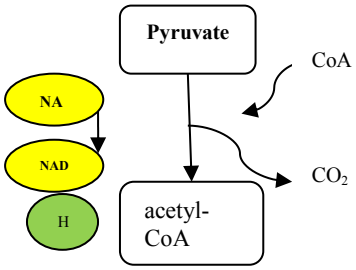
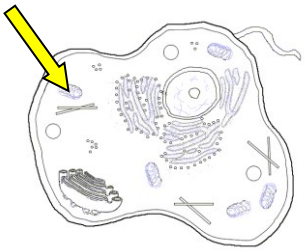
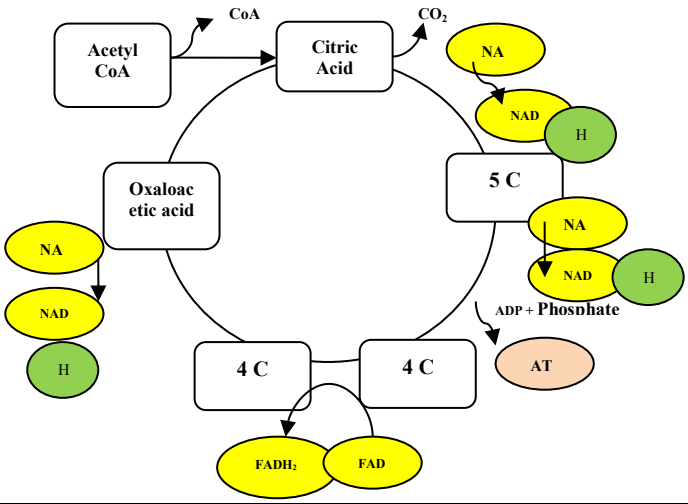
2.1.1.a Glucose

Carbohydrates are an essential nutrient as the major source of glucose for the human body. Glucose $C_6H_{12}O_6$ is a monosaccharide which plays a very important role in human biology. It constitutes the major source of accessible energy for the body cells, in addition to amino acids portions of proteins and fatty acids. Energy in biology is translated in ATP (Adenosine triphosphate) which is often called as the "molecular unit of currency" of intracellular energy

transfer. The overall reaction that takes place is the oxidation of fuel substrates to carbon dioxide and water in the presence of oxygen:

Glucose + Oxygen →Energy + Carbon dioxide + Water

Table 2.1: The mechanisms of energy production through glucose

Metabolic Mechanism	Location	Description
1.Glycolysis Glucose is converted to pyruvate through a series of 10 enzymatic reactions. 7 of these reactions are reversible (gluconeogenic direction). In organs where gluconeogenesis can take place (liver, kidney) there are enzymes which activate the reverse direction of the irreversible glycolytic reaction.	**Cytoplasm** 	
2.Pyruvate decarboxylation Pyruvate enters the mitochondria and through an enzymatic reaction activated by pyruvate dehydrogenase complex it is converted to acetyl-CoA.	**Mitochondrion Matrix** 	
3.Krebs Cycle During the chain of the enzymatic reactions that constitute the tricarboxylic acid cycle (TCA) the metabolic fuel is oxidised. Generally fatty acids and amino acids can also be oxidised through the TCA cycle.(DeFronzo, 2004) The TCA cycle activates electrons transportation (following mechanism)	**Mitochondrion Matrix** 	

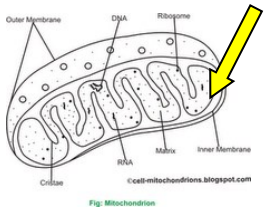
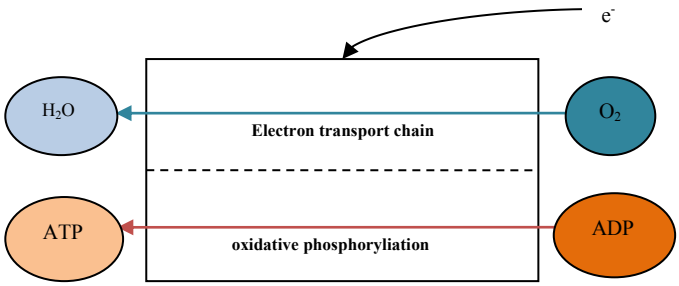
4. Oxidative phosphoryliation	Inner Mitochondrion Membrane	
Process during which ATP is produced, by using the energy released in the electron transport chain (Smeitink, 2004)		

Table 2.1 presents a brief description of aerobic respiration. In cases of insufficient oxygen, for example during intense exercise, muscle cells can perform anaerobic respiration, which incorporates all the metabolic paths described previously, but instead of O_2 as an electron receptor, other electronegative substances are used.

2.1.1.b Pancreas: insulin, glucagon

One of the most important organs that are responsible for glucose regulation is the pancreas. A small region (2% approximately) of the pancreas mass, called the Islets of Langerhans, is responsible for the production of the endocrine hormones. It contains 3 types of cells, a-cell where glucagon is synthesised, b-cell for insulin and amylin synthesis and d-cells for somatostatin synthesis and the PP cells which secrete pancreatic polypeptide. The remaining 98% of the pancreas mass is responsible for exocrine secretions.

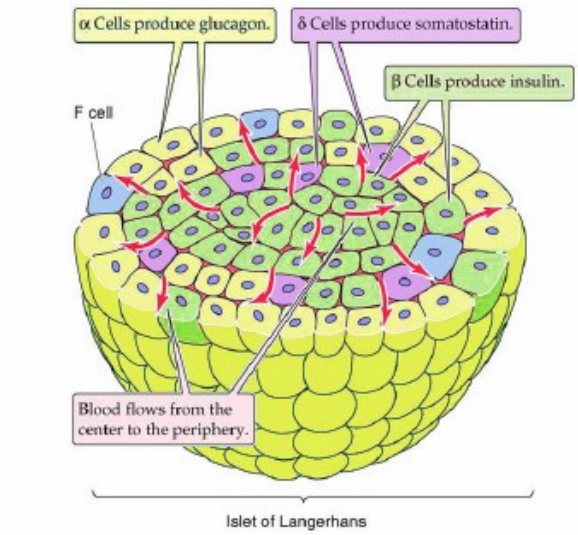


Figure 2.2: Islets of Langerhans adapted from (Parlerm, 2003)

The insulin molecule

Synthesised in b-cells of the pancreas, insulin is a dipeptide consisting of A and B amino chains. Initially a precursor molecule, preproinsulin, is synthesised (Ferrannini and DeFronzo, 2004) which is translated to proinsulin. In this form the A and B chains are linked to a polypeptide, known as a connecting peptide or C-peptide. C peptide is released and insulin is produced. Because both insulin and C-peptide are secreted from b-cells, C-peptide can be used as an indicator of the levels of endogenous insulin production when exogenous insulin is administrated.

Insulin action

Insulin is an anabolic hormone which plays a vital role in human metabolism. The main anabolic actions which insulin performs are:

1. enabling glucose uptake by muscle cells and adipose tissue

Insulin acts as a key that opens up the cell so as to accept glucose. Insulin binds to insulin receptors located on the cellular membrane and a complex series of protein reactions is activated, leading to the translocation of GLUT-4, a glucose receptor, from the intracellular area to the cell membrane and finally the influx of glucose into the cell, where glucose is metabolised and supplies the cell with energy (Nussey and Whitehead, 2002).

2. glycogenesis (glycogen synthesis)

Insulin has several effects which stimulate glycogen synthesis in the liver and in the muscles, such as activation of glucose phosphorylase (required enzyme for the synthesis) and inhibition of the reverse action. Glucose uptake from the liver is not dependent on insulin because the responsible glucose receptor of the hepatocytes is GLUT2, which is not activated by insulin, contrary to glucose uptake from the muscles (Nussey and Whitehead, 2002).

3. glycolysis

Insulin regulates glycolysis, because it provides the metabolic path with available substrate (glucose) and it affects the rate of transcription of the enzymes which catalyse some steps of glycolysis (Meisler and Howard, 1989), (Iynedjian, Gjinovci and Renold, 1988).

4. lipogenesis (adipocytes)

Insulin stimulates the convertion of acetyl CoA to fatty acids and then to triglycerides, by the activation of glycolytic enzymes (Kersten, 2001). Lipogenesis is also amplified because insulin enhances glucose uptake from adipocytes.

5. protein synthesis

Insulin determines protein synthesis by increasing the content of ribosomes with amino acids and by restricting protein breakdown.

6. amino acids transport into cells

The transport rate of amino acids into the cells is increased due to insulin.

Apart from anabolic effects insulin contributes to preventing catabolic actions. In particular, in the liver insulin inhibits glyconeogenesis, glycogenolysis and ketogenesis; in the muscles the breakdown of proteins and in the adipose tissue the breakdown of lipids.
Generally, the body detects that blood glucose levels rise and normally the pancreas secrete insulin to account for that alteration in glucose concentration, as a response to several stimulators. Initially an increase in blood glucose concentration provokes an immediate release of insulin that has already been synthesised and stored in the b-cells. This response is the distinct first phase of the biphasic insulin secretion. Then the newly synthesised insulin is released for as long as the glucose levels are elevated. There are other factors that function as b-cells stimulators, such as certain amino acids, fatty acids, several gastrointestinal hormones and activity of the parasympathetic nervous system. While insulin is being released, glucose can enter the body cells, can be stored as glycogen in the liver until the concentration is between the normal range and insulin release can be stopped.

Glucagon

Another important hormone controlling glucose metabolism is glucagon known as counter-regulatory hormone, because it acts in opposition to insulin, being the major hormone regulating the fuel mobilisation and catabolism. Glucagon's action is located specifically in the liver and is responsible for stimulating the breakdown of glycogen to glucose and for the production of glucose from lactate, glycerol and mainly amino acids. These pathways are the

mechanisms of hepatic glucose production (Griffin and Ojeda, 2004). These mechanisms are better understood than that of insulin (Storey, 2005). Furthermore glucagon is responsible for regulating the rate of oxidation of free fatty acids that enter the liver, and the consequent production of ketones which enter the bloodstream.

Glucagon release is regulated by both insulin and glucose. In case of low blood glucose levels, hypoglycaemia, due to fasting or exercise, the a-cells of the pancreas produce and release glucagon that activates the conversion of glycogen to glucose. Normally, the release of glucagon occurs when blood glucose concentration is 50mg/dl. When blood glucose levels rise above 150 mg/dl glucose production is minimised, with a mechanism which is not fully understood (Storey, 2005).

Other counter regulatory hormones which have catabolic action, similar to glucagon can be seen in Figure 2.3.

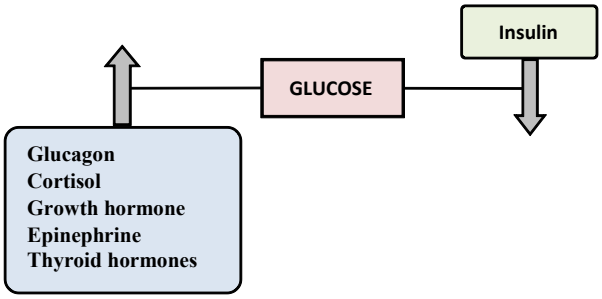


Figure 2.3: Impact of insulin and other counter regulatory hormones on glucose levels

2.1.1.c The Liver

The liver is the main regulator of glucose metabolism. It can store glucose as glycogen when glucose levels are high and release glucose when it is required. Hepatic glucose production is the second source of glucose in the blood apart from exogenous glucose influx, derived from carbohydrates breakdown. In healthy people, hepatic glucose production is high during the fasting state. This rate decreases in response to the rise of blood glucose and the consequent insulin secretion from beta cells. Net hepatic glucose production is defined as the difference between the pathways which stimulate glucose formation (gluconeogenesis, glycogenolysis) and those that contribute to glucose consumption or storage (glycogen synthesis, glycolysis, pentose monophosphate shunt). As it has already been mentioned, the hormones controlling these actions are insulin and glucagon, insulin contributes to glucose disposal and glucagon to glucose production.

In Figure 2.4 the overall flow of fuels and the actions of insulin and glucagon in the liver, muscles and adipose tissue are illustrated:

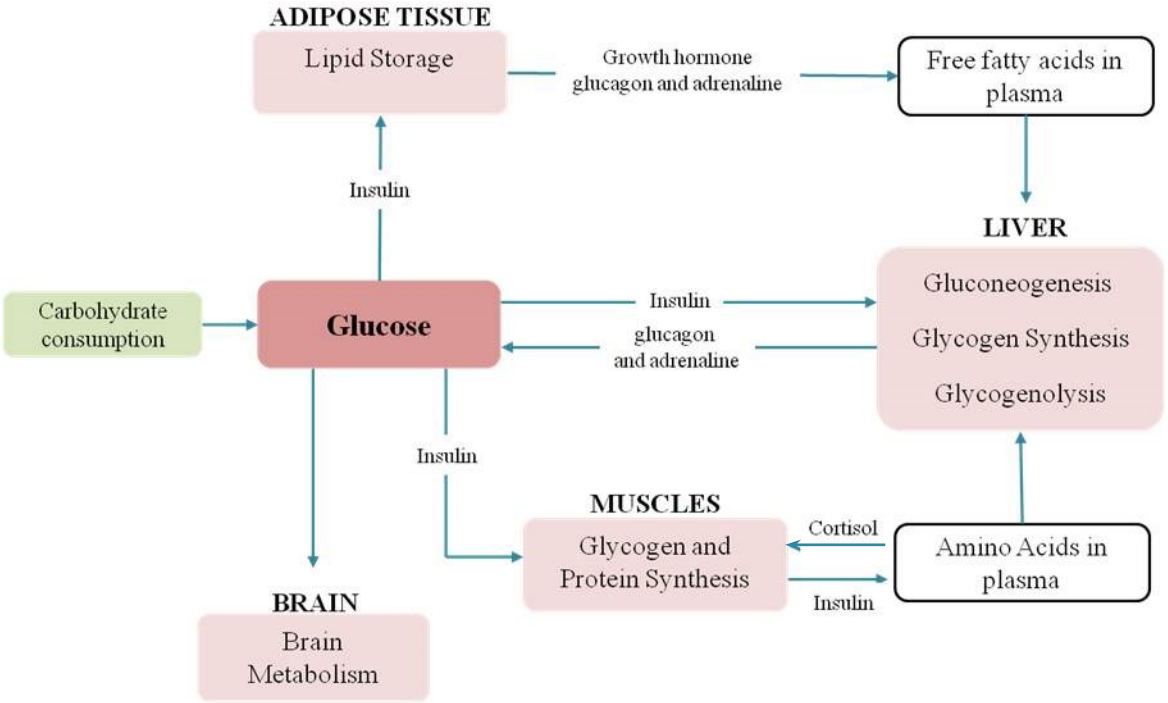


Figure 2.4: The overall flow of fuels and the actions of insulin in the liver, muscles and adipose tissue, adapted from (Pocock, Richards and Richard, 2006)

2.1.2 Pathophysiology and T1DM

T1DM is a catabolic disorder characterised by insufficient or absent insulin circulation, elevated levels of glucagon in the plasma and b-cells inability to respond to metabolic stimulus. It results from autoimmune destruction of b-cells originates from genetic or environmental factors.

It is suggested (Knip *et al.*, 2005) that there is a genetic susceptibility to the disease development, and the exposure to environmental agents triggers the onset of diabetes type 1. A preclinical period up to 13 years has also been identified. This is characterised by hyperglycaemia for a few years progressing to clinical diabetes when the complications begin to appear (Steck and Rewers, 2004), (Khardori, 2014).

2.1.2.a Complications of T1DM

T1DM can cause serious complications in the major organs of the body. Problems in the heart, kidney, eyes and nerves can potentially develop gradually over years. The risk of the complications can be decreased only by optimal glycaemic control. In detail, the long-terms complications encompass:

Macro vascular complications (disease of any large (macro) blood vessels)

An environment of high glucose conditions stimulates the adhesion of monocytes to arterial endothelial cells. The monocytes, in turn, take up lipids and their accumulation in the artery walls lead to increased levels of atherosclerosis (Chait and Bornfeldt, 2009).

Depending on the location of the affected artery, the following diseases can occur:

- Coronary artery disease (coronary arteries-ischemic heart disease)
- Cerebral vascular disease (carotid artery-stroke, Transient ischemic attack)
- Intermittent claudication (iliofemoral and smaller arteries of the lower legs-gangrene)

Micro vascular complications

Caused by wall thickening of small arterioles and capillaries and include:

- Diabetic retinopathy (can lead to glaucoma, cataracts or even blindness)
- Diabetic nephropathy (can lead to chronic renal failure)
- Diabetic neuropathy (leads to ulceration-diabetic foot)

Other complications may include skin infections, hearing complications, increased risk fordeveloping osteoporosis and complications during pregnancy.

2.1.2.b Symptoms of T1DM

Diabetes type 1 onset can be very sudden and usually the symptoms and signs are very obvious and can develop over a few weeks. The most common symptoms are polyuria, polydipsia, polyphagia with weight loss, tiredness, muscle cramps and blurred vision.

Main Symptoms

Polyuria: due to osmotic diuresis (increase in the osmotic pressure within the kidney tubules, caused by the presence of glucose, that leads to a reduced reabsorption of water and to an increased urine output) leading to nocturnal enuresis especially in young children.

Polydipsia: usually as a result of osmotic diuresis (with the amount of water leaving the body being greater than the amount being taken in) leading to dehydration.

Polyphagia with weight loss: weight loss in the presence of normal or increased appetite is due to stored fat breakdown as an alternative supply of energy to the body cells.

Tiredness: caused by muscle wasting, hypovolemia (decrease in volume of blood plasma due to dehydration), hypokalaemia (urinary loss).

Other Symptoms

Muscle cramps: due to muscle fatigue and electrolyte imbalance (hypokalaemia)

Blurred vision: caused by the lens of the eyes becoming very dry

Itchiness around the vagina or penis: caused by glucose excess in the urine

Gastrointestinal symptoms: Nausea, abdominal discomfort or pain, constipation, usually accompany other causes such as neuropathy, pancreatitis, DKA
Younger children (<7years old) present more severe symptoms because they lose approximately the 80% of the islets compared to 60% in children 7-14 years old and 40% in children older than 14 years old.

2.1.2.c Diagnostic Tests for T1DM

Diagnosis of T1DM

- Blood Glucose Test

Fasting Plasma glucose: 2 samples greater than 125mg/dl (i.e. 6.99 mmol/L) according to ADA
Random plasma glucose (for symptomatic patients): 200mg/dl

- Urinalysis for glucose, ketones and protein
- Physical examination

On-going monitoring of diabetes control

- Glycosylated haemoglobin (Hb) or Hb A1c: Glucose molecules react with haemoglobin, forming glycated haemoglobin. Once a haemoglobin molecule is glycated, it remains that way. The HbA1c level is proportional to average blood glucose concentration over the previous four weeks to three months, a period which reflects the life span of a red blood cell. (HbA1c>6.5% indicates DM)

- Fructosamine blood test: Glucose molecules react with the amino group of proteins, forming fructosamines which reflect glucose control in the previous 1-3 weeks
- Oral glucose tolerance test with insulin levels
- C-peptide/ insulin level test
- Islet cell antibodies
- Self-managed blood glucose testing
- Fingerpick blood drop blood glucose tests
- Urine glucose home testing
- Urine ketone home testing

2.1.2. d Treatment

Diabetes type 1 requires administration of exogenous insulin, which replaces the body's own insulin in order to maintain the blood glucose within a normal range. In general, for patients with T1DM, intensive insulin treatment is recommended. Conventional (standard) insulin therapy is suggested only in special cases. In order to achieve tight blood sugar control, intensive insulin therapy requires frequent insulin injections or the use of an insulin pump, to check blood glucose concentration at least 4 times a day and to follow specific eating and exercise plans.

Occasionally, there is a period following the diagnosis of diabetes that the patient doesn't present any symptoms of the previously mentioned and the blood sugar levels improve to normal or near-normal, levels. This so- called "Honeymoon period" is due to remaining islets of Langerhans which begin to recover their ability to produce endogenous insulin. This period may last for several weeks or months.

Insulin schedules

Insulin schedules consist of multiple subcutaneous insulin injections which are administrated throughout the day with regard to blood glucose control (avoid hyperglycaemia or hypoglycaemia). Usually a background or long acting insulin is taken at bedtime, and rapid acting insulin is taken before meals. The schedule is individualised depending on the patient's

characteristics and needs (meal plan, activities). It should also be flexible to adjust to changing daily routines (holidays, fasting).

CSII

Continuous subcutaneous insulin infusion (CSII) therapy or insulin pump is a small, battery-operated pump that is worn on the body and infuses continuously rapid-acting insulin (Medronic, 2008) through a cannula inserted under the skin. The pump can provide the patient with a continuous basal rate of insulin and manually the patient can administrate bolus doses before each meal, according to the current blood glucose level and the content of carbohydrates in the meal.

It can be stated that successful treatment of diabetes type 1 requires the contribution of a physician, nurse, dietician and the patient's and family's appropriate education and motivation. Particularly important is the patient's diet that should be configured according to the patient's nutrition habits, but should consist of a specific caloric plan and specific daily intake of carbohydrates, proteins and fat subjected to timing, size and composition management of each meal. Furthermore daily activity is highly recommended to patients and adjustment of insulin therapy and nutrition should be taken into account.

2.1.2.e Types of insulin

There are three kinds of insulin, according to its origin: a. animal insulin, b. recombinant insulin or "Human" insulin and c. insulin analogues (Mohan, 2002). Animal insulin is extracted from the pancreas of healthy animals (such as beef, pork and salmon) and then is highly purified. Although this product is very cheap (Mohan, 2002) it is used less frequently in the developed countries due to fear of immunogenic reactions caused by contaminated preparations and due to the rapid increase of the demand during the 70s, that could not be covered by the existing supplies. Consequently biosynthetic methods of synthesizing insulin were developed to ensure that there would always be available supplies. The production of "Human" insulin is based on either recombinant DNA technology by using E. coli and yeast cells, or on alteration of the structure of animal insulin. Ultimately, insulin analogues are genetically produced starting from "Human" insulin with further alteration in the amino chains that finally are different from any occurring in nature. These modifications can produce two types of insulin, the rapid acting insulin which is monomeric and hence it is easily absorbed and biologically active; and the long acting insulin, preparations which

contain a high proportion of hexamers and its slow diffusion is appropriate to cover the daily basal rate.

Insulin, regardless of the preparation method, can be classified according to the following three characteristics: the onset (length of time before insulin reaches the bloodstream and begins lowering blood glucose), the peak time (time during which insulin is at maximum strength in terms of lowering blood glucose), and duration (how long insulin continues to lower blood glucose). In Table 2.2 the characteristics of the typical types of insulin can be observed.

Table 2.2: Characteristics of Insulin(American Diabetes Association)

	Rapid acting	**Regular**	Intermediate-acting	**Long-acting**
Onset	5min	30min	2-4hr	6-10hr
Peak time	1hr	2-3hr	4-12hr	Peakless profile
Duration	2-4hr	3-6hr	3-6hr	20-24hr

The following table shows in detail the commercially available types of insulin and their mixtures.

Table 2.3: Commercially available types of insulin and their mixtures

Generic name (U-100 except where noted)	**Brand name**	**Form**	**Manufacturer**	**Cloudy or Clear**
Rapid acting				
Insulin glulisine	Adidra*	analog	Sanofi-Aventis	Clear
Insulin lispro	Humalog*	analog	Eli Lilly	Clear
Insulin aspart	Novolog*	analog	Novo Nordisk	Clear
Regular				
Regular	Humulin R **	human	Eli Lilly	Clear
Regular	Novolin R*, ReliOn (Wal-Mart)	human	Novo Nordisk	Clear
Intermediate-acting				
NPH	Humulin N*	human	Eli Lilly	Cloudy
NPH	Novolin N*, ReliOn(Wal-Mart)	human	Novo Nordisk	Cloudy
Long-acting				
Insulin detemir	Levemir*	analog	Novo Nordisk	Clear
Insulin glargine	Lantus*	analog	Sonofi-Aventis	Clear
Mixtures				
70%NPH/30%regular	Humulin 70/30*	human	Eli Lilly	Cloudy
70%NPH/30%regular	Novolin 70/30*#, ReliOn(Wal-Mart)	analog	Novo Nordisk	Cloudy
50%lispro protamine/50%insulin lispro	Humalog Mix 50/50*	analog	Eli Lilly	Cloudy
75%lispro protamine(NPL)/25%lispro	Humalog Mix 75/25*	analog	Eli Lilly	Cloudy
70%aspart protamine/30%aspart	NovoLog Mix 70/30*#	analog	Novo Nordisk	Cloudy
Less commonly used insulin				
Regular	Humalin R U-500**$	human	Eli Lilly	Clear
50%NPH/50%regular		human	Eli Lilly	Cloudy

** Available in prefilled, disposable pens or cartridges for reusable pens*

*** Note difference between Humulin R and Humulin R U-500*

#Note difference between Novolin 70/30 (70% NPH/30% regular) and NovoLog Mix 70/30 (70% aspart protamine/30% aspart)

$U-500 and U-100 are different concentrations of insulin. U-500 is typically used in very insulin-resistant people

2.2 Literature Review

2.2.1 Modelling the drug delivery system

From the moment a therapeutic agent is administered in the human body until the desired therapeutic effect becomes apparent, there are numerous mechanisms and factors involved that play a substantial role to the drug's therapeutic efficacy. In an effort to maximise the drug's efficacy and increase the patient's safety, modelling the entire drug delivery process has become a very useful tool for understanding, simulating, optimising and predicting patient's response to the drug. This is achieved through pharmacokinetic and pharmacodynamic studies. The pharmacokinetics describe mechanisms such as drug metabolism, transport, absorption, distribution, diffusion and elimination, (the effect of the body on the drug). The pharmacodynamics, on the other hand, describe the effect of the drug on the body and is usually expressed mathematically by dose-response relations. A brief description of the established ways to model the pharmacokinetics and pharmacodynamics is presented below.

2.2.1.a Pharmacokinetic Modelling

Compartmental Models

One of the most common modelling approaches to describe the pharmacokinetic process is the compartmental modelling. This approach assumes that the drug molecules act inside the considered compartments, and explicit mathematical expressions of the drug concentration in each compartment are determined (Hladky, 1990). The simplest case is to represent the human body as a single compartment in which the drug is administered and eliminated, as shown on the left hand side of Figure 2.5. The basic assumption in compartmental modelling is that the concentration of the drug inside the compartment is constant, in other words, there is instant homogeneous distribution of materials within a compartment. A single compartment can be considered only when there is a very rapid distribution of the drug from the central compartment (the plasma) to the peripheral compartment (the equilibrating tissues). Usually, this approach describes intravenously injected well-diffused drugs whose elimination follows first-order kinetics. If that is not the case, usually because of slow diffusion of the drug to the peripheral tissues, additional compartments should be considered (right hand side of Figure 2.5). There are several drawbacks of the compartmental analysis, such as the correlation of the model parameters (e.g. transfer coefficients) to physiological parameters, as well as

difficulties related to the determination of the appropriate number of compartments that should be used to represent the pharmacokinetics of the entire population.

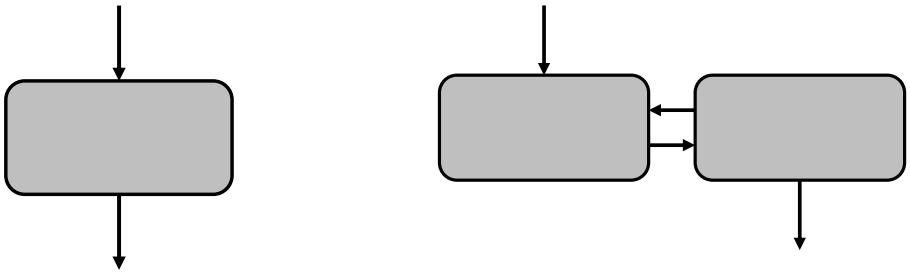


Figure 2.5: Single Compartment (left hand side), two compartmental approach (right hand side)

Physiological Models

To overcome the difficulty of relating the model parameters (compartment's volume, transfer rate between compartments) to physiological features in compartmental modelling, physiological models have been developed. The physiological models take advantage of a priori knowledge of the mechanisms involved in the drug action and the mathematical representation reflects the administration, diffusion and elimination of a drug in every organ of the body. This approach requires deeper understanding of the physiology but provides detailed and explicit representation of the drug delivery system. The advantages of physiologically based models over compartmental/empirical models include the ability to be extrapolated between different species and different drug dosages (Saltzman, 2001), (Cashman *et al.*, 1996). The main drawback of physiologically based models is that sometimes certain parameters cannot be measured and their values are difficult to be accurately predicted.

Figure 2.6 illustrates a schematic of a physiological pharmacokinetic model. The grey arrows represent the routes of a drug administration: inhaled, intravenous, oral, intramuscular. The black arrows show the elimination from several compartments depending on the route of administration.

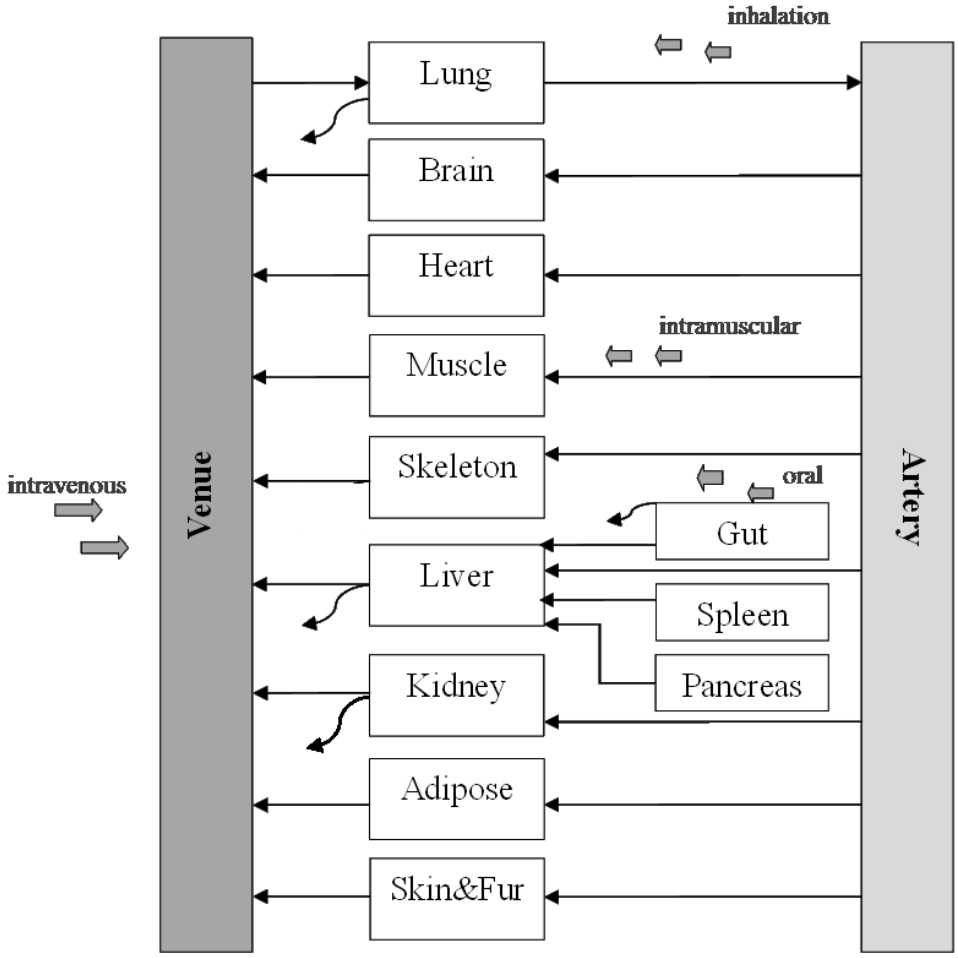


Figure 2.6: physiological modelling, adapted from (http://aiche.confex.com/aiche/2008/webprogram/Paper138436.html)

Simplifications in the previous schemes can be made depending on the exact system which is studied. In Figure 2.6, organs which do not contain important amounts of the drug agent can be neglected (Saltzman, 2001). Every organ can be described with more than one compartment when a more detailed representation is required. Accordingly, the scheme of Figure 2.7 can be changed in cases where wall permeability of either the capillary or cell membrane or both is high, and the corresponding transport through the membranes is rapid. In such cases, the respective compartments can be lumped in two or just one (Sorensen, 1978).

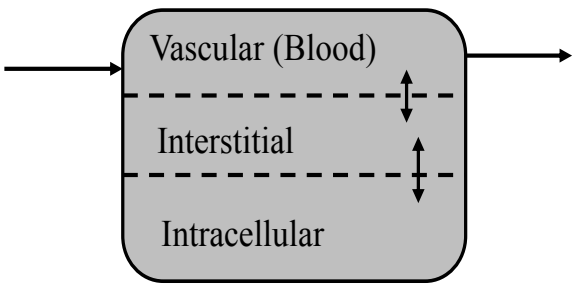


Figure 2.7: Organ compartmental analysis

2.2.1.b Pharmacodynamic Modelling

Modelling the pharmacodynamics of a system (i.e. the effect of a drug on the human body) is essentially connected to pharmacokinetic modelling because the profile of drug concentration (pharmacokinetic model) is required to estimate the parameters that describe the consequent effect. Usually, precise measurements of the drug effect cannot be easily obtained, so in practice the pharmacodynamic model is determined by testing potential models and estimating the parameters when a reference pharmacokinetic model is used.

Pharmacodynamic models assume that the concentration of the drug is in equilibrium with the effect site, which could only hold at steady state, and therefore the pharmacodynamic expression cannot be complete without the combined usage of a pharmacokinetic model.

Table 2.4 briefly presents types of empirical pharmacodynamic models proposed in the literature:

Table 2.4: The most common types of empirical pharmacodynamics models (adapted from (Holford and Sheiner, 1982)

Model	Model Equations	Description
Fixed Effect Model	Effect: Present (1) or Absent (0), or degree of effect	
Linear Model	$E = S \cdot C + E_o$	E=drug effect, C=drug concentration, S=slope parameter, E_o= initial drug effect
Log-linear Model	$E = S \cdot \log C + I$	E=drug effect, C=drug concentration, S=slope parameter, I=constant
E_{max}Model	$E = E_o - \frac{E_{\max} \cdot C}{EC_{50} + C}$	E= drug effect, C=drug concentration, E_{max}= maximum drug effect, E_o= initial drug effect from previous application, EC_{50}=concentration producing half of the maximum drug effect
Sigmoid E_{max}model	$E = \frac{E_{\max} \cdot C^n}{EC_{50}^n + C^n}$	E= drug effect, C=drug concentration, E_{max}= maximum drug effect, E_o= initial drug effect from previous application, EC_{50}=concentration producing half of the maximum drug effect,n= constant affecting the shape of the drug effect-concentration curve

2.2.1.c Applications

A model of a biomedical process is an analogue of the studied system. The reason why a process is modelled determines the complexity of a proposed model. Two of the most common applications of modelling of biomedical systems are the development of virtual patients or patient simulators and the development of reliable predictive tools for control studies. A patient simulator is used for educational purposes such as AIDA developed by (Lehmann & Deutsch, 1992) or it can substitute clinical trials to determine optimal drug doses that produce effective and safe responses, such as the UVa/Padova Simulator (B. P.

Kovatchev, M. D. Breton, *et al.*, 2009) These models have a strong relevance to physiology. The models derived for control purposes are usually simpler and can also be empirical. The aim of these software tools is to provide the doctor with a decision advice, acting as a therapeutic advisory system in a model based control context.

2.2.2 Modelling the glucose-insulin system in T1DM

In the last 35 years a large number of models describing the glucose-insulin interaction system have been developed. Usually, the system is divided in insulin pharmacokinetics and glucose metabolism, which describes mathematically the mechanisms of glucose absorption, distribution and production in the relevant organs. Glucose appears in the blood either as a result of carbohydrates consumption or by being released by the liver. Insulin is administered externally in the subcutaneous tissue. Insulin contributes to glucose metabolism in the liver, where it suppresses the endogenous glucose production and in the adipose tissue and muscle cells where insulin-dependent glucose uptake is taking place. Consequently, the main components that contribute to the entire description of the process are: glucose absorption from the blood through the gastrointestinal tract, insulin absorption from the blood through the subcutaneous tissue, endogenous glucose production, glucose excretion and glucose uptake. The models encountered in the literature describe these processes with several approaches. A selection of models can be seen in Table 2.5. Detailed description of the available models of glucose-insulin interactions is presented below:

Models based on Minimal Model

Modelling the glucose-insulin system for normal and diabetic subjects started in 1970s, when Dr. R. Bergman and co-workers introduced the Minimal model (Bergman, Phillips and Cobelli, 1981), which essentially is a method to estimate pancreatic effectiveness and insulin sensitivity. The model describes the dynamics during an intravenous glucose tolerance test (IVGTT) or an oral glucose tolerance test (OGTT). It consists of two subsystems describing insulin and glucose kinetics at a level of minimal complexity. Glucose subsystem encompasses a plasma compartment and a remote compartment in which insulin is inserted to transfer glucose into the periphery and liver and to inhibit hepatic glucose production; the insulin minimal subsystem involves only a single plasma compartment. Although this model contributed fundamentally to later research work, it has several drawbacks regarding the modelling approach. For example, Caumo (1993) has indicated that the minimal model presents an abnormal behaviour of endogenous glucose production and limited validity in the

unsteady state. Furthermore Cobelli et al., (2009) state that the assumption of insulin secretion in proportion to glucose concentration cannot be experimentally verified. Generally, the model simplifies the complexity of the metabolic system and its validity is restricted to the description of insulin-glucose dynamics during an IVGTT or OGTT (Van Herpe *et al.*, 2007).

In Fisher (1991) two more terms were introduced in the minimal model. One represents the effect of glucose intake from meal consumption; and the other represents exogenous insulin infusion. The limitations of this approach are derived from the limitations of the minimal model approach, such as fixed values of the model parameters. Furthermore this approach has not been validated clinically, but the results are consistent with the literature.

Fabietti et al. (2006) modified the minimal model to focus on patients with T1DM. The glucose kinetics model consists of two compartments, insulin kinetics is described by two compartments, one representing the exogenous, subcutaneous administration of insulin and the other a remote one. External inputs such as meals and glucose boluses are assumed together with liver glucose uptake. A drawback as mentioned by (Wilinska and Hovorka, 2008) is that the model is not capable of representing personalised results, following real time changes of the patient's physiological responses. However, it is able to represent within patient variability, by considering circadian insulin sensitivity variation.

Several models have been introduced which retained the core of the minimal model but altered specific parts to account for certain aspects, such as descriptive representation of the glucose kinetics according to experimental data (Caumo and Cobelli, 1993). Van Herpe *et al.* (2007) have evolved the MM so as to take into consideration the critical ill patients (intravenous glucose and insulin administration).

Further compartmental approaches

Berger and Rodbard (1991) have developed a simulation and optimisation program (GLUCOJECT) for insulin therapy in patients with T1DM. The model used in this program is consistent of two subsystems describing insulin and glucose kinetics at a level of minimal complexity. The insulin subsystem describes the pharmacokinetics of insulin within 3 compartments: subcutaneous insulin depot, plasma insulin compartment and a remote compartment. Glucose kinetics is described by a single compartment of plasma glucose. This program stores glucose values and insulin doses and can reproduce an average 24h glucose and insulin profile. There are no published data referring to its clinical evaluation. The pharmacokinetic model of insulin action of this model was used by (E D Lehmann and

Deutsch, 1992) in combination with a model describing glucose pharmacodynamics, which is based on experimental data from the literature and presented by (Guyton *et al.*, 1978) to describe glucose-insulin interaction of T1DM. This model was used by AIDA, an online educational tool. The authors of AIDA model suggested a generic subcutaneous absorption of insulin (Lehmann *et al.*, 2007). This model is suggested initially from Tarín et al. (2005) and it is incorporated alongside the existing model of insulin kinetics and disposal from Berger and Rodbard. In this way, novel insulin analogues can be simulated and the current insulin dose can exceed the limit of 40 IU per injection, which was assumed in the previous model. This tool, as mentioned by the authors, should be used only for patients' education and not as a treatment tool. Currently, further developments are considered to account for the existing limitations.

Two of the most commonly used physiologically-based compartmental models are those developed by the groups of Hovorka and Cobelli.

The model of the glucoregulatory system developed by Hovorka et al. (2002) and Hovorka et al. (2004) considers the glucose subsystem using 2 compartments representing the accessible and non-accessible pool; the insulin subsystem with a chain of three compartments to describe the rapid acting insulin infusion and distribution (Willinska *et al.*, 2010) and finally a subsystem of insulin action on glucose transport, disposal, and production. Additionally the glucose absorption from the gut as well as the interstitial glucose kinetics have been modelled. This model so far has been validated in the sense that it can reproduce the results obtained from a clinical study of a closed loop insulin delivery in patients with T1DM. The model and its parameters represent a virtual patient. The simulation environment is currently fully validated in order to be used for the development of closed loop insulin delivery systems.

Another simulation environment has been developed from the Universities of Padova and Virginia (Dalla Man *et al.*, 2007), (B. P. Kovatchev, M. Breton, *et al.*, 2009). This model describes accurately the glucose and insulin dynamics during a meal. It consists of a glucose and an insulin subsystem. Glucose subsystem encompasses two compartments while the insulin dynamics are also represented by two compartments. The modelling of glucose rate of appearance coming from the food consumption as well as the endogenous glucose production and glucose utilisation are addressed. One issue that should be taken into account is the diurnal variability of the parameters. This simulator has been accepted by FDA for preclinical closed-loop control experiments by substituting animal trials as well as for clinical trials of closed-loop control based entirely on silico tests.

Models in the form of delay differential equations

There are two kinds of time delays in the physiology of glucose-insulin system. The first delay is related to insulin production triggered by increased glucose levels as well as the time required for insulin to become accessible for utilisation. The other one is the delay between the appearance of insulin in the plasma and its inhibitory effect on the hepatic glucose production. Regarding the pathophysiology of T1DM, there is another delay concerning the exogenous insulin infusion; it represents the required time of subcutaneous infused insulin to be absorbed. These delays can be represented implicitly or explicitly. In other words, they can be expressed by either separating insulin/glucose in two compartments, by using auxiliary variables, or by introducing time delay terms in the functions describing insulin production and endogenous glucose production.

Models assuming physiological delays in the system of insulin – glucose have been developed. In these models circadian insulin secretion oscillations are analysed in the form of differential equations. The initial model suggesting that behaviour has been developed by (Sturis *et al.*, 1991). The delays are modelled by assuming insulin action in two separate compartments and by assuming auxiliary variables representing insulin effects on endogenous glucose production. The model equations were modified by (Tolić, Mosekilde and Sturis, 2000) and insulin secretion was represented as a sigmoid function of glucose concentration.

In order to examine whether oscillatory insulin supply is more efficient, as it mimics the pulsatile secretion of hormones in the endocrine system, Tolić et al. (2000) have suggested that insulin infusion should be sinusoidal. Actually, it was proved that only when hepatic glucose release is near the upper limit oscillatory, will insulin supply be more efficient; otherwise oscillatory and constant insulin infusion produce similar effects.

Bennett and Gourley (2004) instead of the three auxiliary linear equations, proposed in the previous model, introduced a time delay of insulin effect on hepatic glucose production, explicitly in the model. The two-compartment approach for insulin production/utilization delay was maintained. Engelborghs et al. (2001) assumed only the delay related to insulin effect on hepatic glucose production, which was represented explicitly in the model. Because this model is not physiologically complete, it is not further considered. Li et al. (2006) suggested a two time delay model that introduces two explicit time delays in the system.

Finally, Chen et al. (2010) have developed a model for diabetic patients in which the time delays for hepatic glucose production and insulin release from beta cells are maintained, but

exogenous inputs of meal and insulin are described, as well as the effects of hyperglycaemia. Further modifications have been proposed by (Chen and Tsai, 2010).

Physiological Models

One of the most important models developed is the physiological model of Sorensen (1978). It contributed in the understanding of the physiology of the glucoregulatory system and it has been a reference point for subsequent research studies on modelling of the system. It is based on the work of Guyton et al. (1978) and was modified by Parker et al. (1999). Although it describes the complexity of the metabolism it cannot represent the intra-patient variability.

Empirical Models-Hybrid Models

Several research groups have worked on data driven models, in an attempt to overcome the assumptions and simplifications that physiological and physiologically based compartmental models are by default subject to. An approach of using Volterra Models to describe the glucoregulatory system has been proposed by Mitsis et al. (2009). For the particular study the data are obtained from simulation results of the Minimal Model. Eren-Oruklu et al. (2009) have used an ARMA (autoregressive moving-average) model to describe the glucose-insulin dynamics in order to capture the between patients variability. Additionally Ghosh and Maka (2009) has described the system by a NARX model by using data obtained from IVGTT. Finally Mougiakakou et al. (2005) have proposed the combination of compartmental models and artificial Neural Networks as an individualised representation of the glucose metabolism.

Table 2.5: Mathematical models of glucose-insulin system

Mathematical Models				
Compartmental Models				
Number of compartments				
Glucose Kinetics	**Insulin Kinetics**	**Validation**	**Comments**	**Reference**
1	2	IVGTT data	Minimal complexity Healthy subjects	(Bergman, Phillips and Cobelli, 1981)
1	2	Literature data	Minimal model for T1DM	(Fisher, 1991)
2	2	IVGTT data	Healthy subjects	(Caumo and Cobelli, 1993)
1	3	Literature data	No published data for clinical evaluation	(Berger and Rodbard, 1991)
1	2	Literature data	AIDA: educational tool	(E D Lehmann and Deutsch, 1992)
1	1	Literature data	experimental data on critical ill patients	(Hann *et al.*, 2005)
2	2	Literature data	average patient Circadian SI variation	(Fabietti *et al.*, 2006)
2	3	Literature data	critical ill patients	(Van Herpe *et al.*, 2007)
2	3 3 effect of insulin action	Clinical study of closed loop insulin delivery in young people with T1DM	Validated simulation environment	(Willinska *et al.*, 2010)
2	2	Experiments	FDA approval	(Dalla Man, Rizza and Cobelli, 2007), (Dalla Man *et al.*, 2007)
Physiological Models				
6	6	Literature data	average 70kg man	(Sorensen, 1978)
6	6	Literature data	average 70kg man Includes a meal submodel	(Parker, Doyle and Peppas, 1999)
Models in the form of delayed differential equation				
1	2 3 delayed insulin effect	Literature data	Healthy subjects Implicit delays	(Tolić, Mosekilde and Sturis, 2000)
1	2	Literature data	Healthy subjects explicit delays	(Bennett and Gourley, 2004)
1	2	Literature data	Healthy subject explicit delay	(Engelborghs *et al.*, 2001)
1	2	Literature data	Healthy subjects Explicit/implicit	(Li, Kuang and Mason, 2006)
1	2	Literature data	T1DM explicit delay	(Chen, Tsai and Wong, 2010)
Empirical Models				
Volterra Model		Literature data	(Mitsis, Markakis and Marmarelis, 2009)	
ARMA model		Literature data	(Eren-Oruklu *et al.*, 2009)	
NARX model		Literature data	(Ghosh and Maka, 2009)	
Compartmental-Neural Networks		Literature data	(Mougiakakou, Prountzou and Nikita, 2005)	

3. Mathematical Model Development

3.1 Introduction

An essential step for the design of model predictive control is the development of a reliable mathematical model. The model presented in this section is describing glucose metabolism and insulin kinetics for a patient with T1DM in a detailed compartmental approach. The system is analysed at organ-level aiming to provide thoughtful insight and understanding of the physiology. Additionally, in an effort to reduce the intra-patient variability and describe the individualised glucose metabolism, patient-specific variables that are functions of the patient's individual characteristics such as gender, age, weight, height and hematocrit are introduced. However, the pharmacodynamic variables that are related to the effect of insulin on glucose remain uncertain and present inter and intra- patient variability. In the next chapter, the uncertainty in the predictability of blood glucose is investigated by using model analysis techniques to prioritise the variables that need to be identified first to successfully predict the patient's current state.

3.2 Physiologically based Compartmental Model of Glucose Metabolism

The proposed model describes glucose distribution in the involved body compartments, as presented in Figure 3.1, and the effect of insulin on glucose uptake and suppression of endogenous glucose production. The structure of the proposed model is inspired by the Sorensen's model (Sorensen, 1978) that describes the glucose metabolism with actual anatomical compartments. The body is considered to be divided in six compartments, brain, heart, liver, gut, periphery and kidney, where glucose is distributed via blood circulation. The periphery compartment that lumps the muscles and adipose tissue is described by two sub compartments, the interstitial fluid and the tissue, in order to highlight the dependence of glucose diffusion on the prevailing blood flow and capillary permeability as well as the dependence of glucose tissue uptake on insulin concentration. At steady state, an approximation of constant physiological conditions, the blood glucose concentration reflects the net balance of endogenous glucose release in the circulation and glucose uptake. When food is consumed, the contained carbohydrates break down into glucose in the gastrointestinal tract which is absorbed through the small intestine into the bloodstream. Physiologically, an increase in blood glucose triggers pancreatic insulin release, which activates glucose

transporters to mediate glucose translocation into the insulin-sensitive cells (adipose tissue, skeletal and cardiac muscles) and additionally suppresses the endogenous glucose production. In T1DM the pancreatic insulin secretion is replaced by optimal administration of exogenous insulin that mimics the pancreatic response. Glucose appearance in the gut after meal consumption, endogenous glucose production in the liver and glucose excretion from the kidney are described with additional sub models that are well-established in the literature and are embedded into the structure of the model to entirely describe glucose metabolism.

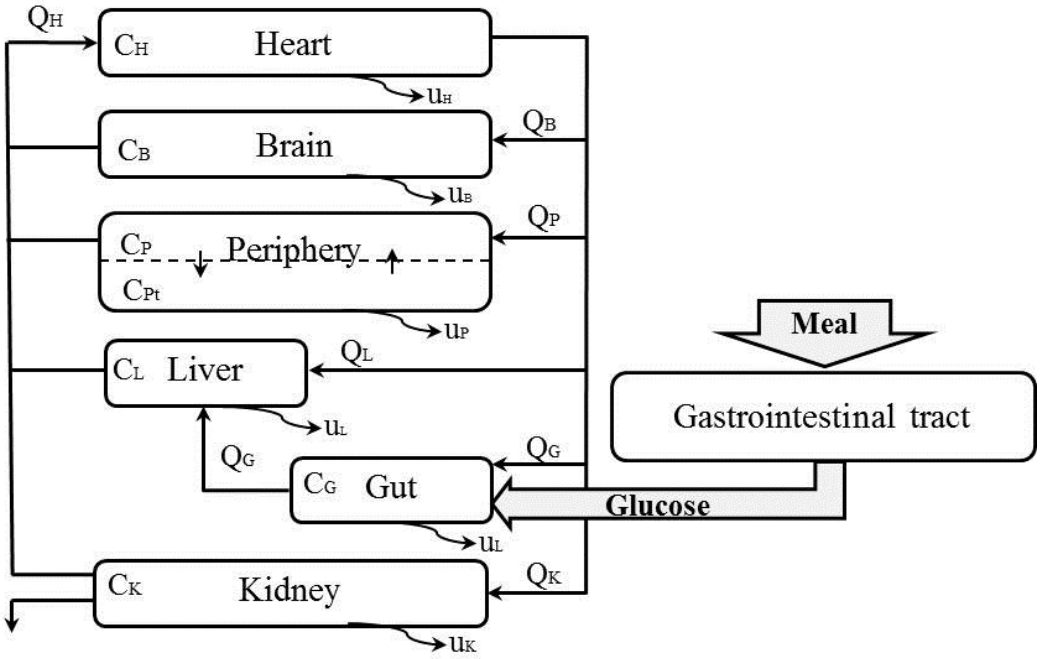


Figure 3.1: Structure of the physiologically based compartmental model of glucose metabolism in T1DM

For the highly perfused organs (brain, liver, gut, kidney) glucose concentration is considered to be in equilibrium with the tissue glucose concentration. The periphery compartment lumps the adipose tissue and muscle cells. Glucose transfer from the blood capillaries to the interstitial fluid and glucose uptake in the periphery is described with two compartments. Homogeneity and instant mixing is assumed for every compartment, imposing all the exiting fluxes to be in equilibrium with the compartment. For the insulin insensitive organs glucose uptake is assumed to be a constant ratio of the available glucose. The core of the model is described with (3.1)-(3.6) and the definition of the involved variables is presented in detail in the notation section at the beginning of this thesis.

The driving force for glucose transport into the compartments is the blood-tissue concentration difference. The concentration in every organ is given by mass balances in every compartment.

Brain (B)

$$V_{g,B}\frac{dC_B}{dt} = Q_B(C_H - C_B) - u_B \tag{3.1}$$

Kidney (K)

$$V_{g,K}\frac{dC_k}{dt} = Q_K(C_H - C_K) - u_K - excretion \tag{3.2}$$

Liver (L)

$$V_{g,L}\frac{dC_L}{dt} = Q_L \cdot C_H + Q_G \cdot C_G - (Q_L + Q_G)\cdot C_L - u_L + BW \cdot EGP \tag{3.3}$$

Gut (G)

$$V_{g,G}\frac{dC_G}{dt} = Q_G(C_H - C_G) - u_G + BW \cdot R_a \tag{3.4}$$

Heart (H)

$$V_{g,H}\frac{dC_H}{dt} = Q_B \cdot C_B + Q_L \cdot C_L + Q_P \cdot C_P + Q_K \cdot C_K - Q_{CO} \cdot C_H - u_H \tag{3.5}$$

Periphery (P)

$$V_{g,Pc}\frac{dC_P}{dt} = Q_P(C_H - C_P) - p(C_P - C_{Pt}) \tag{3.6.1}$$

$$V_{g,P,ISF}\frac{dC_{Pt}}{dt} = p(C_P - C_{Pt}) - u_P \tag{3.6.2}$$

$$u_P = (\lambda_o)\cdot C_{Pt} \tag{3.6.3}$$

where the C_i is the glucose concentration (mg/dl) in *i* compartment, $V_{g,i}$ the accessible glucose volume (dL) of *i* compartment, Q_i the blood flow (dL/min) in *i* compartment, u_i the glucose uptake (mg/min), EGP the endogenous glucose production (mg/kg/min), R_a the rate of glucose appearance in the blood (mg/kg/dL) through the interstitial wall and λ_o the rate of glucose uptake (dL/min).

For (3.1)-(3.6) the blood flow in every organ *i* is described by (3.7). The ratio of cardiac output perfusing every organ is presented in Table 3.1.

$$Q_i = r_{CO,i} \cdot Q_{CO} \tag{3.7}$$

Table 3.1: Ratio of cardiac output at rest (Ferrannini and DeFronzo, 2004)

Tissue	($r_{co,i}$)
Brain	0.11
Liver	0.20
Kidneys	0.13
Gut	0.15
Periphery	0.40

Similarly the glucose uptake in every organ is described with (3.8) and the ratio of glucose uptake $r_{u,i}$ is presented in Table 3.2.

$$u_i = r_{u,i} \cdot Total_uptake \tag{3.8}$$

Table 3.2: Ratio of glucose uptake (Ferrannini and DeFronzo, 2004)

Tissue	($r_{u,i}$)
Brain	0.45
Liver	0.13
Kidneys	0.02
Gut	0.07
Periphery	0.30
Heart	0.03

In the following section the sub models of glucose metabolism functions are described in more detail.

Endogenous Glucose Production (EGP)

Glucose is produced endogenously in the liver with a percentage of approximately 80% through gluconeogenesis and glycogenolysis, and in the cortex of kidney with a percentage of 20% (Cano, 2002) mainly through glyconeogenesis (Gerich, 2010), (Gerich *et al.*, 2001). In this study it is assumed that glucose is entirely produced in the liver, due to limited data availability. Generally, in diabetes, the insufficiency of insulin causes liver to function as being in fasting condition, where the rate of glucose production is high. In particular, when glucose is consumed, there is no indicator to suppress hepatic glucose production (Newgard, 2004). In T1DM, the rate of EGP depends on adequate control of the disease (Roden and Bernroider, 2003). When referring to intensive insulin therapy, it can be assumed that EGP is approximately the same as in normal humans (Roden and Bernroider, 2003), (Davis, Fowler

and Costa, 2000). The model describing the endogenous glucose production in T1DM and used in (3.3) is adapted from (Dalla Man, Rizza and Cobelli, 2007).

$$EGP = (k_{p1} - k_{p2} \cdot M_L - k_{p3} \cdot I_d) \tag{3.9}$$

$$\frac{dI_1}{dt} = k_i \cdot (I_1 - I_p) \tag{3.10}$$

$$\frac{dI_d}{dt} = k_i \cdot (I_d - I_1) \tag{3.11}$$

M_L (mg/kg) denotes the liver glucose mass and I_d (pmol/l) denotes the delayed insulin signal described by a chain of two compartments (I_1, I_d). The model parameters are estimated using available literature data (Boden, Cheung and Homko, 2003).

Rate of glucose appearance (R_a)

The model describing the rate of glucose appearing in the circulation when food is consumed is adopted from (Dalla Man, Camilleri and Cobelli, 2006). This model describes glucose transit from the stomach with two compartments representing the solid and liquid phase, to the upper small intestine which is described with one compartment.

$$q_{sto} = q_{sto1} + q_{sto2} \tag{3.12}$$

$$\frac{dq_{sto1}(t)}{dt} = -k_{21} q_{sto1}(t) + D\delta(t) \tag{3.13}$$

$$\frac{dq_{sto2}(t)}{dt} = -k_{empt} q_{sto2}(t) + k_{gri} q_{sto1}(t) \tag{3.14}$$

$$\frac{dq_{gut}(t)}{dt} = -k_{abs} q_{gut}(t) + k_{empt} q_{sto2}(t) \tag{3.15}$$

$$k_{empt}(t) = k_{\min} + \frac{k_{\max} - k_{\min}}{2} \{\tanh[a(q_{sto} - bD)] - \tanh[\beta(q_{sto} - cD)] + 2\} \tag{3.16}$$

$$R_a(t) = \frac{f k_{abs} q_{gut}(t)}{BW} \tag{3.17}$$

$$a = \frac{5}{2 \cdot D \cdot (1-b)} \tag{3.18}$$

$$\beta = \frac{5}{2 \cdot D \cdot c} \tag{3.19}$$

with q_{sto1}, q_{sto2} (mg) the glucose mass in solid and liquid phase, q_{sto} (mg) the overall glucose mass in the stomach, q_{gut} (mg) is the glucose mass in the small intestine, k_{empt} (min^{-1}) is the rate of gastric emptying, α and β are model parameters, k_{max}, k_{min} (min^{-1}) are the max and min

gastric emptying, k_{abs} (min^{-1}) is the rate constant of intestinal absorption, k_{gri} is the rate constant of grinding, f (dimensionless) is the fraction of intestinal absorption, b and d are percentages of the dose and D (mg) is the amount of ingested meal.

Glucose Renal excretion (excretion)

In diabetes, the threshold of renal glucose reabsorption is exceeded when glucose concentration increases above 180mg/dl and glucose gets excreted by the kidney. It is assumed that renal glucose excretion (mg/min) increases proportionally to increasing blood glucose concentration (Willinska *et al.*, 2010), (Rave *et al.*, 2006).

$$E(t) = \begin{cases} CL_{renal}(G_K - 180) & \text{If } G_K > 180mg/dL \quad (3.20) \\ 0 & \text{If } G_K \leq 180mg/dL \quad (3.21) \end{cases}$$

CL_{renal} (dl/min) is renal glucose clearance.

Glucose diffusion in the periphery

The structure presented in Figure 3.2 is considered to model glucose distribution and uptake in the periphery compartment:

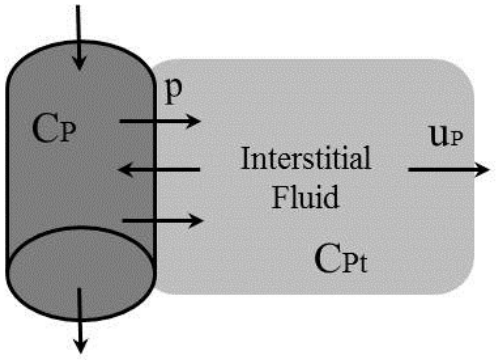


Figure 3.2. Detailed glucose uptake in the periphery

It is assumed that glucose is extracted from the arterial flux with a rate factor given in the current literature (Crone, 1965), (Regittnig *et al.*, 2003):

$$p = Q_P \cdot (1 - \exp(-PS / Q_P)) \quad (3.22)$$

PS is the permeability across the capillary wall, a product of permeability of exchange surface to glucose P and exchange surface area S. This rate factor can increase in case of increased blood flow to the periphery or increased perfusion due to increased capillary exchange area during for example exercise. According to Gudbjornsdottir et al. (2003) PS was increased

significantly during a one-step hyperinsulinemic clamp. The following equation describes the effect of insulin on glucose permeability across the capillary wall.

$$\frac{dPS}{dt} = -k_{2,PS}PS + k_{1,PS} \cdot I_p \tag{3.23}$$

When glucose enters the interstitial fluid it is absorbed by the tissues to provide them with energy, (3.6). The rate of uptake, λ_o (dL/min) is dependent on insulin concentration in the blood and insulin effect is described with (3.24).

$$\frac{d\lambda_o}{dt} = -k_2\lambda_o + k_1 \cdot I_p \qquad with \;\; \lambda_o(0)=\lambda_{basal} = \frac{k_1}{k_2} I_{pbasal} \tag{3.24}$$

$$S_I = k_1 / k_2 \tag{3. 25}$$

SI represents the patient's sensitivity to insulin.

Adaptation to the individual patient

1) Total Blood Volume

The total blood volume (TBV) (dL) is adapted to the patient's height, weight and gender to account for the differences between obese and underweight patients and for males and females. The formula used for men is (Wennesland *et al.*, 1959):

$$TBV_M = 0.285h + 0.316m - 2.820 \tag{3.26}$$

and for women (Brown *et al.*, 1962)

$$TBV_F = 0.1652h + 0.3846m - 1.369 \tag{3.27}$$

where the height (h) is in centimeters and weight (m) in kilograms

2) Cardiac Output

The cardiac output (mL/min) can be efficiently approximated as a proportional relationship to the patient's weight *BW* (kg) according to the equation (Ederle et al., 2000):

$$Q_{CO} = 224BW^{3/4} \tag{3.28}$$

3) *Compartmental Volume*

Plasma proteins comprise approximately 8% of the plasma volume and the erythrocytes about 38% of the total packed red blood cells volume or Haematocrit (Ferrannini and DeFronzo,

2004), (*Hemat*). This percentage of the total blood volume is inaccessible to glucose. Consequently the accessible glucose volume in every compartment is determined as:

$$V_{g,i} = \left(1 - \left(0.08 \cdot (1 - Hemat) + 0.38 \cdot Hemat\right)\right) \cdot (V_{\mathrm{V},i} + V_{C,i}) \tag{3.29}$$

The blood volume of the every compartment i is defined as the sum of venous and capillary volume. The glucose venous volume equals 60% of total blood volume and the capillary the 10% of total blood volume (Gerich et al., 2001), (Enderle, 2011). The compartmental venous and capillary volumes are defined as:

$$V_{V,i} = r_{f,i} \cdot 0.6TBV \tag{3.30}$$

$$V_{C,i} = r_{c,i} \cdot 0.1TBV \tag{3.31}$$

Where $r_{f,i}$ refers to the ratio of total venous volume in compartment *i*. The compartmental venous blood volume is calculated by distributing the total venous blood volume at the body organs at the basis of fractional blood flows (Sorensen, 1978) (3.32):

$$r_{f,i} = Q_i / \sum Q_i \tag{3.32}$$

and $r_{c,i}$ refers to the ratio of total capillary volume respectively (Sorensen, 1978) and is presented in Table 3.3.

Table 3.3: Ratio of capillary volume

Tissue	($r_{c,i}$)
Brain	0.071
Liver	0.18
Kidneys	0.08
Gut	0.13
Periphery	0.53

4) Peripheral Interstitial Volume

The total regional volume for the adipose tissue is defined as

$$V_P = V_{Capillary,\mathrm{P}} + V_{Interstitial,\mathrm{P}} + V_{Intracellular,\mathrm{P}} \tag{3.33}$$

According to Man and Uribarri (Man and Uribarri, 2006) the interstitial volume represents 28% of the total body water while the intracellular volume 60%. Hence, $V_{Interstitial} = 0.47V_{Intracellular}$. The adipose tissue mass is described by:

$$m_{AT} = \left(1.2BMI - 10.8sex + 0.23age - 5.4\right)0.01BW \quad \text{(Deurenberg, et al., 1991)} \tag{3.34}$$

with $d_i = m_i / V_i$ (3.35)

The interstitial volume of the adipose tissue and the muscles is considered to be 10% of the total tissue volume according to (Eckel, 2003) and (Johnson, 2003) respectively. Muscle mass is considered to be approximately 40% of the total body weight (3.36), according to Ackland, Elliott and Bloomfield (2009).

$$m_{muscles} = 0.4BW \tag{3.36}$$

The peripheral volume of the interstitial fluid is calculated via (3.37), using Table 3.4:

$$V_{g,P,ISF} = V_{Interstitial,AT} + V_{Interstitial,musc} \tag{3.37}$$

Table 3.4: Density of muscles and adipose tissue

Tissue	Density (kg/L)	Reference
Adipose Tissue (d_{AT})	0.92	(Gallagher *et al.*, 1998)
Muscles ($d_{muscles}$)	1.04	(Gallagher *et al.*, 1998)

3.3 Insulin Kinetics

When pump therapy is used, rapid/short acting insulin is continuously infused through the subcutaneous tissue. The amount of insulin delivered is programmed and administered at a basal rate which varies depending on the patient's daily requirements, and additional bolus doses that compensate for blood glucose level increase when meal is consumed. The formulation of rapid acting insulin reduces the tendency of insulin monomers to dimerize and further associate into hexamers (Leslie, Taylor and Pozzilli, 1997). Hence, the diffusion in the blood is enhanced with onset of action within 10-20min and maximum serum concentration reached in 45min (Home, 2012). However, the absorption of insulin from the subcutaneous tissue is dependent on the blood flow in the tissue, which causes variable time of onset and maximum effect. Hence, insulin kinetics describe the mechanisms involved from the moment insulin is administered in the subcutaneous tissue until it is fully eliminated from the body. Several models have been proposed in the literature (Tarín *et al.*, 2005), (Kraegen and Chisholm, 1984), (Kuang and Li, 2008), (Nucci and Cobelli, 2000), with compartmental modelling being the most common approach. In this study, the structure to describe insulin kinetics is investigated when an insulin pump is used. Four alternative compartmental models are presented in this section that describe experimental data of insulin kinetics and compared in terms of identifiability, parameter correlations and accuracy, as presented in the following chapter. The models of insulin kinetics are linked with the glucose metabolism model (3.1-3.37) via equations 3.10 and 3.24 which represent, respectively, insulin action on endogenous glucose production and glucose absorption from the periphery.

Model 1

This model considers two different channels for insulin transport for basal infusion and bolus dose, Figure 3.3.

$$\frac{dS_1}{dt} = bolus - k_{sub_1} \cdot S_1 \tag{3.38}$$

$$\frac{dS_2}{dt} = basal - k_{sub_2} \cdot S_2 \tag{3.39}$$

$$\frac{dI_p}{dt} = \frac{k_{sub_1} \cdot S_1 + k_{sub_2} \cdot S_2}{V_{dist}} - k_{e\lim} \cdot I_p \tag{3.40}$$

Model 2

This model describes insulin transport for the bolus dose as one compartment and the basal infusion is considered as a direct input to the plasma compartment as a proportion of the initial basal rate, assuming that rest of the dose is degraded in the subcutaneous tissue, Figure **3.4**.

$$\frac{dS_1}{dt} = bolus - k_{sub_2} \cdot S_1 \tag{3.41}$$

$$\frac{dI_p}{dt} = \frac{k_{sub} \cdot S_1}{V_{dist}} + k_{in} basal - k_{e\lim} \cdot I_p \tag{3.42}$$

The variable and parameter definitions for both models are shown in Table 3.5.

Table 3.5: Variable and parameter definition of Model 1 and Model 2

Symbol	Definitions
S_1, S_2	Insulin mass(mU) in the subcutaneous compartments
k_{sub_1}, k_{sub_2}	intercompartmental transfer rate constants (min^{-1})
k_{elim}	elimination rate constant (min^{-1})
V_{dist}	insulin distribution volume (L/kg)
k_{in}	Proportion of the initial basal rate as direct input
basal	Continuous insulin infusion (U/min)
bolus	Pulse insulin infusion (U/min)

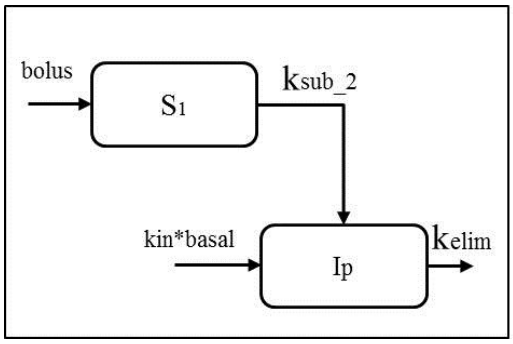


Figure 3.3. Schematic representation of model 1

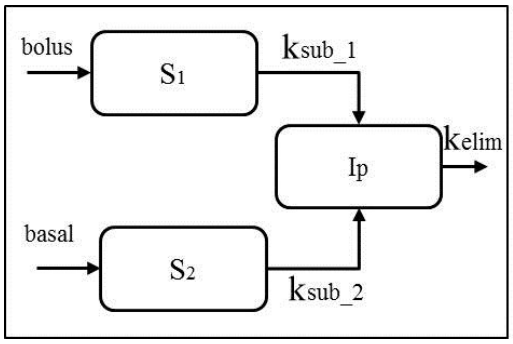


Figure 3.4. Schematic representation of model 2

Model 3

This model consists of three compartments in series, namely two compartments to describe insulin absorption through the subcutaneous tissue (S_1, S_2) and a single compartment for insulin in the plasma (I). This model of insulin kinetics has been widely used in the literature (Wilinska *et al.*, 2005), (Willinska *et al.*, 2010)

$$\frac{dS_1}{dt} = u - k_{sub}S_1 \tag{3.43}$$

$$\frac{dS_2}{dt} = k_{sub}S_1 - k_{sub}S_2 \tag{3.44}$$

$$\frac{dI}{dt} = k_{sub}S_2 - k_{elim}I \tag{3.45}$$

$$I_p = \frac{I}{V_{dist}} \tag{3.46}$$

The variables and parameter definitions are presented in Table 3.6 and the schematic representation in Figure 3.5

Table 3.6: Variable and parameter definition of Model 3

Symbol	Definitions
S_1, S_2	Insulin mass(mU) in the subcutaneous compartments
I	Insulin mass(mU) in the plasma compartment
k_{sub}	Intercompartmental transfer rate constant (min^{-1})
k_{elim}	Elimination rate constant (min^{-1})
V_{dist}	Insulin distribution volume (L/kg)
u	Continuous insulin infusion (U/min)

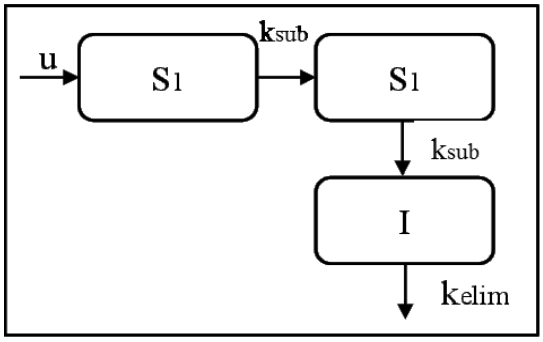


Figure 3.5: Schematic representation of model 3

Wilinska Model (Wilinska *et al.*, 2005)

This model assumes a slow channel of insulin absorption Q_{1a},, Q_2 and a fast absorption channel Q_{1b},.

$$\frac{dQ_{1a}}{dt} = ku - k_{a1}Q_{1a} - \frac{V_{\max,LD}Q_{1a}}{k_{M,LD} + Q_{1a}} \tag{3.47}$$

$$\frac{dQ_{1b}}{dt} = (1-k)u - k_{a2}Q_{1b} - \frac{V_{\max,LD}Q_{1b}}{k_{M,LD} + Q_{1b}} \tag{3.48}$$

$$\frac{dQ_2}{dt} = k_{a1}Q_{1a} - k_{a1}Q_2 \tag{3.49}$$

$$\frac{dQ_3}{dt} = k_{a1}Q_2 - k_{a2}Q_{1b} - k_eQ_3 \tag{3.50}$$

$$I = \frac{Q_3}{V_{dist}} \tag{3.51}$$

The variables and parameter definitions are presented in Table 3.7 and the schematic representation in Figure 3.6**.**

Table 3.7: Variable and parameter definition of Wilinska Model

Symbol	Definitions
Q_1, Q_2, Q_3	Insulin mass(mU) in the accessible, non-accessible subcutaneous compartment, plasma
$V_{max,LD}$,$k_{M,LD}$	Michaelis-Menten coefficients describing saturated degradation
k_{a1}, k_{a2}, k_e	transfer rate constants (min^{-1})
V_{dist}	insulin distribution volume (L/kg)
k	proportion of insulin flux entering the slow channel
u	Continuous insulin infusion (U/min)
a, b	insulin mass administered as continuous infusion and bolus respectively

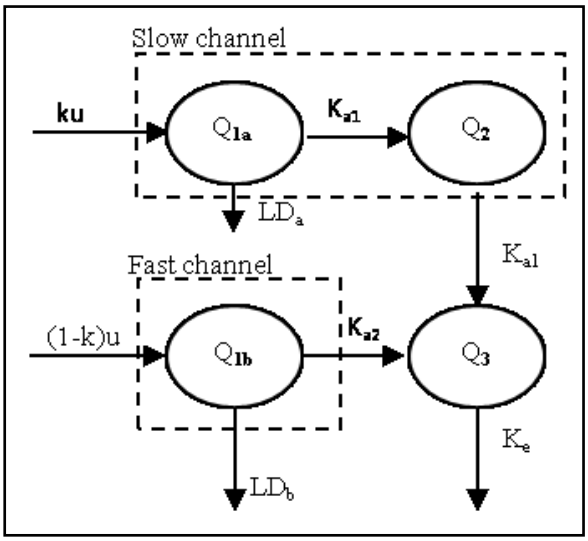


Figure 3.6: Schematic representation of Willinska model

The most suitable model to describe the insulin kinetics through the subcutaneous tissue to the plasma is found in the following chapter.

3.4 Concluding Remarks

In this chapter a mathematical model describing glucose metabolism in T1DM is presented. The core of the model consists of six compartments representing the most important organs associated with glucose metabolism, as introduced in Sorensen (1978). Glucose appearance in the gut after meal consumption, endogenous glucose production in the liver and the kidney as well as glucose excretion from the kidney are described with additional sub models that are well-established in the literature and are embedded into the structure of the model to entirely describe glucose metabolism. The compartmental accessible glucose volumes, the cardiac output and the total blood volume are expressed as functions of patient characteristics, leading towards an individualised representation of the system's dynamics. Unlike Sorensen's model, insulin administration and absorption through the subcutaneous route is considered as simple compartmental representation, due to limited availability of experimental data to describe the involved mechanisms of insulin diffusion, dissociation and absorption. In the next chapter, the most appropriate model to describe the insulin kinetics is selected and the entire model is analysed in terms of influential parameters and variables, parameters correlations and estimation.

4. Model Analysis and Dynamic Optimisation

4.1 Introduction

In this chapter, the most suitable model for insulin kinetics is selected by performing a series of analysis tests. Experimental data obtained in the literature are used to estimate the model parameters. Additionally, the suggested structure of the EGP sub model is evaluated in terms of reliability, using experimental data from the literature to estimate the model parameters and confirm the model's accuracy. Subsequently, the previously presented entire mathematical model of glucose metabolism is analysed in order to identify the most influential parameters that contribute to the model's uncertainty. This uncertainty originates to a large extent from the high intra- and inter-patient variability that dominates the system. Global sensitivity analysis, parameter estimation and correlation are performed to evaluate the model's ability to represent the glucoregulatory system's physiology. Additionally, the model's adaptability to the specific patient and predictive ability are evaluated with data available in the literature and data provided from the UVa/Padova T1DMS simulator.

4.2 Insulin Kinetics: Model Selection

4.2.1 Methods

The experimental plasma insulin concentration profiles used to investigate the accuracy of the proposed insulin kinetic models were obtained by (Boden, Cheung and Homko, 2003). Nine subjects with T1DM (Sex (M/F) 1/8, Age (years), 24±3, Weight (kg), 68.8± 3.1, Height (cm), 169± 4 BMI (kg/m^2), 24.2 ±1.2, duration of T1DM (years), 7.5± 1.5, HbA1c (%),7.6 ± 0.7, insulin dose (units/24 h), 33.3± 5.1) were hospitalised to perform the particular study, which involved an euglycaemic clamp to determine the effect of insulin excess on gluconeogenesis (GNG), glycogenolysis (GL), or both, by measuring GNG (with $^2H^2O$) and GL (EGP-GNG) and during insulin deficiency that developed after approximately 5 to 8h of the subcutaneous insulin injection. Boden et al.(2003) report the mean plasma insulin concentration profiles averaged over all nine patients which were used to evaluate the suggested models.

4.2.2. Parameter Estimation

The values of the parameters of the four models of insulin kinetics listed in Table 4.5 are identified via parameter estimation, performed in gPROMS. The solution method used in

gPROMS to obtain the optimal parameter estimates is to minimise the maximum log likelihood objective function (PSE, 2011a) by solving an optimisation problem.

The goodness of the fit of the proposed model to the experimental data is evaluated with a Pearson's chi-squared test (x^2) (PSE, 2011a), the accuracy of the estimates of the parameters was evaluated with a t-test and the reliability of the estimated values with the confidence intervals. The structural identifiability of the models is investigated by analysing the correlation matrix of the model parameters. Finally, the most suitable model to represent the experimental data was selected by applying the principle of parsimony and the Akaike criterion (Akaike, 1974) is tested.

Figure 4.1 shows the plasma insulin concentration (I_p) profiles produced by the suggested models versus the experimental data. Generally, we can conclude that all models describe relatively well the experimental data. However, a more in-depth analysis reveals the strengths and the weaknesses of each model.

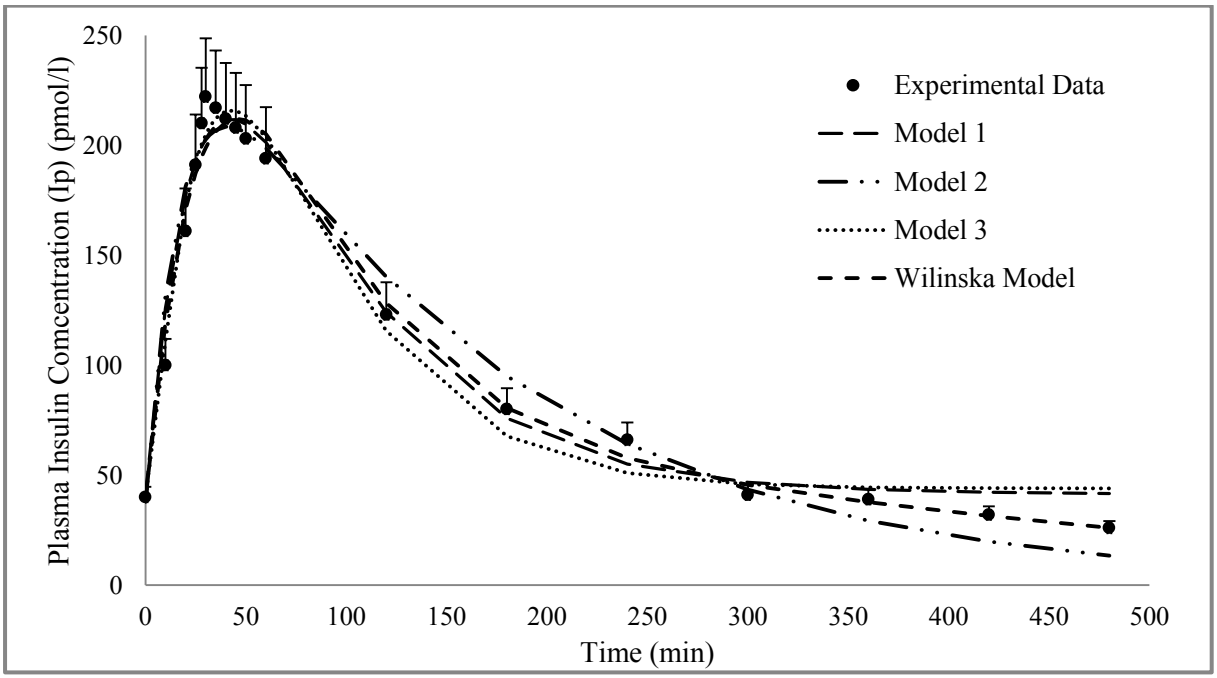


Figure 4.1: Comparison of Model 1, 2, 3 and Wilinska model with experimental data

Figure 4.2 shows the weighted residuals of the models which present more clearly the deviation of each model from the experimental level. The residuals for all models are small in magnitude and thus it is difficult to conclude whether a model is better than the other.

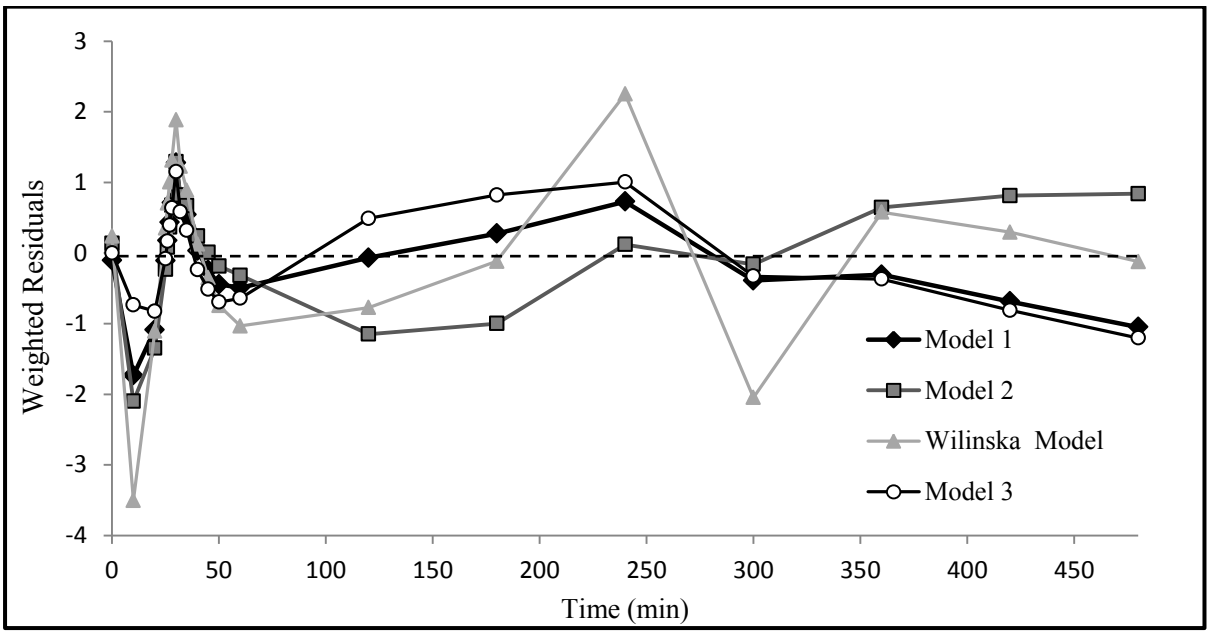


Figure 4.2: Weighted Residuals of the four models

A Pearson's chi-squared test (x^2) is performed and the result that all models describe relatively well the experimental data in Figure 4.1 is confirmed in Figure 4.2. For N-p degrees of freedom, where N is the number of experimental data and p the number of parameters, the x^2-value is obtained for a 95% confidence level. The calculated x^2 are smaller than the reference x^2-value, which indicates that the fit of the considered model is good.

Table 4.1: Goodness of fit of proposed models and model selection

	Model 1	**Model 2**	**Wilinska Model**	**Model 3**
Pearson's chi-squared test(x^2)	23.404	9.1041	13.362	9.0727
x^2-Value (95%, k)	**27.587**	**27.587**	**23.685**	**28.869**
Akaike Criterion	11.28	13.19	15.56	**5.13**

4.2.3 Model Selection

The Akaike criterion (AIC) is applied in order to select the most appropriate model that represents the experimental data. The test is presented in (4.1).

$$AIC = N\ln(WRSS) + 2K \quad (4.1)$$

N denotes the number of data points, K the number of parameters and WRSS the weighted residuals sum of squares.

The Akaike values shown in Table 4.1 indicate that Model 1, Wilinska model and Model 3 are suitable to describe the available experimental data. Model 2 is excluded from the

selection since it has the maximum Akaike value for the same number of model parameters as Model 1 (p=4). In principle, Model 3 should be selected since the AIC value is the smaller, but this choice is verified by analyzing further the remaining three models in terms of structural identifiability. The correlation matrix of the remaining models is calculated. The elements of the correlation matrix C are:

$$C_{ij} = \frac{V_{ij}}{\sqrt{V_{ii}}\sqrt{V_{jj}}} \tag{4.2}$$

with v_{ij} the elements of the variance-covariance matrix. A value of c_{ij} of the elements off-the diagonal close to 1 indicates that there is high correlation between the parameters i and j, whereas a value equal to 0 indicates no correlation.

Table 4.2: Correlation Matrix of the parameters of Model 1

	k_{sub1}	k_{sub2}	k_{elim}	V_{dist}
k_{sub1}	1.00	-0.94	0.98	-0.98
k_{sub2}	**-0.94**	1.00	-0.99	0.99
k_{elim}	**0.98**	**-0.99**	1.00	-0.99
V_{dist}	**-0.98**	**0.99**	**-0.99**	1.00

The correlation matrix of the parameters of model 1 indicates that there is a high correlation among all pairs of estimated parameters, and therefore each parameter cannot be estimated independently. This implies that there are concerns related to the structural identifiability of the model and hence, the structure of the model may be inappropriate to describe the experimental data.

The correlation matrices of Wilinska Model and Model 3 are presented in Table 4.3 and Table 4.4.

Table 4.3: Correlation Matrix of Wilinska Model

	k	k_{a1}	k_{a2}	k_{elim}	k_m	V_{dist}	V_{maxLD}
k	1.00	-0.57	-0.60	0.14	0.99	-0.90	0.97
k_{a1}	-0.57	1.00	-0.10	0.65	-0.64	0.24	-0.69
k_{a2}	-0.60	-0.10	1.00	-0.78	-0.56	0.88	-0.48
k_{elim}	0.14	0.65	-0.78	1.00	0.06	-0.53	-0.05
k_m	**0.99**	-0.64	-0.56	0.06	1.00	-0.86	0.99
V_{dist}	-0.90	0.24	0.88	-0.53	-0.86	1.00	-0.81
V_{maxLD}	**0.97**	-0.69	-0.48	-0.05	**0.99**	-0.81	1.00

The correlation matrix of Wilinska Model shows that there is high correlation between the parameters k and k_m, k and $k_m$and V_{maxLD} and k_{a2}. Whereas, the correlation matrix for Model 3 shows that parameters V_{dist} and k_{elim} cannot be estimated independently.

Table 4.4: Correlation Matrix of Model 3

	k_1	k_{elim}	V_{dist}
k_1	1.00	-0.67	0.70
k_{elim}	-0.67	1.00	-0.90
V_{dist}	0.70	**-0.90**	1.00

In the Wilinska Model and Model 3 there are significant correlations between pairs of parameters. But the model structures can be considered acceptable since both pass the goodness of fit test and both describe adequately the complexity of the physiology (Wilinska *et al.*, 2005). The mean of the parameter estimates for all models are presented in Table 4.5.

Table 4.5: Optimal Mean Parameter Estimates and standard deviations reported in parenthesis. Initial guess and lower-upper bounds of the parameters used for estimation are reported in the 2nd column.

Parameter	Initial Guess [Lower-Upper]	Model 1	Model 2	Wilinska Model	Model 3
k_{sub1}	0.1 [0.05-1.5]	0.36 (±0.28)	-	-	-
k_{sub2}	0.05 [0.001-0.1]	0.016 (±0.048)	0.042 (±0.012)	-	-
k_{in}	0.5 [0-1]	-	0.59 (±0.3)		
k_{elim} [M1,M2]	0.015 [0.001-0.1]	0.017 (±0.0065)	0.011 (±0.004)		
V_{dist} [M1,M2]	1.5 [0.1-5]	3.46 (±1.57)	2.76 (±0.5)		
k_{elim} [WM]	0.037 [0.011-0.1]**			0.012 (±0.023)	-
V_{dist} [WM]	0.42 [0.17-1.25]**			1.12 (±0.3)	-
k	0.67 [0.45-0.82]**	-	-	0.51* (±0.07)	-
k_{a1}	0.011 [0.004-0.029]*	-	-	0.003 (±0.001)	-
k_{a2}	0.021 [0.011-0.040]*	-	-	0.03 (±0.006)	-
k_m	62.6 [62.6-62.6]*	-	-	65.66 (±28.87)	-
V_{maxLD}	3.4 [0.06-7.5]**	-	-	7.09* (±3.4)	-
k_{elim} [M3]	0.33 [0.067-1.34]*				0.418 (±0.338)
V_{dist} [M3]	0.054 [0.016-0.25]*				0.087 (±0.072)
k_{sub}	0.016 [0.01-0.026]*				0.025 (±0.0017)

*Obtained from (Wilinska *et al.*, 2005)

**Bounds relaxed

°M1 refers to Model 1, M2 to Model , M3 to Model 3 and WM to Wilinska Model

The values of the estimated parameters for Wilinska model and Model 3 are in good accordance with the literature (Wilinska *et al.*, 2005).

Key Points

- Good fit to experimental data for the four models as verified from the Pearson's chi-squared test
- Model 3 is selected according to the Akaike Criterion
- Estimated parameters of Model 3 in good accordance with the literature

4.3 Endogenous Glucose Production: Parameter Estimation

The experimental data used for parameter estimation for the EGP submodel (3.9-3.11) are obtained from (Boden, Cheung and Homko, 2003). The purpose of this experiment was to study the mechanisms of endogenous glucose production (3.9-3.11) during insulin excess and insulin deficiency, while maintaining blood glucose concentration constant. Therefore, the parameter related to the effect of glucose to the suppression of EGP, k_{p2}, was kept constant and equal to the mean value obtained from the literature (Dalla Man, Rizza and Cobelli, 2007).

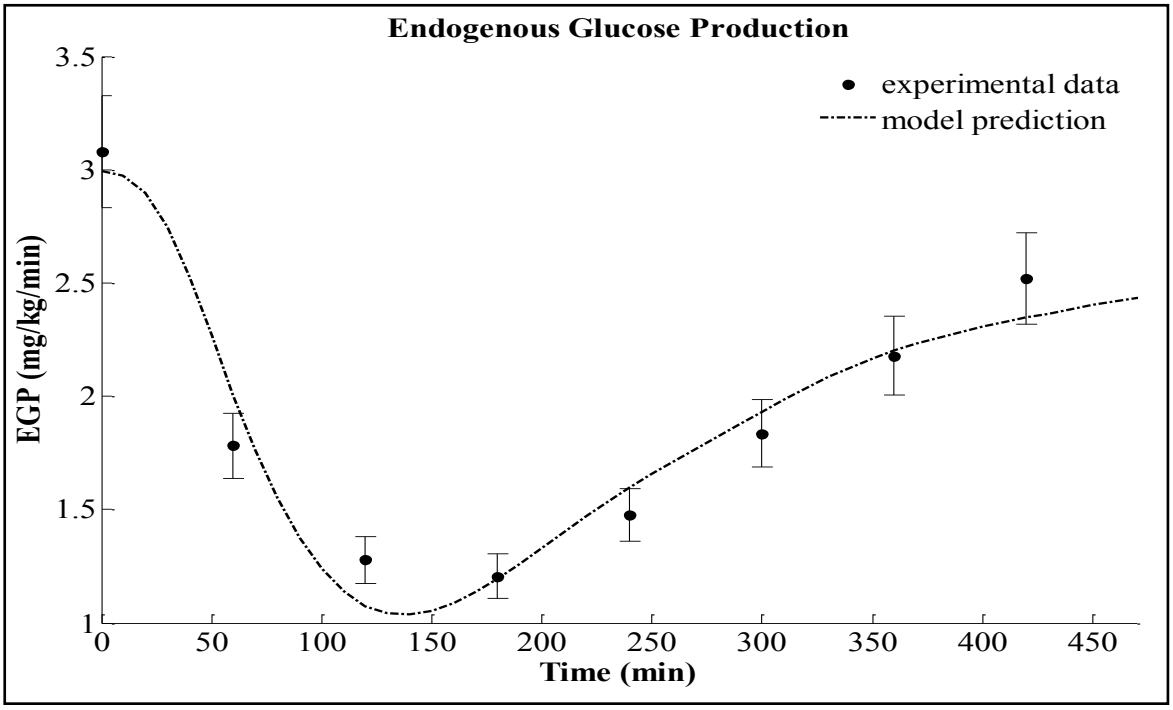


Figure 4.3. Effect of subcutaneous insulin injection on endogenous glucose production

Figure 4.3 shows that the model fits well the experimental data and the values of the estimated model parameters can be seen in Table 4.6. A t-test was performed that indicates accurate estimates of the parameters since the t-value is larger than the reference t-value for 95% confidence level. Additionally, the confidence interval shows the precision of the estimated values for the corresponding parameters and is calculated with (4.3)

$$\text{Confidence Interval}=\pm \frac{t_a}{2}(n-1)\frac{SD}{\sqrt{n}}, \tag{4.3}$$

Considering a a=95% confidence level

Table 4.6: Parameter estimation results

Symbol	Optimal Estimate (mean±SD)	Confidence Interval* (95%)	95% t-value
$\mathbf{k_i}$	0.024±0.0034	0.0085	2.82
$\mathbf{k_{p1}}$	3.058±0.17	0.42	7.33
$\mathbf{k_{p3}}$	0.014±0.0022	0.0053	2.7

Reference t-value (95%):1.94

4.4 Global Sensitivity Analysis

The model's reliability is evaluated with the performance of global sensitivity analysis. The uncertain factors that have a relative influence on the model's measurable output are determined and provide information on the proposed model's structure, in an effort to reduce the model's uncertainty by examining the most influential parameters. The GSA has been performed with the GUI-HDMR software (Ziehn and Tomlin, 2009) which uses an expansion of high dimensional model representation (RS-HDMR) method. This software calculates the sensitivity index (SI) for the parameter of interest. The RS-HDMR method maps the input (parameters) and output relationship as a function of orthonormal polynomials, the metamodel, using random sampling. The metamodel contains up to second order interactions, expressed as components of the orthonormal basis function as derived with ANOVA decomposition. The sensitivity indices are determined from the coefficients of the polynomial approximation. Sobol's sampling set is preferred because it provides evenly uniform distributed points of the input space. The samplings was performed by simulating the model in gPROMS via gO: MATLAB interface, developed by Krieger et al. (Krieger *et al.*, 2014). The SI is scaled between 0 and 1, with a SI=0 indicating a non-influential parameter. The parameters values vary between their upper and lower bounds and for every GSA, a set of

20000 Sobol's distributed points within the range were used to calculate the SI for specified time points. The sum of all the SI converges to 1.

In this study, the effect of the parameters on blood glucose concentration (C_H) was evaluated in two cases. In the first case the sensitivity indices were calculated for all the parameters to investigate their influence in a system with respect to intra- and inter-patient variability. In the second case only the parameters related to the intra-patient variability were included assuming that the weight, the organ volumes, the insulin distribution and the meal absorption can be considered constants for an individual patient and were fixed at their default values. The results are presented in Table 4.7.

Individual Model Parameters

The model parameters are shown in Table 4.7. The range of the parameters Qco and Vg,i is calculated from (3.29)-(3.33) when considering the body weight of 50-115 kg, height of 150-190 cm and age of 18-80 years. The default values are set for a male patient of 170 cm height, 50 years old and 94 kg. The range of the parameters related to the Ra and EGP is adapted from the Uva/Padova Simulator. The default values of the parameters for these subsystems were set at the mean value. The ratio of cardiac output and the ratio of glucose uptake were considered to vary ±5%, a value chosen when performing a series of stochastic simulation studies, while the default values were obtained from Table 3.1 and Table 3.2. The range and the default value of the parameters for insulin kinetics was obtained from (Wilinska *et al.*, 2005). A big variation of the default value in the parameters k_1 and k_2 was assumed to evaluate the predictability of the model. Finally a ±20% variation was assumed for $k_{1,PS}$ and $k_{2,PS}$. The initial guess of the values of the parameters k_1, k_2, and $k_{1,PS}$, $k_{2,PS}$ was selected when performing a set of stochastic simulation studies in comparison with the simulation results provided by the simulator.

Table 4.7: Model parameters default values and range. SIs for of all parameters and for those related to intra-patient variability calculated with GUI-HDMR toolbox

Symbol	Default	Range	Sensitivity Index				Units
			All parameters		Intra-patient parameters		
			480min	720min	480min	720min	
k_{a1}	1.66×10^{-02}	$(1.0\text{-}2.66)\times10^{-2}$	0	0	-	-	min^{-1}
V_{dist}	5.38×10^{-02}	$(1.16\text{-}25.08)\times10^{-2}$	1.12E-06	5.07E-07	-	-	L/Kg
k_{elim}	3.02×10^{-01}	$(6.79\text{-}134.55)\times10^{-2}$	0	0	-	-	min^{-1}
k_1	3.00×10^{-04}	$(0.40\text{-}1.00)\times10^{-03}$	**0.263565**	**0.340726**	**0.791256**	**0.445745**	dL^2 per $pmol\cdot min^2$
k_2	2.00×10^{-01}	$(0.50\text{-}5.00)\times10^{-01}$	**0.096337**	**0.418659**	**0.154249**	**0.565001**	min^{-1}
k_{p1}	$5.38\times10^{+00}$	$(3.56\text{-}7.20)\times10^{+00}$	0	0	7.93E-06	3.21E-05	mg/kg/min
k_{p2}	5.23×10^{-03}	$(2.44\text{-}8.02)\times10^{-03}$	0	0.000721	0	0	min^{-1}
k_{p3}	1.43×10^{-02}	$(0.46\text{-}2.39)\times10^{-02}$	**0.301874**	0.005473	**0.11209**	0.039743	mg/kg/min per pmol/L
k_i	0.78×10^{-02}	$(0.29\text{-}1.62)\times10^{-02}$	3.51E-06	4.19E-05	0	0.000163	$min\text{-}^{1}$
k_{2_PS}	4.00×10^{-03}	$(3.20\text{-}4.80)\times10^{-03}$	0.015557	0.004761	0	3.37E-05	min^{-1}
k_{1_PS}	5.00×10^{-04}	$(4.00\text{-}6.00)\times10^{-04}$	0.000932	0.000138	3.64E-05	2.27E-05	dL^2 per $pmol\cdot min^2$
k_{max}	3.01×10^{-01}	$(0.21\text{-}5.82)\times10^{-01}$	0	0	-	-	min^{-1}
k_{min}	4.00×10^{-02}	$(2.19\text{-}5.82)\times10^{-02}$	0	0.000127	-	-	min^{-1}
k_{abs}	8.84×10^{-03}	$(0.28\text{-}1.49)\times10^{-02}$	**0.160871**	1.67E-05	-	-	min^{-1}
k_{gri}	4.00×10^{-02}	$(2.19\text{-}5.82)\times10^{-02}$	0	8.23E-05	-	-	min^{-1}
B	7.95×10^{-01}	$(6.27\text{-}9.62)\times10^{-01}$	3.63E-05	0.001582	-	-	-
D	2.15×10^{-01}	$(0.92\text{-}3.37)\times10^{-01}$	0	0.001022	-	-	-
CL_{renal}	5.00×10^{-05}	$(4.00\text{-}6.00)\times10^{-01}$	1.33E-04	0	6.32 E-05	0	dL/min
Q_{co}	$6.04\times10^{+03}$	$(3.76\text{-}7.02)\times10^{+03}$	0.003759	0.003217	6.69E-05	2.64E-05	mL/min
V_K	$3.90\times10^{+00}$	$(2.24\text{-}4.86)\times10^{+00}$	0.000289	0.000225	-	-	dL
V_G	$4.44\times10^{+00}$	$(2.55\text{-}5.54)\times10^{+00}$	0.012974	0.008315	-	-	dL
V_P	$1.09\times10^{+01}$	$(0.63\text{-}1.37)\times10^{+01}$	0	0.000374	-	-	dL
V_B	$3.06\times10^{+00}$	$(1.76\text{-}3.82)\times10^{+00}$	6.78E-05	0.010876	-	-	dL
V_L	$5.62\times10^{+00}$	$(3.23\text{-}7.02)\times10^{+00}$	0	0.00272	-	-	dL
V_H	$1.34\times10^{+01}$	$(1.27\text{-}1.35)\times10^{+01}$	3.38E-05	0.000164	-	-	dL
$r_{co,K}$	1.78×10^{-01}	$(1.69\text{-}1.87)\times10^{-01}$	1.33E-05	0.000539	1.16E-05	0.006560	-
$r_{co,G}$	1.95×10^{-01}	$(1.85\text{-}2.05)\times10^{-01}$	0.067301	0.004797	0	3.68E-05	-
$r_{co,P}$	4.39×10^{-01}	$(4.17\text{-}4.61)\times10^{-01}$	4.28E-05	0.00048	6.26E-05	0.003743	-
$r_{co,B}$	1.38×10^{-01}	$(1.31\text{-}1.45)\times10^{-01}$	0.000107	0.003262	1.29E-05	2.34E-06	-
$r_{co,L}$	2.44×10^{-01}	$(2.32\text{-}2.56)\times10^{-01}$	2.75E-05	0.018778	1.04E-05	0.000398	-
$r_{u,K}$	2.00×10^{-02}	$(1.90\text{-}2.10)\times10^{-02}$	0	0.00064	0.000774	0.003097	-
$r_{u,G}$	7.00×10^{-02}	$(6.65\text{-}7.35)\times10^{-02}$	0.02257	0.001398	0.008611	0.003169	-
$r_{u,L}$	1.30×10^{-01}	$(1.24\text{-}1.37)\times10^{-01}$	**0.052423**	**0.137398**	**0.027909**	0.001827	-
$r_{u,H}$	1.80×10^{-02}	$(1.71\text{-}1.89)\times10^{-02}$	0.000969	**0.033467**	0.000112	**0.025256**	-

A meal containing 50 g of carbohydrates and a 10 U bolus were given at 420min. The time points in Table 4.7 refer to 1 hour and 5 hours after meal consumption and were chosen to investigate the influence of the parameters when the sub models of meal absorption and bolus insulin kinetics are active and when all the external disturbances are absorbed and the system is relatively balanced. For the first case the most influential parameters are the k_1, k_2, k_{p3}, k_{abs} and $r_{u,L}$ at 480min and k_1, k_2, $r_{u,L}$ and $r_{u,H}$ at 720min. Hence, the parameters related to glucose absorption from the periphery k_1, k_2 as a function of insulin concentration (3.24) are the most critical since they are related to the patient's sensitivity to insulin and therefore their ability to absorb glucose. For the second case the parameters k_1, k_2, $r_{u,L}$ and $r_{u,H}$ are the most influential.

The time varying parameters for the two cases defined in Table 4.7 are shown in Figure 4.4 and Figure 4.5. Only the parameters with the highest sensitivities are included in the graphs. For both cases, the sensitivities of parameters k_1 and k_2 remain high throughout the performance analysis while both are increased after meal and bolus administration. The sensitivity of k_{p3}, as expected, increases during bolus administration and decreases at the postprandial state when insulin concentration decreases after the bolus peak. Additionally for k_{abs}, a parameter that indicates how fast the blood glucose is absorbed from the small intestine, the sensitivity increases with meal consumption and decreases when glucose has been absorbed. For the ratio of glucose absorption from the liver the sensitivity is high at the fasting state and decreases relatively at the postprandial state. While the ratio of glucose absorption from the heart increases after meal consumption, indicating that both of these parameters influence the glucose regulation in accordance with (3.3) and (3.5).

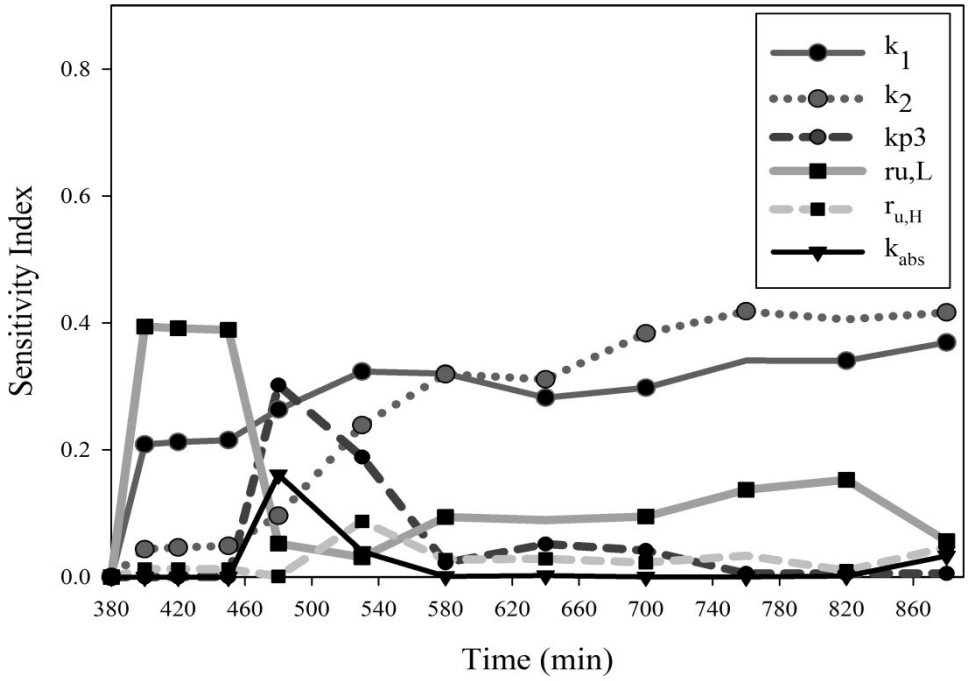


Figure 4.4: Time varying SIs when all parameters are considered

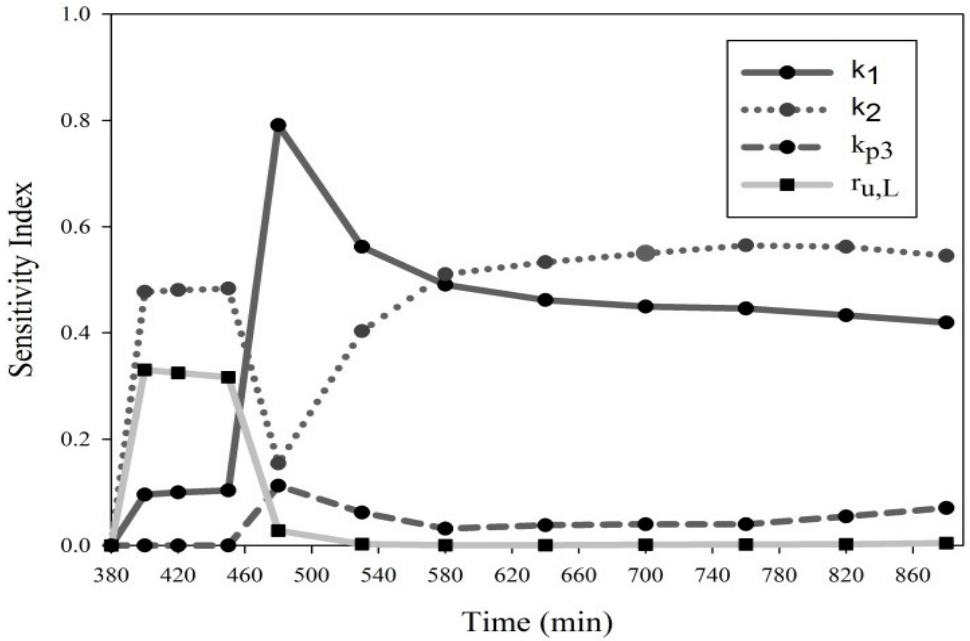


Figure 4.5: Time varying SIs when intra-patient variability related parameters are considered

As a conclusion, it can be stated that the parameters with the most influential role are those related to insulin effect on glucose. The parameters related to insulin distribution, absorption and elimination through the subcutaneous tissue, as well as the parameters related to glucose distribution in the various compartments can be considered as non-influential compared to the insulin-effect related parameters.

4.5 Parameter Estimation

The performance of the proposed model is evaluated with detailed simulation studies performed in gPROMS and its predictive ability is verified by comparison with results from the simulator UVa/Padova T1DMS. In order to obtain individual parameter estimates, an experiment is designed and the following information is required: duration of the experiment (24h), CGMs blood glucose concentration measurements and the time the measurements were taken, time varying control inputs (bolus, basal doses, meal amount,), their variation profiles (timing, meal duration) and plasma insulin concentration profile after a subcutaneous insulin injection. The insulin regimen is set for every patient using their total daily dose (TDD), and the standard clinical rules (5.4-5.8). Although the blood glucose concentration measurements and the control input information can be collected and recorded easily, measurements of plasma insulin concentration require invasive experimental design. However, the GSA concluded that the parameters of insulin kinetics are not as influential and therefore a mean value of the parameters can be considered. In this work individual parameter estimation studies are performed using plasma insulin concentration measurements coming from the "virtual patient" in order to estimate precisely the range of all the parameters. Additionally, it is considered that the patient is not taking any exercise during the experiment.

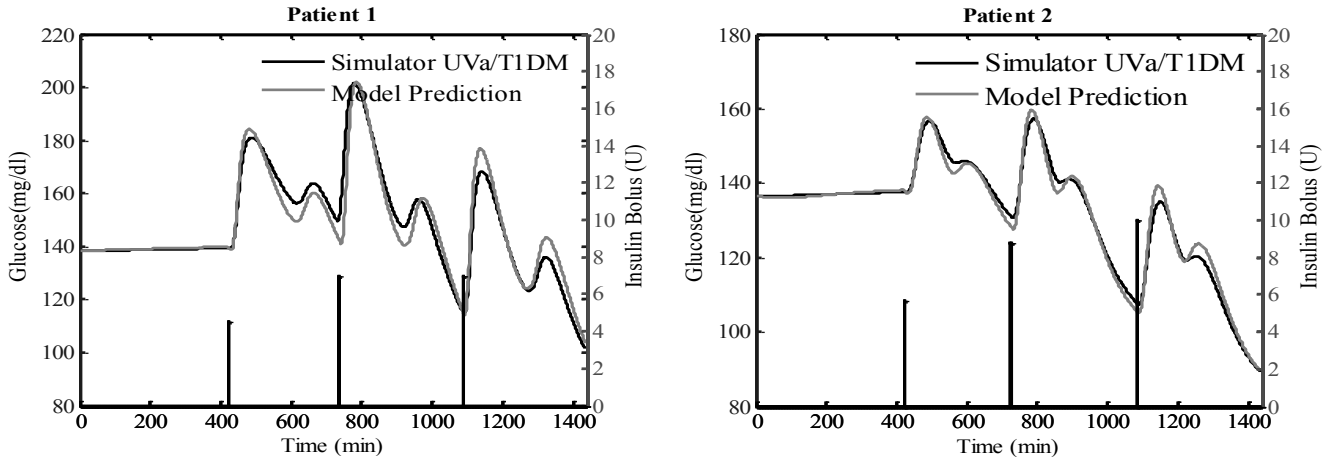
To demonstrate the prediction ability of the proposed model, a specific diet plan of 45g of carbohydrates for breakfast, 70 g for lunch and 70 g for dinner is set and the simulation results are shown for the ten patients. The same experimental conditions are applied in the simulator and the blood glucose and plasma insulin concentration profiles are used as "experimental" data to estimate the most influential model parameters. Hence, the individual parameters of model 3 for insulin kinetics and k_1, k_2, $r_{u,L}$ and k_{p3} and k_{abs} of glucose metabolism are estimated as shown in Table 4.8. The rest of the parameters of the sub model Ra and EGP are estimated for each patient to obtain patient-specific glucose-insulin dynamics. Parameters Qco and V_i are calculated for every patient using (3.28-3.29), parameters $r_{u,K}$, $r_{u,G}$ and $r_{u,H}$ are calculated according to the estimated value of $r_{u,L}$ to maintain the initial ratio as in Table 3.2 and parameters $k_{1,PS}$, k_{2_PS}, $r_{co,i}$ are set to their default values as specified in Table 4.7. The estimated parameter values for all the patients are presented in detail in Appendix B.1.

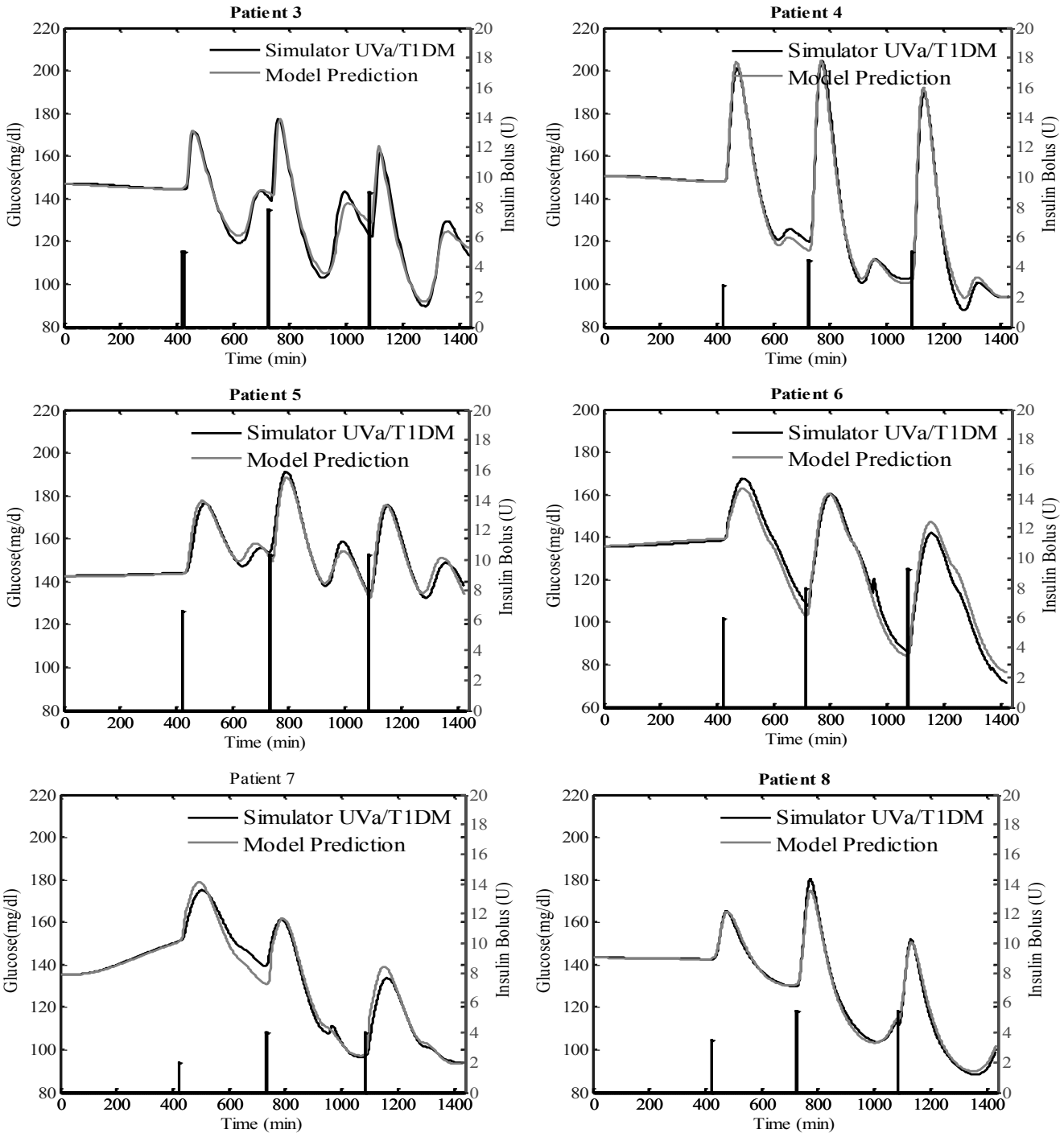
Table 4.8: Optimal parameter estimates presented as mean value (lower-upper) value for the 10 patients

Symbol	Value	Units	Symbol	Value	Units
k_1	1.58×10^{-04} ($2.11\text{-}38.4$) $\times10^{-05}$	dL^2 per pmol·min	k_i	8.15×10^{-03} ($0.294\text{-}1.34$) $\times10^{-02}$	min^{-1}
k_2	2.35×10^{-02} ($1.17\text{-}4.53$) $\times10^{-02}$	min^{-1}	k_{p1}	5.65 (3.97-7.2)	mg/kg/min
$r_{u,L}$	1.7×10^{-01} ($0.6\text{-}1.9$) $\times10^{-01}$	-	k_{p2}	4.73×10^{-03} ($2.44\text{-}7.72$) $\times10^{-03}$	min^{-1}
k_{max}	3.53×10^{-02} ($2.19\text{-}5.82$) $\times10^{-02}$	min^{-1}	k_{p3}	1.49×10^{-02} ($0.0551\text{-}2.39$) $\times10^{-02}$	mg/kg/min per pmol/L
k_{min}	7.62×10^{-03} ($0.373\text{-}1.16$) $\times10^{-02}$	min^{-1}	k_{elim}	1.36 (0.2996-2.1433)	min^{-1}
k_{abs}	1.14×10^{-01} ($0.214\text{-}5.82$) $\times10^{-01}$	min^{-1}	k_{sub}	1.86×10^{-02} ($1.21\text{-}2.46$) $\times10^{-02}$	min^{-1}
b	8.27×10^{-01} ($7.36\text{-}9.29$) $\times10^{-01}$	-	V_{dist}	1.54×10^{-02} ($1.00\text{-}5.16$) $\times10^{-02}$	L/Kg
d	1.91×10^{-02} ($0.98\text{-}3.32$) $\times10^{-01}$	-			

4.6 Simulation Results

The glucose profiles of the proposed model compared to the simulator are shown in Figure 4.6 for the ten patients. A meal plan of 45g, 70g and 70g of carbohydrates is considered at 420min, 720min and 1080min. The right-hand side y-axis represents insulin amount (U). The amount of insulin bolus given to compensate for the glucose increase after each meal is shown with the insulin pulses colored in black. The left-hand side y-axis represents the blood glucose concentration (mg/dl). The glucose profiles as calculated by both models for the particular meal plan and insulin treatment are compared. The black curve shows the glucose profile calculated by the simulator and the grey curve the glucose profile calculated using the proposed model.




Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Simulator UVa/T1DM
Model Prediction
Glucose(mg/dl)
Insulin Bolus (U)
Time (min)

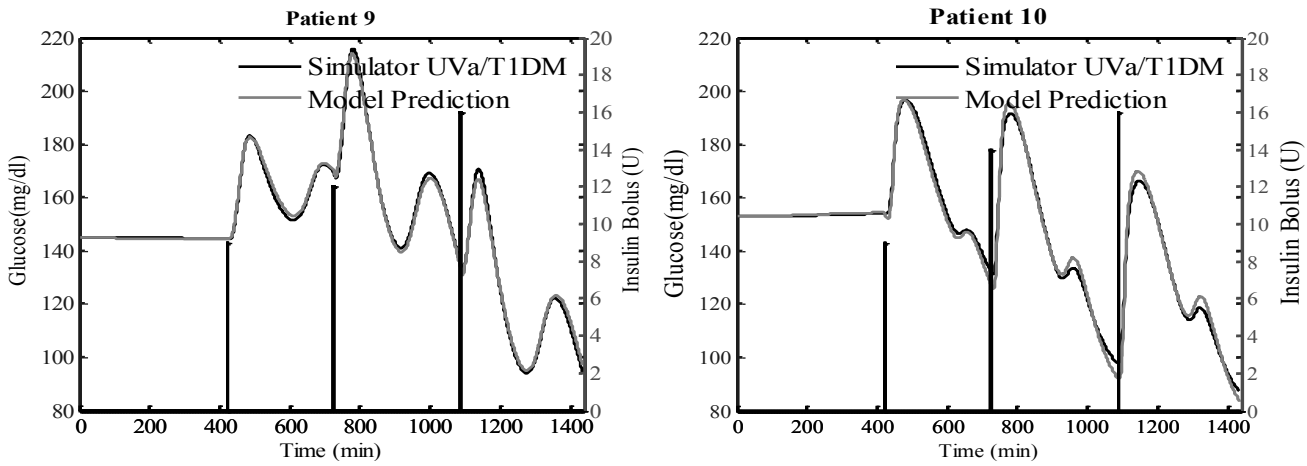


Figure 4.6: Comparison of blood glucose concentration (mg/dl) as predicted from the proposed model with the Simulator, for the 10 adults when a meal plan of 45g, 70g and 70g of carbohydrates are considered at 420min, 720min and 1080min respectively. The insulin infusion (U) is shown at the right axis for every patient.

The simulation results indicate that the proposed model can predict accurately the daily blood glucose concentration profile. The good fit of the model to the UVa/Padova Simulator shows that the estimated values of the most influential parameters, as identified from the previous section are well adjusted for all cases.

In Figure 4.7 the glucose concentration profile in all organs is presented for adult 5, in the presence of 45 g of meal and 6.5 U of insulin bolus. The concentration in the liver is higher as expected since liver can store and produce glucose and thus the capacity of glucose accumulation is higher. It is shown that the concentration in the gut increases rapidly when the meal is consumed before being absorbed into the blood.

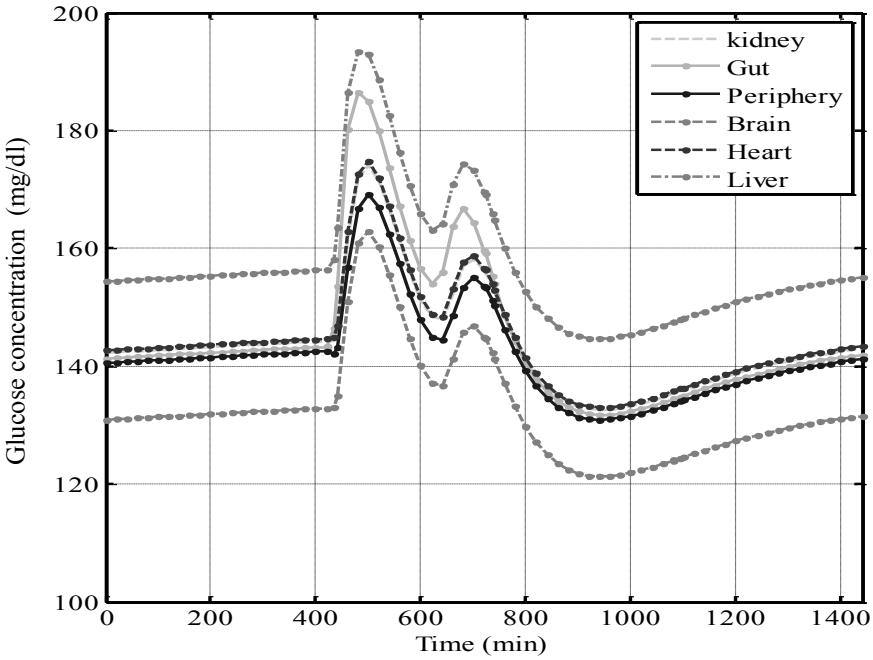


Figure 4.7: Glucose concentration profiles in the organs for a 45 g of CHO meal and a 6.5 U insulin bolus

In Figure 4.8 the rate of glucose uptake by the body organs is presented. The rate of glucose uptake by the brain is considered constant since the brain's glucose requirements remain continuously the same and account for approximately 46% of the total available glucose to be absorbed. Glucose absorption by the periphery account for 29% and the remaining percentage is absorbed by the rest of the organs.

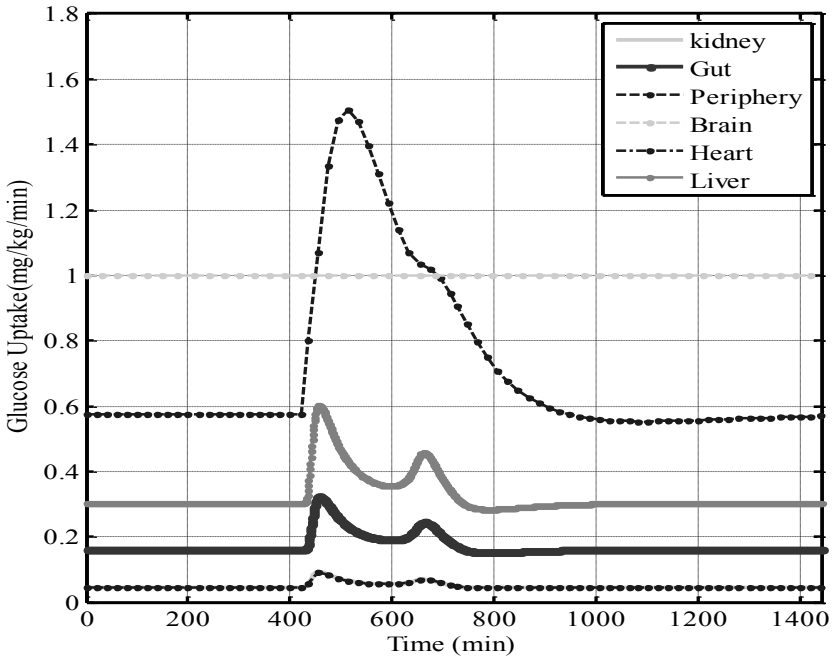


Figure 4.8: Rate of glucose absorption from the organs for a 45 g of CHO meal and a 6.5 U insulin bolus

Figure 4.9 and Figure 4.10 present the EGP profile and the Ra respectively, of 45 g of CHO and 6.5 U of insulin bolus for adult 5. Since the parameters were estimated using the glucose profiles as presented in section 4.5, and no exact EGP and Ra profiles were considered, the profiles of two sub models for adult 5 are compared with the area produced when performing a series of 50 simultaneous stochastic simulations at the UVa/Padova simulator with the corresponding parameters of each model varying 20% of their mean values.

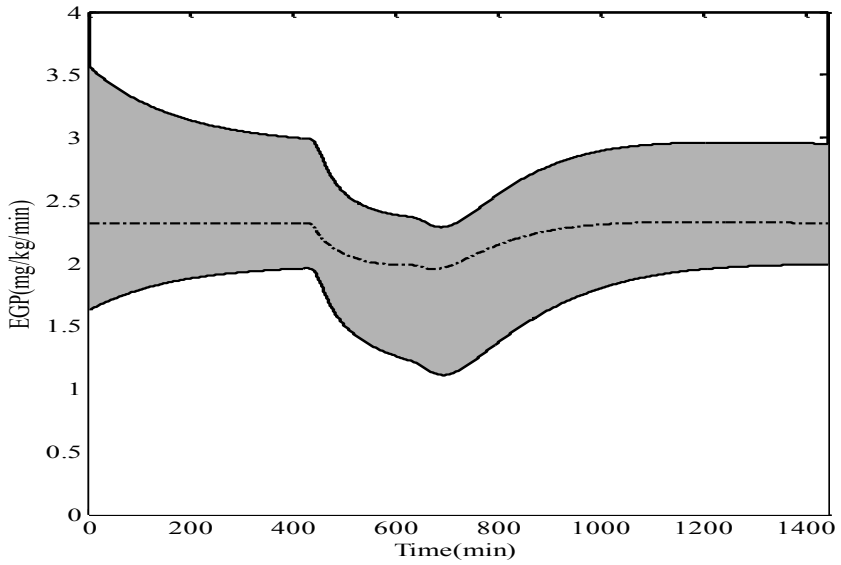


Figure 4.9: Grey area presents the EGP profiles of a stochastic simulation performed in UVa/Padova Simulator for 20% variation of the parameters from their mean value and the dashed line the EGP profile as obtained from the proposed model using the estimated parameter values.

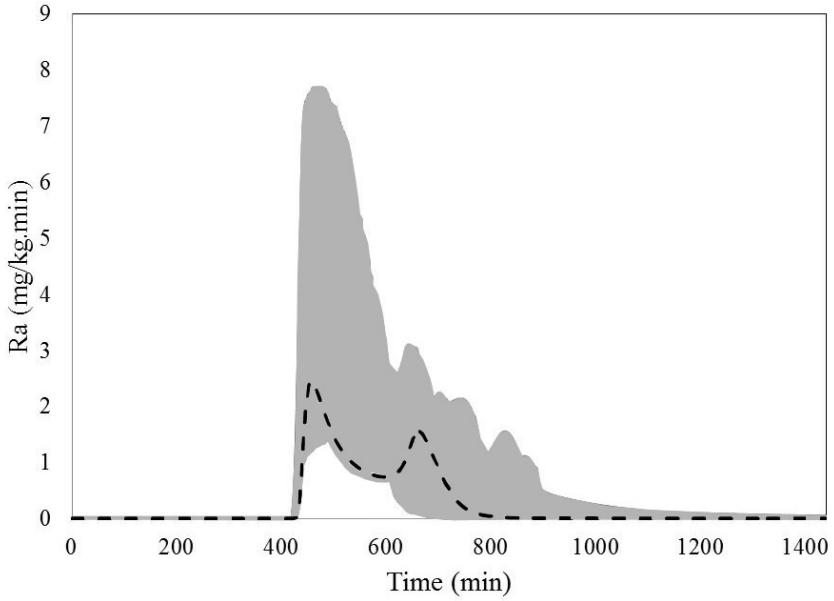


Figure 4.10: Grey area presents the Ra profiles of a stochastic simulation performed in UVa/Padova Simulator for 20% variation of the parameters from their mean value and the dashed line the Ra profile as obtained from the proposed model using the estimated parameter values.

Figure 4.9 and Figure 4.10 show that the model parameters of Ra and EGP sub models as estimated using only blood glucose concentration profiles are well adjusted and the prediction of Ra and EGP profiles is very adequate. Additionally, Figure 4.9 and Figure 4.10 demonstrate that there is a high inter-patient variability.

Key Points

- The simulation results indicate that the proposed model can accurately represent individual glucose-insulin dynamics
- The model states describe the involved physiology of glucose metabolism and insulin interactions at organ level
- The model can be regarded as an educational and simulation tool that increases the level of understanding for the particular system

4.7 Time Delays in the system

Time delay in a system is the time that intervenes from the instant the input, the control or a force is applied until the instant the effect is observed. One of the great challenges of an automated system of insulin delivery is the delayed insulin absorption and action. That means that there is a time lag between the time insulin is given and the time to cause the maximum effect. This time lag is related to the type of insulin used, the route of administration, the detection of a glucose fluctuation and the patient's sensitivity to insulin. The difference in the glycaemic response produced by the same dose of insulin in different individuals indicates that there is a high intra-patient variability involved in glucose-insulin interactions. When this variability is low then a more predictable glycaemic response can be determined, which is important for a closed loop system. In order to reduce the factors that cause variability and deteriorate the prediction of the glycaemic response, open loop simulation analysis is performed to gain deep knowledge of the particular system and use the conclusions as a guideline for the closed loop studies, studied in the next chapter.

In this particular system the input is the insulin dose and the effect is the decrease in the blood glucose concentration. Figure 4.11 reveals the complexity of blood glucose regulation when subcutaneous rapid acting insulin is used. Rapid acting insulin is a human insulin analogue that, due to its chemical structure, reduces aggregation of insulin molecules and therefore accelerates the absorption process. Assuming that the sampling time Ts is 5min (available measurements of glucose concentration in the blood by the sensor), it can be noticed that

insulin requires up to 15min to initiate the decrease of blood glucose concentration, practically to observe a 1mg/dl change of the concentration. This time involves the absorption of rapid acting insulin through the subcutaneous tissue and insulin action can take up to 1-3 hours for its maximum effect.

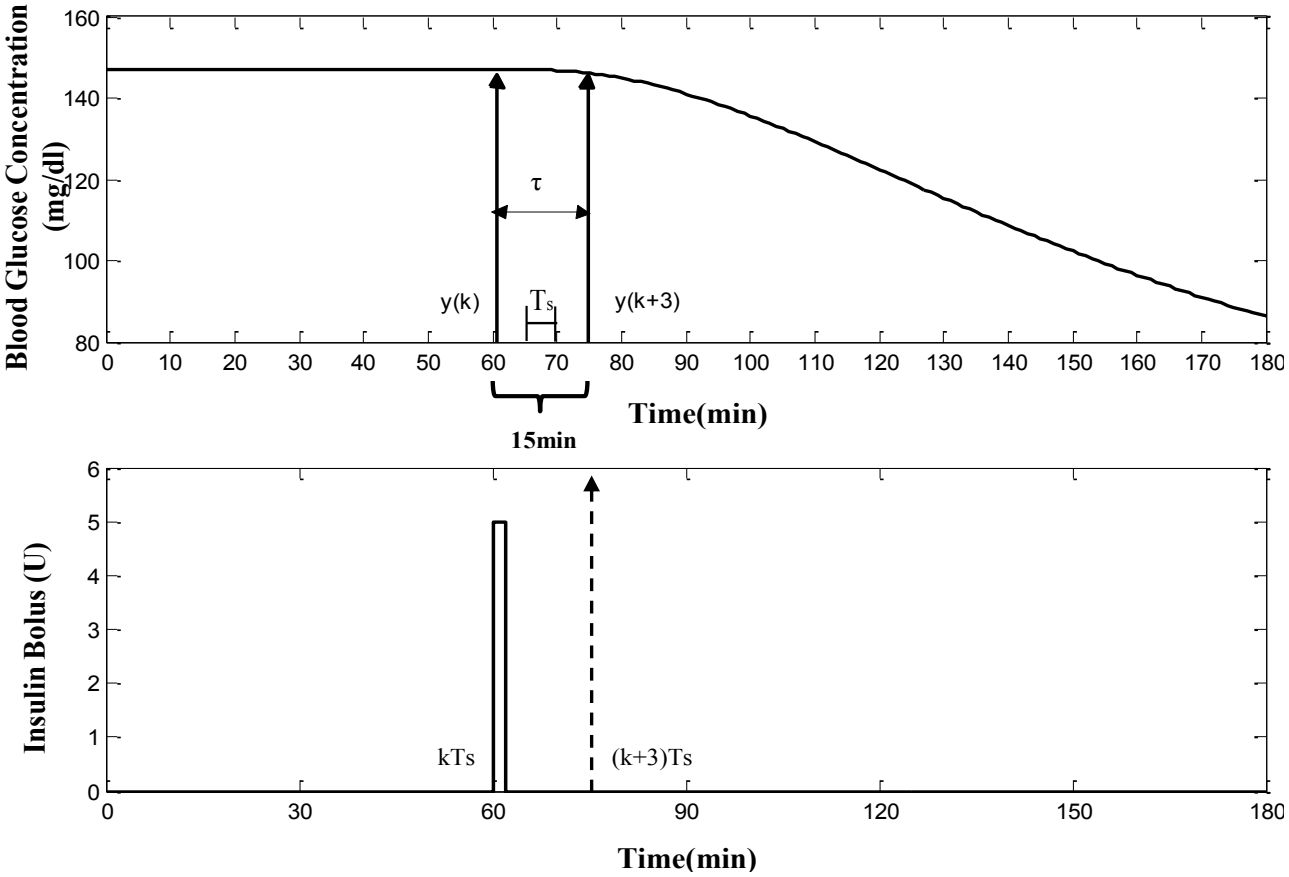


Figure 4.11: Time delay in the system

In Figure 4.12, 1U bolus of rapid acting insulin is given at 60min in four patients. It can be noticed that the time to observe a 10mg/dl decrease of blood glucose concentration is not equal for the four patients. This can be explained since every patient responds differently to insulin and has a different ability to increase the body's glucose uptake by the various tissues. This can be quantified with insulin sensitivity index. The more sensitive to insulin the patient is, the less amount of insulin is required. Patients 4 and 7 with high insulin sensitivity index require less time for their blood glucose to be decreased than patients 3 and 6.

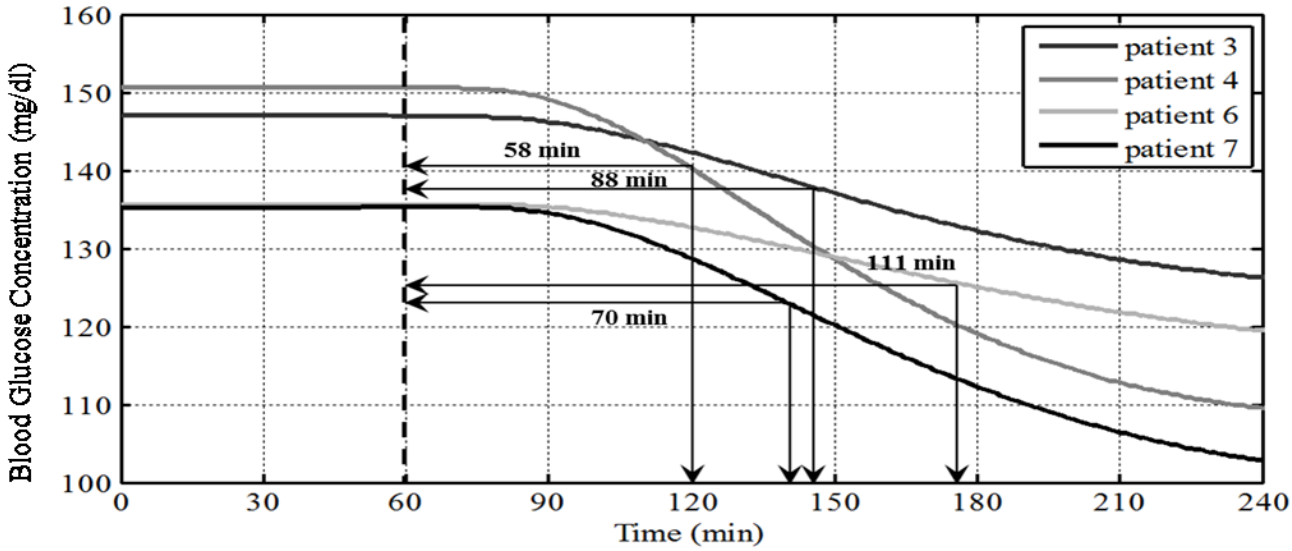


Figure 4.12: Patient dependent time delay

In Figure 4.13 and Figure 4.14 for two patients, low and high insulin sensitive, 3 different bolus doses are given at 400min without considering meal consumption. It can be noticed that the time required for glucose to be decreased by 10mg/dl is dependent on the amount of bolus given. The delayed insulin effect decreases while the amount of insulin bolus increases. This implies that the time delay property cannot be considered constant for an individual patient.

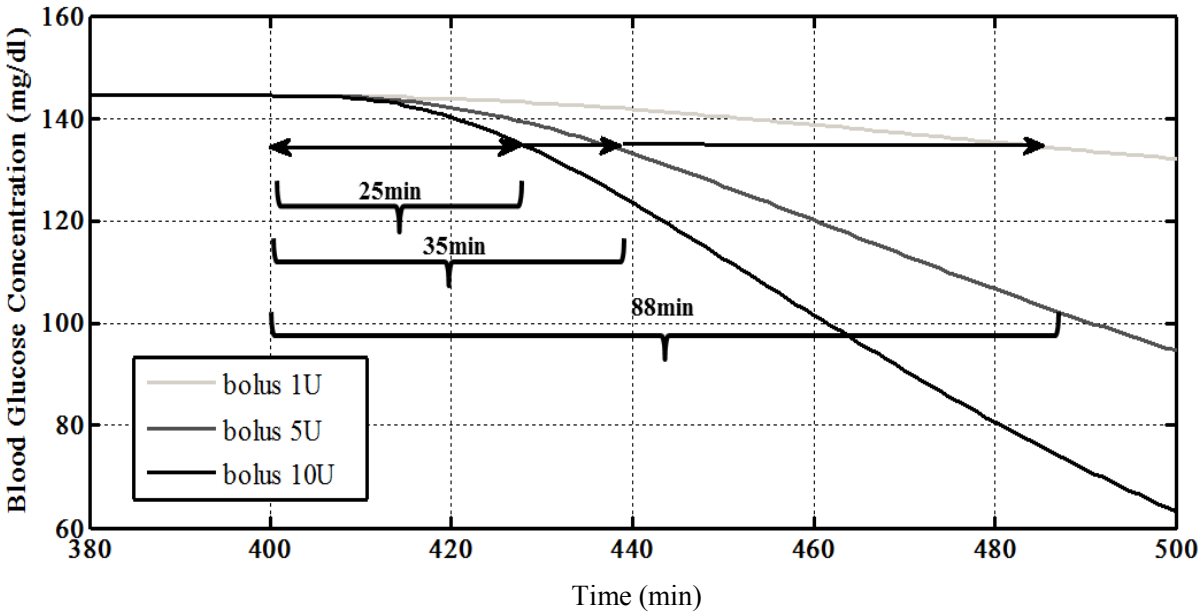


Figure 4.13 : Time delay dependence on patient and bolus (adult 3-low insulin sensitive)

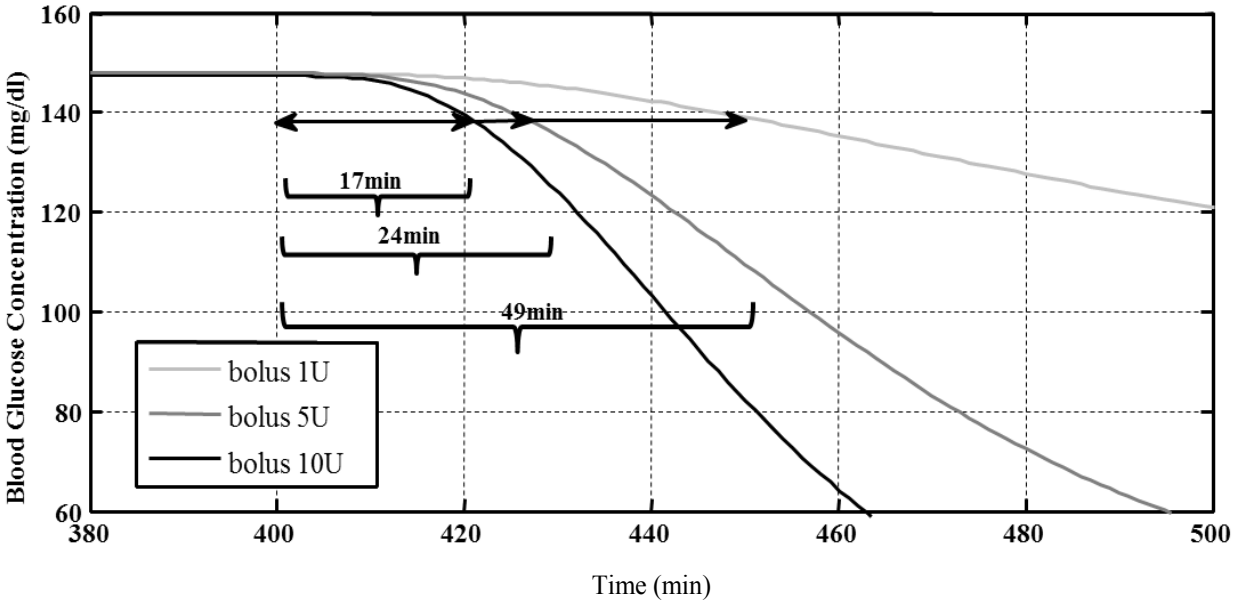


Figure 4.14: Time delay dependence on patient and bolus (adult 4-high insulin sensitive)

In conclusion, the dynamic system involves inherent time delays. These include the delayed insulin absorption and action and also the approximately 10 min delayed glucose appearance in the blood after food consumption due to interstitial glucose kinetics, meaning the route from the mouth to the small intestine and then to the blood. Apart from these delays, there are additional technical delays which involve the delayed detection of blood glucose concentration change because the continuous glucose monitoring devices calculate blood glucose concentration by measuring interstitial fluid (ISF) glucose concentration (Keenan *et al.*, 2009). Hence the time lag of the displayed glucose value and the real blood glucose value consists of the time lag between ISF and blood glucose accounting for the processing requirements as well. This analysis has motivated the performance of patient-specific optimisation studies, to find the optimal timing of insulin dosing to maintain the patient's glycaemic target.

4.8 Dynamic optimisation of insulin delivery

From the previous analysis, it has been evident that, in order for the patients to maintain their blood glucose close to their glycaemic target, the timing of the bolus insulin administration must be optimally decided to achieve safe glycaemic regulation. It has also been evident that each patient presents a unique response to insulin and therefore must be treated differently. Hence, patient-specific optimisation studies are performed to obtain the optimal insulin profile that minimizes the time over which glucose is outside of the normal range. The mathematical formulation of the optimisation problem has the following general form:

$$\min_{d_i} \int_0^{t_f} (w_1 + w_2)dt \tag{5.1}$$

s.t.

$$G = f(x(t), \dot{x}(t), y(t), u(t), d_i) \tag{5.2}$$

$$\sum_{i=1}^{N_{\text{int}}} d_i = 1, \qquad d_i \in \{0,1\} \tag{5.3}$$

$$w_1 \geq 0, \qquad w_1 \geq G - G_{\max} \tag{5.3.a}$$

$$w_2 \geq 0, \qquad w_2 \geq G_{\min} - G \tag{5.3.b}$$

where t_f is the time horizon, G is the blood glucose concentration described by the nonlinear process model presented in Chapter 3, G_{max} (140 mg/dl), G_{min} (70mg/dl) are the upper and lower glucose concentration bounds. (5.3.a) and (5.3.b) are the blood glucose constraints imposed to prevent severe health complications related to hyperglycaemia and hypoglycemia. A window of 4h before the meal was considered, which is long enough to cover the cases of patients with extremely low insulin sensitivity. This time span was discretised every 2min, which is the time the pump requires to deliver an insulin bolus, hence resulting in 120 control intervals. A time invariant, binary variable d_i was considered to be 1 if a bolus was given over time interval *i,* and 0 otherwise. The Mixed Integer Nonlinear Programming problem was implemented and solved in gPROMS.

At t_0=400 mins a breakfast meal of 50 g of carbohydrates is given to the 10 patients. The optimal amount of insulin that can compensate for the forthcoming glucose increase due to the meal intake is calculated using standard medical rules for optimal insulin dosing:

Conventional Optimal Insulin Dosing:

Basal Dose = 60% of the TDD (Walsh and Roberts, 2006) (5.4)

Bolus Dose = CHO/CR+CID (Walsh and Roberts, 2006) (5.5)

where CHO is the carbohydrate meal size in g, CR (g/U) is the carb factor (calculated with the 500 Rule as 500/TDD) which defines the amount of carbohydrates (in g) covered by 1U of insulin. The Correction Insulin Dose, CID, is given to compensate for the difference of high blood glucose from the desired value (target) and is calculated as:

CID=(Current BG-Target BG)/CF (5.6)

where BG refers to blood glucose and equals to C_H in the model (3.5). The correction factor (CF) is calculated with the 1800 Rule as 1800/TDD.

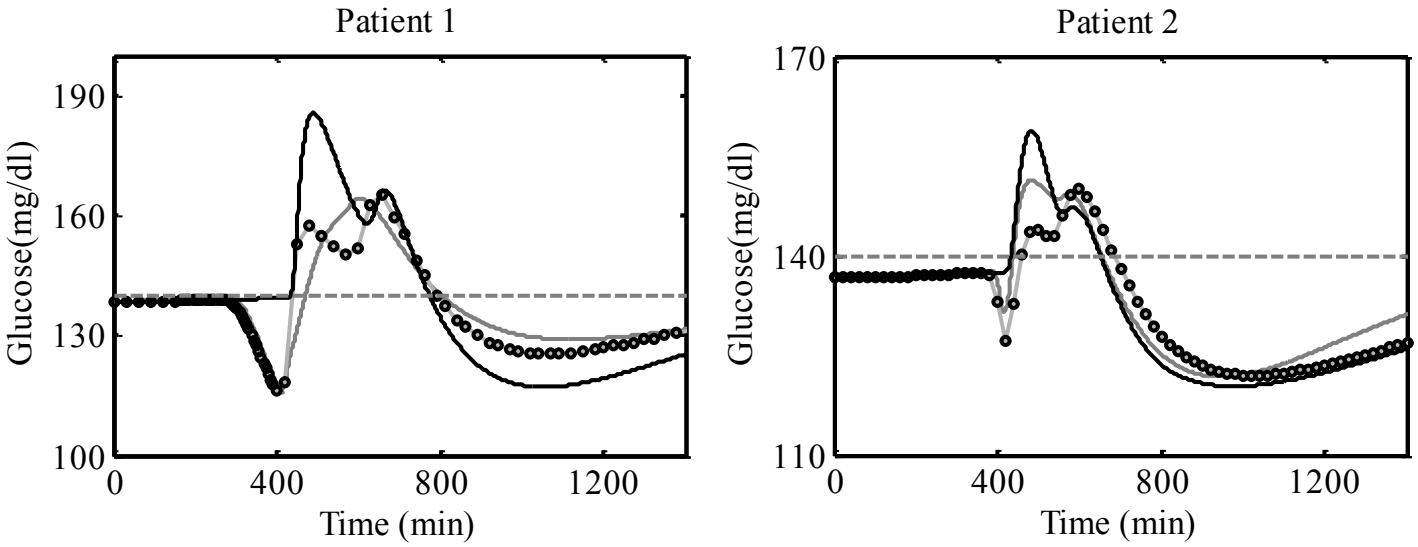
The TDD is set for every patient from their physician. Appropriate adjustments, if necessary, are also defined by their physician.

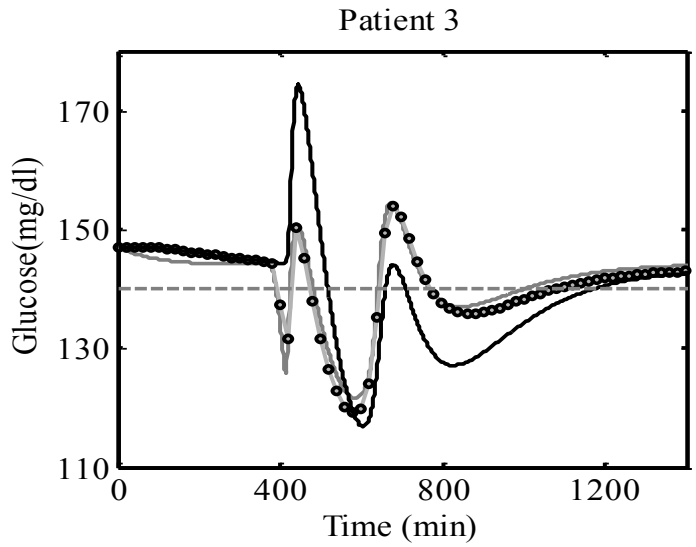
The values of TDD, CF, CR, CID are obtained from the UVa/Padova Simulator for each patient. Hence the administered insulin boluses, calculated as CHO/CR, are:

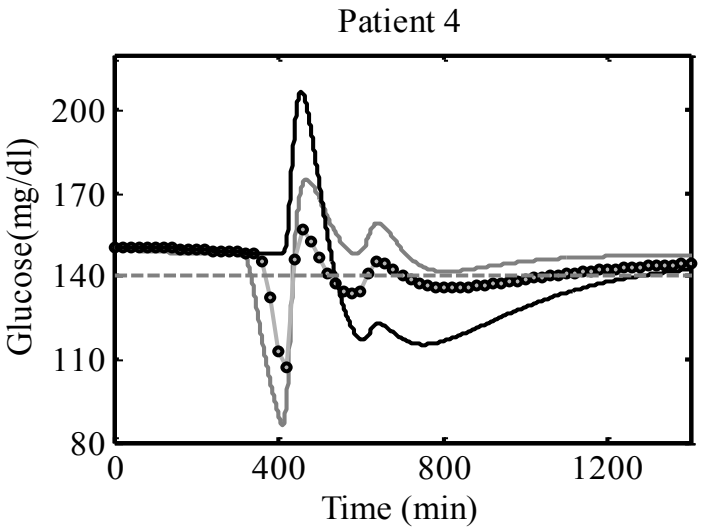
Table 4.9: Insulin bolus to compensate for 50 g of CHO

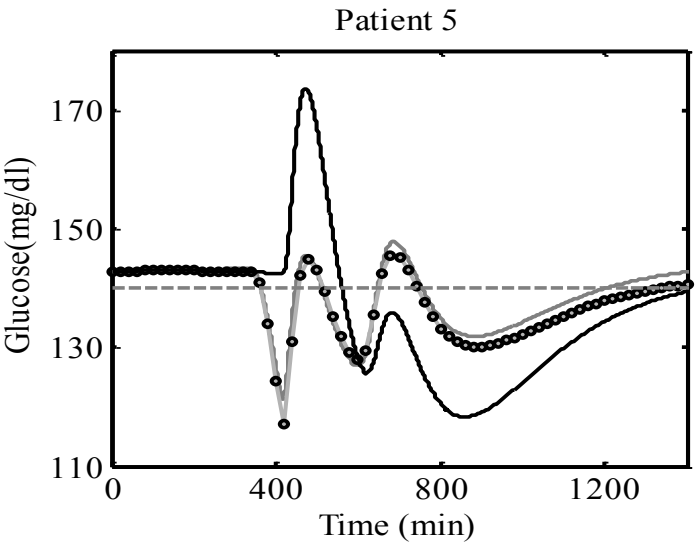
Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient1 0
5.57U	3.165U	5U	6.27U	10U	5.02U	2.27U	3.87U	10U	10U

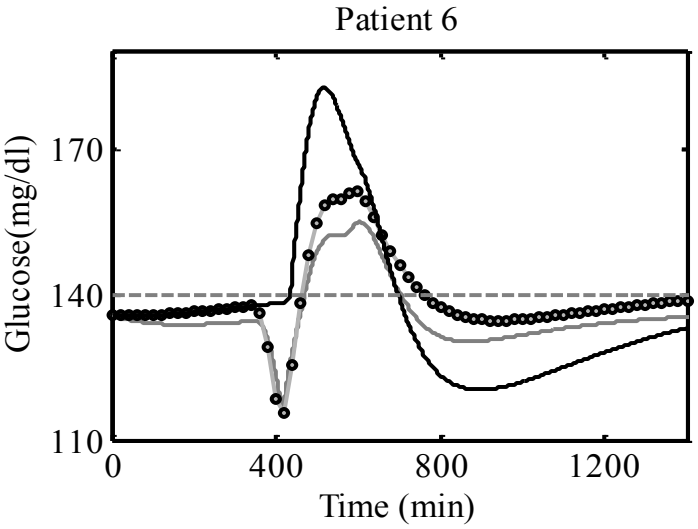
The optimisation results are presented in Figure 4.15 for 8 patients. The grey line shows the optimised glucose profile while the black line shows the simulated profile when the bolus is given simultaneously with meal; the light dotted grey line is the optimised glucose profile when the T1DMS model is used instead of the proposed model in the optimisation, for comparison. The optimal timing of insulin administration for every patient is summarised in Table 4.10. When the bolus is given at the optimal time the glucose profile is improved in terms of maintenance of the concentration within the normal range for all the patients. In Table 4.10 the area between the upper glucose bound and the glucose profile is calculated.

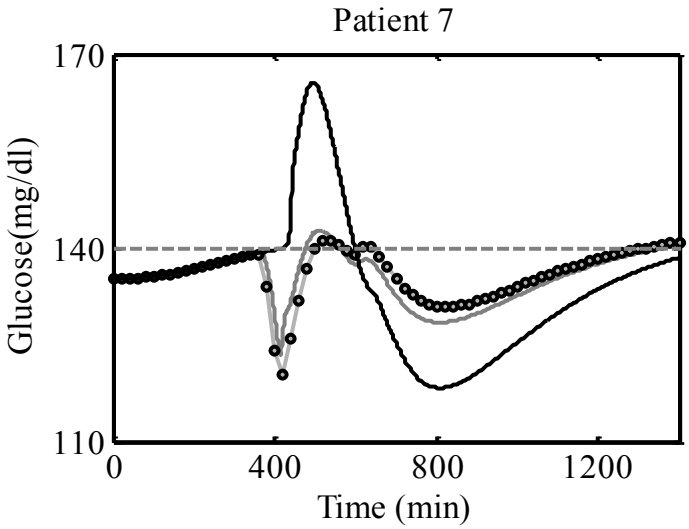


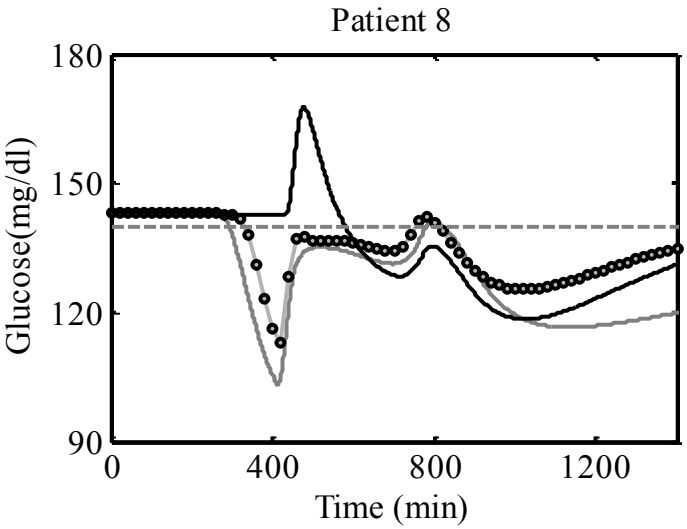

Patient 3
Glucose(mg/dl)
170
150
130
110
0
400
800
1200
Time (min)


Patient 4
Glucose(mg/dl)
200
170
140
110
80
0
400
800
1200
Time (min)


Patient 5
Glucose(mg/dl)
170
150
130
110
0
400
800
1200
Time (min)


Patient 6
Glucose(mg/dl)
170
140
110
0
400
800
1200
Time (min)


Patient 7
Glucose(mg/dl)
170
140
110
0
400
800
1200
Time (min)


Patient 8
Glucose(mg/dl)
180
150
120
90
0
400
800
1200
Time (min)

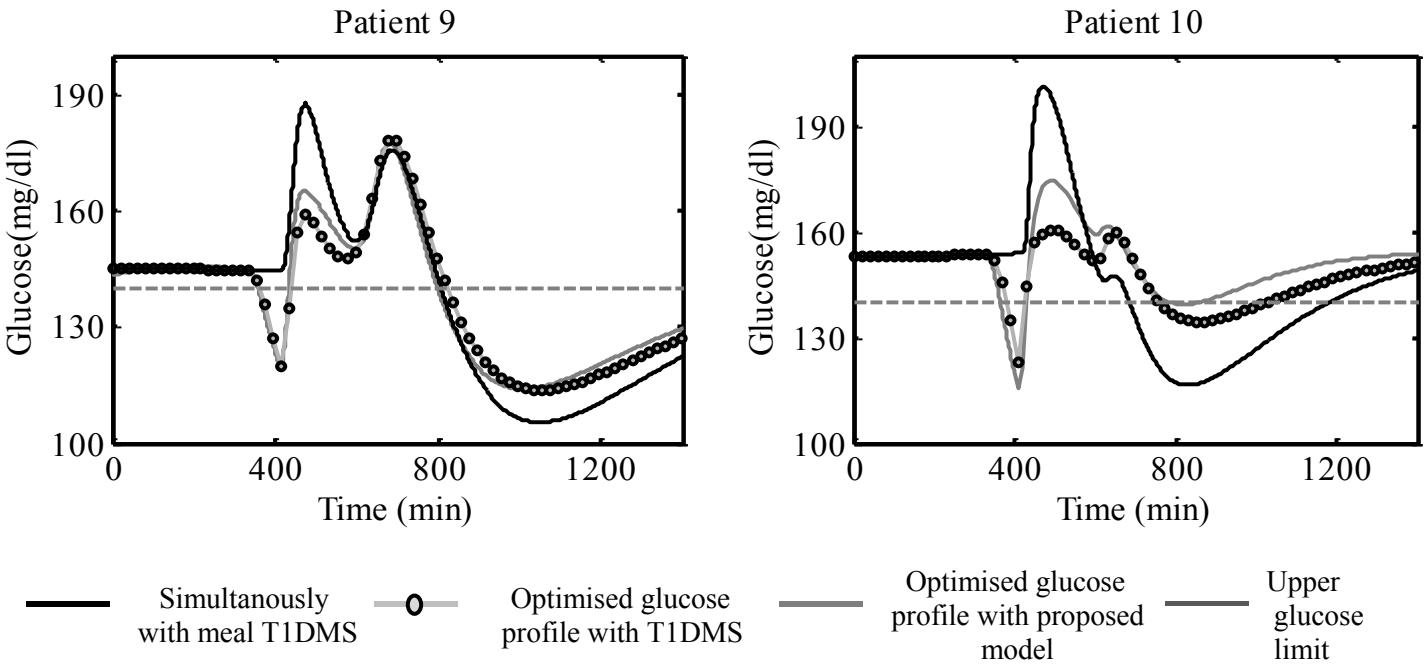


Figure 4.15: Optimisation of bolus timing; light grey: optimised glucose profile using the T1DMS, grey: optimised glucose profile using the proposed model and black line: glucose profile when bolus given simultaneously with food using the T1DMS.

Table 4.10: Area under the curve (outside the normal range)

	Glucose curve	Optimised Glucose curve (T1DMS)	Optimised Glucose curve (proposed model)	Optimal bolus time (T1DMS)	Optimal bolus time (proposed model)
Pat1	8.330e+03	5.126e+03	4.751e+03	140min	110min
Pat2	2.191e+03	1.321e+03	1.8536e+03	36min	16min
Pat 3	5.174e+03	4.482e+03	4.527e+03	32min	32min
Pat4	6.708e+04	5.892e+03	1.195e+04	66min	84min
Pati5	4.064e+03	1.718e+03	2.355e+03	62min	64min
Pati6	2.096e+05	3.945e+03	2.420e+03	62min	48min
Pat7	2.083e+05	2.785e+02	3.266e+02	52min	44min
Pat8	5.972e+04	1.209e+03	1.075e+03	100min	140min
Pat 9	1.165e+04	8.913e+03	3.537e+03	74min	68min
Pat10	1.493e+04	1.262e+04	1.672+04	72min	72min

As illustrated in Figure 4.15 improved glycaemic control can be achieved for both the examined models when the time to provide the insulin dose is optimised. This result is confirmed with Table 4.10, which shows that the area under the curve for the optimised curves is smaller than the simulated curves indicating that the time glucose is spent above the upper glucose bound is less. Additionally, hypoglycemic events are not observed for any of

the patients, despite the considerable difference of the bolus timing between them. This is related to the sensitivity of the patient to insulin as mentioned before and for the specific optimal dose the patient would not reach the lower glucose bound.

If we either compare the graphs or the results in Table 4.10, we can notice that the solution of the optimisation problem using the proposed model or the T1DMS may be different. For some of the patients the optimisation results are similar, indicating a good fit of the parameters, but for other patients (such as patient 4 or patient 2) the optimal time to administer the dose differs from 20 to 40min. This demonstrates that additional experimental data, apart from glucose and insulin profiles are required to capture entirely the dynamics of each patient. However, the trend of the glucose profiles as well as the approximately same timing range confirms that the reliability of the proposed model is acceptable and that it can predict individual patient dynamics.

4.9 Alternative insulin infusion

An alternative to bolus dosing is considered as a piecewise constant infusion rate that holds a constant value over 5 min time intervals. The profile is calculated with optimising criterion the minimum range of glucose outside the normal bounds. The results are demonstrated for two adults, adult 3 and adult 5 for illustrative purposes. Figure 4.17, for patient 3 includes the optimised glucose profile when the bolus is given at the time calculated with the previous optimisation problem (a), the glucose profile when a piecewise approach is considered (d) with time frame of 32 min (Table 4.10) and both are compared with the glucose profile when bolus is given simultaneously with meal (b). The two approaches produce the same effect on glucose, indicating that a stepwise infusion could be considered as a possible mechanism since it provides flexibility and can be better adjusted in an automated delivery system. In Figure 4.17, for patient 5, in order to avoid a big time frame (64 min) which can be restricting from a control point of view and to overcome the issues related to pre-bolusing (risk of hypoglycaemia) a time frame of 30 min is considered. The glucose profiles are compared and additionally the profile when bolus is given 30min in advance (c) is included. The stepwise approach (d) and the 30 min bolus in advance (c) produce comparatively the same results. This case of adult 5 although it is not the optimal, can still be regarded as a considerable alternative for control design.

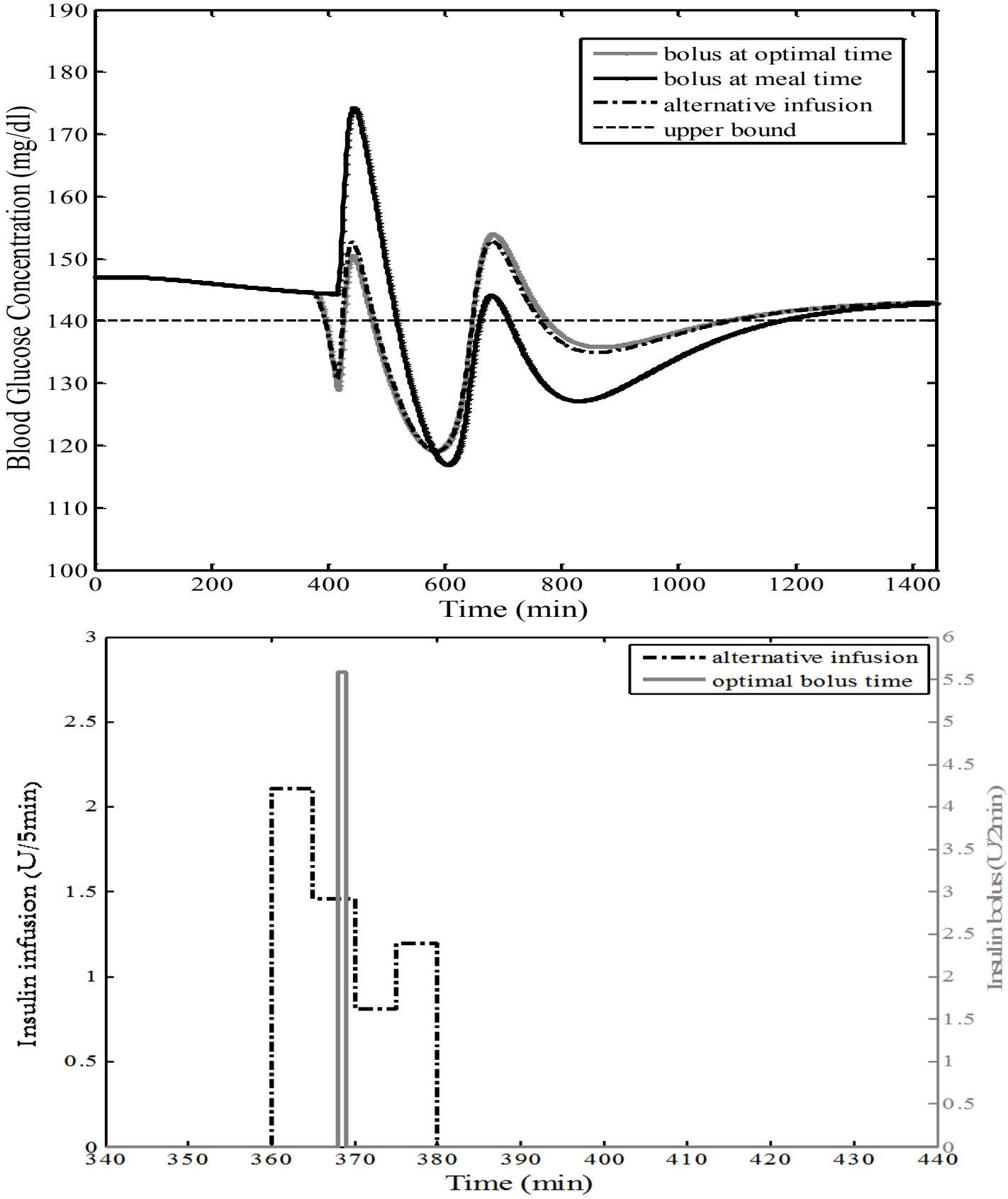


Figure 4.16: Optimal glucose profiles when insulin is given as a bolus and as a piecewise constant infusion (adult 3)

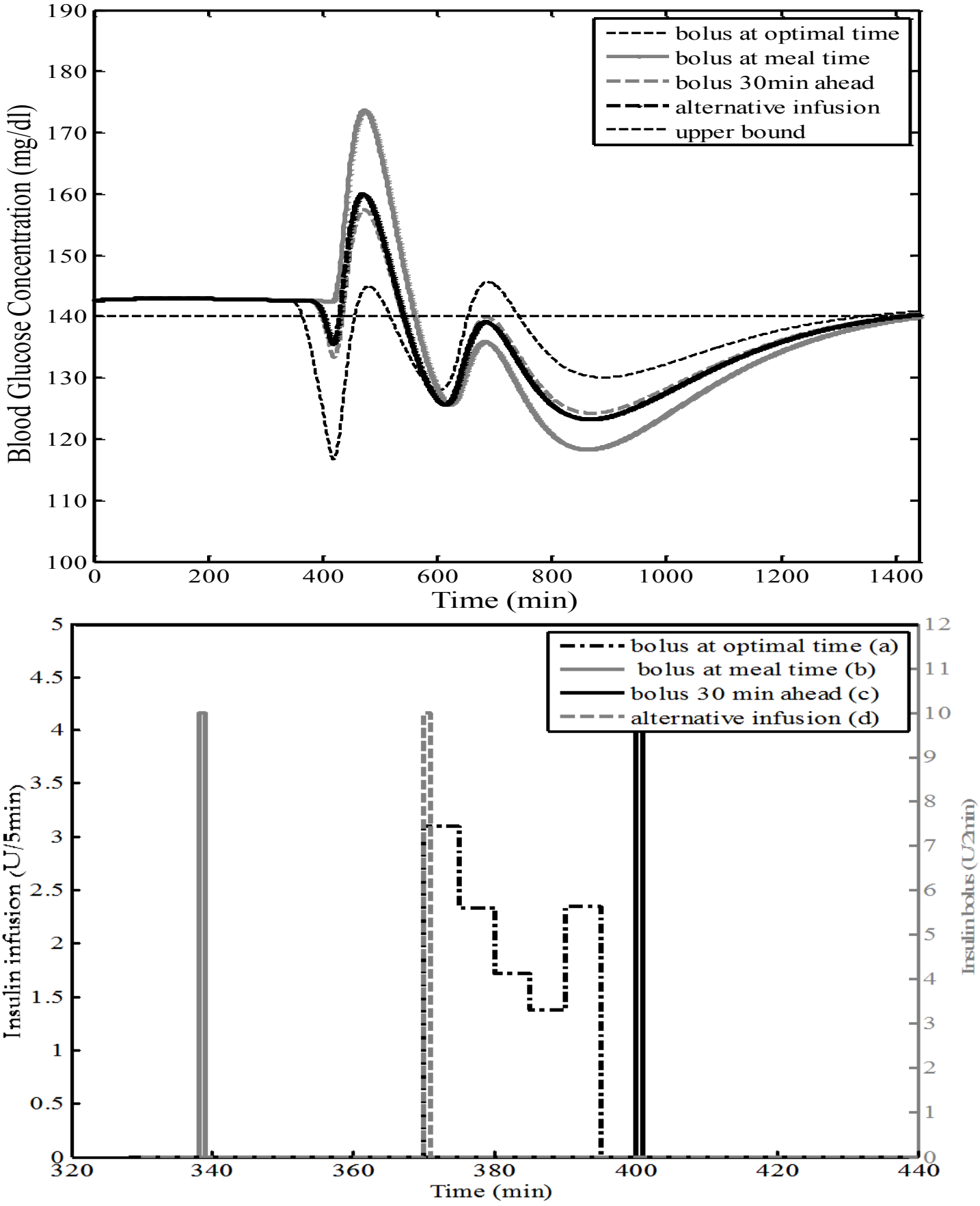


Figure 4.17: Optimal glucose profiles when insulin is given as a bolus and as a piecewise constant infusion (adult 5)

The two figures indicate that the alternative to bolus dosing insulin infusion can produce the exact same effect on blood glucose concentration. Therefore, the stepwise insulin infusion is a potential delivery mechanism that will be considered in the closed loop insulin delivery. The MINLP problem is simplified to NLP reducing the complexity introduced by the binary variables.

Key Points

- Delayed insulin effect on blood glucose (after effect)
- Inter-patient and intra-patient variability of insulin effect
- MINLP solution to identify the optimal time to administer an insulin bolus dose
- Tight glycaemic control when the time lag is considered
- Alternative insulin infusion to be used in the closed loop insulin delivery system

4.10 Concluding Remarks

In this Chapter, the model presented in Chapter 3 is analysed in terms of structure, parameter correlations and identifiability and physiological relevance. GSA was used to determine the most influential model parameters that were estimated from glucose and insulin concentration profiles for each patient. The simulation studies demonstrated that the model is reliable in terms of flexibility and predictive ability. The inherent time lags due to delayed insulin absorption and action have been quantified for the 10 patients and it has been shown that for the same insulin dose the delayed effect on glucose is patient dependent. Therefore, patient-specific optimisation studies were performed to find the optimal timing to give the bolus dose. An alternative, stepwise insulin regimen has been considered and the optimisation results indicate that it can be an attractive alternative for closed loop applications.

5. Closed Loop Control in T1DM- An Overview

5.1 Introduction

In this Chapter an overview of the existing methodologies for closed loop insulin delivery in T1DM is presented. The concept of the artificial pancreas (AP) has been widely considered as the potential treatment of T1DM and many research groups have been extensively working towards this direction. The state-of-the art on the topics related to the AP technology can be found in: (Kovatchev *et al.*, 2010), (Dassau *et al.*, 2013), (Thabit and Hovorka, 2013), (Soru *et al.*, 2012), (Cobelli *et al.*, 2012), (Breton *et al.*, 2012),(Herrero *et al.*, 2013). The Chapter continues with a brief introduction to the theoretical background of Model Predictive Control (MPC) and finally the control oriented model for the application of MPC for insulin delivery is presented.

5.2 Literature review

In the past decades a great effort has been made to develop suitable control algorithms which calculate the appropriate insulin administration rate to maintain the blood glucose concentration within the normal range. Many approaches have been evaluated as can be seen in the following reviews: (Lee and Bequette, 2009), (Bequette, 2005), (El Youssef, Castle and Ward, 2009), (Takahashi, Xiao and Hu, 2008), (Valletta, Chipperfield and Byrne, 2009), (Cobelli *et al.*, 2009), (Doyle, Jovanovic and Seborg, 2007), (Doyle *et al.*, 2014), (Thabit and Hovorka, 2014).

The first clinical approach to automatically regulate blood glucose concentration is the Biostator which was developed in the 1970s, was approved by the Food and Drug Administration (FDA) and made commercially available by Miles Laboratory. Although it is an actual artificial pancreas that reports efficient external glucose control in hospitalised patients (Reece, Coustan and Gabbe, 2004), (Cobelli, Renard and Kovatchev, 2011), the invasive intravenous route of insulin delivery and glucose sensing as well as its large size makes this system inappropriate for everyday use.

The development of more efficient techniques for blood glucose control is inseparable from: the development of fast-acting insulin analogues (e.g. insulin lispro, insulin aspart), which have minimized the time to maximum insulin effect; the use of the less invasive subcutaneous route instead of the intravenous one, which accelerated the progress in the technology of

glucose monitoring systems and insulin pumps; and finally the development of computer-based algorithms, which has enhanced the quality of therapeutic advisory systems.

Several control methodologies have been suggested in the literature such as Proportional-Integral-Derivative (PID), Model Predictive Control (MPC), adaptive control, Sliding Model Control (SMC), fuzzy logic and neural network, as presented in more detail below:

PID

PID control has been widely used as a potential method for blood glucose regulation. The PID controllers operate on the error (difference between the measured output and the desired glucose concentration) in a feedback system and suggest a control signal (insulin infusion) that is applied to the system (patient). The relatively simple implementation has established the PID control as an important alternative for blood glucose regulation. Several clinical trials have been conducted to evaluate overnight glucose control, the effect of exercise, the addition of glucagon, the intraperitoneal infusion etc.

Table 5.1: Clinically Evaluated PID controllers

Control Algorithm	Control Algorithm Reference	Clinical Trial	Summary
ePID with Insulin Feedback (IFB)	(Steil *et al.*, 2006), (Weinzimer *et al.*, 2008), (Steil *et al.*, 2011),	1.(O'Grady *et al.*, 2012) 2.(Sherr *et al.*, 2013)	1. In-clinic overnight closed loop trial suggests 78% of time glucose spent in normal range 2. Effect of afternoon exercise on nocturnal hypoglycaemia: CL better than OL
Fading Memory Proportional Derivative algorithm (FMPD)	(Gopakumaran *et al.*, 2005), (Ward *et al.*, 2008)	(Castle *et al.*, 2010)	Insulin plus glucagon: reduced frequency of carbohydrate treatment
PID	Several PID algorithms were evaluated	(Dauber *et al.*, 2013)	In-clinic closed loop control in children. Improvements in time spent above 300mg/dl and total AUC compared to open loop.
PID	(Steil *et al.*, 2006)	(Renard *et al.*, 2010)	Intraperitoneal insulin infusion
ePID	(Steil *et al.*, 2006)	(Weinzimer *et al.*, 2012)	Evaluation of the effects of pramlintide on CL-delayed time to peak BG and reduced magnitude of BG peak

Although it was reported that glucose spends adequate amount of time in normoglycaemia for several experimental conditions with PID controllers (Doyle *et al.*, 2014), it has also been reported that there is an increased risk of hypoglycaemia due to inappropriate dosing coming

from the integral feature (Bequette, 2005), (Marchetti *et al.*, 2008). Hence, PD controllers are considered instead. However, PD controllers require complementary components such as fault detection algorithms, pump shut-off or feedforward control to address the issue of maintenance of glucose within the upper and the lower level. Another limitation of a PID controller is that it cannot include the inherent time delays of the system, which can lead to hypoglycaemia.

MPC

The limitations of PID control as well as the ability of MPC i) to handle constraints ii) of straightforward applicability iii) to handle time delays and complex nonlinear systems and iv) to calculate the control action in anticipation of the future output, have motivated its wide use for blood glucose regulation. In Parker et al. (1999) a linear MPC for optimal insulin dosing is designed based on the Sorensen model (Sorensen, 1978) which incorporates a state estimator. Additionally, a nonlinear quadratic dynamic matrix control with state estimation is evaluated that takes advantage of the information coming from the nonlinear model.

Magni et al. (2007) evaluated an unconstrained MPC with the internal predictive model being a linearised reduced state space of (Dalla Man, Rizza and Cobelli, 2006) with linear representation of k_{empt} (A.10). Three clinical studies were based on this MPC control design. The first study was conducted in 2008-2009 (n=20 adults, length=14.5h). The study resulted in reduced hypoglycaemic events with closed loop compared to open loop and better glycaemic maintenance in the target range. The second clinical study evaluated a fully integrated artificial pancreas (Breton *et al.*, 2012), (n=11 adolescents and 27 adults, length = 22h). This trial involved the testing of two modular closed-loop control designs, the standard control to range and the enhanced control to range. Both designs are based on combining a range correction module (RCM) and a safety supervision module (SSM). The RCM involves an unconstrained linear MPC algorithm as described in Magni *et al.* (2009) that calculates the correction insulin infusion of a predetermined nominal open-loop profile. The SSM aims to prevent hypoglycaemia, therefore it involves features such as risk analysis of blood glucose data (Kovatchev *et al.*, 2000) and IOB (Insulin On Board) constraints (Ellingsen *et al.*, 2009). The clinical study resulted in an ived glycaemic control with enhanced CTR achieving a 97% near normoglycaemia. Finally, a clinical study (B. Kovatchev *et al.*, 2013) was conducted using an integrated modular control, as explained in Patek *et al.* (2012), to evaluate the performance of the integrated artificial pancreas in outpatient settings. The system consists of a continuous safety module, a control module and an interface module. The safety module is

similar to the one considered in the previous study (Breton *et al.*, 2012), whereas the control module involves the same principles of range correction module as in (L. Magni, Forgione, *et al.*, 2009) and (Magni *et al.*, 2007), as described above, but the control design is individualised in terms of individual cost function. The results indicated no significant difference of the control performance between inpatient and outpatient settings.

In Hovorka et al. (2004) a nonlinear MPC is designed that estimates on line the model parameters which vary with time using Bayesian techniques. A series of clinical studies were conducted using an adaptive algorithm based on MPC as described in Bequette (2005) to evaluate mainly the closed loop performance during the night. In Hovorka et al. (2010) an overnight closed loop study is described which concluded that the applied MPC strategy can reduce the time spent in hypoglycaemia compared to standard open-loop therapy. In (Elleri *et al.*, 2011), (Elleri *et al.*, 2012), (Elleri *et al.*, 2013) overnight studies in children and adolescents are performed using a fully automated closed-loop strategy to investigate the influence of initiation timing after regular meals and exercise. The results indicated that earlier time of closed-loop initiation can achieve tighter glucose control; nonetheless the impact of exercise remains a challenge for the closed loop system.

In Soru et al., (Soru *et al.*, 2012) a model derived by linearising the original (Dalla Man, Rizza and Cobelli, 2007) model around the basal conditions was used. Two MPC approaches were designed to individualise the closed loop system. The first involves the tuning of the cost function and the second the derivation of individual approximate models from system identification and optimal tuning of cost function from real life experiments, such as reference input-output, signals and weights of cost function. An adaptive MPC algorithm including an IOB feature using an ARMAX internal model has been clinically evaluated (Turksoy *et al.*, 2013), (n=3, length (h)=32 or 60h). The study indicated that 62% of the observations were spent in the near normoglycemic range.

Multi-parametric MPC for blood glucose concentration was evaluated in (Dua, Doyle and Pistikopoulos, 2006), (Dua, Doyle and Pistikopoulos, 2009). In mpMPC the online optimisation problem is solved off line via parametric programming (Bemporad *et al.*, 2002) and the objective function as well as the future control actions are obtained as a function of the measured output or states, i.e. the parameters, and the regions in the state or output space were the parameters are valid; hence all the possible control trajectories are calculated in advance, minimising the required computational effort of online MPC. A clinical trial (n=17, length =6.3h) was conducted to evaluate the performance of a personalised artificial pancreas (Dassau *et al.*, 2013) based on linear multi-parametric MPC including an IOB feature

(Ellingsen *et al.*, 2009). The internal linear model (Percival *et al.*, 2010) used in the control design is identified from individual patient data of 3days of open loop studies while the control algorithm is described in (Dua, Doyle and Pistikopoulos, 2006), (Dua, Doyle and Pistikopoulos, 2009), (Dua *et al.*, 2008), (Bemporad *et al.*, 2002). The study resulted in an average of 70% of the trial time in near normoglycemia ensuring the ability of the control design to be further investigated.

A control approach based on zone-MPC was clinically evaluated (Harvey *et al.*, 2014). Details about the "control-to-range" algorithm are described in (Grosman *et al.*, 2010). The internal control-relevant model is individually tuned using *a priori* clinical information (van Heusden *et al.*, 2012). A supportive health monitoring system (Harvey *et al.*, 2012) was used in addition to zone-MPC to prevent hypoglycaemia episodes and to increase the safety of the system. The study (length=24h) involved unannounced meals and exercise as well as an overnight period which resulted in an average of 80% of the trial time near normoglycaemia.

Table 5.2 describes a selection of MPC designs evaluated in clinical trials.

Table 5.2: MPC control Algorithms evaluated in clinical trials

Clinical Studies Reference	Summary
(Hovorka *et al.*, 2014), (Elleri *et al.*, 2012), (Elleri *et al.*, 2013), (Elleri *et al.*, 2011), (Hovorka *et al.*, 2010)	The MPC design of this study is based on (Bequette, 2005) using internal model (Hovorka *et al.*, 2002).
(Kovatchev *et al.*, 2010), (B. Kovatchev *et al.*, 2013)	The linear MPC design is described in (Magni *et al.*, 2007). The model used for validation is found in (Dalla Man, Rizza and Cobelli, 2007) but modified adequately for T1DM. This model is linearised at average population basal conditions. The MPC specifications are tailored to each patient. An interface and safety module are included in (Patek *et al.*, 2012).
(Russell *et al.*, 2012)	Bihormonal closed loop system (El-Khatib *et al.*, 2010) insulin administration with MPC control and glucagon with PD. The internal model is ARMAX with identified model parameters.
(Dassau *et al.*, 2013)	The linear mpMPC design is described in (Percival *et al.*, 2010), the model used is a transfer function with patient-specific parameters. More details on the explicit MPC can be found in (Dua, Doyle and Pistikopoulos, 2006)
(Harvey *et al.*, 2014)	Zone-MPC as described in (Grosman *et al.*, 2010) in

	parallel with health monitoring system (Harvey *et al.*, 2012)
(Breton *et al.*, 2012)	(B. Kovatchev *et al.*, 2009) range correction module and safety supervision module

Although the applied MPC theory for glucose regulation has reduced the occurrence of hypoglycaemic episodes in most clinical studies (Doyle *et al.*, 2014), the challenge remains when the patient is examined in free living conditions (Bequette, 2012), subjected to unannounced disturbances such as a meal. This involves the risk of direct prandial hyperglycaemia that leads to aggressive insulin action and possible postprandial hypoglycaemia. Another important issue is the high intra and inter-patient variability that dominates the system. To address this problem patient specific approximations of the original system (L. Magni, Raimondo, *et al.*, 2009), (van Heusden *et al.*, 2012), and control specifications are considered. Although this approach has minimised the effect of intra-patient variability on the prediction ability of the internal model, inter-patient variability remains an important source of uncertainty that requires advanced control techniques such as robust control (Sakizlis, Dua, *et al.*, 2004), (Pistikopoulos *et al.*, 2009) or complementary components (Breton *et al.*, 2012) to incorporate the effect and control its impact on the system.

Other Algorithms

Fuzzy Logic control has been evaluated as a potential approach for blood glucose regulation. Control-to-range and control-to-target modules have been incorporated in the MD-Logic Artificial pancreas (Atlas *et al.*, 2010) which was tested in a clinical trial. A series of clinical trials based on MD-Logic AP were conducted (Nimri *et al.*, 2014), (Nimri *et al.*, 2012), (Nimri *et al.*, 2013), (Phillip *et al.*, 2013) and the study is still on-going but the results suggest that closed-loop can be implemented as standard overnight treatment. A pump shut off algorithm is proposed using a Kalman filter for blood glucose value and rate of change estimation (Cameron *et al.*, 2012) and evaluated in an in-patient study. A sliding model control has also been considered (Abu-Rmileh, Garcia-Gabin and Zambrano, 2010) which presents simplicity in the implementation but more robust performance compared to a PID.

5.3 Challenges of the closed loop design

The purpose of the artificial pancreas is to ameliorate the living standards of a patient with T1DM. This can be translated to the following requirements of a closed loop system:

1. Safety of the patient
2. Flexibility to adapt to changing patient characteristics
3. Reduced side-effects
4. Minimally invasive therapeutic devices and minimum patient requirements for initialisation and individualisation

These requirements can be very challenging for the development of a fully automated insulin delivery system regardless of the chosen type of control algorithm. The challenges are summarised below:

- Complexity of the system: nonlinearities, time delays, patient specific dynamics, which make the development of representative mathematical models relatively difficult especially models that capture the dynamics of different patients with different characteristics and on top of that the derivation of reliable linear approximate models.
- Delayed insulin absorption due to the subcutaneous route that produces an after effect of insulin on glucose that should be taken into consideration.
- High intra- and inter-patient variability: source of uncertainty that should be taken into account in the control strategy.
- Personalised control design due to high intra and inter-patient variability: there is high demand to develop patient-specific therapeutic methods towards a more personalised health-care that treats every patient according to their needs.
- Hard constraints on glucose concentration. Violation of the constraints can have serious acute and chronic health complications.
- The presence of disturbances such as meal, exercise, stress, illness that have a significant effect on the insulin-glucose dynamics, factors of everyday life that should be taken into account either in the model or the control design.
- Once insulin is delivered to the body it cannot be removed, which makes the development of the automated system very challenging. Glucagon has been suggested as a complementary hormone to counteract the insulin effect.
- The uncertainty of free living conditions that requires a robust control strategy.

5.4 Model Predictive Control

The suggested control strategy for glucose regulation with manipulating insulin infusion, refers to model predictive control theory (Dua, Doyle and Pistikopoulos, 2006, 2009). The standard approach of all the MPC methodologies is the use of a mathematical representation of the controlled system (model) to predict the system's output/states, for a finite time horizon (prediction horizon). The model is used for the formulation of an optimisation problem that minimises an appropriately chosen objective function. Decision variables of this problem are the predicted values of the manipulated variable (insulin) in a generally smaller future time horizon, the control horizon. When the optimal sequence of the future control actions is determined, only the first value is applied on the system and the optimisation problem is then reformulated and solved at the next time instant, when new information of the system is available. The basic concept of MPC is illustrated Figure 5.1.

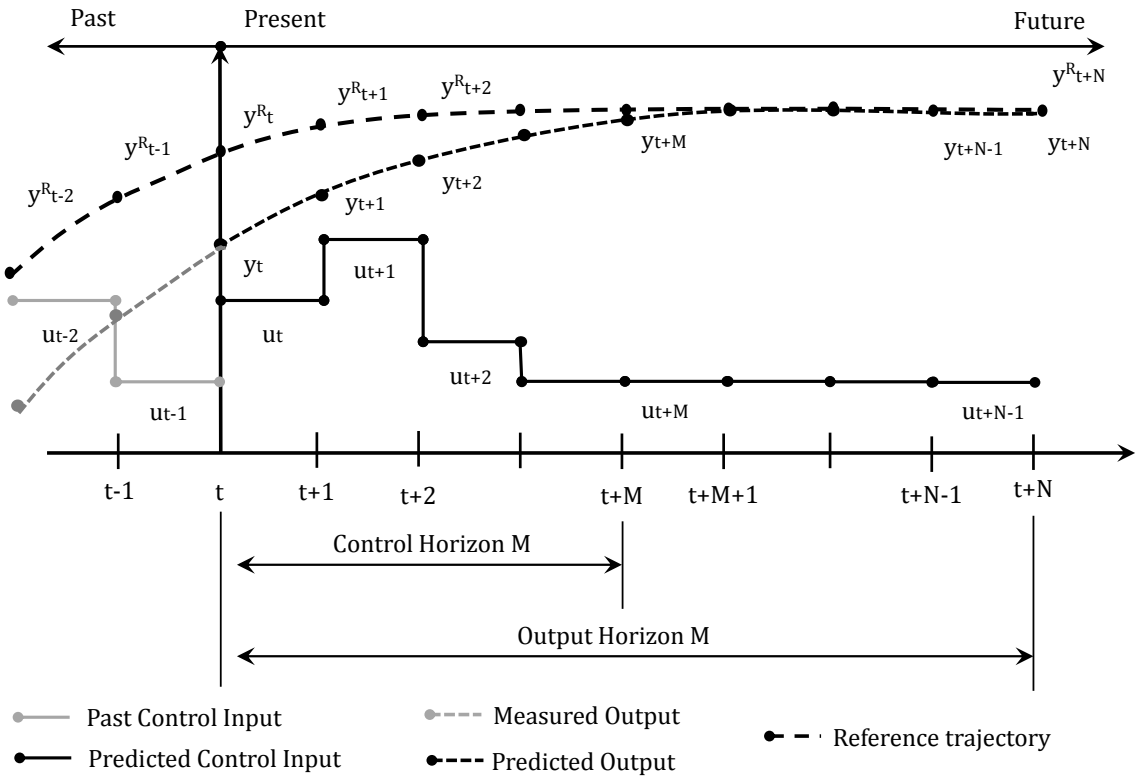


Figure 5.1: Schematic of Model Predictive Control

The appropriate current control action is obtained by solving on-line, at each sampling instant, the finite horizon open-loop optimal control problem:

$$\min_{x,y,u} J = \sum_{k=1}^{N-1} x_k' Q_k x_k + \sum_{k=1}^{N-1} (y_k - y^R)' Q R_k (y_k - y^R) + \sum_{k=1}^{M-1} u_k' R_k u_k + \sum_{k=1}^{M-1} \Delta u_k' R_{1_k} \Delta u_k \quad (5.1)$$

s.t.

$$x_{k+1} = Ax_k + Bu_k + Ed_k$$

$$y_k = Cx_k$$

$$y_{min} \leq y_k \leq y_{max}$$

$$u_{min} \leq u_k \leq u_{max}$$

$$\Delta u_{min} \leq u_{k+1} - u_k \leq \Delta u_{max}$$

The problem is formulated as a quadratic programming problem (APPENDIX B.2) that is solved using established functions and tools in MATLAB.

Table 5.3: definitions of symbols found in (5.1)

Symbol	Definition
A	State matrix
B	Input matrix
C	Output matrix
E	Disturbance matrix
N	Prediction Horizon
M	Control Horizon
Q	Weight Matrix for the states
QR	Weight Matrix for the output deviation from the reference point (blood glucose concentration)
R	Weight Matrix for the input (insulin infusion rate)
R_1	Weight Matrix for the change in the control input
y	System output (blood glucose concentration)
y^R	Reference point
x	System states
u	Control input (insulin infusion rate)
Δu	Step change in control input

The MPC specifications used in the following chapter are presented in detail for each patient in Appendix D.

5.5 Kalman Filter

System Uncertainty

There are two main sources of uncertainty in a wide class of systems that cause a limited ability to accurately represent the real process with a mathematical model:

- Observation uncertainty (measurement "noise")
- Process uncertainty (unmodeled disturbances)

A simple way to describe these two sources of uncertainty is the formulation of a linear state space model as a stochastic system (Rawlings and Mayne, 2009):

$$\begin{aligned} x_{k+1} &= Ax_k + Bu_k + Gw_k \\ y_k &= Cx_k + \upsilon_k \end{aligned} \qquad \text{with} \quad x(0) = x_0 \tag{5.2}$$

The random variable $w_k \in \mathbb{R}^{g}$ is introduced to describe the process uncertainty while the variable υ_k models the noise of the measurement device. Matrix $G \in \mathbb{R}^{n\times g}$ is used to fine tune the effect of the process uncertainty on the states.

Kalman Filter

The linear Kalman Filter is a widely used method for unconstrained state estimation for the system of (5.2) of normally distributed with zero mean process disturbance w_k and measurement noise υ_k :

$w(0) \sim N(0, Q)$ and $\upsilon(0) \sim N(0, R)$

The zero mean is chosen for w and υ because the disturbances and the effects with nonzero mean are considered to be included in the model.

The optimal state estimation is calculated using the following algorithm (5.3-5.7) which includes a two steps approach (Chui and Chen, 2008). The first step predicts the state and covariance estimates using the model equations and previous estimates while the second updates the prediction using information from the observations.

1) Time Update / "Prediction"

   State Prediction:

$$\hat{x}_k^- = A\hat{x}_{k-1} + Bu_{k-1} \tag{5.3}$$

   Projection of the error covariance:

$$P_k^- = AP_{k-1}A^T + Q_{KF} \tag{5.4}$$

2) Measurement Update/ "Correction"

   Computation of the Kalman gain:

$$K_k = P_k^- H^T (HP_k^- H^T + R_{KF})^{-1} \tag{5.5}$$

   State estimate update:

$$\hat{x}_k = \hat{x}_k^- + K_k(z_k - H\hat{x}_k^-) \tag{5.6}$$

Error covariance update:

$$P_k = (I - K_k H)P_k^- \tag{5.7}$$

The choice of Q_{KF} and R_{KF} depends on the examined system. Generally a large Q_{KF} is used when there is no prior knowledge, and this force the states to be determined by the upcoming measurements y_K. A large value of R_{KF} is used for a noisy measurement process.

5.6 Model Approximation

Sources of nonlinearity in the model of glucose-insulin interactions can be found not only in non-linear expressions of specific variables (e.g. gastric emptying), but most importantly in non-linear dependencies among variables (e.g. insulin dependent peripheral glucose absorption). Another challenging inherent source of complexity in this system is the time delay from the moment the input is applied to the effect on glucose being observed. This time lag is related to the subcutaneous route of insulin administration, the detection of a glucose fluctuation and the patient's sensitivity to insulin. The difference in the glycaemic response produced by the same dose of insulin in different individuals indicates that there is a high intra-patient variability involved in glucose-insulin interactions.

However, the internal model used to predict the future output G(t) depending only on past inputs u(k-1),u(k-2),..., is usually considered to be linear because this makes the calculation of the optimal insulin infusion relatively simplified in a model predictive control framework. Hence, the aforementioned challenges of nonlinearity, time delays and patient variability have to be described by a simple linear model.

The accuracy of the internal model used in MPC is essential since it forecasts the future behaviour of the system based on which the controller optimises the control action. Therefore the internal model should accurately represent the patient's specific dynamics. Even if feedback can overcome some issues of inaccurate modelling, in order to achieve efficient control the internal model should be carefully considered.

The original model is linearised at basal state, assuming that $k_{empt}=(k_{max}-k_{min})/2$ and $p=p_b$. The 16 states model is then reduced to 10 states using the redmod function in MATLAB. Further reduction decreases the model's prediction ability. The discretised, with sampling time 5min, reduced linear model is used as the internal model in MPC. Two cases are considered for model linearisation, which will be further used in Chapter 6:

Case 1: Development of patient-specific approximate model

It is assumed that the available patient data are informative enough to estimate the original model parameters as presented in the parameters estimation section (4.5) and develop an approximate model that accurately predicts the patient's dynamics. Hence, the individual model parameters are considered in the linear state-space model.

Case 2: Development of an adjusted mean approximate model

In this case, it is assumed that a priori knowledge of the patient's dynamics cannot be obtained and that only standard clinical tests are available, such as CGMS glucose profiles, TDD, patient characteristics and meal information. Then the approximate model with mean values of the parameters is used but adjusted accordingly for the specific patient. The adjustable parameter is k_{p1} and is an element of the second column of B_d matrix which determines the constant terms of the states that are considered in the linearisation. The individual parameters of the control design that are individually tuned when using the mean approximate model are the body weight, the total daily dose and the upper insulin constraint, the weights of the objective function and the control horizon.

$$x = [C_K \quad C_G \quad C_P \quad C_B \quad C_H \quad C_L \quad C_{Pt} \quad U \quad I_d \quad I_1 \quad S_1 \quad I_b \quad S_2 \quad Q_{sto1} \quad Q_{sto2} \quad Q_{gut}]'$$

$$A = \begin{bmatrix}
-\frac{Q_K}{V_{g,K}} & 0 & 0 & 0 & \frac{Q_K}{V_{g,K}} & \frac{k_{p2}r_{u,K}}{V_{g,K}} & 0 & 0 & \frac{k_{p3}r_{u,K}BW}{V_{g,K}} & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{fk_{abs}r_{u,K}}{V_{g,K}} \\
0 & -\frac{Q_G}{V_{g,G}} & 0 & 0 & \frac{Q_G}{V_{g,G}} & \frac{k_{p2}r_{u,G}}{V_{g,G}} & 0 & 0 & \frac{k_{p3}r_{u,G}BW}{V_{g,G}} & 0 & 0 & 0 & 0 & 0 & 0 & \frac{(1-r_{u,G})fk_{abs}}{V_{g,G}} \\
0 & 0 & -\frac{(Q_P-p)}{V_{g,P}} & 0 & \frac{Q_P}{V_{g,P}} & 0 & \frac{p}{V_{g,P}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -\frac{Q_B}{V_{g,B}} & \frac{Q_B}{V_{g,B}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{Q_K}{V_{g,H}} & 0 & \frac{Q_P}{V_{g,H}} & \frac{Q_B}{V_{g,H}} & -\frac{Q_H}{V_{g,H}} & \frac{Q_L}{V_{g,H}} & 0 & 0 & \frac{k_{p3}r_{u,H}BW}{V_{g,H}} & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{fk_{abs}r_{u,H}}{V_{g,H}} \\
0 & \frac{Q_G}{V_{g,L}} & 0 & 0 & \frac{Q_L}{V_{g,L}} & -\frac{Q_L}{V_{g,L}}+\frac{(1-r_{u,L})k_{p2}}{V_{g,L}} & 0 & 0 & \frac{(1-r_{u,L})k_{p3}BW}{V_{g,L}} & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{fk_{abs}r_{u,L}}{V_{g,L}} \\
0 & 0 & \frac{p}{V_{g,P,ISF}} & 0 & 0 & 0 & -\frac{(p+U)}{V_{g,P,ISF}} & \frac{-1}{V_{g,P,ISF}} & 0 & 0 & 0 & -\frac{k_1}{6.945V_{g,P,ISF}} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_2 & 0 & 0 & 0 & \frac{k_1}{6.945} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_i & k_i & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_i & 0 & k_i * 6.945 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{sub} & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{elim} & \frac{k_{sub}}{k_{elim}} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{sub} & 0 & -k_{sub} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_{gri} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{gri} & -k_{empt} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{empt} & -k_{abs}
\end{bmatrix}$$

$$B = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \frac{1000}{BW} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad B_d = \begin{bmatrix} 0 & -\frac{r_{u,K}BWk_{p1}}{V_{g,K}} \\ 0 & -\frac{r_{u,G}BWk_{p1}}{V_{g,G}} \\ 0 & 0 \\ 0 & -\frac{u_B}{V_{g,B}} \\ 0 & -\frac{r_{u,H}BWk_{p1}}{V_{g,H}} \\ 0 & \frac{(1-r_{u,L})BWk_{p1}}{V_{g,,L}} \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ \frac{1}{meal_duration} & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}, \quad C=[0 \;\; 0 \;\; 0 \;\; 0 \;\; 1 \;\; 0 \;\; 0 \;\; 0 \;\; 0 \;\; 0 \;\; 0 \;\; 0 \;\; 0 \;\; 0 \;\; 0 \;\; 0]$$

$D = [0]$

The accuracy of the patient specific approximate model is presented in Figure 5.2 for patient no2.

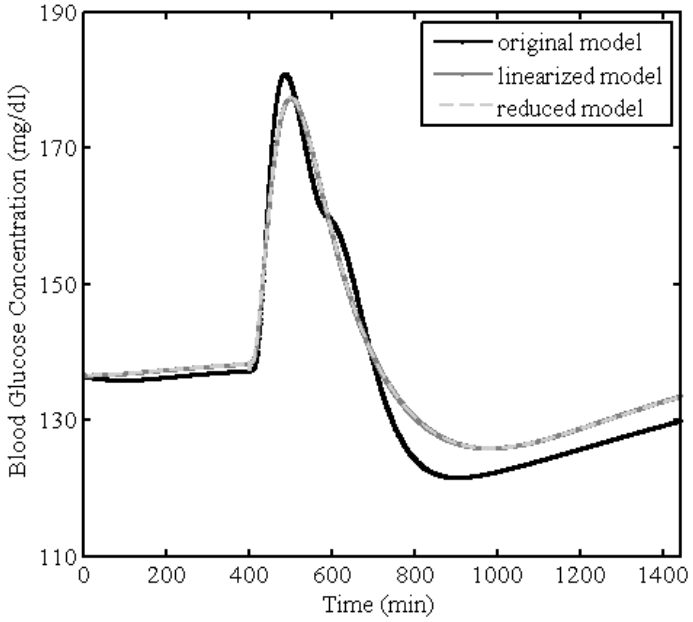


Figure 5.2: Comparison of original model, linearised model and reduced model when 50 g of carbohydrates are consumed and a 5 U bolus is given to patient no2

A measure to calculate the goodness of the fit between the original, the linearised and the reduced model is the normalised mean square error as presented in (5.8).

$$Fit = \left(1 - \frac{\sum_{i=1}^{N} |y_i - \widehat{y_i}|}{\sum_{i=1}^{N} |y_i - \overline{y}|}\right) \times 100 \tag{5.8}$$

The fit is of the patient specific linearised approximate model to the original model is 93.6%. Therefore, the linearised model accurately approximates the original model. The reduced linear model fits at 99.7% the full-states linearised model.

5.7 Concluding Remarks

In this Chapter an overview of the existing methodologies to address the blood glucose regulation problem with a closed loop insulin delivery system was presented. Emphasis is given on the MPC control designs, because MPC will be further used in this thesis. The challenges of an automated system are described of which the uncertainty originated by high patient variability and the unknown disturbances are the most crucial. The theoretical background of MPC formulation and the Kalman filter is presented and more details can be found in Appendix B.2, which will be used in the following Chapter. The proposed model described in Chapter 3 is linearised and reduced to be further used in the control design presented in the next Chapter.

6. Model Predictive Control Studies in T1DM

6.1 Introduction

In this chapter the design of a closed loop insulin delivery system for T1DM is presented. The aim is to maintain the blood glucose concentration within the normal range (80-140mg/dl) by manipulating the control input, the insulin infusion rate. Insulin is given not as the conventional basal/bolus pattern but as a piecewise constant infusion rate that holds a value for specific time intervals. The performance of the developed control design is evaluated in the presence of meal disturbances and other uncertain factors. Apart from the MPC, additional components are introduced to meet the specific requirements of blood glucose regulation under unknown meal disturbances as explained in the following sections.

6.2 Control Objective

The aim of the developed control designs that are presented in the following sections is to efficiently regulate the blood glucose concentration. However, the issues that make glucose regulation rather challenging are the following:

- Complexity of the inherent dynamics (Chapter 3 and 4)
- Time delays (sections 4.7-4.9)
- Intra -patient variability (section 4.5-4.9)

The need of a closed loop system to perform efficiently under free living conditions adds up the following challenges:

- Presence of unknown meal disturbances
- Metabolic uncertainty

Therefore, with the proposed control designs we aim to:

- Develop personalised insulin delivery systems
- Take into account the involved time delays
- Compensate for the unknown meal disturbances
- Address the issue of uncertainty

6.3 Model Predictive Control Strategy for insulin delivery in T1DM

Two general strategies for blood glucose regulation are studied. The first is a systematic strategy which aims for personalised blood glucose control, whereas the second is an "approximation" strategy that can be considered for blood glucose regulation in the absence of informative patient data.

I. Systematic Strategy

It involves the following steps:

Step 1: Collection of CGMs data with available inputs (insulin, meal, exercise) and plasma insulin concentration profile

Step 2: Estimation of the original model parameters for each patient (as described in section 4.5)

Step3: Derivation of linearized patient specific models (as described in section 5.6)

Step 4: Systematic Strategy: Control design

II. "Approximation" Strategy

It involves the following two steps:

Step 1: Mean approximate model (mean values of the parameters of the linearized model – section 5.6)

Step 2: "Approximation" Strategy: Control design

The control designs for the two strategies are different because the first strategy uses the a priori knowledge of the patient dynamics to enhance the closed loop performance in the presence of unknown disturbances and variability by solving an open loop optimisation problem. On the other hand, the second strategy overcomes the effect of inaccurate modelling with feedback by considering an additional controller. The inherent time delays of the system are described with the linear approximate model presented in section 5.6. The internal model predicts the delayed insulin effect and therefore, the efficacy of glucose regulation depends on the controller's ability to compensate for the after effect. The parameters of the control formulation that are individually specified in both cases are the body weight, the total insulin daily dose and the upper insulin constraint, the weights of the objective function and the prediction horizon.

The control designs for each strategy are described in detail in the following sections:

6.4 Systematic Strategy (I): Control designs

In Figure 6.1 a general control strategy to regulate blood glucose concentration is presented. It consists of four parts that are activated depending on the type of meal disturbances d_i, as defined in Table 6.1; an optimisation problem, an MPC controller, a state estimator and a scheduling level. Depending on the type of meal disturbances different combinations of the components are activated to efficiently regulate blood glucose concentration.

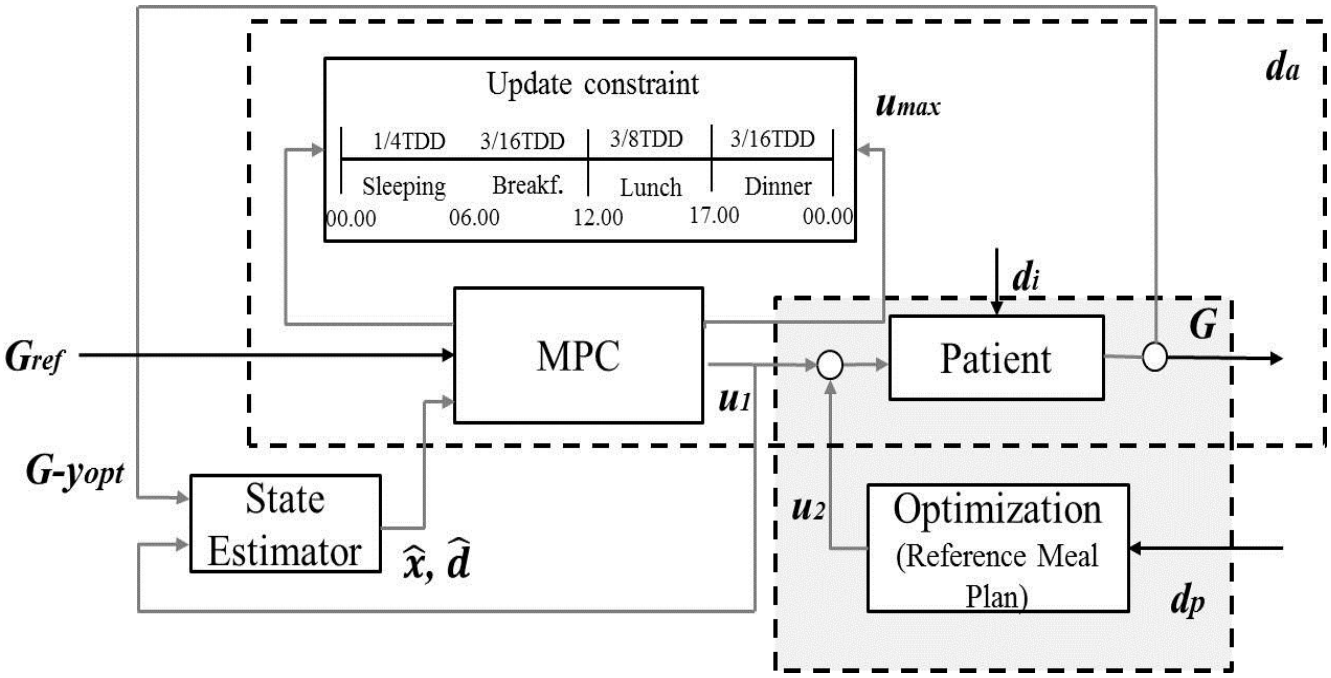


Figure 6.1: General proposed control strategy that consists of three blocks, MPC, State Estimator and optimisation that are activated depending on the nature of the meal disturbances. In the case of predefined disturbances (*dp*) the problem of optimal insulin delivery is an output optimisation problem, in the case of announced disturbances (*da*) the problem is a state feedback MPC involving a scheduling feature for upper insulin constraint. For unknown disturbances (*du*) the entire strategy is activated involving an output feedback MPC.

Table 6.1: Meal disturbance types

Symbol	Disturbance Type
d_p	Predefined
d_a	Announced
d_u	Unknown

Hence, the following control designs (CDs), as presented in Table 6.2 are evaluated for different types of meal disturbances, d_i. When the meal plan is predefined and known in advance then the regulation problem becomes an open-loop dynamic optimisation problem and only the grey block d_p is activated (CD_1). The optimisation problem is solved and the optimal insulin infusion rate that acts to maintain the blood glucose concentration within the

normal range is calculated. CD_2 involves a regulation level with a state feedback MPC and a scheduling level that enhances the overall control performance. This design is activated when the size of meal disturbances becomes known at the moment of meal consumption. CD_3 combines an optimisation problem for a known reference meal plan and a correction output feedback MPC to address the presence of unknown disturbances, which are estimated with a state estimator as explained below. And finally, CD_4 involves the MPC, the scheduling level and the state estimator and is tested in comparison to CD_3 for unknown disturbances.

Table 6.2: Glucose regulation designs

Control Designs	Description	Disturbance type
CD_1	Dynamic Optimisation-Open-loop Control	Predefined
CD_2	Online MPC with scheduling level	Announced
CD_3	Optimisation and Correction MPC	Unknown
CD_4	Online MPC with scheduling level	Unknown

Prediction Horizon

The system involves high input and disturbance delays, as was explained in section 4.7. Therefore, in order to predict the after effect of a given input, the prediction horizon should be at least equal to the time lag. However, every patient has different glucose-insulin dynamics and the time delay factor should be considered as patient-specific. Although the time lag is dependent on the insulin dose (section 4.7) for the insulin infusion rates considered in the closed loop system an assumption of constant patient specific time delays is reasonable. Table 6.3 shows the prediction horizon of the 10 patients that is calculated as the average time to observe a 1mg/dl change in blood glucose concentration when simulation studies of a step change of 0.5U/h insulin dose from 0 to 5U/h were performed.

Table 6.3: Prediction Horizon (N) for the 10 patients

Patient	N	Patient	N
Patient 1	13 ≙ 65min	Patient 6	10 ≙ 50min
Patient 2	11 ≙ 55min	Patient 7	8 ≙ 40min
Patient 3	7 ≙ 35min	Patient 8	11 ≙ 55min
Patient 4	10 ≙ 50min	Patient 9	14 ≙ 70min
Patient 5	13 ≙ 65min	Patient 10	13 ≙ 65min

6.4.1 (CD_1) Dynamic Optimisation: Predefined Disturbances (d_p)

When a patient follows an exact meal plan, meaning that the exact amount and the time of the meal is known in advance, then this information is introduced in the general regulation design

as predefined meal plan and the optimisation block in Figure 6.1 is activated. Hence, if the only uncertainty in the system is caused by the meal disturbances, then in the case of predefined meal plan the feedback control and the open loop control are equivalent (Rawlings and Mayne, 2009). The following optimisation problem is solved:

$$\min_{u_i} \int_0^{t_f} (w_1 + w_2) dt \tag{6.1}$$

$$\text{s.t} \quad G = f(\dot{x}(t), x(t), y(t), u(t)) \tag{6.2}$$

$$\sum_{i=1}^{N} u_{2_i} = TDD \tag{6.3}$$

$$w_1 \geq 0, \qquad w_1 \geq G - G_{max} \quad and \quad w_2 \geq 0, \quad w_2 \geq G_{min} - G \tag{6.4}$$

where t_f is the 24h time horizon, G is the blood glucose concentration described by the nonlinear process model (6.2) for every patient (3.1-3.15); G_{max} (140 mg/dl) and G_{min} (80mg/dl) are the maximum and minimum glucose concentration bounds. The optimal insulin infusion, u_2, appropriate to compensate for the forthcoming glucose increase due to the meal intake can change every 5min, therefore the time intervals are N= 288. The TDD is the total daily insulin dose for every patient. The optimisation studies were formed and solved in gPROMS (PSE, 2011c).

The advantages and disadvantages of CD_1 are summarised as follows:

- Personalised insulin delivery
- Feed forward insulin action to account for delayed insulin effect
- No compensation for unknown disturbances
- Metabolic uncertainty is not considered

6.4.2 (CD_2) Online MPC with Scheduling Level: Announced Disturbances (d_a)

When information concerning the amount of meal is made available only at the time it is given, then the disturbance is considered as "announced" and the control strategy involves a scheduling and a regulation level to enhance the performance of the controller, Figure 6.2.

The day is divided in 4 periods, and in each period the maximum insulin delivery is different. It is assumed that the meal plan follows a specific trend in terms of carbohydrates consumption and for this case it is considered that the maximum amount of carbohydrates is consumed during lunch according to Figure 6.2.

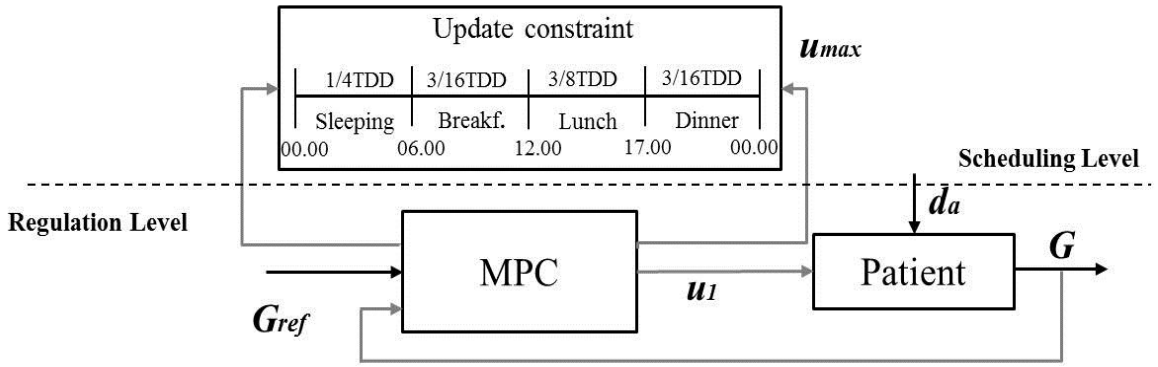


Figure 6.2: Control design CD_2

For each period (sleeping, breakfast, lunch, dinner), the upper insulin limit is changed and therefore a different optimisation problem is solved. The amount of the maximum delivered insulin as determined in the scheduling level can be tailored to every patient according to their lifestyle. This information aims to facilitate the prediction beyond the considered horizon and hence to improve glucose regulation. A fine tuning of the control specifications for every patient R, R1, QR ensures the maintenance of glucose concentration within the normal range, the total insulin delivery to be less than the specified dose and prevent hypoglycaemia in the case of a skipped meal**.**

The advantages and disadvantages of CD_2 are summarised as follows:

- Personalised insulin delivery (patient-specific approximate model, scheduling level tailored to patient's diet)
- Prevention of hypoglycaemia
- Cannot prevent immediate prandial hyperglycaemia due to delayed insulin effect
- No compensation for unknown disturbances
- Metabolic uncertainty is not considered

6.4.3 (CD_3) Optimisation and Correction MPC: Unknown Disturbances (d_u)

In the case of unmeasured meal disturbances, there is no information concerning the amount and the time of the meal. In this case, a nominal controller reacts aggressively to regulate the

glucose deviation from the reference point, which means increased insulin infusion as long as glucose violates the constraints. But this control action involves the risk of postprandial hypoglycaemia due to insulin after effect and also immediate prandial hyperglycaemia. Therefore, a different control design is proposed to compensate for unmeasured disturbances as illustrated in Figure 6.3. It consists of the patient model, an optimizer acting as a reference regulator, an MPC controller acting as the correction control, and a state estimator.

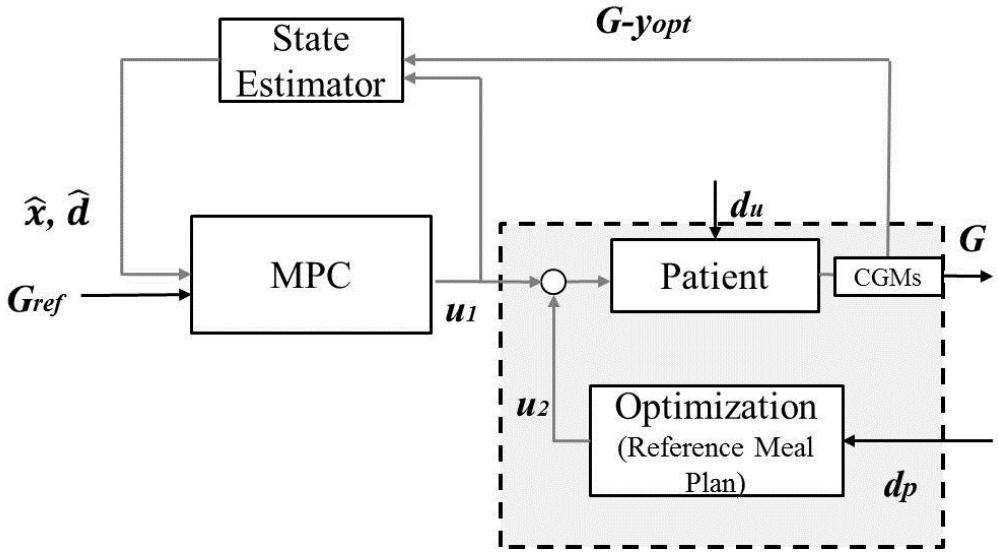


Figure 6.3: Control design CD_3

The proposed control design regulates the glucose concentration when a reference meal plan is considered and additionally responds appropriately to compensate for the deviation from the reference meal when a different size meal is consumed. A similar approach which involves a feedforward and a feedback part has been reposted in (Boiroux *et al.*, 2010). But in our work this approach is used for unknown meal disturbances and the feedforward part is used to enhance the response of the controller due to the delayed insulin absorption. The CGM error is simulated with white Gaussian noise using a signal-to-noise ratio equal to 30.

Optimizer: Reference Regulator

The desired glucose value G_{ref} is set for every patient. A predefined reference meal plan is considered to trigger the control action. Feedback about the current state is obtained by the approximate model output y_{opt}, . y_{opt} is calculated when the optimisation problem for the original non- linear model is solved for the predefined meal plan (described in section 6.4.1) and the optimal insulin infusion is applied to the approximate model.

MPC: Correction Control

MPC aims to find the optimal insulin infusion rate to regulate the difference of glucose as a real measurement coming from the patient, G, and glucose as calculated when solving the reference optimisation problem, y_{opt}. This difference can be regarded as an unknown disturbance of the system that leads to an offset in the set point, $G_{ref,2}$=0. So the correction control is described as a disturbance rejection problem. In order to remove the offset and the nonzero disturbances the original system is augmented with a disturbance model, as presented in (6.6). The output feedback of the patient is obtained as the difference of the actual measurement and the reference control output (G-y_{opt}), from which the state and the integrating disturbance are estimated using a state estimator.

$$\begin{bmatrix} x_{k+1} \\ d_{k+1} \end{bmatrix} = \begin{bmatrix} A & B_d \\ 0 & I \end{bmatrix} \begin{bmatrix} x_k \\ d_k \end{bmatrix} + \begin{bmatrix} B \\ 0 \end{bmatrix} u_k + w_k$$
$$y_k = [C \; C_d] \begin{bmatrix} x_k \\ d_k \end{bmatrix} + \upsilon_k \tag{6.6}$$

where d_k is the integrating disturbance. The matrix $B_d \in \mathbb{R}^{n \times n_d}$ is chosen to be the second column of B_d matrix presented in section 5.6 and matrix $C_d = I \in \mathbb{R}^{n_d \times n_d}$. The variances of variables w and υ are adjusted according to the output data (Odelson, Rajamani and Rawlings, 2006). The new derived augmented linear model ($n = 10, n_d = 1$) is detectable, see (6.7), which means that the states will converge to the real states when a Kalman filter is used, hence this strategy can be employed:

$$rank \begin{bmatrix} I - A & -B_d \\ C & C_d \end{bmatrix} = n + n_d = 11 \tag{6.7}$$

The objective function is modified accordingly to include the nonzero disturbance d.

$$\min_{x,y,u} J = \sum_{k=1}^{N-1} \left(Cx_k + C_d d_k - G_{ref,2}\right)' QR \left(Cx_k + C_d d_k - G_{ref,2}\right) + \sum_{k=1}^{M-1} u'_{1,k} R u_{1,k} \tag{6.8}$$

$$s.t. \;\; \hat{x}_{k+1} = A\hat{x}_k + Bu_{1,k} + w_k \tag{6.9}$$

$$y_{2,k} = C\hat{x}_k + \upsilon_k \tag{6.10}$$

$$y_{2,min} \leq y_{2,k} \leq y_{2,max} \tag{6.11}$$

$$u_{min} \leq u_k \leq u_{max} \tag{6.12}$$

Where the estimated states are:

$$\hat{x} = [x_1 \quad x_2 \quad x_3 \quad x_4 \quad x_5 \quad x_6 \quad x_7 \quad x_8 \quad x_9 \quad x_{10} \quad d]'$$

And $y_2 = G - y_{opt}$. The control specifications for MPC are presented in Table 6.4

Table 6.4: Specifications of MPC and the Kalman Filter

Variable	Value		Variable	Value		Variable	Value
$y_{2,min}$	-10	mg/dl	u_{min}	0	U/min	Q_{KF}	100
$Y2,max$	10	mg/dl	u_{max}	0.2TDD	U/min	R_{KF}	5

The advantages and disadvantages of CD_3 are summarised as follows:

- Personalised insulin delivery (patient-specific approximate model, Kalman Filter)
- Feed forward insulin action to account for delayed insulin effect
- Compensation for unknown disturbances
- Account for metabolic uncertainty as unmeasured disturbance
- A reference meal plan is always considered

6.4.4 (CD_4) Online MPC with Scheduling Level: Unknown Disturbances (d_u)

Control design CD_4 applies the same principles of zero-offset design as CD_3, but instead of the optimizer it includes the scheduling level to enhance the control performance. Therefore, the unknown disturbances are estimated using the augmented system in the state estimator, but now the output and input used for the estimation is the glucose measurement, G, and u_1, respectively, presented in Figure 6.4 for clarity. The CGM error is simulated with white Gaussian noise using a signal-to-noise ratio equal to 30.

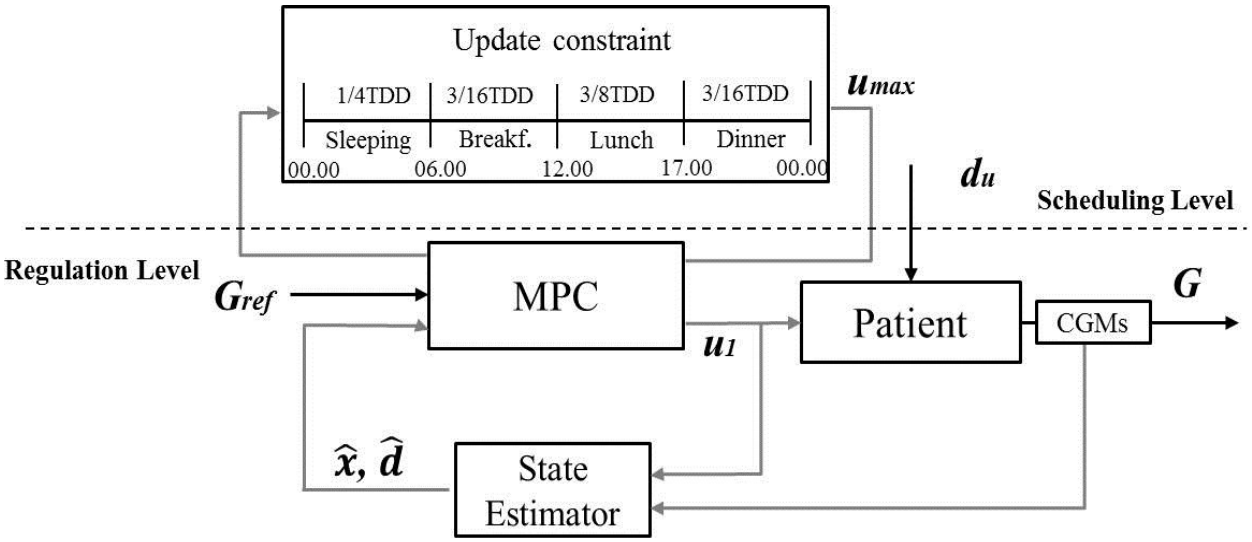


Figure 6.4: Control design CD_4

The advantages and disadvantages of CD_4 are summarised as follows:

- Personalised insulin delivery (patient-specific approximate model, Kalman Filter, scheduling level tailored to patient's diet)
- Compensation for unknown disturbances
- Account for metabolic uncertainty as unmeasured disturbance
- No compensation for delayed insulin effect

6.5 Performance analysis of the four control designs CD_1-CD_4

The previously presented control designs, presented in Table 6.2 are evaluated for different types of meal disturbances, d_i. In all control designs the performance of the controller is evaluated with the results of blood glucose concentration, referred as G.

6.5.1 Control Design 1 (CD_1): Dynamic Optimisation

A predefined meal plan of 45, 70 and 70 g of carbohydrates for breakfast, lunch and dinner is considered given at 420, 720 and 1080 min and the optimisation problem is solved for the entire 24h horizon. A piecewise constant infusion rate that holds a constant value for 5min time intervals is calculated with optimising criterion the minimum range of glucose outside the normal bounds. The TDD is treated as an end-point constraint and is set individually for

every patient. The optimisation problem is solved in gPROMS. The results are presented for all patients in Figure 6.5.

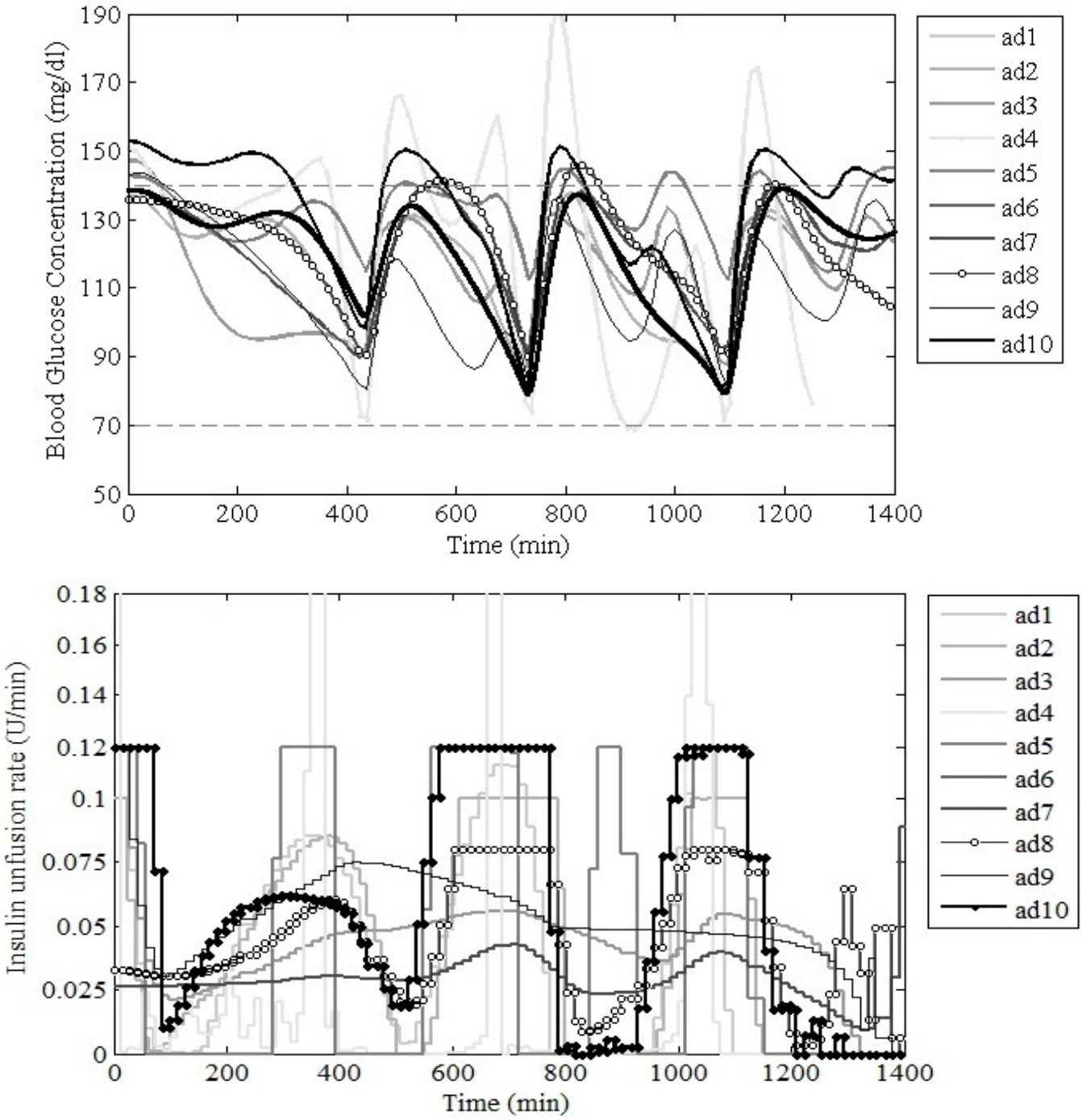


Figure 6.5: Glucose profiles for the 10 adults (upper graph) when optimal insulin infusion (lower graph) is delivered

It can be concluded that very tight glycaemic control is achieved for most of the patients when the meals are known in advance and the patient follows the exact predefined plan. In more detail, the percentage of the time spent outside the euglycaemic range is presented in Table 6.5 for all adults. As confirmed by Figure 6.5, it is difficult to maintain the blood

glucose levels of adults no 4 and no 10 within the normal range. However, if these results are compared to the time spent in normoglycaemia when conventional optimal insulin dosing is applied, it can be stated that superior glucose control can be achieved with optimised insulin infusion for all patents.

Table 6.5: Comparison of the time spent outside the normal glucose range when optimisation of insulin infusion is performed and conventional optimal insulin dosing is administered

%Time	Ad 1	Ad 2	Ad 3	Ad 4	Ad 5	Ad 6	Ad 7	Ad 8	Ad 9	Ad10	Mean
Optimised Insulin Infusion											
G <70	0	0	0	0	0	0	0	0	0	0	0
G <80	0.9	0	0	15.9	0	0	0	0	0	0.9	1.8
80<G<140	99.0	100	96.1	53.5	76.2	90.1	99	90.1	95	48.5	84.7
140<G<180	0	0	3.9	29.8	23.7	9.9	0.99	9.9	4.9	50.5	13.3
180<G<250	0	0	0	2.9	0	0	0	0	0	0	0.29
G >250	0	0	0	0	0	0	0	0	0	0	0
G_{min}	79	80	87	71	112	89	90	90	80	79	86
G_{max}	139	137	147	192	145	146	140	146	144	153	149
Conventional Optimal Insulin Dosing											
G <70	0	0	0	0	0	0	0	0	0	0	0
G <80	0	0	0	0	0	0	0	0	0	0	0
80<G<140	52.2	73.7	42.7	48.9	49.9	52.8	75.8	50.7	26.7	30.9	50.43
140<G<180	40.9	26.2	57.2	41.6	50.1	42.7	24.1	49.2	62.6	58.4	45.3
180<G<250	6.8	0	0	9.5	0	4.4	0	0	10.6	10.6	4.19
G >250	0	0	0	0	0	0	0	0	0	0	0
G_{min}	100	95	102	99	99	103	102	88	93	96	97.7
G_{max}	201	157	175	204	169	186	162	166	216	196	183.2

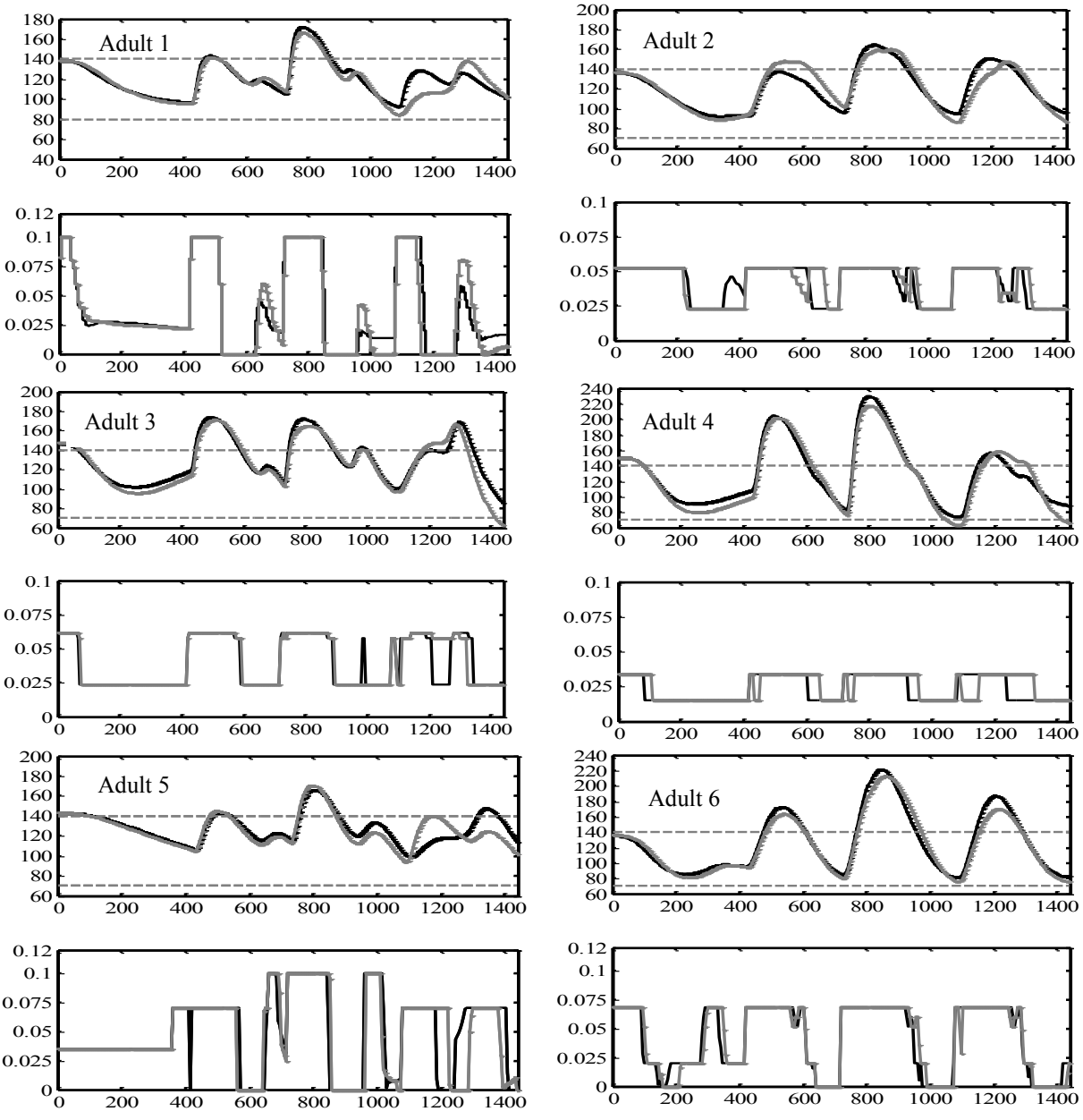
In more detail, no event of hypoglycaemia occurs for either the optimised insulin infusion or the conventional optimal insulin dosing. The time period during which glucose is above 140mg/dl is 36% longer with the conventional insulin dosing than with the optimised insulin infusion, while the time spent above 150mg/dl is 24% larger with the conventional insulin dosing. Hence, when the exact meal plan is known in advance, then the administration of insulin as calculated by the solution of the optimisation problem is a reliable way to tightly maintain the blood glucose concentration within the normal range. However, CD_1 assumes that not only the meal plan is known in advance (something which is not always easy to achieve in practice), but also that there is no model mismatch in terms of patient individual dynamics and that there is no intra-patient variability. However, free living conditions deviate significantly from the ideal simulated conditions. These assumptions are reconsidered and examined in the following sections.

6.5.2 Control Design 2 (CD_2): Online MPC with Scheduling Level

In this section the control design CD_2 for announced disturbances is evaluated for the 10 patients. The patient models are developed in gPROMS, while the control design in MATLAB, gO:MATLAB is used to exchange data between the two environments. The design is validated against:

A. The proposed model
B. The UVa/Padova Simulator

The considered meal plan is 45, 70 and 60 g of carbohydrates for breakfast, lunch and dinner and the meals are given at 420, 720 and 1080 min as previously.



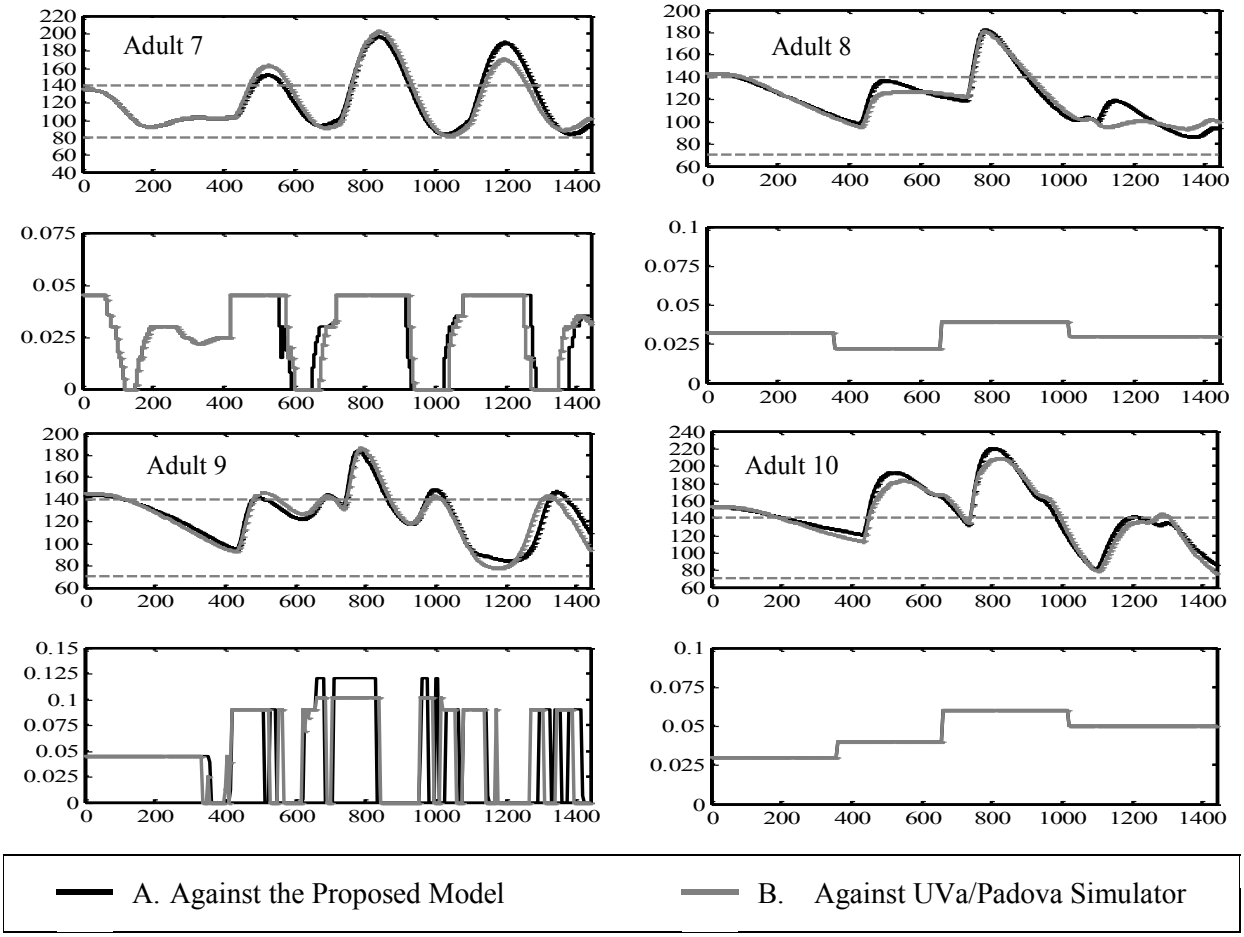


Figure 6.6: MPC control for 10 adults in the presence of announced disturbances.; Upper graphs blood glucose concentration (mg/dl) profiles; lower graphs control action, insulin (U/min). The black lines show the results when CD_2 is validated against the proposed model while the grey lines the results against the UVa/Padova Simulator.

The purpose of Figure 6.6 is first to compare the results produced by CD_2 when evaluated against the proposed model and the UVa/Padova Simulator and second to examine the reliability of CD_2. The results of A and B are very similar, which implies that the proposed model could be generally viewed as a reliable equivalent to the UVa/Padova Simulator. The approximate model used as the internal MPC model can predict the current states for both models and the controller suggests a similar control action for all patients. The observed differences could be due to inaccuracies in the parameter estimation of the proposed model due to the lack of informative data of different meal sizes and insulin infusions. As far as the efficiency of CD_2 is concerned, the results suggest that this strategy is not flexible enough to handle the fluctuations of glucose concentration. The controller suggests the maximum insulin infusion at the announcement of the disturbance, which cannot prevent the prandial hyperglycaemia. The control specifications are fine tuned to ensure the avoidance of hypoglycaemia.

6.5.2.1 Case Study: Skipped Meal

CD_2 is evaluated in the case of a skipped meal. As it can be verified from Figure 6.7 the controller reacts accordingly when the breakfast or the lunch are skipped at 420 and 720 min respectively.

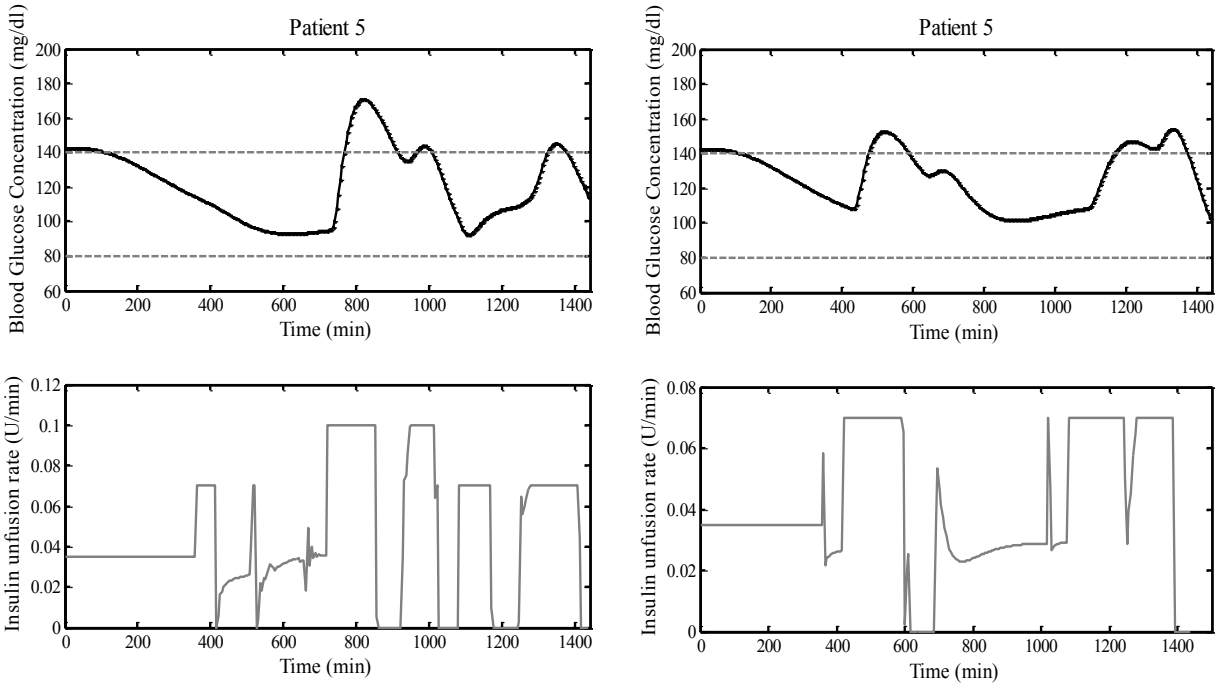


Figure 6.7: Skipped breakfast and skipped lunch for adult 5

6.5.3 Control Design 3 (CD_3): Optimisation and Correction MPC

In this section the CD_3 control design as explained before is evaluated. The ability of the controller to maintain the blood glucose concentration in the normal range is tested for large meal sizes of 75, 100 and 90 g and for normal meal sizes of 45, 75 and 60 g of carbohydrates given for breakfast at 420 min, lunch at 720 min and dinner at 1080 min respectively, as shown in Table 6.6. The reference meal plan is 20, 30 and 25 g respectively. The total insulin amount does not exceed the TDD for each patient plus approximately 6 U to compensate for the large meal sizes. The results from CD_3 are compared to the CD_4 for the same meal sizes and presented in Table 6.7 and Table 6.8.

Table 6.6: Evaluation of CD3 with two meal scenarios

	Scenario 1	**Scenario 2**
Breakfast	75 g	45 g
Lunch	100 g	75 g
Dinner	90g	60 g

Table 6.7: CD_3 predefined reference meal plan (Scenario 1)

	% time <70	% time <80	% time 80<G <140	% time 140<G <180	% time 180<G <250	% time >250	G_{min} (mg/dl)	G_{max} (mg/dl)
Adult1	0	1.3	72.9	18.3	8.6	0	89	203
Adult2	0	0	71.5	22.9	5.5	0	81	190
Adult3	0	2.3	65.0	20.5	12.0	0	70	228
Adult4	0	0.3	25.0	56.9	17.8	0	76	247
Adult5	0	0	55.5	29.2	14.9	0	79	239
Adult6	0	3.1	60.4	14.6	21.9	0	71	226
Adult7	0	0	67.0	20.1	12.8	0	82	205
Adult8	0	4.9	68.4	19.5	7.0	0	77	194
Adult9	0	1.4	59.2	23.4	13.1	2.8	72	265
Adult10	0	2.4	50.3	23.4	24.8	2.4	76	259
Mean	**0**	**1.6**	**59.5**	**24.9**	**13.8**	**0.52**	**77**	**226**
SD	**0**	**1.6**	**14.1**	**11.9**	**6.2**	**1.1**	**5.7**	**26.9**

Table 6.8:CD_4 unknown disturbances (Scenario 1)

	% time <70	% time <80	% time 80<G <140	% time 140<G <180	% time 180<G <250	% time >250	G_{min} (mg/dl)	G_{max} (mg/dl)
Adult1	1.4	4.5	53.8	22.2	19.4	0	62	238
Adult2	4.5	7.9	54.9	25.3	11.8	0	63	202
Adult3	4.1	5.5	45.8	37.1	11.4	0	46	249
Adult4	5.2	12.8	52.7	12.5	7.6	14.2	62	326
Adult5	0	0	43.1	29.8	27.1	0	85	246
Adult6	6.3	12.7	52.4	9.9	20.9	3.9	54	270
Adult7	6.6	12.8	52.8	9.1	16.1	8.6	58	288
Adult8	5.2	9.3	51.7	29.5	9.4	0	65	199
Adult9	0	0	39.2	33.7	20.5	6.5	90	303
Adult10	0	2.1	36.1	27.1	29.5	5.2	72	281
Mean	**3.4**	**6.8**	**48.3**	**23.6**	**17.4**	**3.8**	**66**	**260**
SD	**2.6**	**5.1**	**6.7**	**10.0**	**7.4**	**4.9**	**13.4**	**41.4**

Table 6.7 shows that with CD_3, on average 59.5% of the time is spent within the normal glucose range, while with CD_4 the percentage of the time spent in the normal range is 48.3%. With CD_3 there is no event of hypoglycaemia and the minimum observed glucose value is 71mg/dl for adult 6, in contrast to CD_4 where an average 3.4% of the time is spent in hypoglycaemia with a minimum observed glucose value of 46 mg/dl. Additionally, the time spent in hyperglycaemia (>180mg/dl) is much higher for CD_4 with a 21.2% of the time, while for CD_3 the respective percentage is 14.3%. The 10 adults respond, as expected, relatively different from each other, but as it can be observed from Table 6.7 there is no event of hypoglycaemia in all the studied adults and only adult 9 and adult 10 spend time above 250 mg/dl. However, for CD_4 the results are significantly different with the glucose values being distributed towards the extremes for most of the adults. A Mann-Whitney test was performed to compare CD_3 and CD_4. The *p*-value is calculated for each glucose range and for the ranges

G<70 (p-value= 0.002), G<80 (p-value=0.036), 80<G<140 (p-value= 0.013), it was indicated that the null hypothesis for equal medians is rejected at 5% significance level. Therefore CD_3 can be regarded as a potential strategy to compensate for unknown meal disturbances in terms of minimizing hypoglycaemia and maintaining glucose levels within the safe range. The glucose profile and the control action with both CD_3 and CD_4 are presented in Figure 6.8 for adult 1 for illustrative purposes.

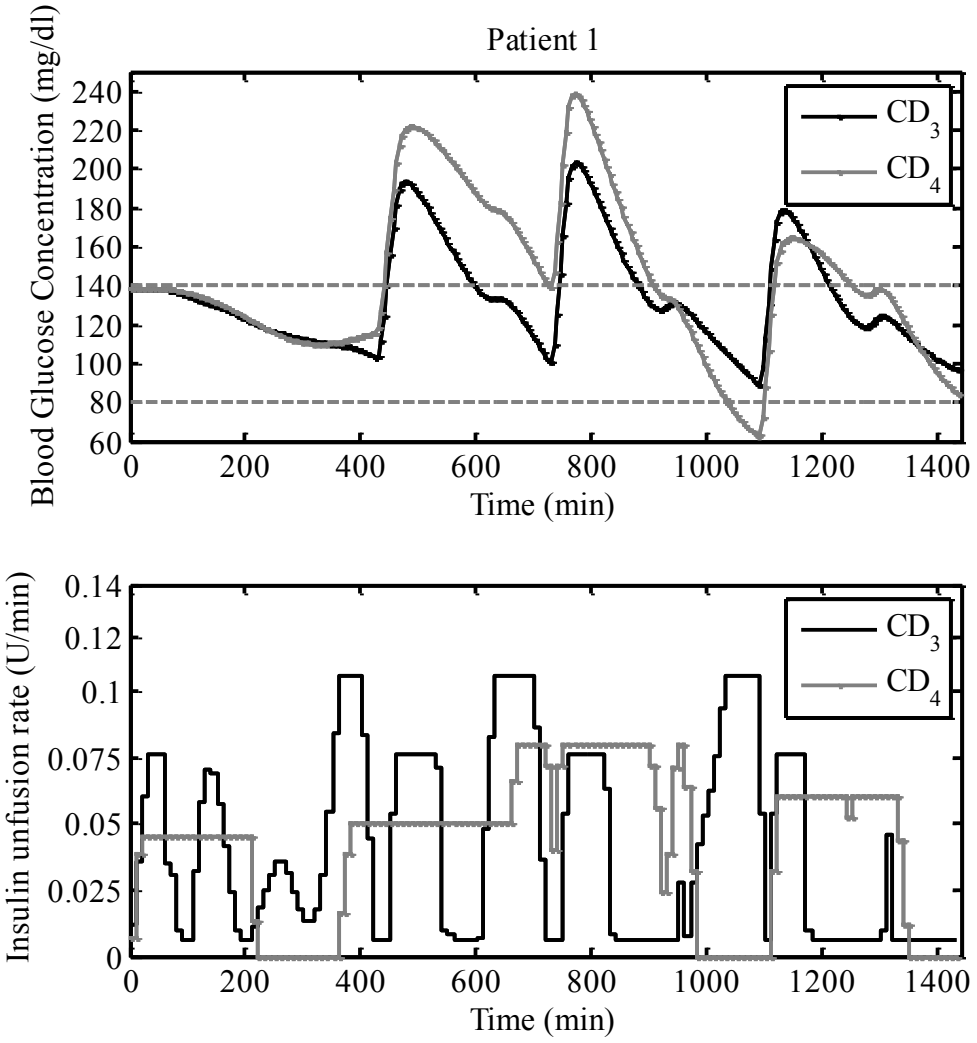


Figure 6.8: Comparison of glucose regulation with CD3 and CD4 for adult 1. The meals are given 420, 720 and 1080 and contain 75, 100 and 90 g of carbohydrates respectively (Scenario 1)

The control designs CD_3 and CD_4 are evaluated for different meal sizes and presented for adult 1 in Figure 6.9.

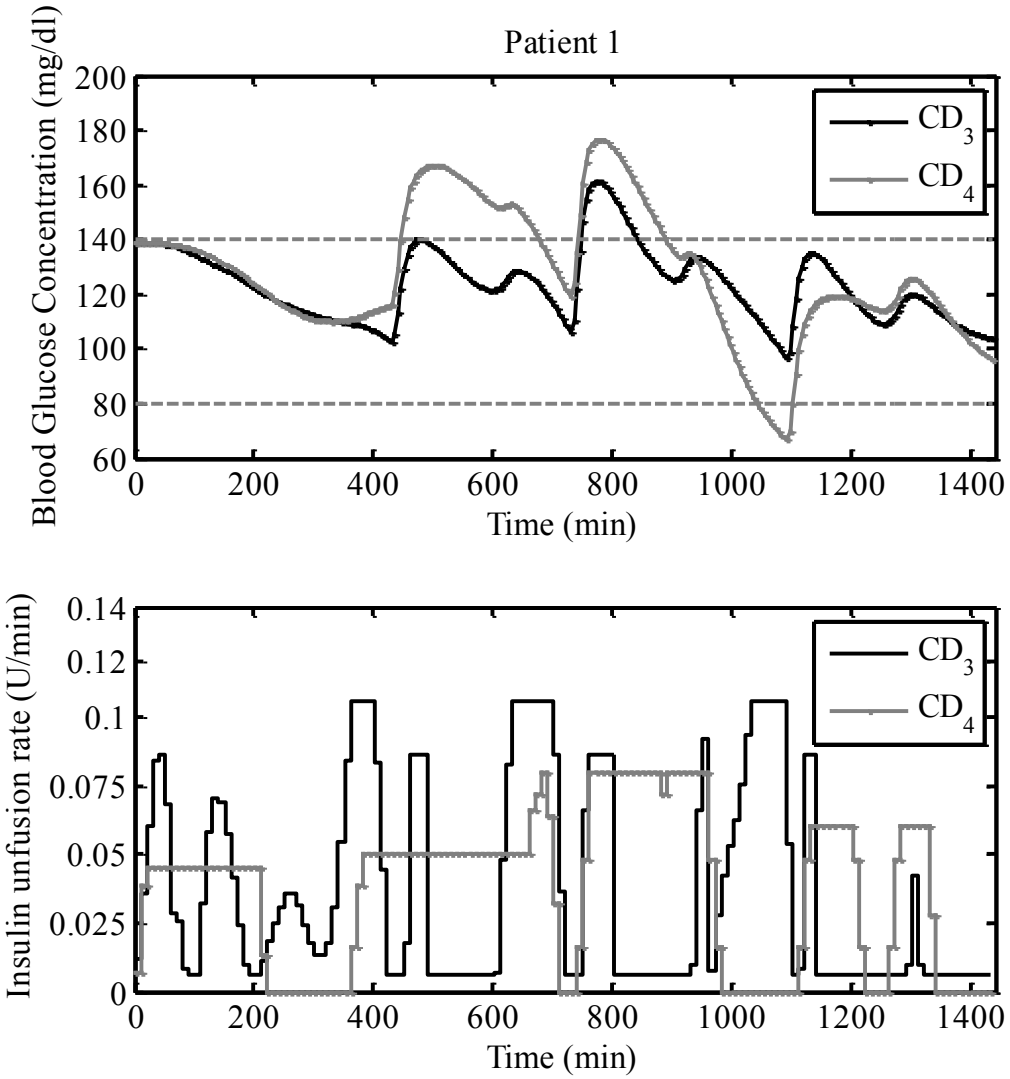


Figure 6.9: Comparison of glucose regulation with CD_3 and CD_4 for adult 1. The meals are given 420, 720 and 1080 and contain 45, 75 and 60 g of carbohydrates respectively (Scenario 2)

Figure 6.8 and Figure 6.9 confirm that tighter glycaemic control can be achieved when CD_3 is used and a feed forward reference action is applied to enhance the control performance in the presence of unknown disturbances.

Key Results for the Systematic Strategy Control Designs

- Control Design 1: Tight glycaemic control
- Control Design 2: Not flexible enough, but no event of hypoglycaemia for the study data
- Control Design 3: Good glycaemic control; 85% of the time spent near normoglycaemia for Scenario 1; no event of hypoglycaemia for the study data
- Control Design 4: Not efficient glycaemic control; 72% of the time spent near normoglycaemia for Scenario 1, with 3.4% in hypoglycaemia

6.6 "Approximation" Strategy (II): Control Designs

In this section the "approximation" strategy is evaluated and compared with the systematic strategy. The general control design applied in this approach is presented in Figure 6.10. This design differs from Figure 6.1 in the grey box that now instead of an optimisation problem a second MPC is considered. Additionally, the y_{opt} becomes y_{ref}, as calculated when the reference tracking problem with known meal disturbance is solved and the optimal insulin infusion is applied. Finally, CD_2 and CD_4 are the same as presented previously.

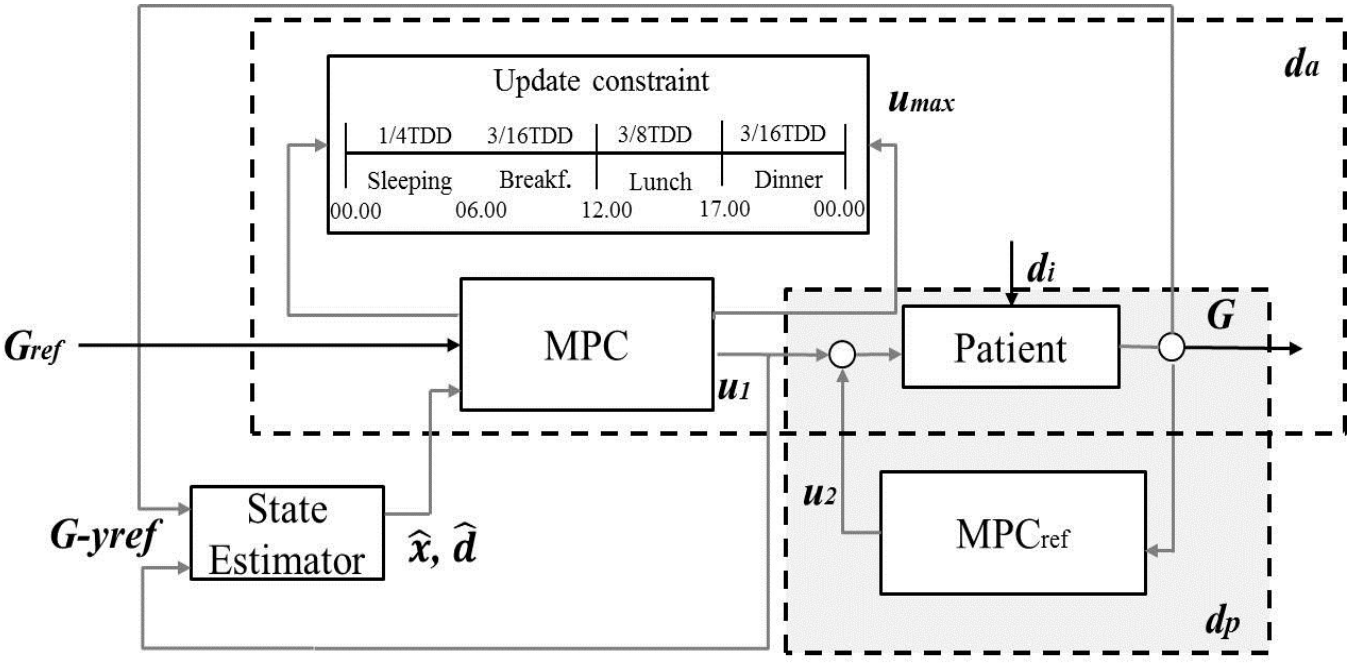


Figure 6.10: General control design for "Approximation" Strategy

Effect of Mean Approximate model

In order to illustrate the effect of using the mean approximate model instead of the patient-specific approximate model, we consider the control design CD_3 of section 6.4.3 but assuming that the internal control model is now the mean approximate model. This assumption in the context of Strategy I is not correct since, if there is no information of the exact patient dynamics, the optimisation problem will not calculate the optimal insulin infusion for each patient. However, for analysis purposes, assuming that u_2 is available and can be applied, we investigate the effect of using mean approximate internal models rather than exact in the control design. Figure 6.11 is a control variability grid analysis (CVGA) plot (Magni *et al.*, 2008) which has been established as a very useful tool to evaluate the performance of different control strategies in a population of patients. The area is divided in zones, each one representing the level of euglycaemic maintenance. For each patient a dot is

plotted that shows the extreme glucose excursions for a given control strategy applied for a specific period. The performed closed loop experiment involves the consumption of 45, 75 and 60 g at 420, 720 and 1080 for all patients (Scenario 2). The black dots represent the CD_3 closed loop performance with a patient specific internal model while the white dots represent the same closed loop experiment but for the mean approximate model. We can see that the white dots are more distributed, with patients found in zone upper B and lower D in contrast to the black dots which are mostly found in zone A and lower B. Figure 6.12 shows the cumulative distribution of the data for both cases. It can be seen that the data coming from the patient-specific model produce a sharper profile indicating that the patients are within tight glycaemic control for most of the time. The light grey area which represents the profiles from the mean model is wider confirming the distributed results presented in Figure 6.11.

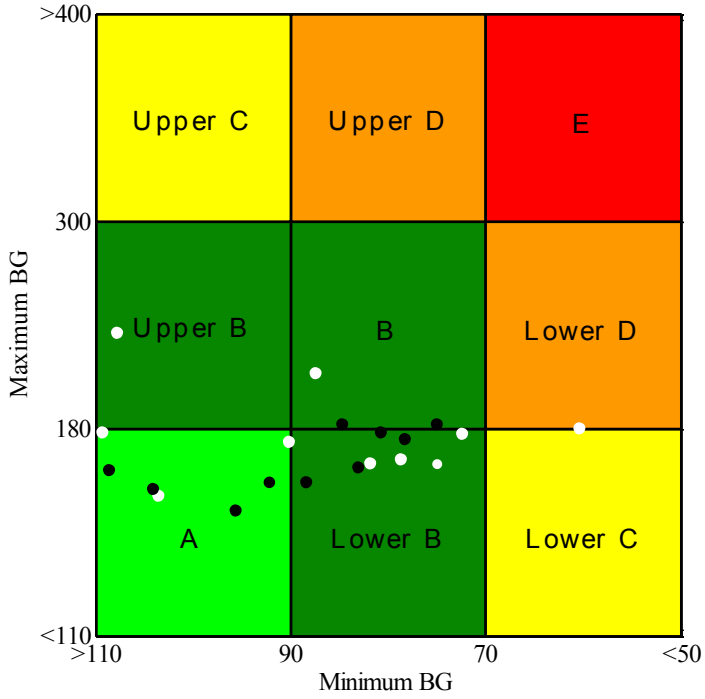


Figure 6.11: CVGA of CD_3 for patient specific approximate model (black dots) versus mean approximate model (white dots)

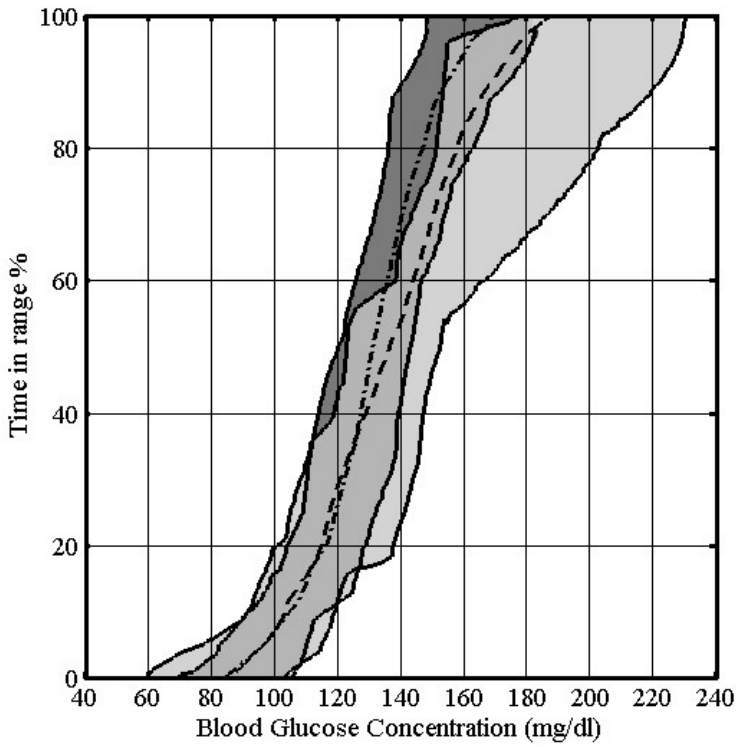


Figure 6.12: Cumulative distribution of blood glucose concentration. The light grey area shows the range of closed loop glucose distribution when the mean approximate model is used for the ten patients; whereas the dark grey area shows the range of closed loop glucose distribution when the exact patient model is used (Strategy I). The dashed line is the mean cumulative glucose distribution of the light grey area while the dash-dot line the mean of the dark grey area.

6.6.1 Comparison of CD_3: Strategy I and Strategy II

The performance of CD_3 for Strategy I and Strategy II is compared in Figure 6.13 for Scenario 2 for all patients. It can be noticed that the results of Strategy II are undoubtedly satisfactory since all patients are in zones A and B. When compared to the results from CD_3 of Strategy I with mean model (as explained above) we can see that the additional MPC acts efficiently to compensate for the effects of poor model and tighter glycaemic control can be achieved. Figure 6.14 shows the cumulative distribution of CD_3 for Strategy I and II. We can observe that both areas are very sharp and tight indicating that most of the time glucose is maintained tightly within the normal range.

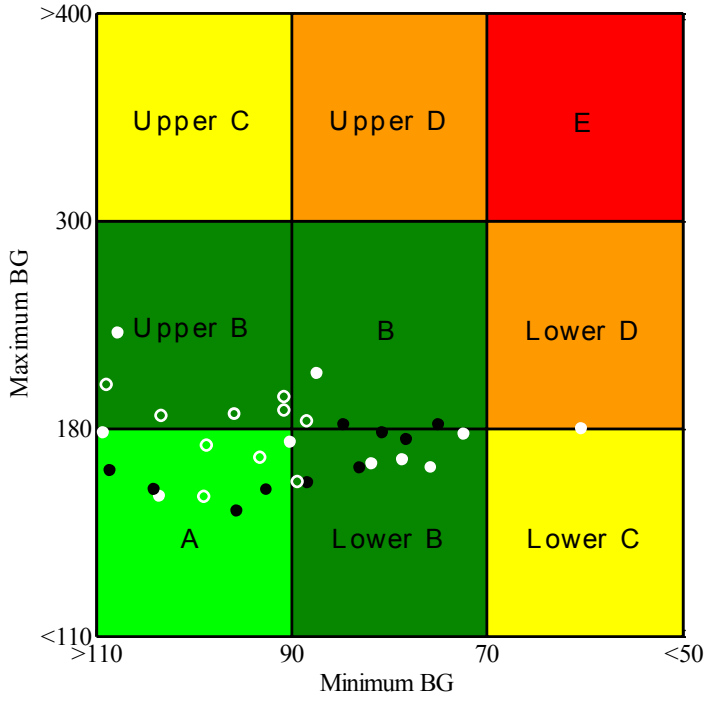


Figure 6.13: CVGA of CD_3 for patient specific approximate model (black dots), Strategy I, versus mean approximate model (white dots) and versus CD_3 Strategy II (white circles)

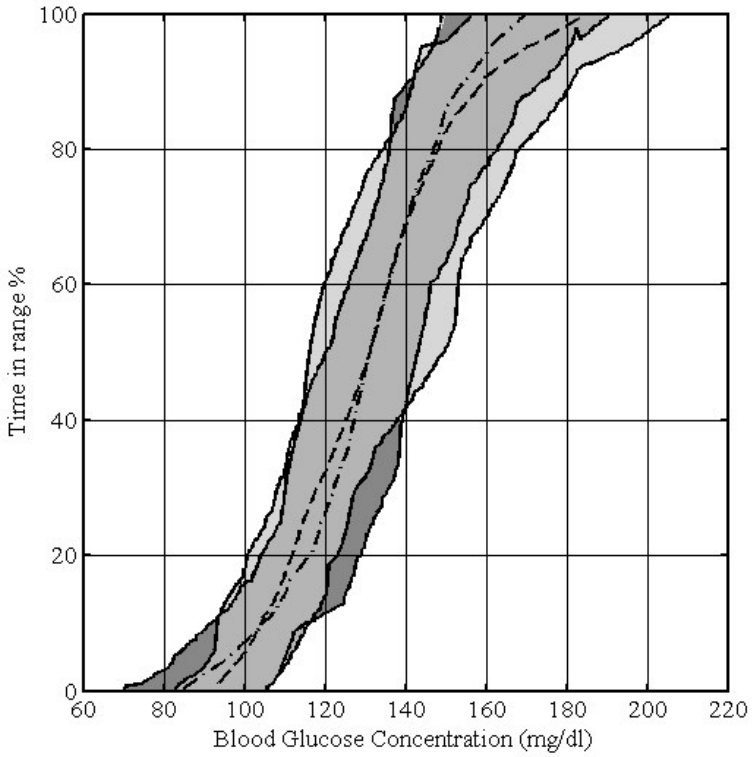


Figure 6.14: Cumulative distribution of blood glucose concentration. The light grey area shows the range of closed loop glucose distribution of Strategy II for the ten patients; whereas the dark grey area shows the range of closed loop glucose distribution for Strategy I. The dashed line is the mean cumulative glucose distribution of the light grey area while the dash-dot line the mean of the dark grey area.

Figure 6.15 confirms the results found in Figure 6.14 for Scenario 2, now for Scenario 1. It can be observed that Strategy I and II present similar behaviour even for larger meal sizes and optimal control is achieved for both cases.

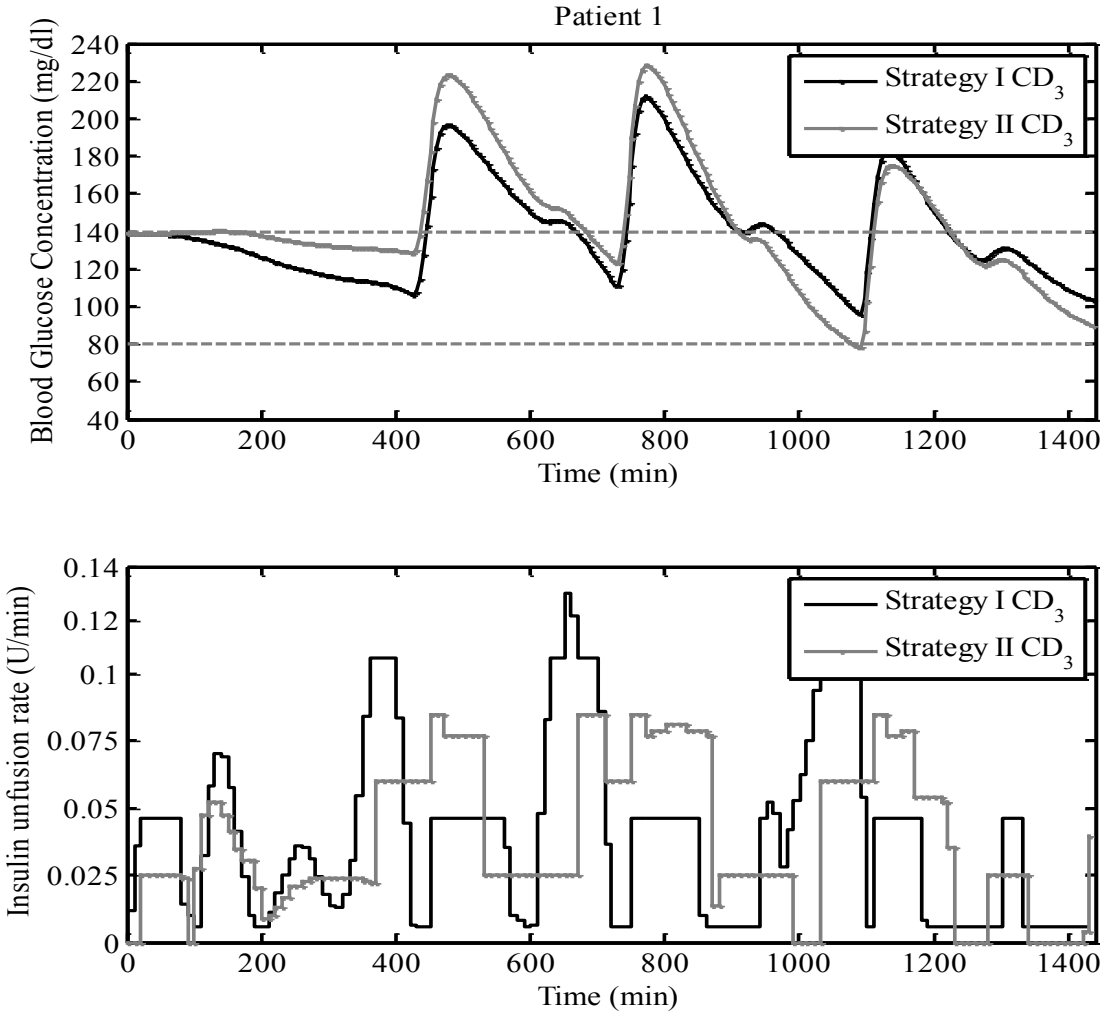


Figure 6.15: Comparison of glucose regulation with CD_3 for both Strategy I and Strategy II applied on adult 1. The meals are given 420, 720 and 1080 and contain 75, 100 and 90 g of carbohydrates respectively (Scenario 1)

Key Results for the "Approximation" Strategy Control Designs

- Compensation for model mismatch with feedback coming from an additional controller
- Control Design 3: Good glycaemic control

6.7 Case Study: Skipped Meal

In this section the case of a skipped meal is evaluated for both the Systematic Strategy and the "Approximation" Strategy, as shown in Figure 6.16 This graph shows the advantage of

Strategy I over Strategy II. We can see that optimisation of the insulin delivery over the entire horizon is much more efficient than the optimisation over the prediction horizon in such an unstable system with long time delays. The insulin action proposed by the solution of the optimisation problem is adequate for each sampling period since the reference meal disturbance is known in advance and insulin is delivered smoothly long before the occurrence of glucose fluctuation. Therefore in the case of a skipped meal the drop of glucose profile is not as severe as in the "Approximation" Strategy because the compensation for a meal disturbance starts early having a smooth effect on glucose. On the other hand, in the "Approximation" Strategy the reference meal announcement is obtained within the framework of the prediction horizon and the action of the controller although it is produced earlier than the meal disturbance, it is sharper than in Strategy I, causing a big drop on blood glucose concentration.

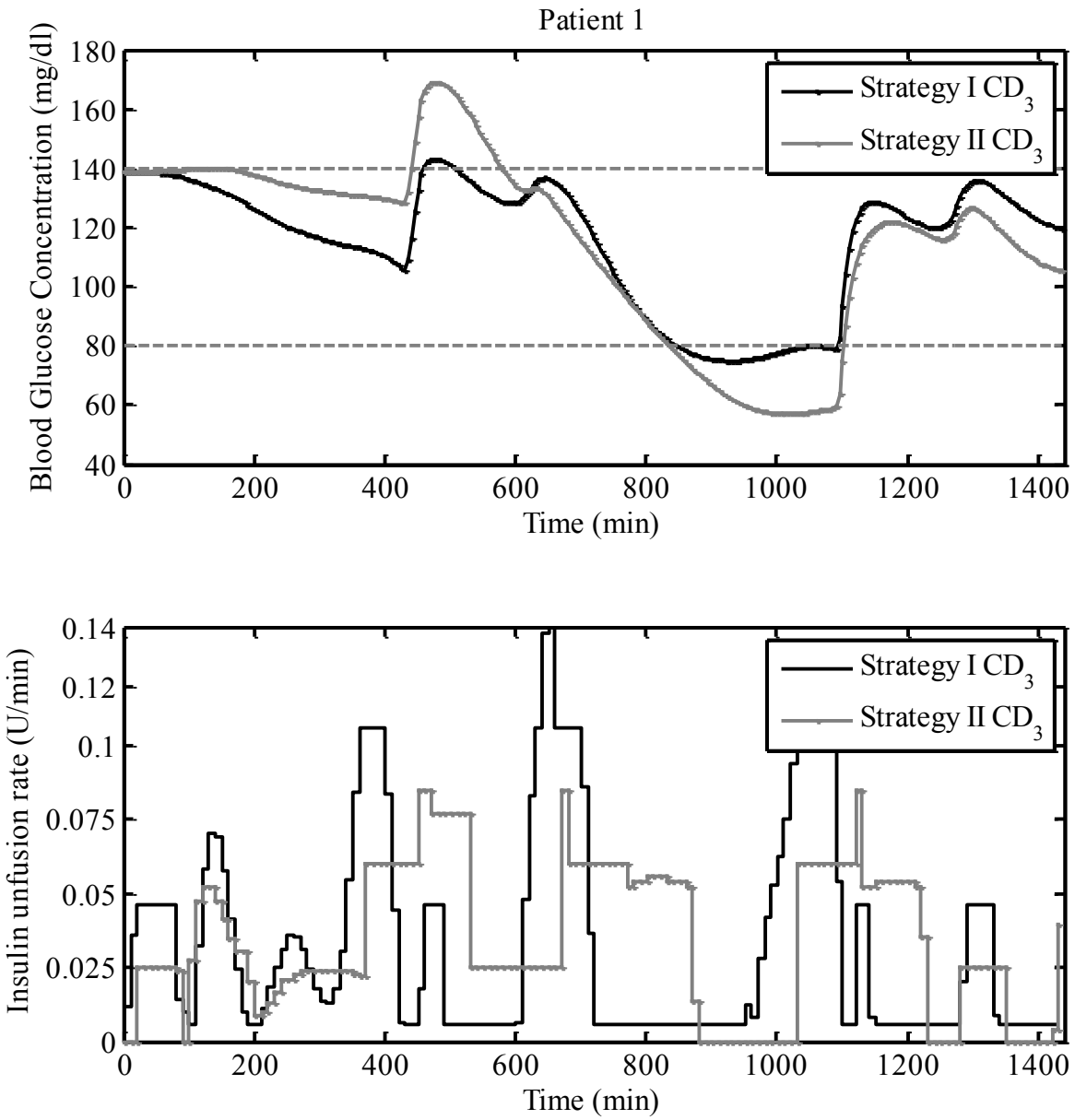


Figure 6.16: Skipped lunch for adult 1 and Scenario 2

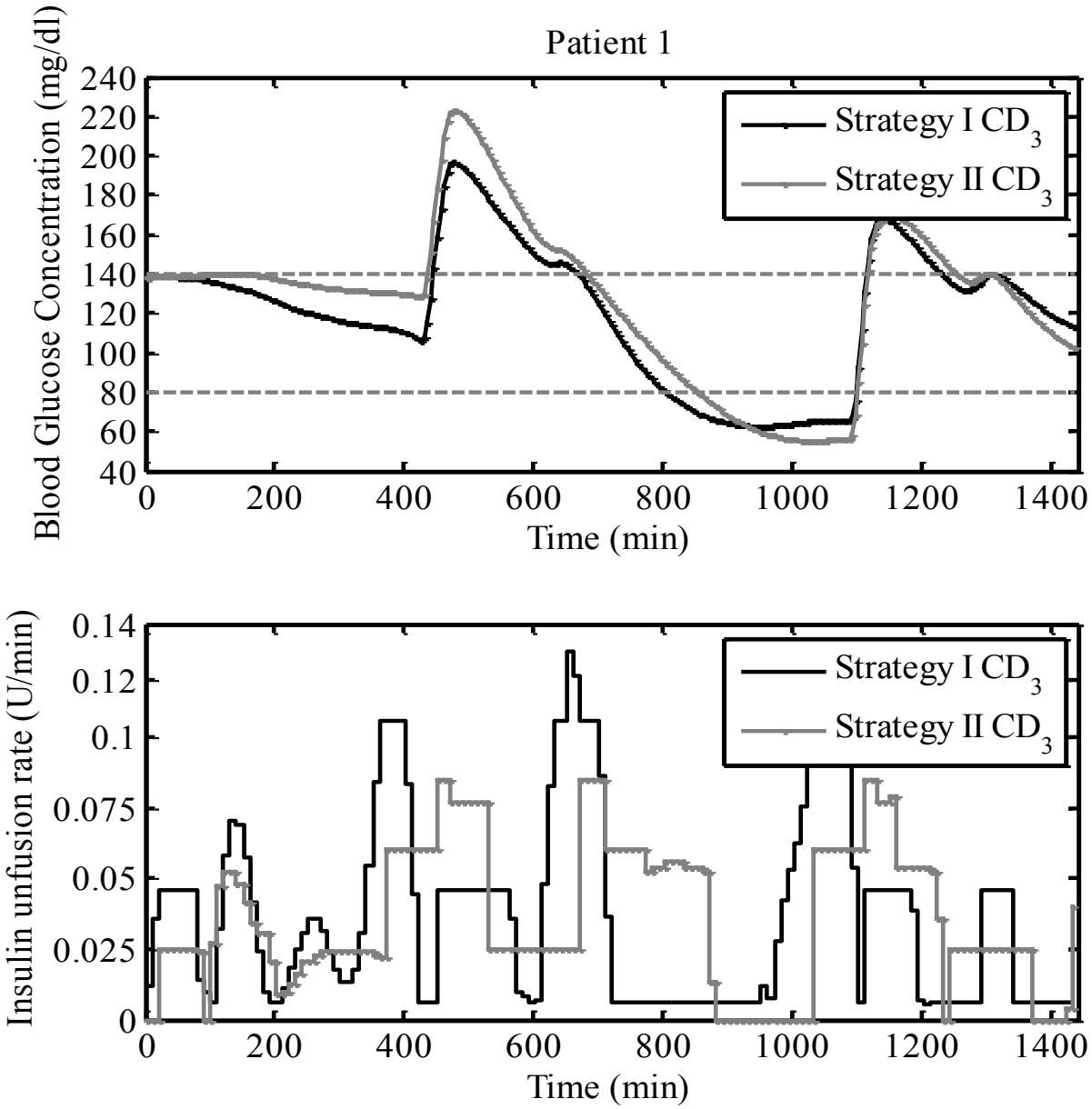


Figure 6.17: Skipped lunch for adult 1 and Scenario 1

The same conclusions are supported with Figure 6.17 for Scenario 1. The drop in glucose concentration is greater since the considered meal disturbances are bigger which means more insulin is required to compensate for the glucose increase. Therefore, the reference meal plan can be adequately adjusted according to the patient's meal habits in case of normal consumption of larger meals.

6.8 Case Study: Variable Meal Time

Figure 6.18 shows the glucose profile for adult 1 for the Systematic Strategy when a meal of 50 g is given 30min before or 30min after, or simultaneously with the predefined 30 g reference meal. It can be noticed that good glycaemic control is achieved even at the case

when a meal is consumed 30min before the considered reference meal which triggers the control action and no event of hypoglycaemia is occurring.

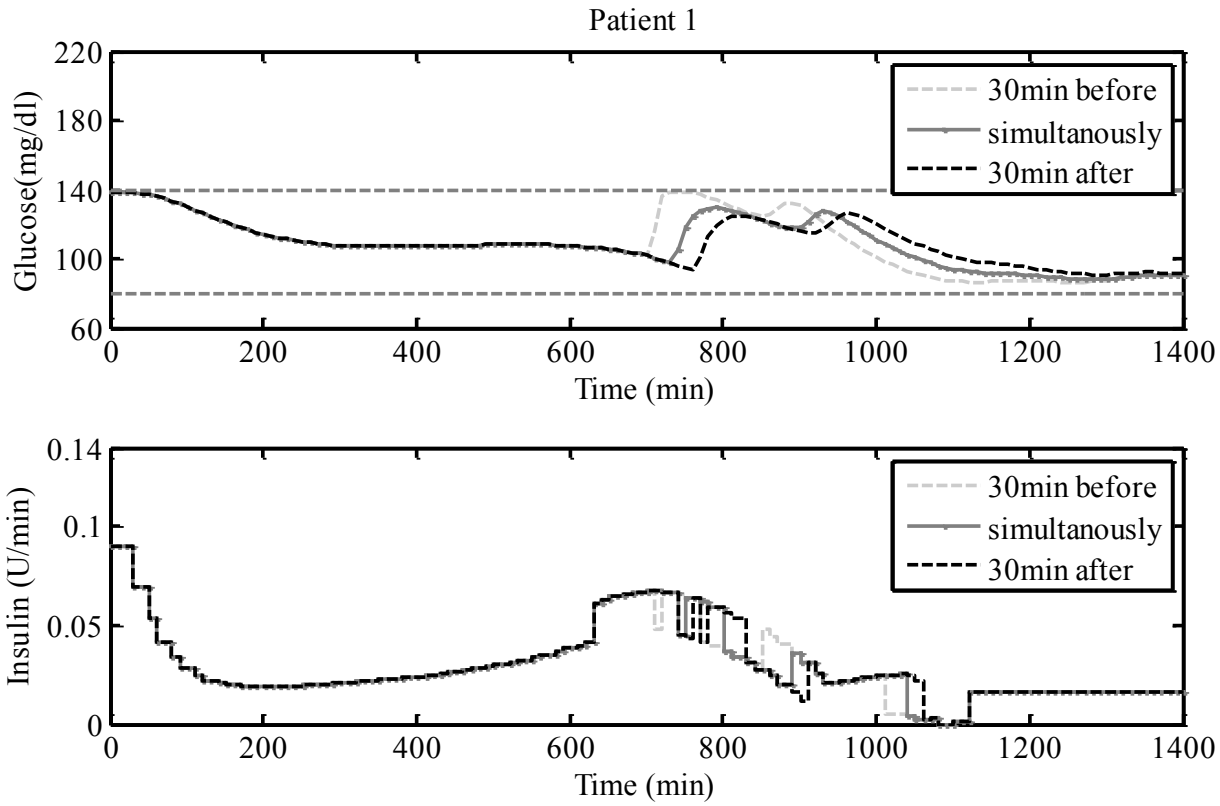


Figure 6.18: Evaluation of CD_3 with Systematic Strategy (I) when a meal of 50 g is given 30 min in advance, 30 min after and simultaneously with the reference meal of 30 g

The results of Figure 6.18 are compared with Figure 6.19 for the exact conditions, but for the "Approximation" Strategy. Once more, we can see that good glycaemic control is achieved and no event of hypoglycaemia is occurring. Additionally, the advantage of considering the Systematic Strategy is confirmed since it can maintain glucose tightly within the range, although the increased postprandial glucose values observed in the "Approximation" Strategy do not raise a potential issue for the patient's safety.

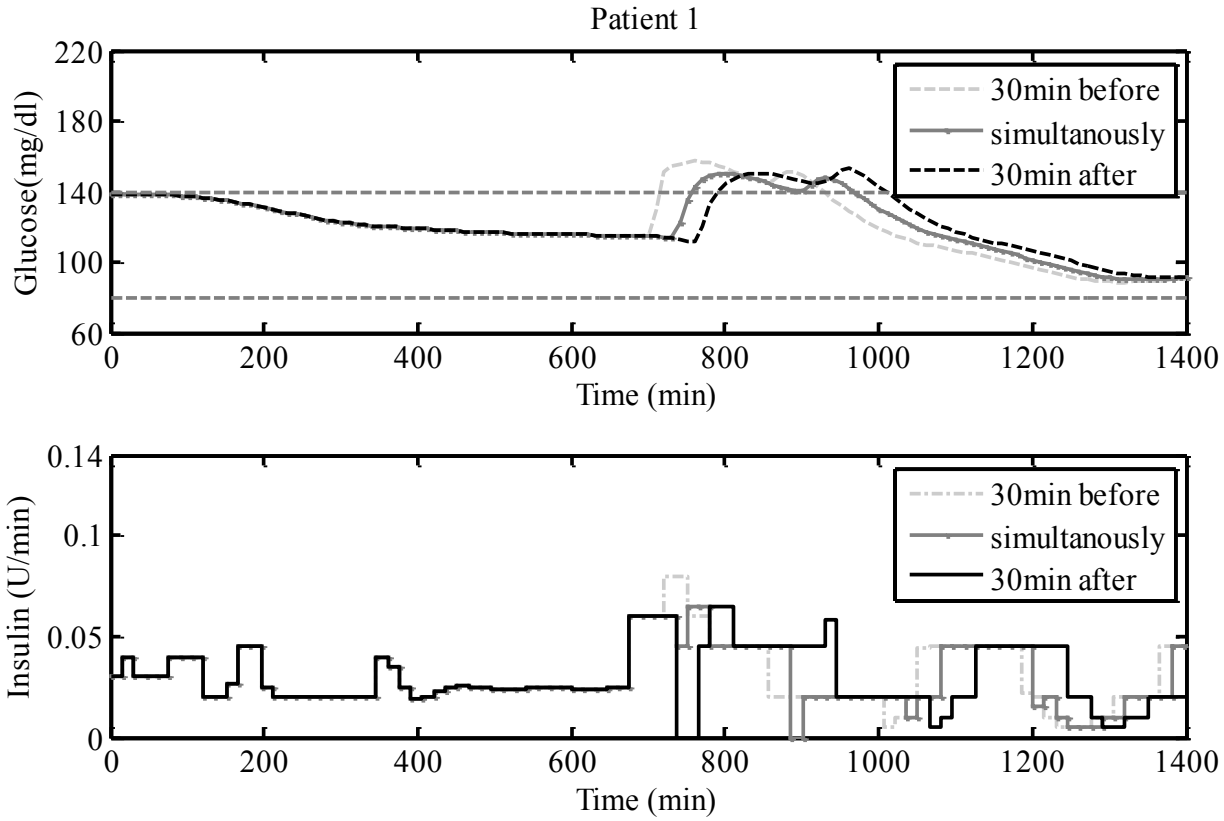


Figure 6.19: Evaluation of CD_3 with "Approximation" Strategy (II) when a meal of 50 g is given 30min in advance, 30 min after and simultaneous with the reference meal of 30 g

The results of Figure 6.18 and Figure 6.19 are confirmed in Figure 6.20 and Figure 6.21 for a different meal size. Good glycaemic control is achieved, i.e. no event of hypoglycaemia is occurring, when a meal of 80 g of carbohydrates is consumed 30 min in advance, 30 min after or simultaneously with the time of the considered predefined meal of 30 g.

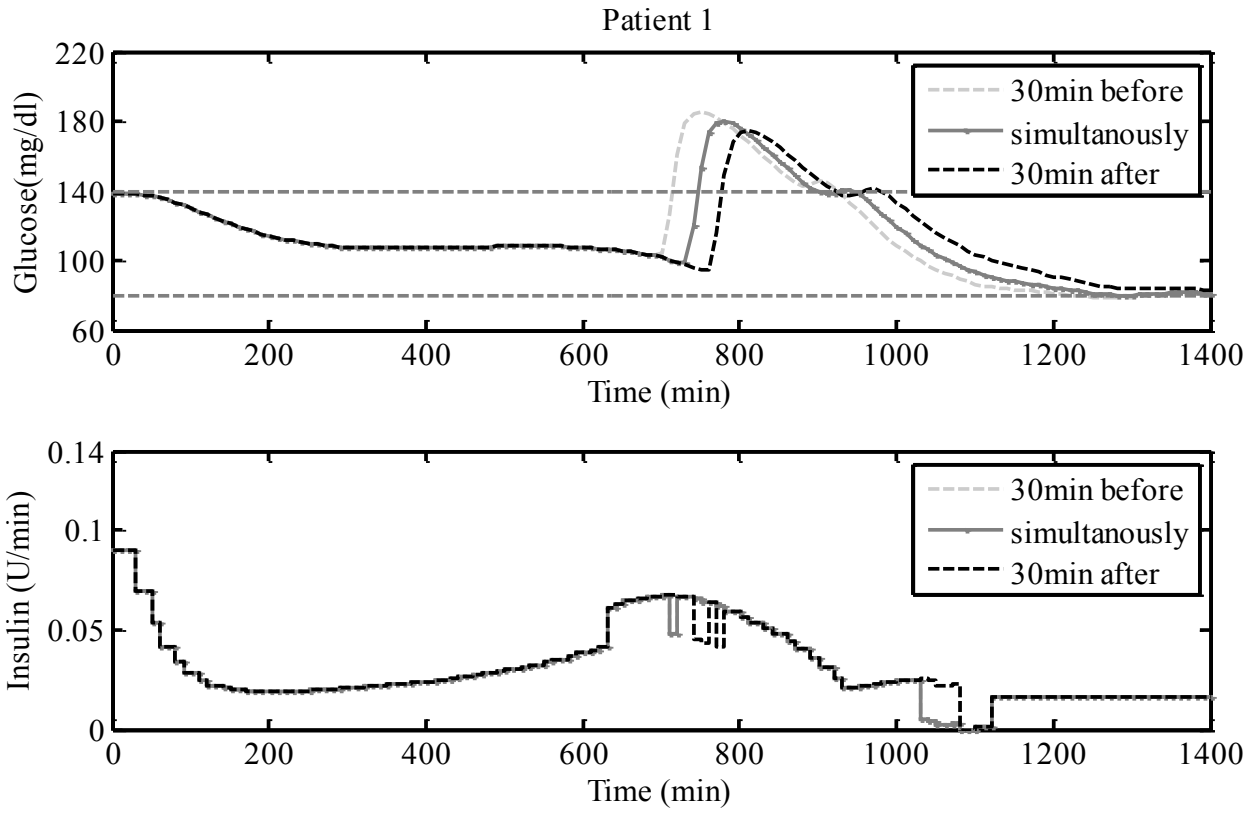


Figure 6.20: Evaluation of CD_3 with Systematic Strategy (I) when a meal of 80 g is given 30 min in advance, 30 min after and simultaneous with the reference meal of 30 g

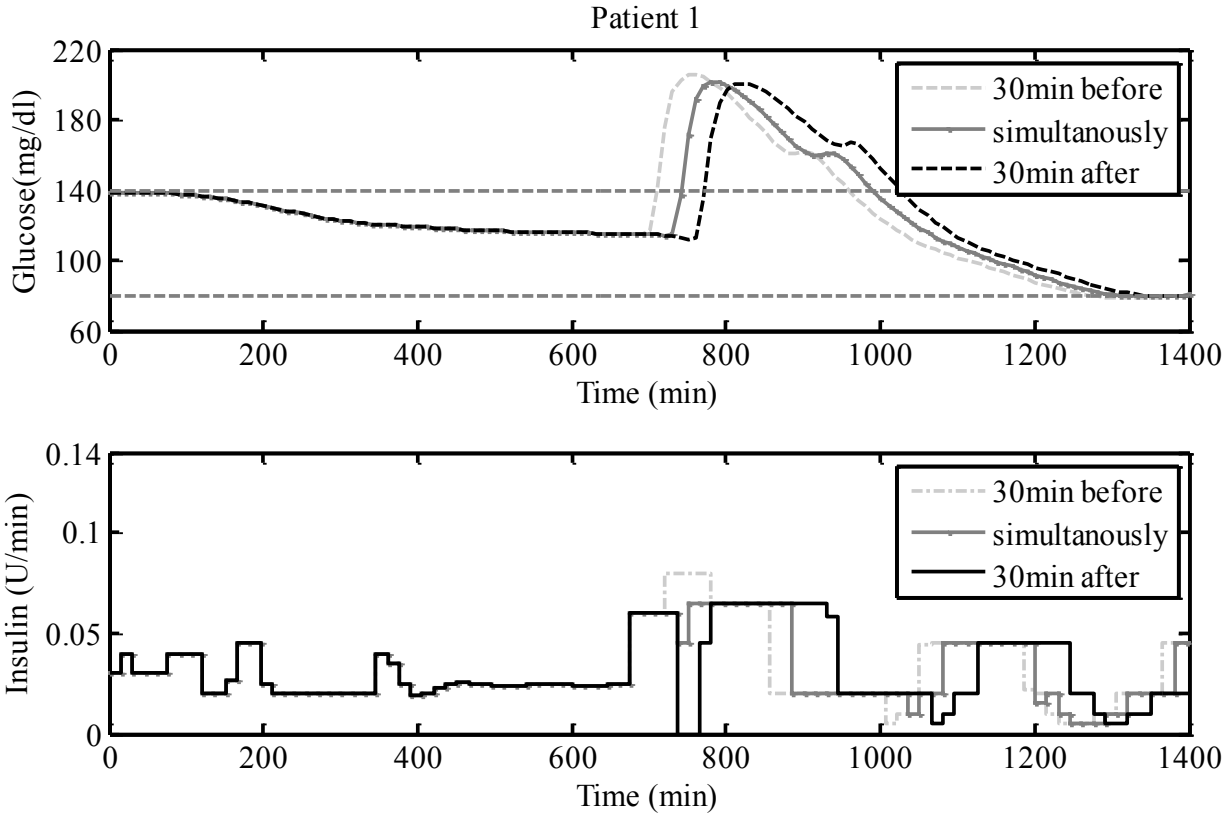


Figure 6.21: Evaluation of CD_3 with "Approximation" Strategy (II) when a meal of 80 g is given 30 min in advance, 30 min after and simultaneous with the reference meal of 30 g

The main assumption of CD_3 is that all the predefined meals will be consumed. Nonetheless, the reference meal plan can be determined individually depending on the patient's lifestyle.

6.9 Case Study: Intra-patient Variability

The impact of intra-patient variability on glucose regulation is evaluated by imposing a circadian sinusoidal variation on the parameter k_1 (3.24). This is related to insulin dependent glucose absorption and is very influential according to the sensitivity analysis presented in Chapter 4. The choice of the parameter as well as the imposed variation is in good agreement with the literature (Fabietti et al., 2006). The amplitude of the wave is 30% of the nominal value of k_1, according to (6.13):

$$k_1 = k_{1,mean}\left(1 - 0.3sin\left(\frac{2\pi}{24}\right)\right),\ 0 \le t \le 24 \tag{6.13}$$

The complete circadian cycle of parameter k_1 is presented in Figure 6.22 for adult1.

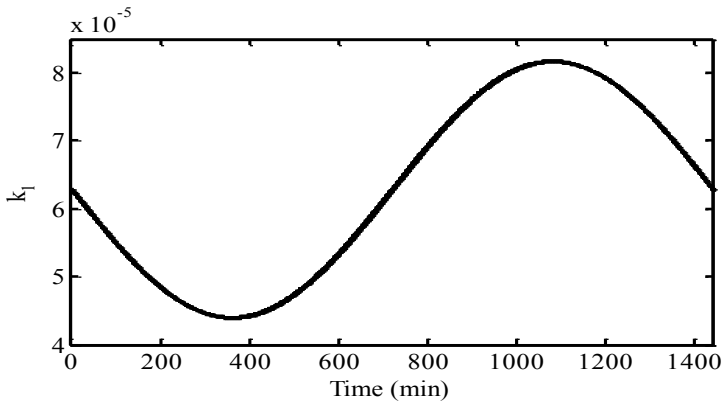


Figure 6.22: Complete circadian cycle of k1 with a 30% change in magnitude

The impact of parameter k_1 variation on glucose concentration is shown in Figure 6.23. The light grey line shows the glucose concentration profile when CD_1 is applied with no intra-patient variability considered. This profile is compared to the darker grey line that shows the influence of intra-patient variation on glucose profile, when no further control action is applied, but only CD_1. It can be noticed that the profile changes according to the sinusoidal variation with increased values of glucose concentration when the value of k_1 decreases and low values of glucose concentration with the increase of k_1.

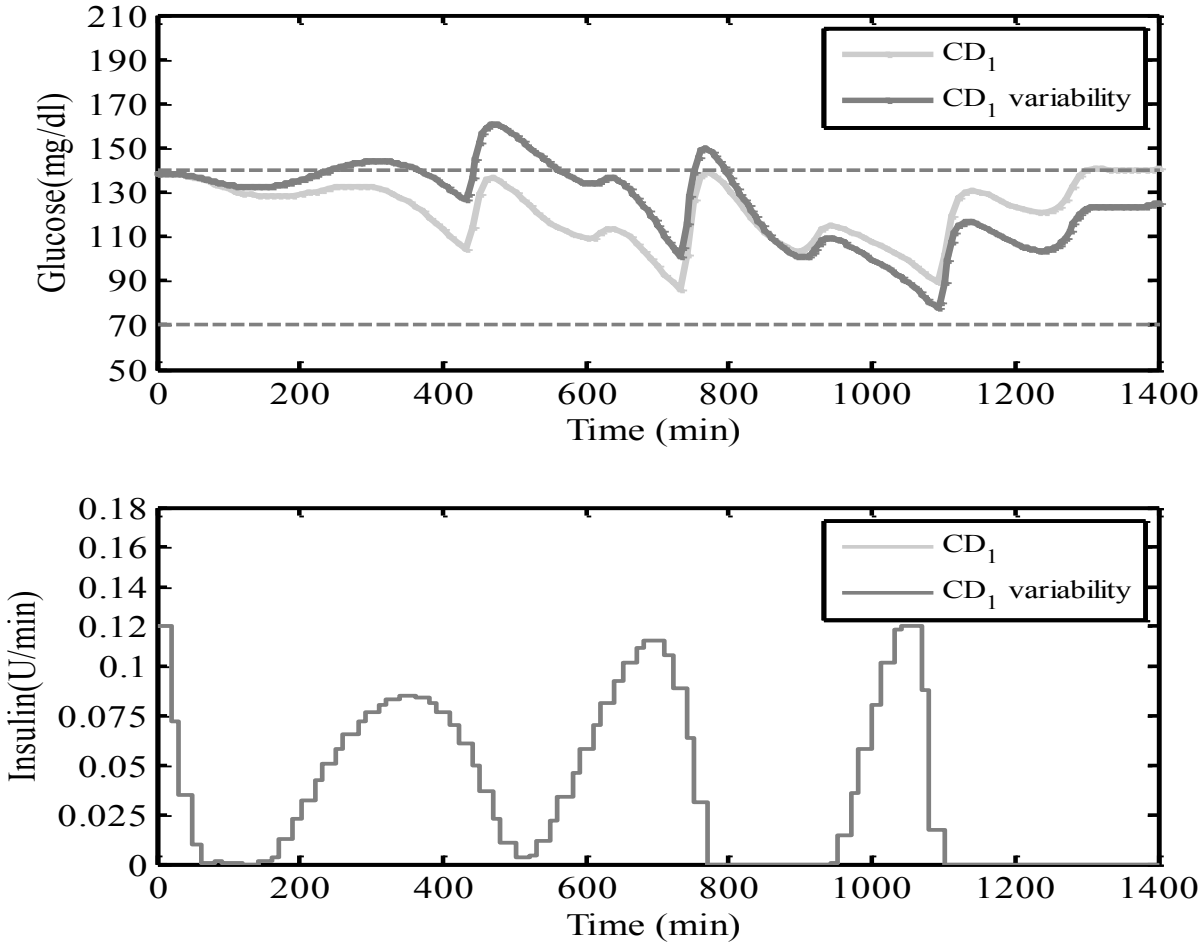


Figure 6.23: glucose profile when CD_1 is applied with no considered variability and CD_1 in the presence of variability for Scenario 2 adult 1.

To address this fluctuation in the case of unknown meal plan, CD_3 is applied for both Systematic and "Approximation" strategies. The results are presented in Figure 6.24.

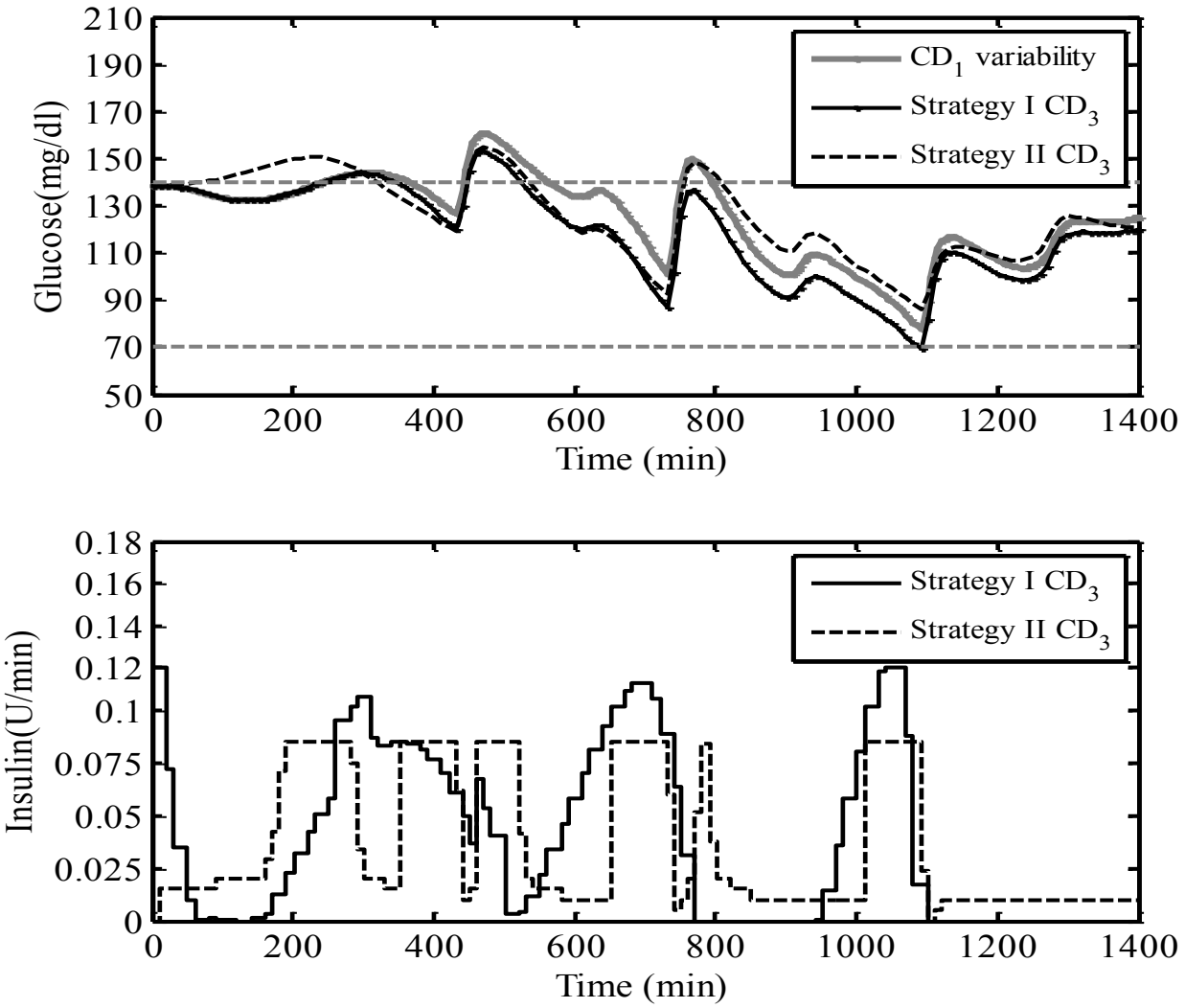


Figure 6.24: CD_3 performance in the presence of intra-parient variability for Strategy I and Strategy II, comparison of glucose profile when CD_1 is applied in the presence of variability for Scenario 2 adult 1.

It can be observed that both control strategies respond accordingly to decrease the glucose concentration when it tends to increase due to the imposed variability. Additionally, when glucose tends to decrease, both control designs achieve to maintain the concentrations above the hypoglycaemic level. This graph also shows the flexibility of "Approximation" Strategy when glucose concentration tends to decrease due to the imposed variability. The two considered controllers respond adequately so as not to deliver more insulin than required, whereas in the "Systematic" Strategy the reference insulin delivery is pre-calculated and administered anyway. Therefore, in this strategy the controller cannot act to prevent the impact of the variability, however in the presence of unknown disturbances and imposed variability the controller maintains glucose concentration within the normal range.

6.10 Conclusions

The key actions taken to address the control objectives presented in Section 6.2 are summarised as follows for the control designs of the Systematic Strategy and the "Approximation" Strategy:

Actions	**Systematic Strategy**	**"Approximation" Strategy**
➢ Develop personalised insulin delivery systems		
- Development of patient-specific approximate models	✓	×
- Specify individually the parameters: BW,TDD,u_{max}, QR,R,R_1	✓	✓
- Scheduling level tailored to patient's diet	✓	✓
- Solution of patient-specific optimisation problem	✓	×
- Patient-specific prediction horizon	✓	✓
- Flexibility to determine the reference meal plan according to patient's diet	✓	✓
➢ Take into account the involved time delays		
- Describe the inherent time delays in the linear approximate models	✓	×
- Include the time lag in the prediction horizon	✓	✓
- Enhance the feed forward action of the controller	✓	✓
➢ Compensate for the unknown meal disturbances		
- Consider an augmented state space system to describe the unknown disturbance as extra state using a Kalman filter	✓	✓
➢ Address the issue of uncertainty		
- Metabolic uncertainty as unmeasured disturbance	✓	✓
- Evaluation of performance robustness in several conditions	✓	✓

6.11 Concluding Remarks

Two general strategies of glucose regulation are presented. The Systematic Strategy involves the steps towards a patient-specific closed loop insulin delivery that takes advantage of the a priori knowledge of the system dynamics. The "Approximation" Strategy compensates for the effect of poor knowledge of the patient's dynamics with the inclusion of an additional controller.

The complications of the system such as the occurrence of disturbances that have a major effect on the system's dynamics, the large time delays and the patient variability make the use of a simple controller for the solution of the closed loop inappropriate as this can lead to poor control performance. Therefore, the proposed frameworks involve an MPC, a state estimator, an optimizer/MPC_{ref} and a scheduling feature.

In the case that the disturbances are known in advance, the results indicate that good control can be achieved. In particular, glucose can be maintained within or close to the normal range despite intra- patient variability, differences in meal sizes and/or timing and skipped meals. The proposed methodology of *Optimisation and Correction MPC* (Control Design 3) considers that a reference meal is given and thus it is assumed that the patient always consumes a breakfast, a lunch and a dinner. In the case of skipping one of these meals it was shown that efficient glycaemic control cannot be achieved, especially by the "Approximation" Strategy. On the contrary, when the meal is announced at the time it is given then the controller responds adequately in the case of a skipped meal. The proposed methodology can be formulated according to the patient's needs and the issue of skipping a meal can be addressed either by manually providing this information or by compensating for the after effect.

7. Concluding Remarks & Future Directions

7.1 Project summary

The proposed mathematical model of glucose-insulin interactions in T1DM is a physiologically based compartmental model that describes glucose metabolism in actual anatomical compartments, inspired by the work of (Sorensen, 1978). Glucose is distributed in six organs (heart, brain, liver, kidney, gut, and periphery) via blood circulation and it is absorbed by the tissue cells to provide them with energy. Insulin, through the subcutaneous route, is distributed via the blood circulation to enhance glucose uptake by the periphery (adipose tissue and muscle cells) and to signal the liver to suppress the endogenous glucose production and therefore, maintain the blood glucose concentration within the normal range. The pharmacokinetic parameters and variables of glucose metabolism (distribution volumes, blood flows, and cardiac output) are expressed as functions of age, weight, gender and height to account for the individual patient characteristics. The rate of glucose appearance in the blood after meal consumption, the endogenous glucose production and the glucose excretion from the kidneys are described with models obtained by the literature that have been clinically validated and are embedded in the proposed model structure. Regarding the insulin kinetics, four potential models are presented, and a series of evaluation tests have indicated the most suitable model to describe experimental data obtained by the literature (Boden, Cheung and Homko, 2003). Additionally, the model used for endogenous glucose production was evaluated with clinical data, obtained again by the literature (Boden, Cheung and Homko, 2003). A global sensitivity analysis was performed to determine which model parameters have a significant influence on the measured output. The GSA specified that the most influential parameters are those related to insulin effect on glucose. Particularly the parameters k_1 and k_2, linked to insulin sensitivity, have the most significant effect on blood glucose concentration.

The model of UVa/Padova simulator (Dalla Man, Rizza and Cobelli, 2006) was implemented and simulated in gPROMS. The commercial version of the T1DMS was used to obtain the patient-specific glucose-insulin profiles. These profiles, for 10 examined adult patients, were treated as experimental data to estimate the parameters of the proposed model and obtain individualised dynamic glucose and insulin profiles. The estimated parameters were the most influential ones as identified using GSA. The parameters of the R_a and EGP sub models were

also estimated. The remaining, non-influential parameters were kept at their mean values. The simulated results indicated that the proposed model can accurately predict individualised glucose profiles and that the model parameters are well adjusted for all patients.

Therefore, this model is used as a virtual patient for closed loop studies, and after simplification, as a predictive tool in the context of model based control, according to the framework presented in Figure 7.1:

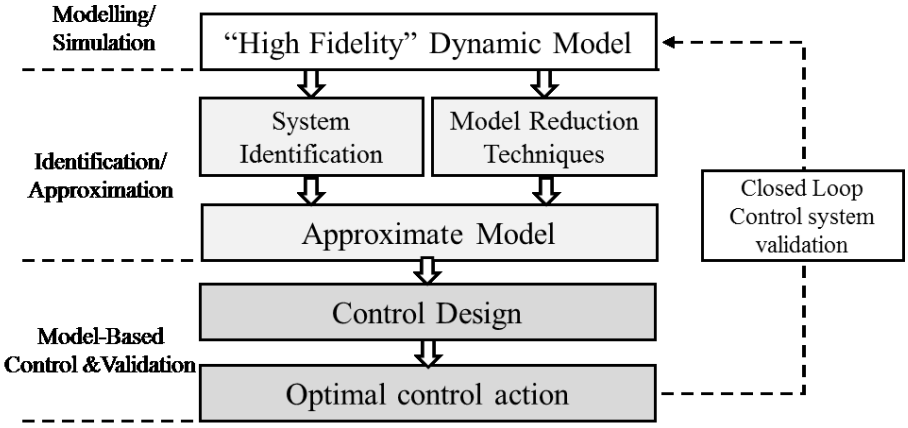


Figure 7.1: Framework of closed loop validation studies in the context of model predictive control

The meal disturbances in the system have a significant effect on glucose dynamics and trigger the system away from the steady state. Depending on the nature of the meal disturbances different control designs are developed. In the presence of known disturbances the problem becomes an open loop optimisation problem over the entire examined time horizon. When the disturbance is announced at the time it occurs then the control design involves an MPC controller and a scheduling level which specifies several time periods according to the daily meal plan of the patient during which the upper insulin bound is different; a different optimisation problem is solved in each time period. Finally, in the case of unknown disturbances it became obvious that a nominal state feedback MPC controller is inadequate to efficiently regulate the blood glucose concentration, and hence a different control design is proposed. The feed forward ability of MPC that acts in anticipation of the future fluctuations due to disturbances is enhanced when considering a reference meal plan of specific size and time that is always given to the patient. This is inspired by the function of the healthy pancreas that provides the system with already stored insulin when receiving a signal of increased blood glucose and then it produces new insulin to compensate for the rest of the increased glucose. Therefore, in the case of the artificial pancreas, the system is ready to provide the optimal insulin infusion to compensate for a small reference meal, in order to overcome the effect of long time delays and to prevent the prandial hyperglycaemia induced

by a large meal. An open loop optimisation problem is solved for the considered meal plan and the solution is incorporated into the control action. Then an MPC controller acts on the difference of glucose concentration, resulting from the unknown meal disturbance, and the expected glucose, resulting from the reference meal plan when the optimal insulin infusion is given. The performance of this control design presents a significant improvement over the nominal state feedback MPC for unknown disturbances. Cases of imposed variability in the meal time, variability in the parameters related to insulin sensitivity and skipped meals are tested to evaluate the reliability of the proposed control design.

In the case of limited patient information of the glucose-insulin dynamics a mean approximate model with adjusted parameters related to obvious patient characteristics is considered. The performance of this control strategy is evaluated for all the aforementioned disturbance types and cases. Necessary modifications in the general control design are considered. It was evident that even though the patient-specific control design outperforms the approximate control design, the approximate strategy shows a general applicability towards the development of closed loop artificial pancreas.

7.2 Key contributions of this thesis

The key contributions of this work are summarised:

Modelling & Model Analysis (Chapters 3 and 4)

- Development of a novel physiologically based compartmental model of glucose-insulin interactions in T1DM that combines actual anatomical compartments and functions that have already been validated in the literature.
- Description of fundamental pharmacokinetic properties with individual patient characteristics.
- Original insights of the insulin kinetics model, in terms of model identifiability, parameter estimation and correlation. The model structure was developed by comparison of alternative models with experimental data and a series of model analysis tests.
- Determination of the model parameters with the most influential effect on the measured output through global sensitivity analysis. The results confirmed that the influence of pharmacodynamic parameters is more significant than the influence of pharmacokinetic parameters.

- Estimation of the patient parameters for 10 adult patients using data obtained from the UVa/Padova T1DMS treated as clinical data. Ten individual glucose-insulin dynamic systems that describe precisely the glucose-insulin interactions are developed.
- Investigation of time delays on the system was investigated with open loop optimisation studies. Solution of an MINLP problem to find the optimal timing to administer a bolus insulin dose. A continuous insulin infusion as an alternative to the conventional basal- bolus insulin treatment was considered and the optimisation results showed that it can be applied in closed loop studies.

Closed loop control for optimal insulin delivery (Chapters 5-6, Appendix A, C)

- Development of two general control strategies: a systematic strategy that aims towards a personalised insulin delivery system and an "approximation" strategy that compensates for lack of patient information.
- Inclusion of features such as a scheduling level which is modifiable for each patient, the personalised reference optimisation problem, the patient specific MPC controller, to develop individual closed loop insulin delivery systems.
- Consideration of the known disturbance rejection problem as a personalised open loop optimisation problem.
- Assessment of unknown disturbances as disturbance rejection with zero offset towards a robust MPC design.
- Investigation of the effect of uncertain factors such as variability in the meal time and size, skipped meal and variability in insulin sensitivity on the system in the closed loop formulation. The control design presents feasible performance under the imposed uncertainty which encourages its further consideration.
- Evaluation of the performance of the control strategies by triggering the system with large meal sizes.
- Preliminary results using explicit Model Predictive Control for closed loop insulin delivery.

7.3 Publications from this thesis

Journal Articles

Stamatina Zavitsanou, Nicki Panoskaltsis, Athanasios Mantalaris, Michael C. Georgiadis, Alexandra Bargiota, Georgios Koukoulis, Efstratios N. Pistikopoulos, A modelling framework for the control of type 1 diabetes, submitted to Journal of Process Control.

Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, Efstratios N. Pistikopoulos, In-silico Closed Loop Control Validation Studies for Optimal Insulin Delivery in T1DM, submitted to IEEE Transactions on Biomedical Engineering.

Book Chapters

Eirini G. Velliou, **Stamatina Zavitsanou**, Eleni Pefani, Alexandra Krieger, Michael C. Georgiadis, Efstratios N. Pistikopoulos, A framework for modelling, optimization and control of biomedical systems, Chapter 1 in Modelling, Control and Optimization of Biomedical Systems (in preparation).

Stamatina Zavitsanou, A. Mantalaris, Michael C. Georgiadis, Efstratios N. Pistikopoulos, Type I Diabetes Mellitus: Modelling, Model Analysis, Optimisation and Glucose Regulation, Chapter 5 in Modelling, Control and Optimization of Biomedical Systems (in preparation).

Conference Proceedings

Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, Efstratios N. Pistikopoulos, 2014, Optimisation of insulin dosing in patients with type 1 diabetes mellitus, Computer Aided Process Engineering, Vol.33, Elsevier, pp 1459-1464,

Stamatina Zavitsanou, Nicki Panoskaltsi, Athanasios Mantalaris, Michael C. Georgiadis, Efstratios N.Pistikopoulos, 2011, Modelling of the Insulin Delivery System for patients with Type 1 Diabetes Mellitus, Computer Aided Process Engineering, Vol. 29, Elsevier, pp.1499-1503

Oral Presentations

Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, Efstratios N. Pistikopoulos , Modelling and Robust Model Predictive Control of Insulin Delivery in Type 1 DM, 2012 AIChE Annual Meeting, Pittsburgh, PA, US. 28 October - 2 November 2012.

Poster Presentations

Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, Efstratios N. Pistikopoulos, 2014, Optimisation of insulin dosing in patients with type 1 diabetes mellitus, 24st European Symposium on Computer Aided Process Engineering (ESCAPE 24), Budapest, Hungary, 15-18 June 2014.

Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, Nicki Panoskaltsis, Efstratios N.Pistikopoulos, Optimisation of insulin dosing in patients with Type I diabetes mellitus, ATTD, Vienna, 5-8 February, 2014

Stamatina Zavitsanou, Athanasios Mantalaris, Michael C. Georgiadis, Efstratios N. Pistikopoulos, Capturing the Dynamic Uncertainty in the Glucoregulatory System of Type 1 Diabetic Patients Using Simulated Data Sets, ATTD, Barcelona, 8-11 February, 2012

Stamatina Zavitsanou, Nicki Panoskaltsis, Athanasios Mantalaris, Michael C. Georgiadis, Efstratios N.Pistikopoulos, 2011, Modelling of the Insulin Delivery System for patients with Type 1 Diabetes Mellitus, 21st European Symposium on Computer Aided Process Engineering (ESCAPE 21), Chalkidiki, Greece, 29 May - 01 June 2011.

7.3 On-going and Future Directions

Model Validation

The proposed model describes accurately individual glucose-insulin profiles. However, validation with clinical data is required to increase the level of confidence for further consideration. The validation of the model with simulated data as experimental data indicates the applicability of the model to represent patient-specific dynamics. Further all model parameters can be estimated precisely using data that are collectable during clinical practice. Nonetheless the ideal simulation environment deviates significantly from the real system which is dominated by high intra- and inter-patient variability. Therefore, the performance of the model needs to be evaluated with real patient data.

Model Extension

There are many conditions of everyday life that influence the hormone levels leading to disruption of the homeostasis and consequently to variations in glucose metabolism. Conditions such as stress, illness, exercise have a significant effect on glucose distribution

and absorption from the involved organs. In the case of T1DM, the complications increase because glucose regulation with exogenous insulin under these conditions can be very challenging. In order to achieve tight glycaemic control with exogenous insulin, the patient needs to fully understand the underlying phenomena of alterations in insulin sensitivity during exercise, the different metabolic effect during mild and vigorous exercise, the role of epinephrine that triggers the release of stored glucose in the blood stream under stressful conditions or illness. The determination of indicators for such conditions has been proposed in the literature in order to enhance the prediction of blood glucose concentration under free living conditions. A multivariable model including the galvanic skin response and the energy expenditure as additional inputs was proposed by Turksoy et al. (Turksoy *et al.*, 2013) for the closed loop system. Towards this direction an extended version of the proposed model including the representation of glucose dynamics during exercise could decrease the uncertainty of glucose predictability. Stress and illness, which do not constitute a deterministic condition, can be regarded as model uncertainty that should be addressed in the closed-loop system.

Robust closed loop insulin delivery

One of the key challenging issues of closed loop insulin delivery is the high intra- and inter-patient variability. Even though there has been an effort towards patient-specific glucose dynamics predictions with the introduction of patient-specific variables and parameters, as well as personalised glucose regulation with the determination of time horizons, TDD, scheduling feature and weights of the cost function tailored for each patient, the glycaemic variability remains an unpredictable quantity. The factors that influence the ability to predict the blood glucose concentration are summarised in Kildegaard et al. (2009) and involve the metabolic variability, meal variability, insulin and glucose monitoring variability and lifestyle variability. All these factors can significantly affect the blood glucose predictability and make the system very challenging to control. In the context of MPC there is a need towards robust control designs for insulin delivery systems. Robust control concerns the systems that are uncertain in the sense that the actual behaviour of the system cannot be described with predictions based on the nominal system (Rawlings and Mayne, 2009). Therefore, in the presence of uncertain predictions, robust control ensures that the control actions do not violate the constraints and that the optimisation solution always exists (Richards, 2005). The uncertainty of the system can be due to unknown additive disturbances, model mismatch and

simplifications (Rawlings and Mayne, 2009). The system can be expressed as the LTI system with unmeasured disturbance (Bemporad and Morari, 1999):

$$x_{t+1} = Ax_t + Bu_t + Hw_t, \quad x(0) = x_0 \tag{7.1}$$

$$y_t = Cx_t + Kw_t$$

With $w(t) \in W$ and W is a bounded set.

Another way to include the uncertainty in the system is with parametric uncertainty:

$$x_{t+1} = A(\theta)x_t + B(\theta)u_t \tag{7.2}$$

$$\Theta = \{\theta_{lb} \leq \theta_k \leq \theta_{ub}; \forall\theta \in \mathbb{R}^q\}$$

$[A(\theta), B(\theta)] \in \Omega$, where Ω is a pre-specified polytope.

These types of uncertainties (7.1-7.2) can occur in the same application. The problem traditionally is approached by minimising the worst-case scenario (maximum w) based on open loop predictions but this can lead to over-conservative control performance (Sakizlis, M.P. Kakalis, *et al.*, 2004), (Bemporad and Morari, 1999). Many different proposals of feedback Robust MPC have been proposed and can be found in the literature (Rawlings and Mayne, 2009), (Langson *et al.*, 2004), (Maciejowski, 2002).

On-line parameter estimation

A complementary approach to decrease the system uncertainty is to estimate on-line the model parameters which contribute significantly to the system dynamics. This method aims to address the uncertainty originated from the metabolic variability such as alterations in insulin sensitivity. A Bayesian approach was used by (Hovorka *et al.*, 2004) to update the values of certain parameters. An on-line parameter estimation formulated as a least-squares problem is evaluated in (Krieger and Pistikopoulos, 2014) for the case of anaesthesia. The relevance of the underlying physiology to the model parameters that need to be updated provides useful directions for the problem simplification.

Model reduction techniques

In the considered insulin-delivery system the internal model used for the control design is a large linear model. Combined with the involved large time horizons the development of the optimal control design (offline; development of mpMPC) can be indeed very challenging due

to the increased computational complexity. Model reduction techniques can be used as an alternative to overcome the limitations of large or inaccurate models by deriving simple but precise models to describe the dynamics of non-linear, complex systems. In this case, the development of explicit multi-parametric MPC could be feasible.

Explicit Model Predictive Control / Robust mp-MPC

In order to overcome the significant online computations involved in the closed-loop optimal control implementation an alternative solution of the on-line optimisation problem has been proposed (Pistikopoulos *et al.*, 2002), (Pistikopoulos, Georgiadis and Dua, 2007a), (Pistikopoulos, Georgiadis and Dua, 2007b), which relies on a parametric optimisation-based approach. In essence, the online solution of the optimisation problem is replaced by the off line derivation of the explicit mapping of the optimal decisions in the space of the plant uncertainty. The ability to solve off-line the MPC optimisation problem makes the mp-MPC technology ideal for implementation on a simple hardware like a chip, "MPC-on-a-chip", for portable or embedded devices (Pistikopoulos, 2012). For the closed loop insulin delivery system, although there has been tremendous progress in the involved device technology (insulin pump, smartphones, CGMS) and their interconnectivity a controller solved offline through simple function evaluation and implemented on a chip can enhance the reliability of the entire system. In Dassau *et al.* (2013) the performance of mp-MPC has been clinically evaluated for the closed loop delivery of insulin resulting in very encouraging outcomes using this technology. Appendix C focuses with the development of mpMPC controllers in the context of the proposed control designs presented in section 6.4.3. Further in-silico validation studies are required to gain confidence in the mpMPC control formulation. The derivation of robust mp-MPC has gained vast consideration in the literature. The combination of the two involved theories has been examined in (Bemporad, Borrelli and Morari, 2003), (Manthanwar, Sakizlis and Pistikopoulos, 2005), (Sakizlis, M.P. Kakalis, *et al.*, 2004), (Kouramas, Sakizlis and Pistikopoulos, 2009), and can be a promising potential for the challenging system of insulin delivery.

Further Developments towards the Artificial Pancreas

Towards the development of an artificial pancreas the validation of the proposed closed loop strategy in a real experimental set-up is required. This implies firstly the validation of the proposed model and secondly the derived control strategy. The use of the UVa/Padova Simulator for the derivation of the approximate model as well as the virtual patient has

presented efficient glucose regulation in the closed loop system (Appendix A.2). Additionally, the testing of the derived control strategy on the UVa/Padova Simulator as the virtual patient in many cases has shown good control performance. Further in-silico validation can increase the level of confidence for the proposed closed loop design. The substitution of online MPC in the presented control designs with mpMPC will improve the reliability of the automated closed loop insulin delivery system. Towards this direction Appendix C explains the formulation of the system but further simulation studies are required to define efficiently the system's specifications to achieve tight glycaemic control. Additionally, incorporation of complementary components such as Insulin-on-Board and hypoglycaemia alarms could improve the closed loop control performance especially in the case of skipped meals.

APPENDIX A

A.1 Model of UVa/Padova Simulator

Glucose Metabolism: A two compartment model is used to model the glucose subsystem with G_p and G_t representing the plasma and tissue glucose mass (mg/kg) respectively.

$$\frac{dG_p}{dt} = EGP + R_a - U_{ii} - E - k_1 G_p + k_2 G_t \qquad G_p(0)=G_{pb} \qquad (A.1)$$

$$\frac{dG_t}{dt} = k_1 G_p - k_2 G_t - U_{id} \qquad G_t(0)=G_{tb} \qquad (A.2)$$

$$G = \frac{G_p}{V_g} \qquad G(0)=G_b \qquad (A.3)$$

The EGP (mg/kg/min) is the endogenous glucose production, the Ra (mg/kg/min)the rate of glucose appearance in the bloodstream after meal consumption, U_{ii} and U_{id} (mg/kg/min) are the insulin independent and insulin dependent glucose utilisation, E(mg/kg/min) is the renal glucose excretion, k_1,k_2 (min^{-1}) are rate parameters of glucose kinetics and Vg(dl) is the glucose distribution volume.

Rate of glucose appearance (Ra) from meal

$$\frac{dQ_{sto1}}{dt} = -k_{kgri} Q_{sto1} + D\delta(t) \qquad Q_{sto1}(0)=0 \qquad (A.4)$$

$$\frac{dQ_{sto2}}{dt} = -k_{empt} Q_{sto2} + k_{gri} Q_{sto1} \qquad Q_{sto2}(0)=0 \qquad (A.6)$$

$$\frac{dQ_{gut}}{dt} = -k_{abs} Q_{gut} + k_{empt} Q_{sto2} \qquad Q_{gut}(0)=0 \qquad (A.7)$$

$$Q_{sto} = Q_{sto1} + Q_{sto2} \qquad Q_{sto}(0)=0 \qquad (A.8)$$

$$R_a = \frac{f k_{abs} Q_{gut}\,(t)}{BW} \qquad Ra(0)=0 \qquad (A.9)$$

$$k_{empt} = k_{min} + \frac{k_{max}-k_{min}}{2}\left\{\tanh\left(a_1\left(Q_{sto} - b \cdot D(t)\right)\right) - \tanh\left(b_1\left(Q_{sto} - d \cdot D(t)\right)\right) + 2\right\} \qquad (A.10)$$

$$a_1 = \frac{5}{2 \cdot D \cdot (1-b)} \qquad (A.11)$$

$$b_1 = \frac{5}{2 \cdot D \cdot d} \qquad (A.12)$$

With Q_{sto1}, Q_{sto2} (mg) the glucose mass in solid and liquid phase, Q_{sto} (mg) the overall glucose mass in the stomach, Q_{gut} (mg) is the glucose mass in the small intestine, k_{empt} (min^{-1}) is the

rate of gastric emptying, a_1 and b_1 are model parameters, k_{max}, k_{min} (min^{-1})are the max and min gastric emptying, kabs (min^{-1}) is the rate constant of intestinal absorption, k_{gri} is the rate constant of grinding, f (dimensionless) is the fraction of intestinal absorption, b and d are percentages of the dose and D (mg) is the amount of ingested meal.

Endogenous Glucose Production (EGP)

$$EGP = k_{p1} - k_{p2}G_p - k_{p3}I_{del2} \qquad EGP(0)=EGP_b \qquad (A.13)$$

$$\frac{dI_{del1}}{dt} = -k_i(I_{del1} - I_p) \qquad I_1(0)=I_{pb} \qquad (A.14)$$

$$\frac{dI_{del2}}{dt} = -k_i(I_{del2} - I_{del1}) \qquad I_d(0)=I_{pb} \qquad (A.15)$$

With I_{del2} (pmol/l) the delayed insulin signal (chain of two compartments), k_{p1} (mg/kg/min) the extrapolated EGP at zero glucose and insulin, k_{p2} (min-1) the liver glucose effectiveness, k_{p3} (mg/kg/min per pmol/l) the insulin action on the liver and k_i (min^{-1}) the rate parameter for the delay between insulin signal and action

Insulin dependent glucose utilization

$$U_{id} = \frac{V_m G_t}{k_{m0}+G_t} \qquad U_{id}(0)=U_{idb} \qquad (A.16)$$

$$V_m = V_{m0} + V_{mx}X_{disp} \qquad V_m(0)=V_{m0} \qquad (A.17)$$

$$\frac{dX_{disp}}{dt} = -p_{2u}X_{disp} + p_{2u}(I_p - I_{BASAL}) \qquad X_{disp}(0)=0 \qquad (A.18)$$

$$U_{tot} = U_{ii} + U_{id} \qquad (A.19)$$

With X_{disp} (pmol/L) insulin in the interstitial fluid, V_{m0} (mg/kg/min) and k_{m0} (mg/kg) the Michaelis–Menten related parameters, V_{mx} (mg/kg/min per pmol/liter) the disposal of insulin sensitivity and p_{2u} (min^{-1}) the rate constant of insulin action on peripheral glucose utilization.

Glucose Renal Excretion

$$E = \begin{cases} k_{e1}(G_p - k_{e2}) & if\ G_p > k_{e2} \\ 0 & if\ G_p \le k_{e2} \end{cases} \qquad E(0)=0 \qquad (A.20)$$

With k_{e1} (min^{-1}) the glomelural filtration rate and k_{e2}(mg/kg) the glucose renal threshold

Insulin Kinetics

$$\frac{dI_{sc1}}{dt} = -(k_d + k_{a1}) \cdot I_{sc1} + u(t) \qquad I_{sc1}(0)=I_{sc1ss} \qquad (A.21)$$

$$\frac{dI_{sc2}}{dt} = k_d I_{sc1} - k_{a2} I_{sc2} \qquad I_{sc2}(0)=I_{sc2ss} \qquad (A.22)$$

$$\frac{dI_l}{dt} = -(m_1 + m_3) I_l + m_2 I_p \qquad I_l(0)=I_{lb} \qquad (A.23)$$

$$\frac{dI_p}{dt} = -(m_2 + m_4) I_p + m_1 I_l + k_{a1} I_{sc1} + k_{a2} I_{sc2} \qquad I_p(0)=I_{pb} \qquad (A.24)$$

$$I = \frac{I_p}{V_i} \qquad I(0)=I_b \qquad (A.25)$$

$$m_3 = \frac{HE_b m_1}{1-HE_b} \qquad (A.26)$$

With I_l (pmol/kg)the insulin mass in liver, I_p (pmol/kg) insulin mass in the plasma, I (pmol/l) the plasma insulin concentration, I_{sc1}(pmol/kg) the amount of non-monomeric insulin in the subcutaneous space, I_{sc2} (pmol/kg) the amount of monomeric insulin in the subcutaneous space, u(t) (pmol/kg/min) the exogenous insulin infusion rate, m_1,m_2,m_3,m_4 (min^{-1}) the rate parameters of insulin kinetics, V_I (L/kg) the insulin distribution volume, k_d (min^{-1}) the rate constant of insulin dissociation, k_{a1} (min^{-1}) the rate constant of non- monomeric insulin absorption and k_{a2} (min^{-1}) the rate constant of monomeric insulin absorption.

A.2 Model Predictive Control Framework

The general framework used for the control design to regulate the BG concentration is presented in Figure A.2.1, as also showed in Chapter 7. It involves the development of a high fidelity model that accurately predicts the glucose-insulin dynamics in T1DM, the simplification of the original model with system identification or model order reduction techniques to derive a reliable approximation of the system dynamics and finally the design of the appropriate control strategy. In the MPC formulation one of the key components is the approximate model that needs to be relatively simple to facilitate the computational complexity, but also very informative to include the entire system dynamics. In this section, the involved steps of closed loop insulin delivery are presented while emphasis is given on the importance of developing a reliable, patient-specific approximate model for MPC.

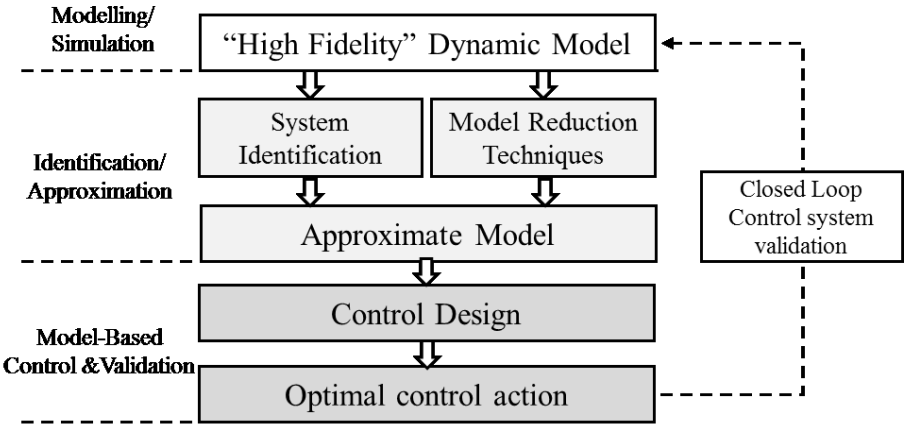


Figure A.2.1: Framework for MPC controllers design

1. "High Fidelity" Model

The mathematical model used in this study as a virtual patient for closed loop control validation studies as well as to derive approximate models necessary for model based control is the model developed by the Cobelli group (Dalla Man, Rizza and Cobelli, 2007), (Dalla Man *et al.*, 2007), and presented in section A.1. The model is simulated in gPROMS using individual patient parameters obtained from the commercial UVa/Padova Simulator for 10 adults.

2. The Approximate Model

Two methods are employed to derive an accurate linear approximate model suitable for control purposes. The first presented method is system identification and the second model linearisation and reduction.

System Identification

The linear model describing the dynamics of the glucose-insulin interactions was determined using the System Identification Toolbox of MATLAB. Due to the complexity caused by the inherent nonlinearities of the system the linear model was built by identifying two separate transfer functions describing the insulin-glucose and food-glucose interactions. The two models are then combined by taking into account the involved time delays for each component and then it is converted in a state space formulation.

$$G(s) = k_p \frac{(1+T_z)s}{(1+T_{p1}s)(1+T_{p2}s)(1+T_{p3}s)} \exp(-T_{delayU}s) \times Insulin(s)$$
$$G(s) = k_p \frac{(1+T_z)s}{(1+T_{p1}s)(1+T_{p2}s)(1+T_{p3}s)} \exp(-T_{delayF}s) \times Food(s) \quad \text{(A.27)}$$

The time delays are replaced with a second order Padé approximation:

$$\exp(-\theta s) \approx \frac{1 - k_1 s - k_2 s^2}{1 + k_1 s + k_2 s^2} \tag{A.28}$$

The applied methodology is presented for patient no2. Input/ Output data obtained from simulating the original model are used to identify the process model. The identified values of the model parameters of (A.27) are shown in Table A.2.1

Table A.2.1: Identified parameters of transfer function models

Effect of Insulin		**Effect of Meal**	
Symbol	Value	Symbol	Value
k_p	4.271e-07	k_p	1.933
T_z	-13.931	T_z	1.917e+05
T_{p1}	51.953	T_{p1}	1.214e+07
T_{p2}	5.912 e+02	T_{p2}	1.295e+02
T_{p3}	1.184e+10	T_{p3}	1.297e+02
T_{delay}	50	T_{delay}	16.8

The accuracy of the identified transfer functions is shown in Figure A.2.2 for the effect of a meal containing 90 g of carbohydrates on BG concentration and in Figure A.2.3 for the effect of 10U of insulin. The approximation error is 11.79% and 6.8% respectively.

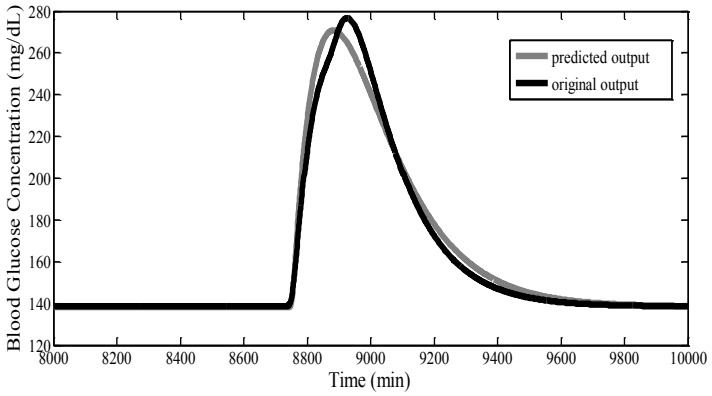


Figure A.2.2: Comparison of original model and TF for meal effect on glucose when 90 g of carbohydrates are consumed

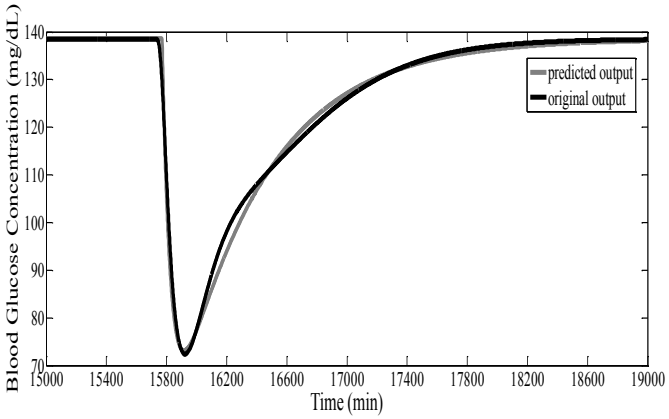


Figure A.2.3: Comparison of original model and TF for insulin effect on glucose when a bolus of 10U is given

The involved time delays are included in the converted state space model as additional states. The resulting continuous state space model is discretised with sampling time $t_s = 5$ min that represents the time to receive a BG reading with a continuous blood glucose monitoring system.

The glucose profile when 45 g of carbohydrates and 6U of insulin are given is shown in Figure A.2.4 for the original model and the identified state space model.

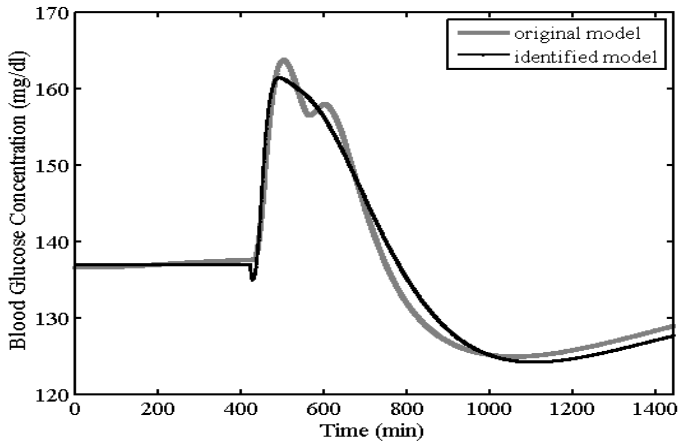


Figure A.2.4: Comparison of original model and state space model

The fit of the model to the original data is calculated with (5.8) and is: Fit=84.5%

The identified model as seen in Figure A.2.4 represents accurately the system dynamics in the presence of meal disturbances. Hence, it can be regarded as a reliable prediction tool for closed loop studies.

The advantage of this model is that it distinguishes the time delay factors coming from insulin and from food; hence it can be used straightforwardly in time delay control approaches. The disadvantage is that the resulting state space model is large (10 states) and that the states are

artificial in terms of not describing the physiological states and therefore the information inside the system is limited.

Linearisation

The model of UVa/Padova Simulator is linearised. The linear model involves 12 states:

$x = [G_p \quad G_t \quad X_{disp} \quad Q_{sto1} \quad Q_{sto2} \quad Q_{gut} \quad I_{del1} \quad I_{del2} \quad I_{sc1} \quad I_{sc2} \quad I_l \quad I_p]'$

When the model is linearised at the steady state, an approximation of constant physiological conditions, the glucose concentration does not coincide with the profile of the original model in the presence of meal disturbances and insulin boluses, resulting in large off-set. To overcome the difficulty to find stable equilibrium points during meal consumption and insulin absorption, that trigger the system away from the steady state, and to capture the dynamics of the system during fasting, prandial and postprandial conditions of different meal size and insulin boluses, a series of parameter estimation studies are performed to estimate the values of specific parameters of the linear model related to meal and insulin absorption that are described with nonlinear equations. The parameter estimation studies are performed in gPROMS and involve the design of patient specific in silico experiments of different meal plans and insulin regimens that take into consideration:

1) Effect of one meal on BG concentration- no bolus is considered (Experiment A)
2) Effect of one bolus on BG concentration –no meal is considered (Experiment B)
3) Effect of one meal and bolus given simultaneously (Experiment C)
4) Steady state –no bolus and meal are considered (Experiment D)
5) Day simulation with different meal sizes and bolus doses (Experiment E)

The values of the estimated parameters are presented in Table A.2 for the 10 adults.

Physiologically based Model Reduction

In order to reduce the computational complexity in a control application caused by the relatively large size of the previously presented 12 states linear physiological model, physiologically based model order reduction is used to mathematically transform the model equations such that to provide the same dynamical behaviour but in a smaller size system. The involved time delays of the system both in glucose absorption from food and in insulin absorption through the subcutaneous tissue does not allow the lumping of many compartments and further simplification of the model. The equations to be reduced are the states $[\mathrm{I_{sc1}}\ \mathrm{I_{sc2}}\ \mathrm{I_l}\ \mathrm{I_p}]'$. The compartments $\mathrm{I_{sc1}}$ and $\mathrm{I_p}$ are forced to be left unmodified since they are used in other equations in the model.

The linear equations are described with the general formulation:

$$\frac{\mathrm{dy}}{dt} = Ky \tag{A.29}$$

where y=$[I_{sc1}\ I_{sc2}\ I_l\ I_p]^T$ and K=$\begin{bmatrix} k_d + k_{a1} & 0 & 0 & 0 \\ k_d & -k_{a2} & 0 & 0 \\ 0 & 0 & -(m_1 + m_3) & m_2 \\ k_{a1} & k_{a2} & m_1 & -(m_2 + m_4) \end{bmatrix}$

The new system is described by (A.31) where $\widehat{\mathrm{K}}$ is the new set of parameters with rank n = 2. The new parameters are found by solving a maximum likelihood parameter estimation problem in gPROMS that determines the values of the new set of parameters that maximise the probability that the new mathematical equations will predict the dynamics of the original model that is used to specify suitable experiments obtained from the experiments.

$$\frac{d\hat{y}}{dt} = \hat{K}y \tag{A.30}$$

The set of the reduced equations is defined as:

$$\frac{d}{dt}\begin{bmatrix} I_{sc1} \\ I_p \end{bmatrix} = \begin{bmatrix} A(9,9) & A(9,10) \\ A(10,9) & A(10,10) \end{bmatrix}\begin{bmatrix} I_{sc1} \\ I_p \end{bmatrix}$$

The values of the parameters are presented in Table A.2 for the 10 patients.

Hence, the states of the reduced model are:

$$x_{red} = [G_p \quad G_t \quad X_{disp} \quad Q_{sto1} \quad Q_{sto2} \quad Q_{gut} \quad I_{del1} \quad I_{del2} \quad I_{sc1} \quad I_p]'$$

Further reduction of the model states lead to loss of the system dynamics. The model is discretised with t_s=5 min. Figure A.5 compares the dynamic model with the state space reduced order model and Figure A.6 shows the accuracy of the linearised model.

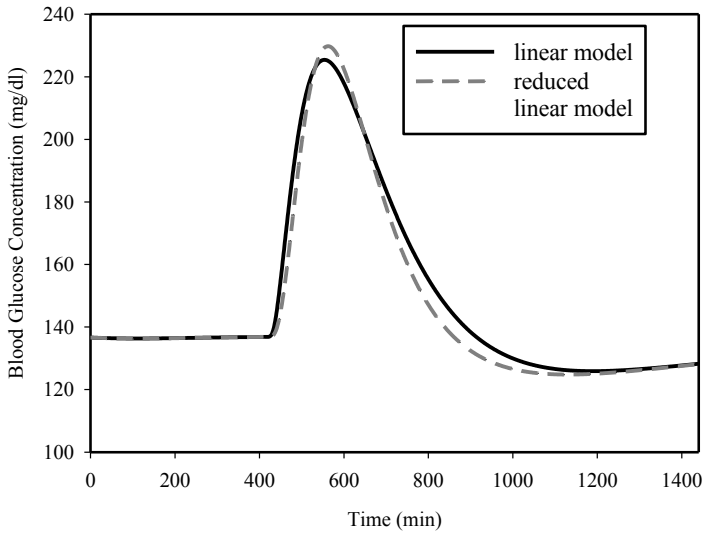


Figure A.2.5: Comparison of full state and reduced linearised model for patient no2.

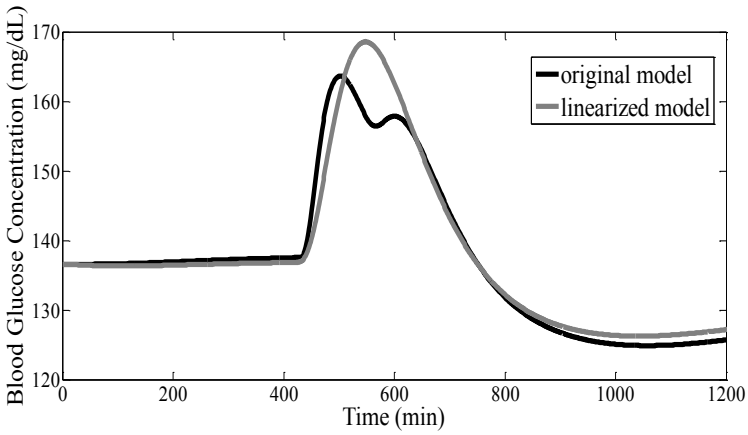


Figure A.2.6: Comparison of original model and linearised model when 50 g of carbohydrates are consumed and a 5 U bolus is given to patient no 2

The model accuracy is calculated using (5.8) for patient no 2 is 81%. Although the performance error for both models is similar, the linearised model is used for the rest of this study, since it enfolds information of the states of the original model, and the patient specific parameters can by identified with a systematic approach.

Table A.2.2: Estimated parameters of linearised model for10 adults

	Experim.	**Patient 1**	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
A(2,2)	C,D,E	-0.10475	-0.12086	-0.30005	-0.1493	-0.21861
A(2,3)	C,D,E	-0.01763	-0.01307	-0.01682	-0.065476	-0.00679
A(5,5)	A	-0.00516	-0.01893	-0.00897	-0.018062	-0.00361
A(6,4)	A	0.01314	0.00157	0.00314	0.0098701	0.01552
B_d(2,1)	C,D,E	1.627	0.17399	2.2616	3.9858	0.50847
			Reduced Model			
A(9,9)	B,E	-0.043407	-0.018901	-0.020299	-0.018992	-0.025647
A(9,10)	B,E	2.8998E-5	0.0	-1.073E-6	-6.346E-6	2.2079E-5
A(10,9)	B,E	0.003991	0.001407	0.0010587	0.0024120	0.004241
A(10,10)	B,E	-0.026149	-0.021764	-0.01929	-0.021041	-0.04864
		Patient 6	**Patient 7**	**Patient 8**	**Patient 9**	**Patient 10**
A(2,2)	C,D,E	-0.07788	-0.13319	-0.08963	-0.17237	-0.21344
A(2,3)	C,D,E	-0.024081	-0.049294	-0.01747	-0.00375	-0.01069
A(5,5)	A	-0.015856	-0.014347	-0.00743	-0.02216	-0.01217
A(6,4)	A	-0.000119	6.3868E-4	0.00442	-3.458E-7	-1.407E-5
B_d(2,1)	C,D,E	3.516	1.5165	1.4351	0.72648	2.1189
			Reduced Model			
A(9,9)	B,E	-0.012480	-0.020122	-0.025168	-0.018841	-0.017661
A(9,10)	B,E	-4.983E-8	-1.460E-8	-2.548E-8	-1.053E-7	-3.308E-8
A(10,9)	B,E	8.2755E-4	0.001284	0.0018019	0.001677	0.001356
A(10,10)	B,E	-0.018837	-0.013686	-0.014726	-0.030188	-0.022085

The advantage of the linearised model over the previously presented model is that the states represent the states of the original model and therefore the deep knowledge of the system's behaviour facilitates the design of control studies. Yet again, this model is large which makes the design of explicit MPC relatively difficult.

The matrices of the linear state space model are presented below. The matrix B_d accounts for the basal level of the states.

A=

$$\begin{bmatrix}
-(k_{p2}+k_1) & k_2 & 0 & 0 & 0 & k_{abs}f/BW & -k_{p3} & 0 & 0 & 0 & 0 & 0 \\
k_1 & -k_2 - f(V_m,k_{km0},G_t) & -f(V_{mx},k_{km0},G_t) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -p_{2u} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & p_{2u}/V_i \\
0 & 0 & 0 & -k_{gri} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & k_{gri} & -k_{empt} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & k_{est} & k_{empt} & -k_{abs} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -k_i & k_i & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_i & 0 & 0 & 0 & k_i/V_i \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_d+k_{a1} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_d & -k_{a2} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_1+m_3 & m_2 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_{a1} & k_{a2} & m_1 & m_2+m_4
\end{bmatrix}$$

$$B=\begin{bmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & \frac{1}{D} \\ 0 & 0 \\ 0 & 0 \\ \frac{6000}{BW} & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix},\ B_d=\begin{bmatrix} k_{p1} - U_{ii} \\ k_{est1} \\ -p_{2u} * I_{BASAL} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},\ C=\begin{bmatrix} \frac{1}{V_g} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},\ D=\begin{bmatrix} 0 & 0 \end{bmatrix}$$

3. Control Design

The proposed control design regulates the glucose concentration when a reference meal plan is considered and additionally responds appropriately to compensate for the deviation from the reference meal when a different size meal is consumed.

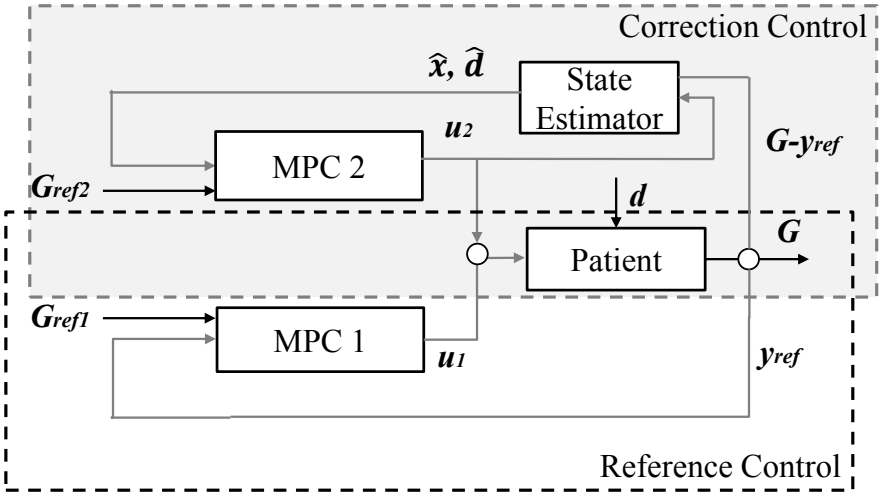


Figure A.2.7: Proposed control strategy to compensate for unknown meal disturbances consisting of two controllers, the reference control that regulates glucose for a reference meal plan and the correction control that regulates the difference of the glucose due to real and reference meal plan.

MPC 1: Reference Control

The desired glucose value G_{refl} is set by the endocrinologist for every patient. A predefined reference meal plan is considered to trigger the control action. Feedback about the current state is obtained by the model output y_{ref} as calculated when the reference tracking problem with announced disturbance is solved and the optimal insulin infusion is applied.

MPC 2: Correction Control

MPC 2 aims to find the optimal insulin infusion rate to regulate the difference of glucose as a real measurement coming from the patient, G and glucose as calculated when solving the

reference control problem, y_{ref}. This difference can be regarded as an unmeasured disturbance of the system, that leads to an offset in the set point, $G_{ref,2}$=0. So the correction control is described as a disturbance rejection problem. In order to remove the offset and the nonzero disturbances the original system is augmented with a disturbance model, as presented in Chapter 8. In order to reduce the computational effort the states describing the meal absorption $[\mathrm{Q_{sto1}} \quad \mathrm{Q_{sto2}} \quad \mathrm{Q_{gut}}]'$ are removed from the state space model. The output feedback of the patient is obtained as the difference of the actual measurement and the reference control output (G-y_{ref}) and the state feedback is obtained by a state estimator that provides information about the current state of the patient and the additional disturbance.

The matrix $B_d \in \mathbb{R}^{n \times n_d}$ is chosen to be the $\mathrm{B_d}$ matrix of Section A.3 and matrix$C_d = I \in \mathbb{R}^{n_d \times n_d}$. The new derived augmented linear model ($n = 7, n_d = 1$) is detectable, see (A.31), which means that the states will converge to the real states when a Kalman filter is used, hence this strategy can be employed:

$$rank\begin{bmatrix} I - A & -B_d \\ C & C_d \end{bmatrix} = n + n_d = 8 \tag{A.31}$$

The estimated states are:

$\hat{x} = [G_p \quad G_t \quad X_{disp} \quad I_{del1} \quad I_{del2} \quad I_{sc1} \quad I_p \quad d]'$

And $y_2 = G - y_{ref}$. The control specifications for MPC 2 are presented in Table A.2.3:

Table A.2.3: Specifications of MPC 2 and the Kalman Filter

Variable	Value		Variable	Value		Variable	Value
$y_{2,min}$	-10	mg/dl	u_{min}	0	U/min	$\hat{Q}$	100
$Y_{2,max}$	10	mg/dl	u_{max}	0.02	U/min	$\hat{R}$	5

4. Simulation Results

In this section the control designs are evaluated for predefined, announced and unknown disturbances for 10 adults with T1DM, provided by the Simulator. The model is developed in gPROMS, while the control designs in MATLAB and gO:MATLAB to exchange data between the two environments. The control designs are denoted as follows:

CD_1	Online MPC, with predefined disturbance
CD_2	Online MPC with scheduling level for announced disturbance
CD_3	Reference and Correction MPC for unmeasured disturbance
CD_4	Online MPC, with unmeasured disturbance

A. Predefined and Announced Disturbances

The results are illustrated in Figure A.2.8. Meal of 45 70 and 60 g of carbohydrates is consumed at 420, 720 and 1080 min.

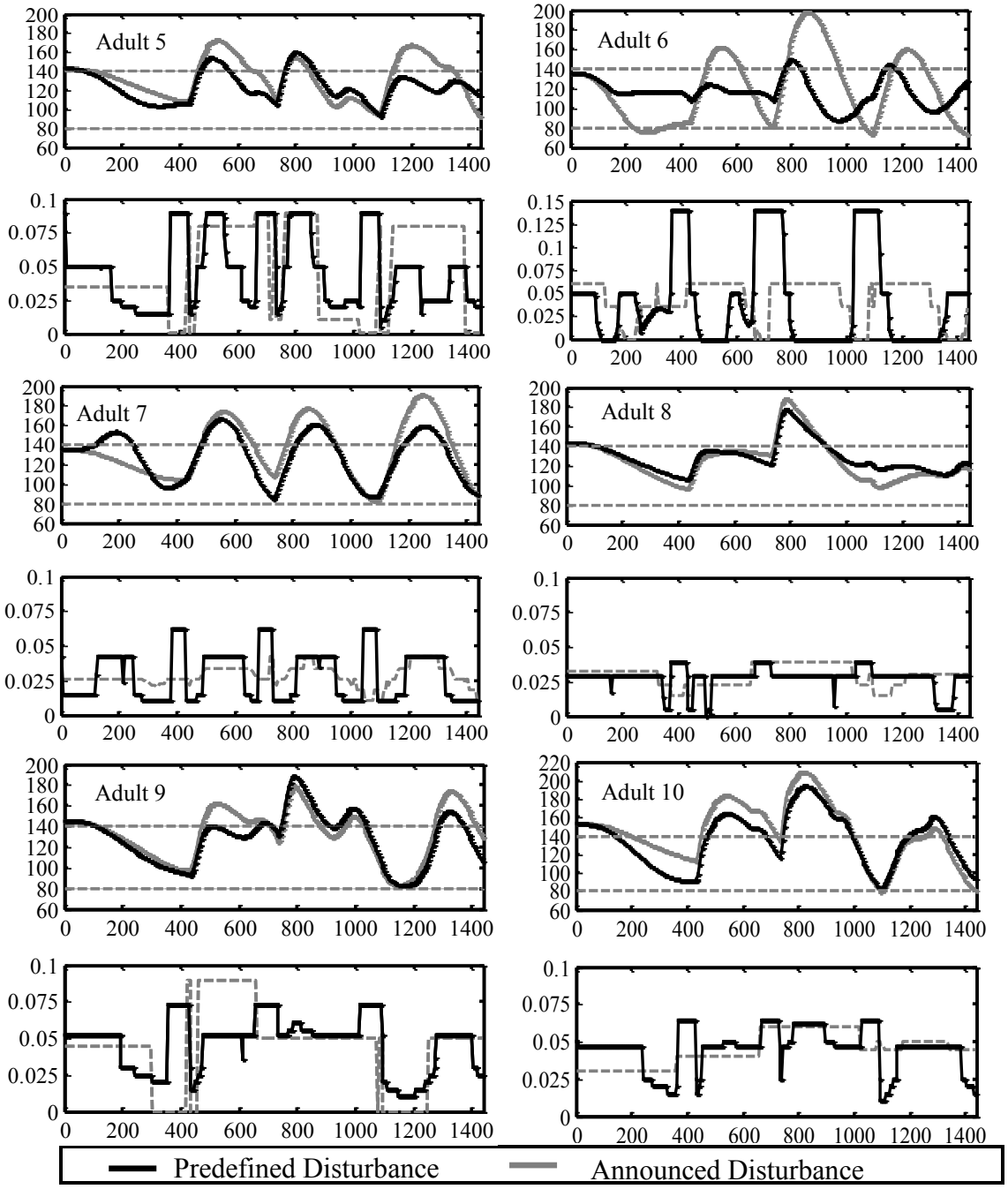


Figure A.2.8: MPC control for 10 adults of UVa/Padova Simulator for measured and announced meal disturbances; Upper graphs blood glucose concentration (mg/dl) profiles; lower graphs control action, insulin (U/min)

It can be noticed that tight glycaemic control can be achieved in the presence of predefined or announced disturbances.

B. Unknown Disturbance rejection

In this section the CD_3 control design as explained before is evaluated. The ability of the controller to maintain the blood glucose concentration in the normal range is tested for large meal sizes of 75, 100 and 90 g of carbohydrates given for breakfast at 7:00 am, lunch at 13:00 pm and dinner at 18:00pm respectively. The reference meal plan is 20, 30 and 25 g respectively. The results are compared to the CD_4 for the same meal sizes and presented in Table A.2.4 and Table A.2.5.

Table A.2.4: CD_3 (predefined meal plan)

	% time <70	% time <80	% time 80<G <140	% time 140<G <180	% time 180<G <250	% time >250	G_{min} (mg/dl)	G_{max} (mg/dl)
Adult1	0	1.7	44.4	38.9	14.9	0	72	247
Adult2	0	0	68.4	28.4	3.1	0	83	187
Adult3	0	5.9	36.4	49.3	8.3	0	76	233
Adult4	0	0	52.8	44.8	2.4	0	87	181
Adult5	0	1.7	59.7	18.4	20.1	0	76	228
Adult6	0	5.5	56.6	14.9	22.9	0	76	226
Adult7	0	0	67.0	20.1	12.8	0	82	205
Adult8	0	6.2	57.6	28.8	7.3	0	75	226
Adult9	0	2	57.6	27	12.5	0	71	250
Adult10	0	2.1	45.5	24.0	21.9	6.5	76	276
Mean	**0**	**2.5**	**54.6**	**29.46**	**12.62**	**0.65**	**77.4**	**225.9**
SD	**0**	**2.4**	**10.1**	**11.4**	**7.4**	**2.0**	**5.0**	**28.9**

Table A.2.5:CD_4 (unmeasured)

	% time <70	% time <80	% time 80<G <140	% time 140<G <180	% time 180<G <250	% time >250	G_{min} (mg/dl)	G_{max} (mg/dl)
Adult1	0.3	2.4	54.5	15.3	24.3	3.5	69	269
Adult2	0	2.1	54.5	25.7	17.7	0	74	205
Adult3	4.5	5.9	44.4	38.2	10.1	1.4	43	256
Adult4	7.6	10.7	20.5	46.2	22.6	0	59	249
Adult5	0	0	49.6	23.6	26.7	0	83	237
Adult6	4.8	6.2	48.2	11.4	31.5	2.4	53	252
Adult7	6.6	12.8	52.8	9.1	16.1	8.6	58	288
Adult8	7.6	9.7	50.3	32.3	6.9	0	59	208
Adult9	0	0	44.7	35	14.2	5.9	85	283
Adult10	0	2.8	31.0	30.0	30.2	6.2	73	295
Mean	**3.1**	**5.3**	**45.0**	**26.7**	**20.0**	**2.8**	**65.6**	**254.2**
SD	**3.4**	**4.6**	**11.0**	**12.0**	**8.4**	**3.1**	**13.4**	**31.2**

Table A.2.4 shows that with CD_3, on average the 54% of the time is spent within the normal glucose values, while with CD_4 the percentage of the time spent in the normal rage in 45%. With CD_3 there is no event of hypoglycaemia and the minimum observed glucose value is 71mg/dl for adult 9, in opposition to CD_4 that an average 3.1% of the time is spent in

hypoglycaemia with a minimum observed glucose value of 43mg/dl. Additionally, the time spent in hyperglycaemia (>180mg/dl) is much higher for CD_4 with a 22.8% of the time, while for CD_3 the respective percentage is 13.3%. The glucose profile and the control action with both CD_3 and CD_4 are presented in Figure A.2.9 for adult 6 for illustrative purposes.

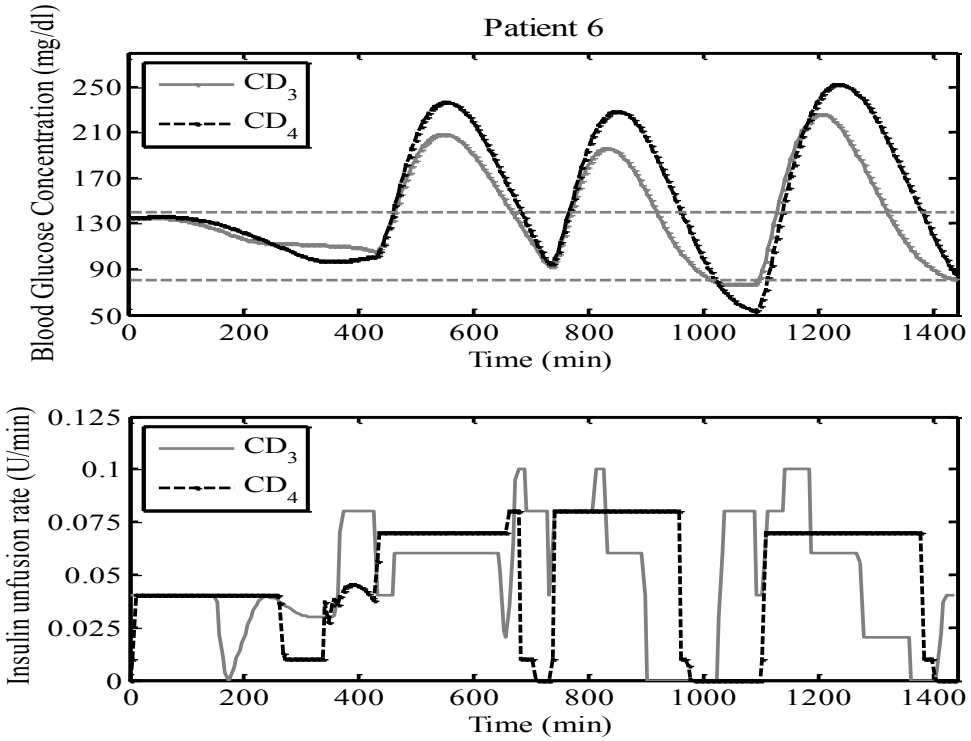


Figure A.2.9: Comparison of glucose regulation with control design 3 and 4 for adult 6. The meals are given at 420, 720and 1080 min and contain 75, 100 and 90 gof carbohydrates respectively.

Variable Meal Time

Figure A.2.10 shows the glucose profile for adult 6 when a meal of 50 g is given 30min before, 30min after and simultaneously with the predefined 30 g reference meal. It can be noticed that good glycaemic control is achieved in all cases with no occurring event of hypoglycaemia. When the meal is consumed 30min before the predetermined meal time prandial hyperglycaemia is occurring since insulin is not acting yet.

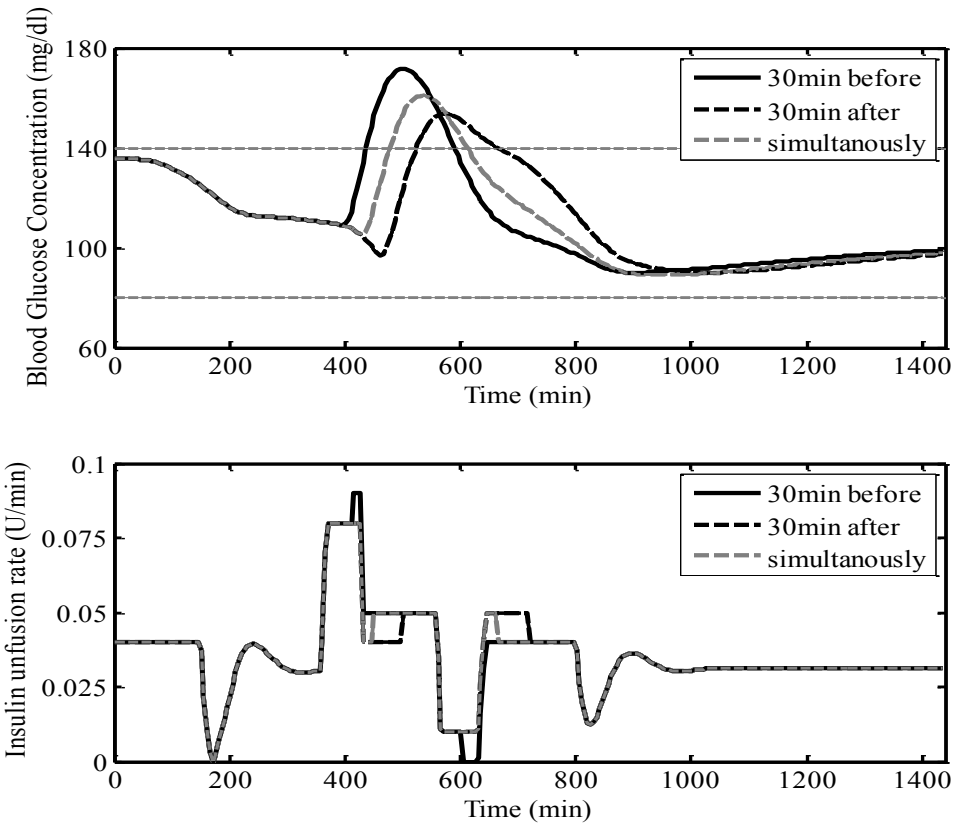


Figure A.2.10: Evaluation of CD_3 when a meal of 50 g is given 30min in advance, 30 min after and simultaneous with the reference meal of 30 g

C. Concluding Remarks

The closed loop control validation studies show that the proposed control design CD_3 can efficiently regulate the blood glucose concentration when tested for large meal sizes. There is no reported event of hypoglycaemia while the mean maximum glucose value being 226 mg/dl. When this control design is compared with CD_4 it becomes obvious that superior control can be achieved when the feed forward action of the MPC controller is enhanced in the presence of unknown meal disturbances. Further closed loop validation studies are required to verify the reliability of the proposed control performance. Hence, the proposed control strategy can be regarded as a potential strategy to compensate for the unknown meal disturbances since the validation studies performed for the UVa/Padova Simulation model as well as the proposed model, shown in Chapter 6, indicate promising closed loop glucose regulation.

APPENDIX B

B.1 Parameter Estimation

The estimated parameters for each patient are presented in detail in the following tables. The reported confidence interval for each value is a measure of the estimated precision, indicating that the smaller the interval the more reliable the estimated value is.

Table B.1: The optimal estimated values for each parameter for the 10 patients and the corresponding (95%) confidence interval that indicates that there is 0.95 probability the value of the parameter to be within the interval

Patient		**k_1**	**k_2**	**k_{elim}**	**k_{sub}**	**V_{dist}**	**$r_{u,L}$**
	Estimate	6.29E-05	1.17E-02	8.96E-01	1.21E-02	2.24E-02	0.15
1	SD	1.18E-06	4.37E-04	1.44E-01	3.08E-05	3.58E-03	3.74E-02
	CI	(±2.32E-06)	(±8.57E-04)	(±2.81E-01)	(±6.04E-05)	(±7.03E-03)	(±0.073)
	Estimate	1.09E-04	1.42E-02	1.35E+00	2.04E-02	1.00E-02	0.22
2	SD	1.59E-06	2.45E-04	1.14E-01	2.75E-05	8.51E-04	0.036
	CI	(±3.12E-06)	(±4.79E-04)	(±2.24E-01)	(±5.40E-05)	(±1.67E-03)	(±0.051)
	Estimate	2.67E-04	4.53E-02	3.00E-01	1.88E-02	5.16E-02	0.12
3	SD	6.03E-06	1.06E-03	2.83E-03	1.17E-05	4.88E-04	1.20E-02
	CI	(±1.188E-05)	(±2.09E-03)	(±5.56E-03)	(±2.31E-05)	(±9.61E-04)	(±0.002)
	Estimate	2.74E-04	2.22E-02	1.97E+00	1.97E-02	1.00E-02	0.11
4	SD	2.20E-05	2.05E-03	8.32E-02	8.71E-06	4.23E-04	4.70E-03
	CI	(±4.33E-05)	(±4.03E-03)	(±1.63E-01)	(±1.71E-05)	(±8.30E-04)	(±0.009)
	Estimate	4.59E-05	1.63E-02	1.34E+00	1.94E-02	1.01E-02	0.17
5	SD	1.98E-06	1.62E-03	1.10E-01	2.47E-05	8.31E-04	1.20E+02
	CI	(±3.88E-06)	(±3.17E-03)	(±2.15E-01)	(±4.85E-05)	(±1.63E-03)	(±0.042)
	Estimate	1.79E-04	3.40E-02	2.14E+00	1.51E-02	1.03E-02	0.06
6	SD	8.44E-06	1.62E-03	1.06E-01	5.79E-06	5.10E-04	4.70E+00
	CI	(±1.68E-05)	(±3.18E-03)	(±2.09E-01)	(±1.14E-05)	(±1.00E-03)	(±0.001)
	Estimate	3.83E-04	2.94E-02	1.47E+00	1.66E-02	1.00E-02	0.19
7	SD	2.19E-05	1.69E-03	7.83E-02	1.05E-05	5.32E-04	2.90E-02
	CI	(±4.29E-05)	(±3.32E-03)	(±1.54E-01)	(±2.06E-05)	(±1.04E-03)	(±0.057)
	Estimate	1.56E-04	2.07E-02	1.21E+00	1.96E-02	1.00E-02	0.19
8	SD	2.80E-05	3.29E-03	5.61E-02	1.52E-05	4.64E-04	6.84E-03
	CI	(±5.51E-05)	(±6.45E-03)	(±1.10E-01)	(±2.98E-05)	(±9.10E-04)	(±0.13)
	Estimate	2.11E-05	1.66E-02	1.13E+00	2.46E-02	1.00E-02	0.07
9	SD	2.79E-06	2.34E-03	1.85E-02	9.23E-06	1.64E-04	5.43E-03
	CI	(±5.47E-06)	(±4.59E-03)	(±3.62E-02)	(±1.81E-05)	(±3.22E-04)	(±0.001)
	Estimate	7.86E-05	2.44E-02	1.76E+00	1.98E-02	1.00E-02	0.17
10	SD	1.37E-05	3.89E-03	1.12E-01	1.53E-05	6.35E-04	3.24E-02
	CI	(±2.69E-05)	(±7.63E-03)	(±2.19E-01)	(±2.99E-05)	(±1.25E-03)	(±0.063)
Mean ± SD		**1.58E-04 ±1.18E-04**	**2.35E-02 ±1.03E-02**	**1.36E+00 ±7.26E-01**	**1.86E-02 ±4.48E-03**	**1.54E-02 ±1.80E-02**	**1.7E-1 ±0.07**

Table B.2: The optimal estimated values for sub model EGP for the 10 patients, the standard deviation and the confidence interval

		k_i	k_{p1}	k_{p2}	k_{p3}
1	Estimate	3.58E-03	6.52E+00	6.12E-03	2.08E-02
	SD	6.34E-05	2.28E-02	1.34E-04	1.42E-04
	CI	(±1.24E-04)	(±4.46E-02)	(±2.63E-04)	(±2.79E-04)
2	Estimate	2.94E-03*	5.03E+00	6.13E-03	1.13E-02
	SD		2.17E-02	1.03E-04	1.03E-04
	CI		(±4.25E-02)	(±2.02E-04)	(±2.01E-04)
3	Estimate	1.30E-02	5.26E+00	2.44E-03*	1.08E-02
	SD	7.81E-05	6.52E-03		2.48E-05
	CI	(±1.53E-04)	(±1.28E-02)		(±4.86E-05)
4	Estimate	1.34E-02	7.19E+00	2.44E-03*	2.39E-02*
	SD	3.66E-04	4.93E-02		
	CI	(±7.17E-04)	(±9.67E-02)		
5	Estimate	8.18E-03	4.00E+00	7.72E-03	6.64E-03
	SD	2.15E-04	6.49E-02	3.78E-04	2.69E-04
	CI	(±4.21E-04)	(±1.27E-01)	(±7.40E-04)	(±5.27E-04)
6	Estimate	1.19E-02	6.53E+00	2.44E-03	1.70E-02
	SD	1.07E-04	1.37E-02		5.76E-05
	CI	(±2.11E-04)	(±2.69E-02)		(±1.13E-04)
7	Estimate	1.24E-02	7.20E+00*	2.44E-03*	2.39E-02*
	SD	1.69E-04			
	CI	(±3.31E-04)			
8	Estimate	4.44E-03	6.42E+00	6.01E-03	2.17E-02
	SD	2.56E-04	7.99E-01	3.10E-03	2.46E-03
	CI	(±5.02E-04)	(±1.57E+00)	(±6.08E-03)	(±4.82E-03)
9	Estimate	4.32E-03	3.97E+00	6.63E-03	7.62E-03
	SD	9.26E-05	5.63E-02	2.50E-04	1.19E-04
	CI	(±1.82E-04)	(±1.10E-01)	(±4.89E-04)	(±2.33E-04)
10	Estimate	7.29E-03	4.35E+00	4.99E-03	5.51E-03
	SD	9.23E-04	4.93E-01	1.55E-03	5.79E-04
	CI	(±1.81E-03)	(±9.66E-01)	(±3.03E-03)	(±1.13E-03)
Mean ± SD		**8.15E-03 ±4.23E-03**	**5.65E+00 ±1.28E+00**	**4.73E-03 ±2.09E-03**	**1.49E-02 ±7.35E-03**

*Optimal value at bound

Table B.3: The optimal estimated values for sub model Ra for the 10 patients, the standard deviation and the confidence interval

		b	**D**	**k_{abs}**	**k_{max}**	**k_{min}**
1	Estimate	8.80E-01	2.93E-01	5.82E-01*	2.19E-02*	4.55E-03
	SD	9.91E-04	7.88E-04			2.01E-05
	CI	(±1.94E-03)	(±1.55E-03)			(±3.93E-05)
2	Estimate	7.47E-01	2.00E-01	2.14E-02*	3.04E-02	1.04E-02
	SD	8.79E-03	4.84E-03		4.83E-04	1.53E-04
	CI	(±1.72E-02)	(±9.49E-03)		(±9.46E-04)	(±2.99E-04)
3	Estimate	8.50E-01	1.88E-01	3.25E-02	5.82E-02*	5.72E-03
	SD	3.08E-03	9.28E-04	6.79E-04		3.48E-05
	CI	(±6.04E-03)	(±1.82E-03)	(±1.33E-03)		(±6.82E-05)
4	Estimate	7.36E-01	1.75E-01	5.31E-01	2.51E-02	8.93E-03
	SD	7.62E-03	6.59E-03	1.43E-01	4.72E-04	2.21E-04
	CI	(±1.49E-02)	(±1.29E-02)	(±2.80E-01)	(±9.26E-04)	(±4.34E-04)
5	Estimate	7.71E-01	2.01E-01	2.21E-02	4.47E-02	5.03E-03
	SD	8.71E-03	4.47E-03	1.45E-03	2.62E-03	1.58E-04
	CI	(±1.71E-02)	(±8.76E-03)	(±2.85E-03)	(±5.14E-03)	(±3.11E-04)
6	Estimate	8.15E-01	1.09E-01	2.14E-02*	4.32E-02	1.16E-02
	SD	1.39E-02	3.72E-03		2.16E-03	1.27E-04
	CI	(±2.72E-02)	(±7.28E-03)		(±4.23E-03)	(±2.49E-04)
7	Estimate	9.29E-01	1.73E-01	2.14E-02*	2.19E-02*	9.63E-03
	SD	1.83E-03	2.84E-03			9.72E-05
	CI	(±3.59E-03)	(±5.57E-03)			(±1.91E-04)
8	Estimate	8.60E-01	1.38E-01	4.71E-02	2.81E-02	5.73E-03
	SD	1.28E-02	8.56E-03	5.53E-03	2.14E-03	2.42E-04
	CI	(±2.51E-02)	(±1.68E-02)	(±1.09E-02)	(±4.20E-03)	(±4.75E-04)
9	Estimate	8.25E-01	3.32E-01	8.34E-02	2.36E-02	3.73E-03
	SD	8.16E-03	1.23E-02	7.21E-03	8.05E-04	1.41E-04
	CI	(±1.60E-02)	(±2.41E-02)	(±1.41E-02)	(±1.58E-03)	(±2.76E-04)
10	Estimate	8.54E-01	9.82E-02	4.40E-02	5.61E-02	1.09E-02
	SD	1.59E-02	7.87E-03	9.05E-03	8.30E-03	3.70E-04
	CI	(±3.12E-02)	(±1.54E-02)	(±1.77E-02)	(±1.63E-02)	(±7.26E-04)
Mean ± SD		**8.27E-01 ±6.10E-02**	**1.91E-01 ±7.40E-02**	**1.41E-01 ±2.20E-01**	**3.53E-02 ±1.41E-02**	**7.62E-03 ±2.95E-03**

*Optimal value at bound

B.2 MPC to QP

The MPC problem, as presented in section 5.4, is formulated in:

$$\min_{x,y,u} J = \sum_{k=1}^{N-1} x_k' Q_k x_k + \sum_{k=1}^{N-1} \left(y_k - y_k^R\right)' Q R_k \left(y_k - y_k^R\right) + \sum_{k=1}^{M-1} u_k' R_k u_k + \sum_{k=1}^{M-1} \Delta u_k' R_{1_k} \Delta u_k$$

s.t

$$x_{k+1} = Ax_k + Bu_k + Ed_k \quad \text{A.4.1}$$

$$y_k = Cx_k \quad \text{A.4.2}$$

The prediction of y is obtained by the iteration of the model A.4.1-A.4.2 that can be written in matrix –vector form:

$$\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \vdots \\ x_N \end{bmatrix} = \underbrace{\begin{bmatrix} A \\ A^2 \\ A^3 \\ \vdots \\ A^N \end{bmatrix}}_{\bar{A} \in \mathbb{R}^{Nnx \times n_{x0}}} x_0 + \underbrace{\begin{bmatrix} B & 0 & \dots & 0 & 0 \\ AB & B & \dots & 0 & 0 \\ A^2B & AB & \dots & 0 & 0 \\ \vdots & \vdots & \dots & \dots & \dots \\ A^{N-1}B & A^{N-2}B & \dots & AB & B \end{bmatrix}}_{\bar{B} \in \mathbb{R}^{Nn_x \times Nn_u}} \begin{bmatrix} u_0 \\ u_1 \\ u_2 \\ \vdots \\ u_{N-1} \end{bmatrix} \quad \text{A.4.3}$$

$$+ \underbrace{\begin{bmatrix} E & 0 & \dots & 0 & 0 \\ AE & E & \dots & 0 & 0 \\ A^2E & AE & \dots & 0 & 0 \\ \vdots & \vdots & \dots & \dots & \dots \\ A^{N-1}E & A^{N-2}E & \dots & AE & E \end{bmatrix}}_{\bar{E} \in \mathbb{R}^{Nn_x \times Nn_d}} \underbrace{\begin{bmatrix} d_0 \\ d_1 \\ d_3 \\ \vdots \\ d_{N-1} \end{bmatrix}}_{D}$$

The predictions of y are obtained by:

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ \vdots \\ y_N \end{bmatrix} = \begin{bmatrix} C & 0 & \dots & 0 \\ 0 & C & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & C \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ \vdots \\ x_N \end{bmatrix}$$

Hence, in a general form:

$$Y = \Phi x_0 + \Gamma U + \Gamma_d D \quad \text{A.4.4}$$

Where:

$\Phi=\begin{bmatrix} CA \\ CA^2 \\ CA^3 \\ \vdots \\ CA^N \end{bmatrix} \in \mathbb{R}^{Nn_x \times 1}$, $\Gamma=\begin{bmatrix} CB & 0 & \dots & 0 & 0 \\ CAB & CB & \dots & 0 & 0 \\ CA^2B & CAB & \dots & 0 & 0 \\ \vdots & \vdots & \dots & \dots & \dots \\ CA^{N-1}B & CA^{N-2}B & \dots & CAB & CB \end{bmatrix} \in \mathbb{R}^{Nn_x \times Nn_y}$, and

$\Gamma_d=\begin{bmatrix} CE & 0 & \dots & 0 & 0 \\ CAE & CE & \dots & 0 & 0 \\ CA^2E & CAE & \dots & 0 & 0 \\ \vdots & \vdots & \dots & \dots & \dots \\ AC^{N-1}E & CA^{N-2}E & \dots & CAE & CE \end{bmatrix} \in \mathbb{R}^{Nn_d \times Nn_y}$

R is introduced to include the setpoints:

$R=\begin{bmatrix} y_1^R \\ y_2^R \\ y_3^R \\ \vdots \\ y_N^R \end{bmatrix}$

The weighing matrices Q, R, QR and R_1 are given by:

$$\bar{Q} = diag(Q, \dots, Q, P) \in \mathbb{R}^{Nn_x \times Nn_x}$$

$$\bar{R} = diag(R, \dots, R) \in \mathbb{R}^{Mn_u \times Mn_u}$$

$$\overline{QR} = diag(QR, \dots, QR) \in \mathbb{R}^{Nn_y \times Nn_y}$$

$$\overline{R_1} = diag(R_1, \dots, R_1) \in \mathbb{R}^{Mn_u \times Mn_u}$$

The objective function is written as:

$$\min_{x,y,u} J = \varphi_x + \varphi_y + \varphi_u + \varphi_{\Delta u}$$

Where:

$\varphi_x = \mathrm{X}'\overline{\mathrm{Q}}\mathrm{X}$

$\varphi_y = (\mathrm{Y} - \mathrm{R})'\overline{\mathrm{QR}}(\mathrm{Y} - \mathrm{R})$

$\varphi_u = \mathrm{U}'\overline{\mathrm{R}}\mathrm{U}$

$\varphi_{\Delta u} = \Delta U'\overline{R_1}\Delta U$

Hence, the problem is formulated as a QP problem, (Rawlings and Mayne, 2009), (Maciejowski, 2002):

States

$\varphi_x = (\bar{A}x_0 + \bar{B}U + \bar{E}D)'\bar{Q}(\bar{A}x_0 + \bar{B}U + \bar{E}D)$

$= (\bar{B}U + b)'\bar{Q}(\bar{B}U + b)$ With $b = \bar{A}x_0 + \bar{E}D$

$= (U'\bar{B}' + b')\bar{Q}(\bar{B}U + b) = U'\overline{B'}\bar{Q}\bar{B}U + b'\bar{Q}\bar{B}U + U'\bar{B}'\bar{Q}b + b'\bar{Q}b$

$= U'\bar{B}'\bar{Q}\bar{B}U + 2(b'\bar{Q}\bar{B})U + b'\bar{Q}b = U'[\bar{B}'\bar{Q}\bar{B}]U + [2b'\bar{Q}\bar{B}]U + b'\bar{Q}b$

$H_x = \bar{B}'\bar{Q}\bar{B}$

$G_x = 2b'\bar{Q}\bar{B} = 2(\bar{A}x_0 + \bar{E}D)'\bar{Q}\bar{B} = N_x x_0 + N_d D$

With $N_x = 2\bar{A}'\bar{Q}\bar{B}$ and $N_d = 2(\bar{E})'\bar{Q}\bar{B}$

Output tracking error

$\varphi_y = (Y - R)'\overline{QR}(Y - R) = (\Phi x_0 + \Gamma U + \Gamma_d D - R)'\overline{QR}(\Phi x_0 + \Gamma U + \Gamma_d D - R)$

$= \big(\Gamma U - (R - \Phi x_0 - \Gamma_d D)\big)'\overline{QR}\big(\big(\Gamma U - (R - \Phi x_0 - \Gamma_d D)\big)$ With $b_y = R - \Phi x_0 - \Gamma_d D$

$= \big(U'\Gamma' - b_y'\big)\overline{QR}(\Gamma U - b_y)$

$= U'\Gamma'\overline{QR}\Gamma U - b_y'\overline{QR}\Gamma U - U'\Gamma'\overline{QR}b_y + b_y'\overline{QR}b_y = U'[\Gamma'\overline{QR}\Gamma]U - \big[2b_y'\overline{QR}\Gamma\big]U + b_y'\overline{QR}b_y$

$H_y = \Gamma'\overline{QR}\Gamma$

$G_y = 2b_y'\overline{QR}\Gamma = 2(R - \Phi x_0 - \Gamma_d D)'\overline{QR}\Gamma = M_\chi \chi_0 + M_d D$

With $M_x = -2\Phi'\overline{QR}\Gamma$ and $M_d = -2\Gamma_d'\overline{QR}\Gamma$

Input

$\varphi_u = \mathrm{U}'\overline{\mathrm{R}}\mathrm{U}$

$H_u = \bar{R}$

Input step change

$$\Delta U = [\Delta u_0 \; \Delta U_1 \ldots \Delta u_{M-1}]'$$

Δu_0 is defined as u_{-1}-u_0

$$\Delta U = \underbrace{\begin{bmatrix} 1 & 0 & 0 & \ldots & 0 & 0 \\ -1 & 1 & 0 & \cdots & 0 & 0 \\ 0 & -1 & 1 & \ldots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & 0 & \vdots \\ 0 & 0 & 0 & \cdots & -1 & 1 \end{bmatrix}}_{H_{R1}} U + \underbrace{\begin{bmatrix} -1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}}_{G_{R1}} u_{-1}$$

$$H_{\Delta u} = H_{R1}' R_1 H_{R1}$$

$$G_{\Delta u} = G_{R1}' R_1 G_{R1}$$

Hence the MPC problem is reformulated in the general QP problem:

$$\min_U J = \frac{1}{2} U' H U + G_{QP}' U + c \qquad \text{A.4.4}$$

With

$$H = H_x + H_u + H_y + H_{\Delta u}$$

$$G_{QP} = G_x + G_u + G_y + G_{\Delta u}$$

Constraints

Constraints are imposed on the input, *u*, the output *y*, and the input step change Δu. In the QP formulation they are expressed as:

$$GU \leq W \qquad \text{A.4.5}$$

Constraints on the states

$$X_{min} \leq x_1, x_2 .. x_N \leq X_{max}$$

$$With\ X_{min} = \begin{bmatrix} x_{min} \\ x_{min} \\ \vdots \\ x_{min} \end{bmatrix}, X_{max} = \begin{bmatrix} x_{max} \\ x_{max} \\ \vdots \\ x_{max} \end{bmatrix}$$

But using A.4.3, it becomes:

$$\begin{bmatrix} \bar{B} \\ -\bar{B} \end{bmatrix} U \leq \begin{bmatrix} X_{max} \\ -X_{min} \end{bmatrix} + \begin{bmatrix} -\bar{A} \\ \bar{A} \end{bmatrix} x_0 + \begin{bmatrix} -\bar{E} \\ \bar{E} \end{bmatrix} D$$

Constraints on the outputs

$$Y_{min} \leq y_1, y_2 .. y_N \leq Y_{max}$$

$$With\ Y_{min} = \begin{bmatrix} y_{min} \\ y_{min} \\ \vdots \\ y_{min} \end{bmatrix},\ Y_{max} = \begin{bmatrix} y_{max} \\ y_{max} \\ \vdots \\ y_{max} \end{bmatrix}$$

Using A.4.4, we have:

$$\begin{bmatrix} \bar{\Gamma} \\ -\bar{\Gamma} \end{bmatrix} U \leq \begin{bmatrix} \Upsilon_{max} \\ -\Upsilon_{min} \end{bmatrix} + \begin{bmatrix} -\Phi \\ \Phi \end{bmatrix} x_0 + \begin{bmatrix} -\Gamma_d \\ \Gamma_d \end{bmatrix} D$$

Constraints on the inputs

$$U_{min} \leq u_0, u_1, .. u_N \leq U_{max}$$

Which is written as:

$$\begin{bmatrix} I \\ -I \end{bmatrix} U \leq \begin{bmatrix} U_{max} \\ -U_{min} \end{bmatrix}$$

$$With\ U_{min} = \begin{bmatrix} u_{min} \\ u_{min} \\ \vdots \\ u_{min} \end{bmatrix},\ U_{max} = \begin{bmatrix} u_{max} \\ u_{max} \\ \vdots \\ u_{max} \end{bmatrix}$$

Constraints on the input step change

$$\Delta U_{min} \leq \Delta u_0, \Delta u_1, .. \Delta u_N \leq \Delta U_{max}$$

$$\begin{bmatrix} H_{R1} \\ -H_{R1} \end{bmatrix} \Delta U \leq \begin{bmatrix} \Delta U_{max} \\ -\Delta U_{min} \end{bmatrix} + \begin{bmatrix} G_{R1} \\ -G_{R1} \end{bmatrix} u_{-1}$$

APPENDIX C

Multi parametric MPC is an ideal control method for drug delivery applications and in particular for the system of automated insulin delivery for T1DM. The ability to obtain the control actions, as functions of the patient measurements, on-line via simple function evaluations makes the mpMPC suitable for portable applications (Pistikopoulos *et al.*, 2002), (Pistikopoulos, Georgiadis and Dua, 2007b), (Pistikopoulos, Georgiadis and Dua, 2007a) In essence, in mpMPC the online solution of the optimisation problem is replaced by the off line derivation of the explicit mapping of the optimal decisions in the space of the plant uncertainty. mpMPC is applied in the context of *Optimisation and Correction MPC (Control design 3)* presented in Section 6.4.3. The framework is illustrated in Figure.C.1:

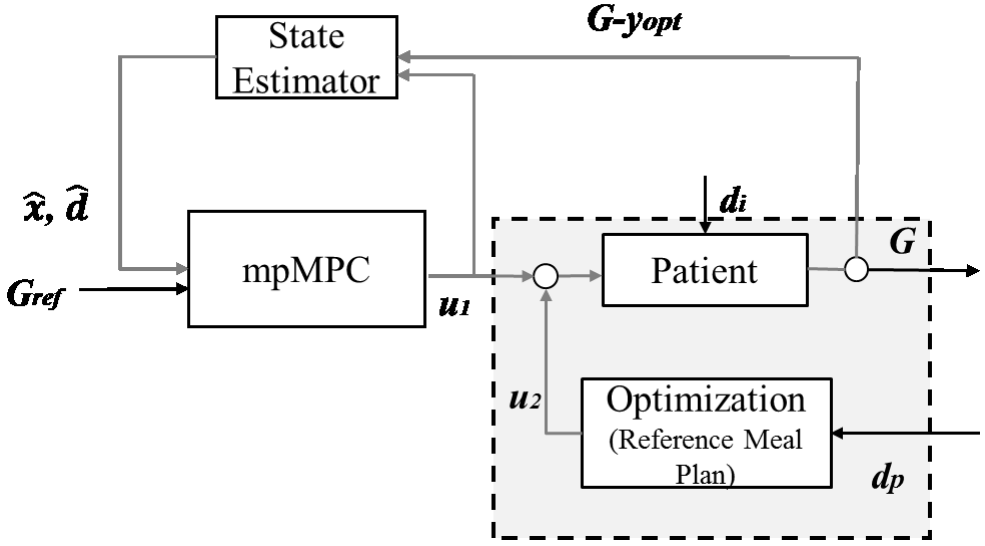


Figure C.1: Proposed framework for closed loop insulin delivery (see section 6.4.3)

An example is illustrated for adult 6. The virtual patient is the UVa/Padova Simulator. A nominal mp-MPC is designed using the linear state-space model presented in Appendix A.2 with estimated states:

$\hat{x} = [G_p \quad G_t \quad X_{disp} \quad I_{del1} \quad I_{del2} \quad I_{sc1} \quad I_p \quad d]'$

The exact formulation of section 6.4.3 is applied here.

The MPC problem is given in equation 6.8. The explicit solution of the quadratic problem (QP) (Bemporad et al., 2002) is obtained:

$\min_U J(\theta) = \frac{1}{2}U'HU + \theta'FU + \frac{1}{2}\theta'Y\theta$ (C.1)

s.t. $GU \leq W + E\theta$

For the specific example the parameters θ of the mp-QP problem are defined as:

$\theta = [G_p \quad G_t \quad X_{disp} \quad I_{del1} \quad I_{del2} \quad I_{sc1} \quad I_p \quad d \quad G \quad yset]$

The multi-parametric Quadratic Programming (mp-QP) problem and can be solved with standard multi-parametric programming techniques (Pistikopoulos, Georgiadis and Dua, 2007b).In this study, Parametric Optimization Software was used (Parametric Optimization Solutions (ParOS) Ltd, 2003) to obtain the explicit controller description, which is the optimal map of the control variables as function of the parameters of the system. This optimal map consists of 8 critical regions and the corresponding control laws. Each of the critical regions is described by a number of linear inequalities $A_i x \leq b_i$ for $i \in \{1 \ldots, n_{CR}\}$, where n_{CR} is the number of critical regions and the corresponding control lows are piecewise linear functions of the parameters: $U = K_i \theta + c_i$, where i is the index of solutions.

The performance of the controller is illustrated in the following graph:

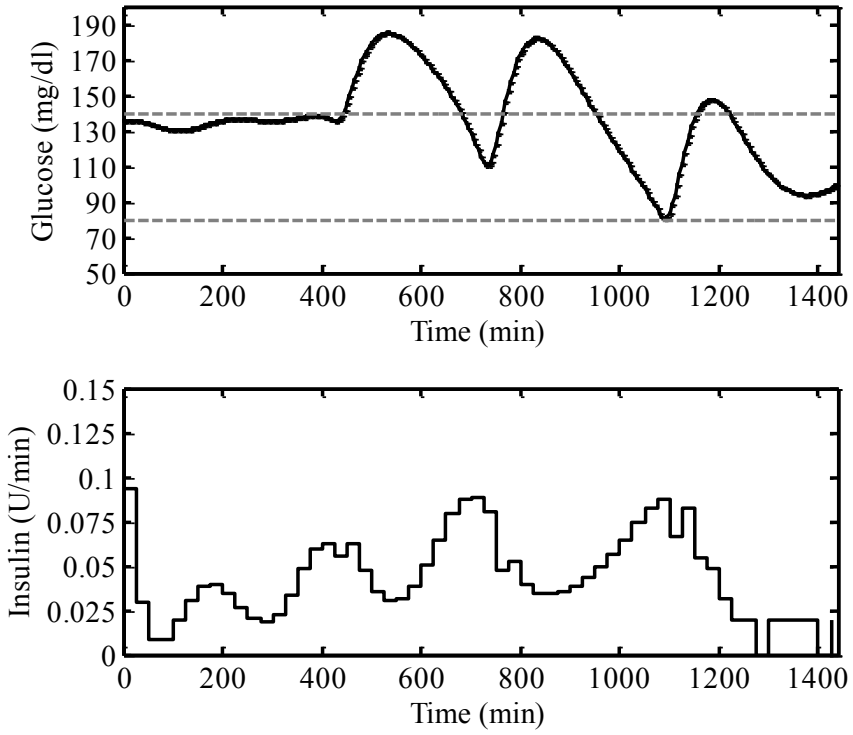


Figure C.2: Performance of mpMPC controller for adult 6, when 45, 80 and 70 g of carbohydrates are consumed at 420, 720 and 1080 min

Glucose regulation is achieved with 92.7% of the time spent between 80 and 180mg/dl and no event of hypoglycaemia occurs.

Figure C.3 shows the performance of the controller in the case of a skipped meal at 720 min. We can see that 12.8% of time is spent in hypoglycaemia with a minimum glucose value of

50mg/dl. It is obvious that further improvement of the control specifications is required to prevent the deep drop in glucose concentration.

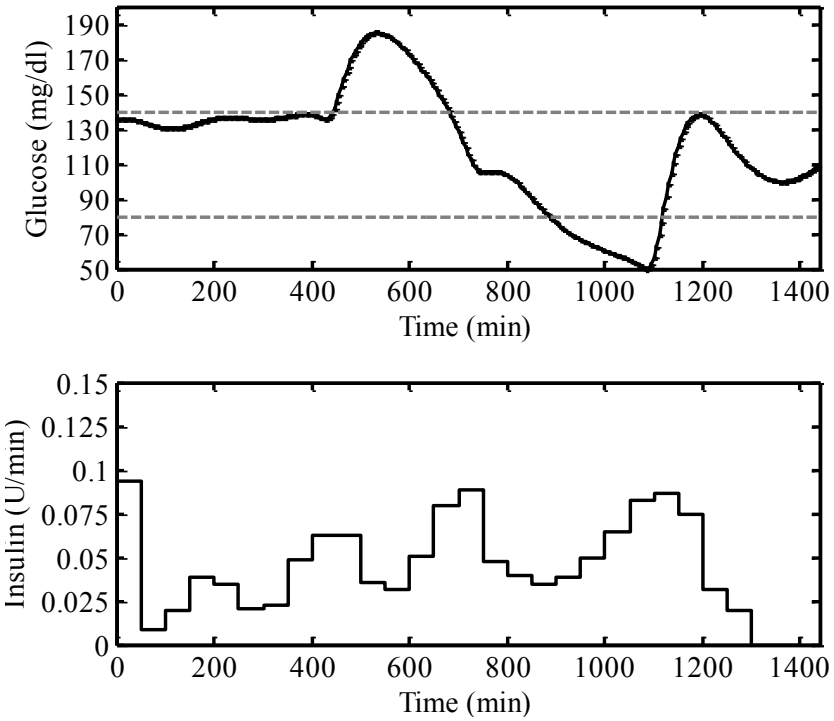


Figure C.3: Skipped meal at 720 min. Breakfast 45 g and lunch 60 g at 420 and 1080 min

An example of the function to obtain the control law and the description of the CR is presented below:

---------- Feasible region 7 ----------
U_1 = -7.49397*Gp +6.48152*Gt -0.800111*x_{disp} -0.597714*I_{del1} -0.0377123*I_{del2} -0.00655881*Isc1 -2.9359*Ip +399.73*d +35.048*G -35.048*Gp0 -0.000779129
U_2 = +0.02
-0.0187475*Gp +0.0162147*Gt -0.00200163*x_{disp} -0.00149529*I_{del1} -9.43444e-05*I_{del2} -1.64081e-05*Isc1 -0.00734469*Ip +1*d +0.0876791*G -0.0876791*Gp0 <= +5.19828e-05
+0.0187475*Gp -0.0162147*Gt +0.00200163*x_{disp} +0.00149529*I_{del1} +9.43444e-05*I_{del2} +1.64081e-05*Isc1 +0.00734469*Ip -1*d -0.0876791*G +0.0876791*Gp0 <= -1.94914e-06
+0.00487771*Gp -0.00437426*Gt +0.00024091*x_{disp} +0.000336128*Idel1 +9.02606e-06*I_{del2} +7.02158e-08*Isc1 +0.00030467*Ip -0.199185*d -0.0350229*G +1*Gp0 <= +48.2489
+0.0241355*Gp -0.0216076*Gt +0.00125817*x_{disp} +0.0016757*I_{del1} +4.83288e-05*I_{del2} +1.33944e-06*Isc1 +0.00188703*Ip -1*d -0.170413*G -0.00718897*Gp <= +0.888008
-0.0244884*Gp +0.0219608*Gt -0.00120948*x_{disp} -0.00168752*I_{del1} -4.5315e-05*I_{del2} -3.52516e-07*Isc1 -0.00152959*Ip +1*d +0.175831*G -0.175831*Gp0 <= -0.000168087
-1*Gp <= +50
+1*Gp <= +250
-1*Gt <= +50
+1*Gt <= +300
-1*x_{disp} <= +700
+1*x_{disp} <= +100
-1*I_{del1} <= +50
+1*I_{del1} <= +100

$-1*I_{del2} <= +50$
$+1*I_{del2} <= +100$
$-1*I_{sc1} <= +50$
$+1*I_{sc1} <= +150$
$-1*Ip <= +50$
$+1*Ip <= +80$
$-1*G <= +10$
$+1*G <= +10$

Concluding Remarks

The advantages of using mpMPC control method in drug delivery systems are summarised:

✓ Suitable for portable applications

✓ Testing off-line of different scenarios to ensure the patient's safety

✓ Advantages of MPC over other control designs

Further in-silico validation is required to improve the mpMPC performance in the context of the proposed framework.

APPENDIX D

Table D.1: MPC tuning parameters and specifications for CD_2 CD_3 and CD_4

	Adult1	Adult2	Adult3	Adult4	Adult5	Adult6	Adult7	Adult8	Adult9	Adult10
ts (min)	5	5	5	5	5	5	5	5	5	5
N (min)	65	55	35	50	65	50	40	55	70	65
M(min)	60	40	30	40	40	45	35	50	40	40
	CD_3									
Q_R	100000	100000	10000	100000	100000	1000	10000	100000	100000	1000000
R	1	0.01	0.001	1	0.01	0.001	1	1	0.001	0.01
R_1	1	0.01	1	1	0.01	0.01	1	1	0.001	1
u_{max} *(U/min)*	0.2TDD	0.2TDD	0.2TDD	0.2TDD	0.2TDD	0.2TDD	0.2TDD	0.2TDD	0.2TDD	0.2TDD
u_{min} *(U/min)*	0	0	0	0	0	0	0	0	0	0
y_{max} *(mg/dl)*	10	10	10	10	10	10	10	10	10	10
y_{min} *(mg/dl)*	-10	-10	-10	-10	-10	-10	-10	-10	-10	-10
	CD_2 - CD_4									
Q_R	100000	10000	10000	1000	100000	1000	100000	100000	1000	100000
R	0.1	0.001	0.001	0.0001	0.01	0.001	0.001	0.01	0.001	0.001
R_1	0.05	0.001	0.001	0.0001	0.01	0.001	0.0	0.01	0.01	0.001
Δu_{max} *(U/min)*	0.01	0.01	0.01	0.008	0.01	0.01	0.008	0.008	0.008	0.008
Δu_{min} *(U/min)*	-0.01	-0.01	-0.01	-0.005	-0.01	-0.01	-0.005	-0.005	-0.005	-0.005
u_{max}-CD_2 *(U/min)*	0.1	0.15	0.1	0.05	0.15	0.1	0.08	0.1	0.1	0.12
u_{max} CD_4 *(U/min)*	-	-	-	-	-	-	-	-	-	-
u_{min} *(U/min)*	0	0	0	0	0	0	0	0	0	0
y_{max} *(mg/dl)*	140	140	140	140	140	140	140	140	140	140
y_{min} *(mg/dl)*	80	80	80	80	80	80	80	80	80	80

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