IN SILICO TESTING OF GLUCOSE CONTROLLERS:

METHODOLOGY AND SAMPLE APPLICATION

by

Ludovic Jean Chassin

Thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

in

Measurement and Information in Medicine

City University

April 2005

Abstract

Diabetes mellitus designates a range of metabolic disorders characterised by hyperglycaemia due to deficient or absent insulin secretion, insulin action, or both. In particular, Type 1 diabetes is characterised by a total lack of endogenous insulin secretion which has to be replaced by exogenous insulin to control the plasma glucose concentration.

An extracorporeal wearable artificial pancreas (AP) has been a research aim for over three decades. The research is motivated by the need to improve glucose control. Results of a major study, the Diabetes Control and Complications Trial (DCCT), have demonstrated that improvements in glucose control prevent or delay long term complications, which are the main causes of morbidity and mortality in subjects with Type 1 diabetes.

Prior to a clinical evaluation, performance of new medical devices can be tested *in silico*. Such an approach has been adopted extensively by the pharmaceutical industry in the development of new drugs. *In silico* testing benefits from relatively low financial, human, and time costs by comparison with the resources required for a full clinical evaluation.

The aims of the present thesis are to identify components of the AP, integrate them into a simulation environment, and design an *in silico* evaluation strategy for the development of closed-loop algorithms with the ultimate goal to assess safety and efficacy prior to clinical evaluation.

In the present work, submodels of metabolic processes were linked to represent the characteristics of the glucoregulation in Type 1 diabetes. The submodels were associated with sets of parameters to account for variability in population and individual responses to meals and insulin therapy. The model of glucoregulation in Type 1 diabetes was extended by models of subcutaneous (sc) glucose sensing and sc insulin delivery to represent all aspects of the AP.

A systematic approach was developed and employed to evaluate, *in silico,* the potential and limitations of an AP glucose controller. This was exemplified by evaluating a nonlinear model predictive controller. The robustness of the AP was explored by hypothesising various perturbations induced by different system components.

A further objective included the establishment of a qualitative grading scheme of glucose control from the clinical viewpoint. This was followed by a comparison between results from simulations and a clinical trial of 24 hours, which gave the proof of concept of *in silico* testing. It was found that despite discrepancies due to initial conditions and meal differences, the simulations indicated well the outcome of the clinical trial.

In conclusion, the thesis demonstrates the significant potential of *in silico* testing to make predictions about system behaviour aiding the assessment of safety and efficacy of control algorithms during the development of an AP.

Acknowledgment

I would like to thank my supervisor Dr. Roman Hovorka for his generous advice, availability, patience, sympathy and his constant positive attitude during the work on the entire thesis.

Many thanks to my friends and colleagues for their encouragements and in particular to Dr. Malgorzata E. Wilinska for her comments, listening and for keeping me energised with coffees.

I am also grateful to Dr. Thomas Vering for supporting me in the continuation and completion of this PhD study.

I would like to extend my thanks to Diana Kasparova who has done much to boost my optimism towards the end of the PhD.

Lastly, I want to thank immensely my parents and my Grandmother for their invaluable lifelong support with a special gratitude to my father who gave me the taste for curiosity and the strength to persevere.

Glossary

ADA	American Diabetes Association
ADICOL	ADvanced Insulin infusion using a COntrol Loop
AP	Artificial pancreas
CHO	Carbohydrate
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
IG	Interstitial glucose
IVGTT	Intravenous glucose tolerance test
MDI	Multiple daily injection
mM	Millimoles per litre
MPC	Model Predictive Controller
MTT	Meal tolerance test
mU	Milliunits of insulin
OGTT	Oral glucose tolerance test
PG	Plasma glucose
U	Units of insulin
WHO	World Health Organisation

Table of Contents

Table of Figures

Table of Tables

1 Introduction and Thesis Structure

1.1 Background and Motivations

Type 1 diabetes is a widespread metabolic disease characterised by a total loss of insulin secretion resulting in elevated glucose (hyperglycaemia). Exogenous insulin is needed to maintain normoglycaemia and to avoid death. The aim of the treatment is to limit hyperglycaemia while avoiding low glucose (hypoglycaemia).

Results from the Diabetes Control and Complications Trial (DCCT) (1) and the United Kingdom Prospective Diabetes Study (UKPDS) (2) have demonstrated the importance of intensive insulin therapy to achieve better glucose control and to avoid or at least delay diabetes complications. Near normal glucose control is difficult to achieve requiring patient compliance and a considerable health care infrastructure. It is associated with an increased risk of hypoglycaemia (1).

The emergence of advanced glucose measuring and insulin delivery devices has improved self management of diabetes (3-5). The development of new insulins with various pharmacokinetic and pharmacodynamic characteristics (6-8) have played an important role in the progress toward a more physiological insulin profile (9).

Education has a major role to play in the improvement of glucose control (10) but this implies an effort and compliance which can be difficult to achieve in some subject groups such as in adolescents or the elderly. To reduce the burden and to achieve an optimum insulin delivery reproducing more closely the physiological insulin release, an automated insulin delivery device is therefore desired.

Approaches to tight glucose control rely on the intensified insulin therapy represented by two types of strategy. The multiple daily injection (MDI) consists of three to four insulin injections and glucose measurements daily (11,12) and the use of different insulins (fast and slow acting) in attempting to mimic the pancreatic insulin release.

The second approach employs the continuous subcutaneous insulin infusion (CSII) through an insulin pump (11,13,14). Changes in insulin requirements can be handled

with more flexibility. This facilitates a closer match to the pancreatic insulin release. However, the outcome of the CSII is dependent on user attitudes (15).

Both approaches are still suboptimal. Several studies illustrate the presence of large glucose deviates from the target glucose concentration (16). Periods of hypoglycaemia and hyperglycaemia periods can be largely unnoticed.

Combining a continuous glucose monitor, with an insulin pump controlled by an algorithm, an optimised insulin delivery could be achieved in a closed-loop fashion (17-21). For management, costs and safety reasons, the widespread application of the artificial pancreas (AP) is likely to employ the subcutaneous glucose measurements and the subcutaneous insulin infusion which unfortunately introduce considerable delays and variability (22-24). Therefore, the extracorporeal AP is still awaiting the solution of a range of issues and especially the development of a reliable continuous glucose monitor.

Safety and efficacy aspects of the AP need to be extensively addressed in a range of situations and under different conditions. This represents a high demand for clinical testing at a considerable cost. The potential for setbacks is considerable and limits the development of such devices.

Considerable knowledge has been compiled about the characteristics of the whole body glucose metabolism and its control by exogenous insulin. Physiological modelling enables physiological systems to be described mathematically and therefore enables implementation of temporal models on a computer. This suggests that the use of glucoregulatory simulators has the potential to accelerate the development of the AP and the control algorithm in particular.

Many studies have focused on the development of a control algorithm for closed-loop systems. However, it appears that none encompassed a systematic and complete *in silico* testing. The objective of the project Advanced Insulin Infusion using a Control Loop (ADICOL) was to develop a treatment system that continuously measures and controls glucose values in subjects with Type 1 diabetes. The modular concept of the ADICOL's biomechanical artificial pancreas consisted of a minimally invasive

subcutaneous glucose sensor, a handheld PocketPC computer, and an insulin pump (Disetronic D-Tron) delivering subcutaneously insulin lispro. The ADICOL project demonstrated the feasibility of a closed-loop glucose control during fasting and fed conditions with a wearable, modular extracorporeal artificial pancreas. The development of a control algorithm for closed-loop control was a critical task of the ADICOL project. It became clear that a comprehensive simulation environment was needed to support the development of the algorithm. As such an environment was not available, the project described in this thesis was initiated as part of the ADICOL work.

1.2 Aims

The primary aim of the thesis is to facilitate the development of glucose controllers by designing, implementing, and validating an *in silico* testing environment. The secondary aim is to develop a methodology to test systematically glucose controllers and exemplify its use in the assessment of a model predictive controller (MPC) developed in parallel with the simulation environment during the ADICOL project.

1.3 Objectives

There are four technical and two clinical objectives.

1.3.1 Technical objectives

The technical objectives are

- To develop a model of the whole body glucoregulatory processes in subjects with Type 1 diabetes treated by the CSII;
- To create a population of virtual subjects with Type 1 diabetes representing inter and intra-subject variability;
- To create a simulation environment facilitating testing of an extracorporeal AP consisting of a glucose sensor, a control algorithm, and an insulin pump;

- To develop a methodology for *in silico* systematic testing of glucose controllers in a simulation environment.

1.3.2 Clinical objectives

The clinical objectives are

- To define clinically relevant criteria to assess glucose excursions during closed-loop control;

- To assess clinical validity of the simulator by comparing simulated and real clinical trials.

1.4 Thesis Structure

A review of diabetes mellitus is given in Chapter 2 starting with a general overview of glucose metabolism and then focussing on Type 1 diabetes and the current standard treatments are presented.

Chapter 3 reviews approaches to simulation and modelling in diabetes. Decision support systems are also reviewed. This is followed by a review of closed-loop control algorithms. A non-linear MPC is described in greater detail as it is used in the following chapters to demonstrate the performance of the simulation environment.

Chapter 4 describes a model of the glucoregulatory processes. The model consists of submodels, which are individually presented.

Chapter 5 describes the simulation environment which includes an insulin pump model, a calibration model, and a measurement model. The chapter also describes the generation of 18 synthetic subjects with Type 1 diabetes and the approaches taken to represent inter- and intra-subject variability.

The methodology to evaluate glucose controllers in a virtual environment is presented in Chapter 6.

Chapter 7 defines clinically relevant criteria for the assessment of glucose excursions during closed-loop control and focuses on the clinical validity of the simulator by comparing results obtained in the simulated and clinical studies.

A general discussion is presented in Chapter 8. This is then followed by conclusions summarising the achievement of the objectives and outlining future work.

Appendix A contains Matlab/Simulink® plots of glucose control in synthetic subjects controlled by the MPC.

Appendix B includes Matlab/Simulink® block diagrams representing the model of subjects with Type 1 diabetes, and the measurement and insulin pump models.

Appendix C contains publications.

2 Type 1 Diabetes and its Treatment

2.1 Introduction

Diabetes is a widespread metabolic disorder affecting glucose homeostasis and characterised by chronic hyperglycaemia (elevated blood glucose). The worldwide increase in incidence has enormous cost implications due to the long term complications (25). In Sweden in 1994, resources expenditure was three times higher to treat complications compared to what was spent on control of the disease (26) and accounted for 2% of the total hospital admissions in the US in 1987 (27). The predictions are alarming (28) with projected 221 million cases in 2010 against estimated 124 million cases in 1997 (29).

There exist several types of diabetes but the vast majority is accounted for by Type 1 and Type 2 diabetes. The former subgroup is characterised by an absolute deficiency in insulin secretion whereas the latter is characterised by a relative lack of insulin secretion and/or insulin action. Treatment is essential to prevent long term complications but is not easily achieved.

In this chapter, a general overview of glucose metabolism is presented and is followed by the description of the types of diabetes with a focus on Type 1 diabetes, its treatment and complications.

2.2 Glucose Metabolism

2.2.1 Generalities

Glucose is the primary energy source for the metabolism of cells. Blood circulation is its conveyor within the body ensuring its distribution. For some organs, in particular the brain, glucose is the only usable substrate. However, if glucose is vital, at high concentrations it is also toxic to the cells. In healthy people, blood glucose is finely controlled and remains stable at a level normally falling in a range of 3.9 to 6.1mM (30) with a slight transient elevation following

meals very rarely exceeding 7.8mM (31) and with a return to normal within two to three hours.

The glucose homeostasis is maintained through different pathways of glucose absorption, endogenous production, utilisation, and storage under the main control of antagonist hormones glucagon and insulin. The glucose concentration is constantly balanced by glucose appearance and its utilisation by the tissues.

2.2.2 Systemic Glucose Appearance

Two sources of glucose contribute to systemic glucose appearance. First, the endogenous source originates from various organs such as the liver and the kidneys. Second, the exogenous source is from the digestion of food. In the latter case, the rate of appearance of glucose is dependent on various factors such as the type of carbohydrates, meal composition, gastric motility and emptying, and intestinal absorption (32-35).

2.2.3 The Pancreas

The pancreas is a hook shaped flat organ measuring about 12.5-15cm and located behind the stomach. It has both an exocrine and endocrine role. The exocrine pancreas secretes the pancreatic juice that aids the digestion while the endocrine pancreas through a specialised group of cells constituting the islets of Langerhans secretes insulin (ß-cells) and glucagons (α-cells).

2.2.4 Insulin

Insulin is the predominant controlling factor of plasma glucose (PG). It is a hormone made up of two polypeptide chains and secreted by the pancreas β-cells. Insulin has a potent hypoglycaemic and sparing effect. Numerous substances inhibit and stimulate insulin secretion but glucose itself has by far the most stimulating effect. Other components such as certain amino acids (resulting from protein hydrolysis during digestion) and gut hormones known as the glucagon-like peptide (GLP-1) and the gluco-dependent insulinotropic

polypeptide (GIP) are also involved in insulin release (36,37). It is believed that neuromediators (38) have a feed forward effect on insulin secretion.

Insulin is delivered through the portal vein allowing fast distribution and therefore exercises a quick response to elevated plasma glucose. By binding to insulin receptors, insulin enables glucose to enter the cells where it is metabolised.

The glucose uptake by the liver represents about one third of the ingested glucose (39) and the liver is the most important organ for postmeal glucose uptake in addition to the systemic glucose removal (40). The remaining glucose is taken up by an increased glycolysis (transforming glucose into pyruvate), glycogenesis (glucose polymerisation into glycogen) in the muscle, and increased lipogenesis (synthesis of fatty acids), insulin stimulating triglyceride storage in the adipose tissue while glycogenolysis (the production of glucose from stored glycogen) and gluconeogenesis (the transformation of pyruvate and certain amino acids into glucose) is reduced.

Although the liver is central to glucoregulation, in terms of glucose storage capacity muscles represent a larger reservoir. Of the 500g of carbohydrates (CHO) which can be stored as glycogen, 25% are retained by the liver while the remaining 75% are retained in the muscle (41).

When the glucose level is normalised, insulin secretion is strongly inhibited and returns to a level controlling the endogenous glucose production mainly driven by the hepatic glucose output (42).

Because of its key role, a deficiency in insulin secretion and/or insulin insensitivity will result in a departure from a normal healthy glucose profile. At the same time, insulin is not needed at all time and has to be disposed of by the body. Most of secreted insulin is degraded by the liver (43), the remaining insulin being catabolised by most tissues.

Some tissues do not need insulin to utilise glucose such as the control nervous system and the brain.

2.2.5 Glucagon

The counterregulatory hormones are catecholamine, glucocorticoides, growth hormone, and glucagon which have synergic effects but the latter is by far the most potent. Glucagon is secreted by the α-cells in response to a low glucose concentration and has an opposite effect to insulin. Its role is to preserve the glucose concentration constant between meals or during an extended fasting period. Numerous factors contribute to the production of glucose to prevent hypoglycaemia. Glucagon stimulates glycogenolysis (the glucose production from stored glycogen) and gluconeogenesis from pyruvate, glycerol (resulting from adipose triglycerides degradation and metabolised by the liver) and certain amino acids by series of complex enzymatic reactions. Glycerol can have a significant role in prolonged fasting (44) and glycogen from the muscle can only be used indirectly by a complex biochemical process producing lactic acid which can be converted into glucose by the liver (41).

Should these first barriers to prevent hypoglycaemia be insufficient, another hormone, epinephrine, which is secreted by the adrenal medulla (41), can quickly contribute to a glucose rise.

2.2.6 Conclusion

In healthy people, glycaemia is principally maintained through the antagonist insulin/glucagon hormone actions. The liver is set into an uptake or storage mode by insulin and when glucose concentration drops, glucagon stimulates glucose production from stored glycogen and through glycogenesis and gluconeogenesis processes. In Type 1 diabetes mellitus, a metabolic disorder characterised by hyperglycaemia, insulin not secreted and needs to be replaced by exogenous inputs to regulate glucose storage and utilisation.

2.3 Diagnostic Categories

2.3.1 Type 1 Diabetes Mellitus

Type 1 diabetes is characterised by absolute deficiency of insulin secretion and was for this reason previously called insulin dependent diabetes mellitus or IDDM.

Type 1 diabetes is usually diagnosed at an early age, most commonly under 20 years. Its prevalence is characterised by a large geographical variation with about 30 cases per year per 100 000 of the population in Finland down to 0.5-2.0 cases per year per 100 000 of the population in Japan (45) strongly suggesting ethnic and environmental factors. Moreover, a seasonal variation seems to be present.

Type 1 diabetes is believed to be an auto-immune disease in which the pancreatic ß-cells are perceived as a foreign body and are destroyed by the immune system.

Symptoms include frequent thirst and urination, blurred vision, weight loss and hyperphagy. Diagnosis is critical as elevated glucose can lead to coma and death.

2.3.2 Type 2 Diabetes

Type 2 diabetes is also characterised by wide differences in its prevalence ranging from less than 1% in Mapuche Indian, Chile, to about 50% in Pima Indian, USA (45). In developing countries it represents almost 100% of the cases and represent a large number of newly diagnosed diabetic subjects in developed countries (46,47).

Type 2 diabetes is characterised by a relative lack of insulin secretion and sensitivity. Insulin deficiency is due to failing of the ß-cell to secrete enough insulin which is needed in a greater quantity to compensate for the insulin

resistance associated with Type 2 diabetes. Type 2 diabetes is very insidious and can develop over years before being diagnosed. It is usually found in people over 40 years old, a decade earlier in newly westernised countries and accounts for the majority of diabetic cases representing about 97% of the population affected by the disease worldwide (29). The rate of increase is epidemic and it already affects more than 150 million persons.

It is believed that the origin of type 2 diabetes is multifactorial. These include a sedentary life style, obesity, and some nutritional related factors. Most common symptoms include thirst, urination, and tiredness.

2.3.3 Other Types of Diabetes

Gestational diabetes mellitus is characterised by glucose intolerance occurring during pregnancy, in most case reversibly. It is estimated that it affects 135,000 pregnant woman annually in the U.S.(30).

Various genetic defects can lead to diabetes. Some affect the ß-cell function resulting in reduced insulin secretion, other affect insulin action mostly because of a genetic defect of the insulin receptor .

Partial or total pancreatectomy can also induce a relative or total lack of endogenous insulin secretion inevitably resulting in diabetes.

Lastly, some drug and chemicals can induce diabetes by impairing insulin secretion or insulin action. Contact with certain toxins or medications will induce diabetes with a variable severity.

2.4 Type 1 Diabetes

The focus of the present work is on subjects with Type 1 diabetes, a much less common form than Type 2 diabetes but still highly prevalent in the developed countries. Type 1 diabetes accounts approximately for 10-15% of diabetes cases in developed countries (48) and is the most common chronic disorder in children.

The exact cause of Type 1 diabetes is not fully understood but aetiological studies suggested risk factors including genetically mediated hereditary factors (49). Several genes are implicated in an increased susceptibility to develop diabetes. Particularly strong associations have been found with the human leukocyte antigen (HLA) DR3 and/or DR4 present in 95% of Caucasians with Type 1 diabetes (45).

In most cases, Type 1 diabetes is the result of an autoimmune disorder causing the subject's immune system to attack its own tissues. More specifically, in the case of Type 1 diabetes the immune system targets the pancreatic ß-cells which secrete insulin. Several antigens have been implicated including islet cell antibodies (ICA) and glutamate decarboxylase (GAD), the latter being present in a majority of recent onset Type 1 diabetes subjects (45).

Several nutritional factors are also suspected to induce Type 1 diabetes, in particular the milk proteins, but this still lacks solid evidence (50). An exposure to certain infections is also suspected to trigger an autoimmune reaction (51) and infant's day-care seems to play a role in the incidence of diabetes (52). Other possibilities include physical injuries, pancreatectomy, or contact with specific toxins.

2.5 Diabetic Complications

If glucose is vital to the cells, an excessive glucose concentration is also toxic and leads directly or indirectly to a large panel of complications with huge cost implications. In 1997, the United States health care expenditure for diabetes was about 15% of the total budget of which 95% were associated with diabetes complications.

Complications fall into two categories, acute complications, that develop quickly, and chronic complications also qualified as long term complications.

The acute complications are due to large deviations from normoglycaemia. These include hypoglycaemia and severe hypoglycaemia usually defined as

plasma glucose below 3.3 and 2.8mM, respectively, and hyperglycaemia when plasma glucose is above the level of 13.9mM.

Although not due to diabetes itself but ironically to its treatment, the most immediate complication is a drop in plasma glucose due to an oversupply of insulin. This can happen in a number of situations, most commonly, due to an overestimated insulin bolus at the meal time, or an unexpected alcohol intake, or exercise.

A large insulin excess leads to pronounced hypoglycaemia, and possibly death. Fortunately, in most cases the subject will experience symptoms which can be autonomic (due to the body reaction to hypoglycaemia) or, if plasma glucose further decreases, neuroglycopenic (due to the brain glucose deprivation). However, it has been reported that repeated hypoglycaemia can diminish hypoglycaemia symptoms and couterregulation, resulting in a condition known as hypoglycaemia unawareness (53,54).

Acute hyperglycaemic complications correspond to diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemia. Although not as immediate as hypoglycaemia, DKA is a serious condition and may cause death among subjects with Type 1 diabetes. DKA is the result of a build up of catabolic by-product in the blood stream due to shortage of insulin.

Chronic hyperglycaemia is responsible for tissue damage. The long term complications can be grouped into the microvascular and macrovascular complications.

The microvascular complications affect the retina. Retinopathy is induced by vasopermeability and non perfused areas. At an advanced stage this results in haemorrhage and severe ischemia responsible for a non-reversible vision loss.

Nephropathy is another common microvascular complication. It affects various parts of the kidneys. This condition is well characterised by an increased capillary pressure and protein leakage. Ultimately, a major dysfunction and

kidney failure will occur. Subjects survival is then subject to renal replacement therapy.

Neuropathy is another type of long term microvascular complication. It is responsible for a large number of non traumatic amputations. As opposed to retinopathy and nephropathy, this complication affects various organs of the body by damaging the nervous system. A foot ulceration and neuropathic oedema are some of the most common occurrences due to neuropathy. Other complications related to the nervous system damage include gastroparesis, diarrhoea, neuropathic bladder, erectile failure, and anomalous cardiovascular reflexes.

The second family of long term complications involves large blood vessels. It is a leading cause of cardiovascular disease in diabetes subjects. Because of the aetiology of Type 2 diabetes this family of complications is more frequent in Type 2 diabetic subjects because these often pre-exist and constitute the background for the development of the disease. However, poorly controlled subjects with Type 1 diabetes are also affected because of the high level of the plasma insulin concentration combined with high plasma glucose at other times.

Lastly, subjects with diabetes are more prone to infections. Combined with a decreased sensation, this can lead to pain free ulcer which then can possibly lead to amputation.

2.6 Standard Diabetes Treatment

Insulin was discovered in the early 1920s. Before then Type 1 diabetes led to death as insulin is the only hypoglycaemic agent in the body. The hypoglycaemic effect of insulin has no redundancy and is still the only available treatment.

To avoid short and long term complications, subjects with Type 1 diabetes need to self inject insulin with the aim to match their insulin needs. The principle is simple but the insulin therapy adjustment is in practice very complex explaining in part the difficulties for a closed-loop system.

An early treatment offered very crude means to control blood glucose. Relying on urine glucose strip, it was lacking precision and reliability. At high plasma glucose concentration, glucose passes into the urine but the urine test measurements do not reflect the plasma glucose concentration. It is influenced by a variable dilution.

In healthy subjects, glucose is constantly monitored and insulin release is constantly adapted to the needs. The objective of the treatment is to replace the absence of endogenous insulin by exogenous insulin. Ideally the insulin injection should reproduce basal and postprandial insulin profiles. At present, the two most common types of treatment are based on multiple daily injections (MDI) or the continuous subcutaneous insulin infusion (CSII) using an insulin pump.

Three main insulin types are now available: long, intermediate, and fast acting insulin analogues. These provide a different onset, peak, and duration of action (6,8,55-57).

2.6.1 Multiple Daily Injections

Treatment with multiple daily injections (MDI) is the most commonly employed approach to control blood glucose in Type 1 diabetes.

The strategy of the MDI treatment is to use insulin with various time action profiles to reproduce the basal rate with long and intermediate acting insulins and the postprandial insulin surge with fast acting insulin (58). The long acting insulin is, ideally, a slow, peak-free insulin (59,60) mimicking the basal needs. The fast acting insulin is quickly absorbed with an early peak action (61).

With the multiple daily injections, two types of treatments have been developed making use of the insulin characteristics by combining fast acting and intermediate acting insulins or mixing long acting and fast acting insulins.

The conventional therapy consists of two injections per day with intermediate and fast acting insulin given at breakfast and in the evening. The aim is to avoid

symptomatic hyperglycaemia and severe hypoglycaemic episodes. The insulin regimen is dictated by the subject's lifestyle and finger prick glucose measurements.

Another type of insulin treatment is called the intensive therapy. It has gained popularity and is widely promoted because of its superior results compared to the conventional therapy (1,62). It consists of a mixture of long, intermediate, and fast acting insulin but the difference lies in the more tailored approach than that adopted by the conventional therapy. It consists of a minimum of three injections per day. Insulin is injected before each meal in addition to long acting insulin which covers the basal needs.

Combined with educational training, the intensive therapy leads to improved treatment (10) and enhanced life quality (63).

The improvement in insulin therapy has been made possible thanks to a progress in insulin engineering but also in the availability of reliable and easy-to-use monitoring devices (64). Measurement devices are numerous and have become more and more advanced often keeping track of past events therefore facilitating optimisation of insulin treatment and helping in the adoption of the intensive insulin therapy.

Injections classically rely on syringes but devices known as insulin pens facilitate the insulin administration by combining an insulin cartridge with a highly pressurised air mechanism. Their usage characteristics have promoted their dissemination and improved self care (65).

The main objective for glucose control is individually tailored insulin delivery. An approach employing a continuous infusion of fast acting insulin is increasingly used because of its numerous advantages to provide an improved insulin delivery. This is presented in the next subsection.

2.6.2 Continuous Subcutaneous Insulin Infusion

The continuous subcutaneous insulin infusion (CSII) is seen as an alternative to MDI. CSII dates back to the late 1970s with the first report of a portable insulin pump (66). Initially very bulky, burdened by a limited battery life and insulin aggregation, insulin pumps have became popular during the last ten years (67). They have the size of a pager, equipped with a long-life battery and far more stable insulin.

As opposed to MDI, during CSII insulin is infused continuously with a pre-programmed user-defined profile and an additional bolus at meal time. This provides for a more regular insulin delivery facilitating a more physiological plasma insulin profile.

There are two types of insulin pumps, either internal, delivering insulin intraperitonealy but requiring surgery to be implanted, or external, employing the subcutaneous delivery route and being minimally invasive. External pumps have entered into routine use. The use of internal pumps is limited and the present section focuses on external pumps.

An advantage of insulin pumps is related to the use of fast acting insulin permitting fast changes in the plasma insulin profile. This allows for a greater flexibility to adapt to the subject's lifestyle.

The downside of the use of fast acting insulin is an increased risk of hyperglycaemia and ketoacidosis. Because of its short-term action, an insulin infusion discontinuation will lead to hyperglycaemia faster than with regular insulin (68-70). However, pumps can be equipped with a pressure sensor to detect occlusion (71). However, complications are due to the catheter dislocation or a possible mechanical failure. This risk implies frequent measurements and a more extensive education of pump users (68). Studies have shown that fast acting insulin lispro is safe and an insulin of choice for pumps (71).

Many studies have demonstrated the association between a good glucose control and the reduction of the long term complication (62,72-75). Some studies focused on comparing MDI and CSII in terms of efficacy and safety (13,76). Results shown some improvements in metabolic control (77,78) but also an improvement in the number of hypoglycaemia events (13,79,80) usually associated with the tight glucose control.

CSII has been shown to improve insulin sensitivity (78) which is important because of the deleterious effect of excessive insulin delivery needed in the insulin resistant patient. Insulin has been associated with weight gain which in turn increases the risk of complications. A relatively low weight gain has been reported in a review by Bode et al (67).

With CSII, an insulin sensitive subject can benefit from a high resolution of insulin delivery, usually as low as 0.1U/h which is not possible with the MDI approach. CSII can enhance the control of subjects experiencing hyperglycaemia due to the dawn phenomenon (81).

CSII is ideal for some but not for all. An important factor for the choice of a pump is related to the subject's compliance. A meal content estimation and regular monitoring are a requirement for a successful and safe pump use. Despite its advantages, the adoption of the insulin pump can be slowed down by its initial cost and an expensive maintenance (82).

2.6.3 Other Insulin Delivery Approaches

Other types of insulin delivery are under development. Iontophoresis can be employed to deliver insulin by circulating an electric current provoking the migration of insulin molecules through the dermal route (83,84).

Inhaled insulin is being investigated (85-88). The pulmonary delivery route presents appealing properties such as convenience, non-invasiveness, and the speed of absorption (85). However, a large amount of insulin is not absorbed

(87) and clearance mechanisms are still unclear. But progress is being made (86,88).

Other controlled release approaches are being elaborated employing various materials. Biocompatible and biodegradable materials such as hydrogel (89,90) or microspheres (91-93) could be employed.

A large amount of work has been devoted to pancreatic transplantation (94-97). The first transplantation was performed in the 1960s. This treatment can offer a full normalisation of glycaemia but its use is limited by the availability of sources of the pancreatic cells and requires a lifetime of immunosuppressive treatment (98) which is known to weaken the immune system.

3 Simulation and Modelling to Support Treatment of Type 1 Diabetes

3.1 Introduction

Glucoregulation is an extensively studied system. Over the last three decades, different approaches have been applied to distil complexities and intricacies of the glucose metabolism on the whole body, organ, or cellular level.

The present review is concerned with modelling and simulation of the glucoregulatory system on the whole body level. Specific subsystems are also reviewed. A review of model-based decision support systems is also included. The focus is on approaches related to Type 1 diabetes. Models describing insulin secretion are therefore excluded. Finally, a review of closed-loop approaches to treat Type 1 diabetes is presented. A non-linear model predictive controller is described in detail as it is used extensively throughout the thesis to exemplify the utility of the simulation environment.

3.2 Modelling of Glucose Metabolism

Modelling and simulation of the glucoregulatory system has a long history as a tool to explain, quantify, predict, and teach. As all models have a restricted validity, their use has to be limited to a specific domain. By definition, a model can only be an approximation of the system behaviour. However, it can be sufficient for its intended purposes.

A large proportion of models to represent the glucoregulatory system adopt a compartmental approach which offers suitable means to describe fluxes between different body organs and/or tissues in terms of the mass balance expressed in a mathematical form.

Simple models have been proposed by Cobelli *et al* (99-101), resorting to a single compartment model. These models require assumptions which are not fully compatible with the glucose system. Others have also adopted simple linear models leaving out many of the non-linearities present in the physiology such as

saturation processes (102). Specifically, Ackerman *et al* (103) introduced one of the first models to represent glucose and insulin kinetics employing two linear differential equations. This two compartment model had two parameters for the glucose kinetics and two parameters for the insulin kinetics.

More complex structures were proposed by Cerasi *et al* and Insel *et al* (104,105). A three compartment model was proposed by Ferrannini (106) representing the distribution and exchange of glucose among the different body pools. However, the representation failed to partition the peripheral and hepatic glucose disposal.

Salzsieder *et al* (107) developed a model-based system to optimise the insulin therapy. The model was described by fourth-order differential equations. The approach consisted of identifying subject's metabolism characteristics, and employed simulations to derive an optimised insulin therapy.

A study by Boroujerdi *et al* (108) focused on representing glucose transport processes. This explanatory model was employed in various simulations to increase our understanding of glucose utilisation in subjects with diabetes. The model included insulin dependent and independent glucose disposal and a glucose saturable flux into the intra cellular space.

New technologies such as the positron emission tomography (PET) combined with the use of tracers have enabled to increase our understanding and knowledge. The technique has provided deep understanding of glucose transport leading to a 15 compartment model (109).

In line with a detailed description of the glucoregulatory system, Guyton *et al* (110) resorted to a set of 32 differential equations. This model was further expanded by Sorensen (111) and included additional components such as the glucose counteregulation and disturbances such as meal and exercise.

Structurally complex models are useful for their explanatory powers. But they require complicated experimental methods to derive subject specific parameters.

At times, it is important to reduce model complexity and thus the number of parameters while retaining the representation of the fundamental physiological processes. The primary advantage of the so called "minimal model approaches" is that they facilitate the parameter estimation of individual subjects without excessively complicated clinical tests.

Two widely used clinical experiments can be used to estimate characteristics of the carbohydrate metabolism using model-based techniques. These tests are (i) the intravenous glucose tolerance test (IVGTT) and (ii) the meal tolerance test (MTT) or the oral glucose tolerance test (OGTT).

In 1979, Bergman *et al* (112) adopted a minimal approach to derive insulin sensitivity (S_I) and glucose effectiveness (S_G) from data collected during the IVGTT. Insulin sensitivity describes the ability of insulin to stimulate glucose disappearance and glucose effectiveness describes the ability of glucose to promote its own disappearance. However, unlabelled IVGTT could not distinguish between the glucose production and the glucose disposal. This limitation was overcome by developing labelled IVGTT. The minimal model of the glucose kinetics (113-115) during the labelled IVGTT facilitates the estimation of the hepatic glucose production during the IVGTT.

As opposed to the IVGTT which can be considered unphysiological, other more physiological tests were employed to characterise a subject. Recently, Breda *et al* (116) have employed the oral glucose tolerance test to derive indices of insulin secretion and insulin action for a particular subject. An insulin secretion model during the MTT by Hovorka *et al* (117) gives indices describing the ability of the pancreas to secrete insulin under fasting and postprandial conditions.

A number of models (110,118,119) have been adopted in simulation studies (120-124) according to particular requirements. These models were employed to test control or advisory algorithms and strategies to optimise insulin therapy (124-129).

A simulator has incorporated the subcutaneous insulin kinetics and allowed experiments with various insulin inputs and the resulting glucose profile to be executed. The simulator was only valid for an average subject (130). Lehmann and Deutsch have extended the capabilities of the system by including a parameter estimation process. However, the parameter individualisation process was not evaluated (131).

The relationship between plasma and interstitial fluid glucose has been investigated following the availability of minimally invasive or non invasive subcutaneous glucose sensors (23,132-134). A model of the subcutaneous glucose kinetics has been recently developed (64,135,136). Wilinska *et al* proposed 9 models. Important findings about the temporal variation in interstitial glucose (IG) to plasma glucose ratio were found. The study provided background information for the new model implemented in the simulator; 2 of the 9 models were used in the simulator as described in Chapter 4.

Modelling studies identified the importance of the insulin delivery route and algorithms (137,138). Cobelli *et al* (138) employed a previously developed model of glucoregulation (118) replacing endogenous insulin secretion by a controlled insulin delivery in the liver or plasma compartment. It outlined and explained the potential and limitations of the peripheral insulin and hepatic delivery route (138).

To model the absorption and kinetics of different types of insulin, compartmental modelling has again been widely used. A two compartment model representing plasma glucose and the interstitial glucose space was developed for actrapid (139), a fast acting insulin. A three compartment model was developed by Puckett *et al* to model the kinetics of human insulin given as boluses (140). Another three compartment model dividing the subcutaneous space into two subcompartments was developed to describe the kinetics of fast acting insulin (141).

The kinetics of insulin Lispro, which is used in insulin pumps, have been modelled using a three compartment structure employing bolus injection and used for the development of a closed-loop insulin delivery device (142). A model

of monomeric insulin was developed by Trajanoski *et al* (143). The study suggests that a change in the absorption rate was not influenced by the varying volume and the injection depth. The model was then used in simulations to test a glucose controller (124).

Stimulated by the need for a better therapy, some models were placed in a simulation framework. These simulators were used in various ways to educate subjects with diabetes or to test open loop and/or closed-loop insulin delivery systems.

Models in simulators developed for educational purposes are usually characterised by a representation of an average subject. Therefore these systems do not provide individualised advice but rather enable the influence of different insulin regimens, meals, or exercise to be understood.

An educational simulator was developed using a heuristic model of physician's predictions (144) to derive the glucose profile from insulin injections in an average subject. It included the influence of food intake and exercise.

In Glucosim (138), a complex model is employed to describe the glucoregulation in subjects with Type 1 diabetes representing the glucose kinetics and the pharmacokinetics of subcutaneous insulin. Glucosim can be employed to simulate virtual experiments. However, the model does not support an individualised insulin optimisation.

An Interactive Diabetes Advisor (AIDA) (145-147), one of the most promoted simulators dedicated to education, contains a model that represents both endogenous and exogenous glucose inputs. Although AIDA is limited by its representation of an average subject, the glucose utilisation is well described by distinguishing between the insulin independent and insulin dependent components.

Another approach to modelling adopts the representation of the input/output relationship without attempting to represent explicitly the physiological

knowledge. A typical example can be found in a published simulated study by Sano (148) who related the intravenous insulin infusion and the blood glucose level using a linearised model.

The model by Ackerman *et al* (103) which adopted the input output relationship representation was modified to represent a subject with Type 1 diabetes by setting the insulin response parameter to zero. It was used in simulated studies (127) to obtain knowledge about insulin therapy.

Parker *et al* (122) employed a pharmacokinetic-pharmacodynamic approach by using a fundamental model by Sorensen.

A two-compartment model of carbohydrate metabolism has been recently developed (42). It provides novel information about certain characteristics of the glucose/insulin kinetics. In particular, the study using glucose tracers has enabled the partitioning of three different insulin effects on the glucose transport/distribution, disposal, and hepatic glucose production.

In summary, modelling and simulation have complementary aims and may use different approaches and reach different levels of complexity. Key elements when building a model are to define its objectives and the type and complexity of its structure.

3.3 Decision Support Systems

Decision support systems are intended to help in the decision making process and are used in a wide range of systems, tools, technologies, and domains such as in economics for risk analysis, management of various organisational processes, or in medicine to facilitate diagnosis, treatment optimisation, or disease management.

In Type 1 diabetes, numerous decision support systems have been employed to aid in the optimisation of insulin therapy. A wide variety of approaches for data analysis and feature extraction have been employed such as time series

analysis (149,150), fuzzy logic (151-153), and causal probabilistic networks (154-157). The systems give advice on insulin dosing on a visit-to-visit, day-to-day, or dose-by-dose basis depending on the exact objectives. Decision support systems in diabetes are numerous but a few stand out.

In Utopia, the time series analysis technique of subject specific data was employed (150) to adjust insulin regimen on a visit-to-visit basis through the establishment of a subject's modal-day which implied a certain consistency of the subject's lifestyle.

Hovorka *et al* (158) developed a model-based system, which employed individualised parameter estimation using past glucose measurements and insulin administration to generate advice on insulin therapy. The system was shown to improve glucose control.

A diabetes advisory system (DIAS) (157) is a decision support system which employs a causal probabilistic network model of the glucose metabolism and the Bayesian parameter estimation to predict the glucose profile from historic plasma glucose measurements, food intake and insulin doses.

Others adopted a rule-based approach, see for example Skyler *et al* (159). Diabetex (160) is a knowledge-based system that can accept various modes of insulin delivery. However, it has poor capabilities to individualise treatment. Stadelmann *et al* (161) have extended Diabetex with a decision module to take into account special situations.

A mathematical model of the glucose/insulin interactions was used in the development of the decision support system Kadis (162). However the parameter estimation procedure requires numerous clinical experiments which render its extensive use difficult.

The objectives of the decision support systems are different from these of an automated closed-loop system. They should not be regarded as a substitute but rather complementary to the treatment process.

3.4 Closed-Loop Control

The development of an "artificial endocrine pancreas" for subjects with Type 1 diabetes has been subject to extensive research since the 1970s. Considerable research has been dedicated to the development of insulin delivery algorithms to close the loop. Several approaches have shown promising results under simulated conditions but few results are available about their clinical performance.

The present review covers the main control strategies developed for a closed-loop system. The approaches can be divided into three categories according to the type of control employed to drive the insulin delivery: (i) non-adaptive approaches, (ii) adaptive or optimal control approaches, and (iii) model predictive approaches.

3.4.1 Non Adaptive Approaches

These control approaches have the advantage of being relatively simple but are limited in their ability to cope with the variability and delays.

The initial work was carried out by Pfeiffer *et al* (163) developing the glucose controlled insulin infusion system (GCIIS) leading to the development of the "Biostator" (164,165), one of the most well known feedback control system still in use in experimental settings. The system employed *ex vivo* blood glucose measurements and the intravenous insulin infusion. It used a proportional integral derivative (PID) controller coupled with measurement noise rejection techniques. The insulin infusion was linked to the rate of glucose change by an algorithm developed by Albisser *et al* (166) with modifications, for example, by Botz (167), Marliss *et al* (168), and Kraegen *et al* (169). These and similar algorithms were reviewed by Broekhuyse *et al* (170), who concluded that none of the algorithms was superior and that further work was required to achieved normalisation of the glucose concentration.

Another method was developed to close the loop (171). The intravenous insulin infusion was modified on hourly basis according to hourly plasma glucose measurements. Good control was obtained overnight. The overall amount of insulin given intravenous and insulin delivered by an insulin pump via the subcutaneous route on the basis of a 4 to 5 days insulin requirement study were strongly correlated. The nocturnal basal insulin requirements remained constant for several months apart from special conditions such as illness. The authors concluded that insulin infusion rates need to be customised to the individual.

3.4.2 Adaptive and Optimal Control Approaches

Due to the presence of the inter- and intra-subject variability, optimal and adaptive control approaches characterised by the ability to adapt to new circumstances are appealing.

Advanced algorithms used, for example, include the pole-placement technique (125). A similar concept was adopted by Shichiri *et al* (17,172). The optimal control theory was employed by Swan (173), Ollerton (174), and Fisher and Teo (127).

A study was carried out focussing on robustness to deal with parameter variations and uncertainty using the H-infinity theory but made the assumption of the continuous plasma glucose measurement (120). The H-infinity theory was shown to provide a good compromise between the performance and robustness requirements. However, in another study using the same approach (175), it was concluded that the uncertainty needed to be well characterised and it was necessary to restrict the uncertainty included on the eight parameters problem to that associated the three most highly sensitive parameters.

Self-tuning controllers were tested under simulated conditions. Self tuning controllers are a special group of controllers in which the parameter estimation procedure is performed automatically. Such approaches used the subcutaneous glucose measurements and the subcutaneous insulin infusion or the peritoneal insulin administration (176), and the intravenous glucose measurement and the

intravenous insulin infusion (121). Results were promising demonstrating insensitivity to variable subject responses but the development did not progress beyond the simulation stage.

Candas and Radziuk (129) employed a similar approach but the aim was to maintain euglycaemia with exogenous insulin and glucose infusions. The performance of the controller was evaluated in an animal study (three pigs were studied) and plasma glucose stability was documented. It was concluded that a model mimicking the glucoregulation provided valuable information for the development of an artificial pancreas.

Adaptive control was employed along a finite preview optimal control law in a simulation and animal study using a linearised model (177). The intravenous measurements with a small dead time of 4 minutes and intravenous insulin infusion were used. The adaptive component was beneficial to control adjustments due to inter-subject variability. The preview component had a positive effect but had to be carefully chosen to avoid hypoglycaemia prior to the glucose load.

3.4.3 Model Predictive Approaches

Model predictive control (178) is an emerging methodology known to facilitate control of systems with long time delays and open loop characteristics.

The strategy of model predictive control is shown in *Figure 3.1* (179). Based on a model, the output trajectory $\hat{y}(t+k \mid t)$, k=1...N, is estimated for any given control sequence $u(t+k \mid t)$ over a prediction horizon N. The model primary use is to determine optimum control sequence, which results in a desired (target) trajectory.

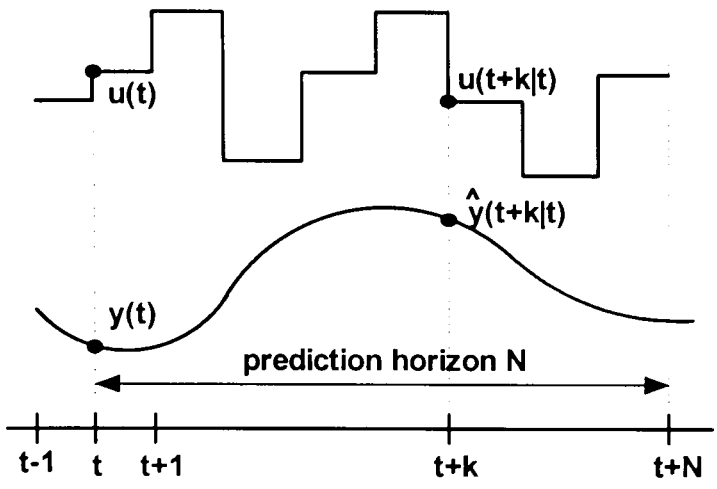

Figure 3.1: Strategy of model predictive control.

The control action is the first insulin infusion rate u(t+1) of a control sequence u(t+1) ... u(t+N), which is calculated by minimising an objective function composed of two components, (i) the adherence of the predicted glucose to the target trajectory y(t+i) and (ii) the variation in the control sequence.

The first generation of control approaches was designed for intravenous glucose sampling and intravenous insulin infusion. The subcutaneous delivery of insulin is less invasive than the intravenous insulin delivery and is suitable for the use with a wearable extracorporeal artificial pancreas.

It has been well recognised that the subcutaneous insulin delivery poses problems to efficient glucose control due to the additional delay associated with the absorption of subcutaneously infused insulin (138) and only with the availability of fast-acting insulin (57,180), the next generation of control algorithms could have been developed. When combined with adaptive capabilities, model predictive control promises to tackle successfully problems associated with control of glucose concentrations in subjects with Type 1 diabetes. Algorithms developed with such an approach assume a model representation of the underlying system and, usually, the model adopts a linearised version of one of the many models of the glucoregulatory system (80,130,181,182).

An early study using the intravenous glucose measurements and the intravenous insulin infusion route in dogs pointed out the potential of the model predictive control by comparing a simple glucose projection technique with the direct control. A sparing effect on the insulin administration was found (166). This represents an advantage over the Biostator algorithm, which tends to administer too much insulin and generates spikes because of the derivative component in its control law.

More advanced predictive control schemes were employed later. For example, Lynch and Bequette (183) and Parker *et al* (122,122) have recently used model predictive control but limited its use to simulations. In the latter study, good results were obtained for measurement delays less than 10 minutes. A preliminary identification of each subject had to be performed. A non-linear predictive control with subcutaneous insulin infusion using neural networks was proposed by Trajanoski *et al* (123,124). The approach has been evaluated in simulated studies. The results confirmed the limitations due to the delays but have provided insights into the performance of the closed-loop when minor fluctuations of blood glucose are present, e.g. in the preprandial state. The authors recommend additional information, e.g. timing of meals, to be provided to such algorithms when the subcutaneous-subcutaneous route is considered.

3.4.4 Non-linear Model Predictive Controller

In parallel with the work described in the thesis, a new nonlinear MPC has been developed to maintain normoglycemia in subjects with Type 1 diabetes (184,185). The controller employs a novel non-linear model of the glucose kinetics based on a detailed dual-tracer study by Hovorka *et al* (42). The controller adopts Bayesian parameter estimation to facilitate adaptive behaviour. The controller is designed to work with subcutaneous measurements and subcutaneous insulin infusion. Its structure is presented in *Figure 3.2*. The model predictive controller is used in Chapters 6 and 7 to demonstrate the use of the simulator described in the thesis. The two applications were developed hand in hand. The simulator assisted in tuning and testing the MPC, the MPC supported the assessment of the simulator validity, see Chapter 7. The MPC is described in

a greater detail in the present section to facilitate conceptual understanding of its structure and functions.

The MPC controller is designed to be used with subcutaneous glucose sampling and subcutaneous infusion of insulin Lispro by insulin pump. In principle any glucose sampling/control frequencies, equidistant or non-equidistant, are possible without changes to the controller design.

The model gave glucose predictions with a mean square error proportionally related to the prediction horizon with the value of 0.2mM per 15 min.

The block diagram of the controller is shown in *Figure 3.2*. The controller includes the following components: parameter optimiser, target projector, dose optimiser, and safety schemes 1-4.

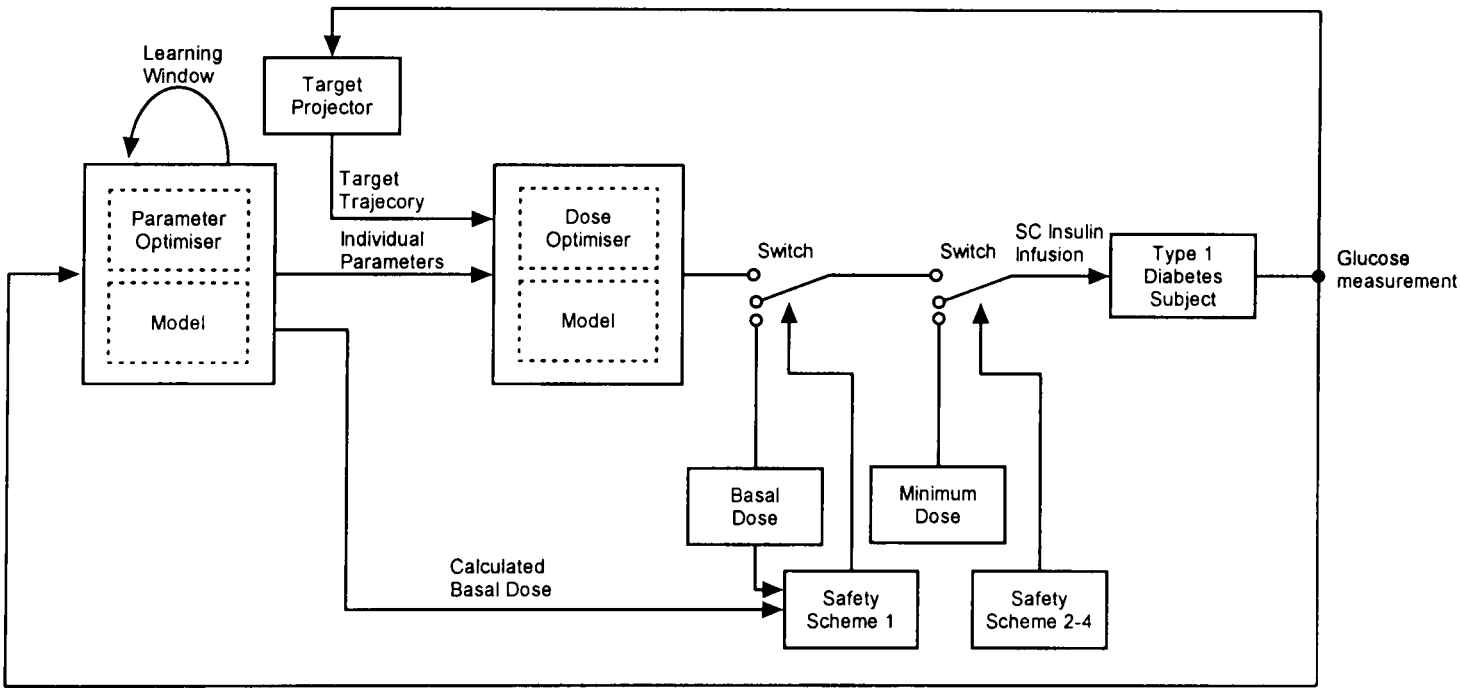

Figure 3.2: Block diagram of the model predictive algorithm.

The parameter optimiser estimates model parameters employing glucose measurements from a "learning window", i.e. a time period immediately preceding the control time. Three lengths of the learning window are predefined, fast, medium, and long, to be able to deal with both a time-invariant (or slowly varying) underlying system, which is best identified over a long learning window, and a time-variant system best identified over a shorter learning window.

The dose optimiser calculates a sequence of insulin infusion rates, which gives best fit to the target trajectory. From this sequence, the first element is returned and is suggested to be infused by the insulin pump. The remaining elements in the sequence are discarded. The dose optimizer adopts non-linear function minimisation as the underlying model is non-linear.

The target projector calculates target trajectory, i.e. the desired glucose profile. The target glucose concentration is 6.0mM. When starting above the target value, the target trajectory is linearly declining with a maximum decrease set to a conservative value of 2mM per hour to reduce the risk of an undershoot. When starting below the target trajectory, a faster exponential normalisation of glucose values is specified reflecting the need to recover faster from low glucose values.

For safety the control systems must be able to cope with exceptional circumstances. Four safety schemes protect against system failures and minimize the risk of insulin overdosing and subsequent hypoglycaemia.

Safety scheme 1 monitors the relationship between a "normal" (model-independent) basal insulin rate, determined from total daily insulin dose, and a "model" basal rate determined by the MPC. Basal rate corresponds to the insulin infusion rate, which maintains glucose concentration at normoglycaemia.

When model-based basal rate becomes substantially higher than the model-independent basal rate, the MPC-derived infusion rate is deemed to be too high due to the system failure and is overridden by the model-independent basal rate. This signals that "estimated" subject's insulin resistance is transiently increased above a plausible threshold. The model-independent basal rate is used rather than a minimal dose (alternating 0.0 and 0.1U/h to avoid pump occlusion) to provide an insulin supply comparable to that delivered without the use of the closed-loop control.

Further safety schemes limit the insulin infusion to a minimum dose of 0.1U/h when glucose is declining too fast (safety scheme 2), when glucose is below a specific threshold (safety scheme 3), or when glucose is administered

intravenously within the last 30min (safety scheme 4; designed for clinical tests only).

3.4.5 Conclusion

In conclusion, modelling of glucoregulation processes have fulfilled several of its purposes by allowing better understanding, increased knowledge, and facilitated patient management and education. Modelling was intensively employed to achieve an artificial pancreas (AP) but a comprehensive simulation environment for adequate testing of the AP is not available. Having in this chapter reviewed the various modelling approaches to the glucose metabolism in men, the next chapter is presenting a Type 1 diabetic model within a closed loop system employing CSII and subcutaneous glucose measurements.

4 Simulating Carbohydrate Metabolism in Type 1 Diabetes

4.1 Introduction

This chapter describes a model to simulate glucose excursions during fasting and fed conditions in Type 1 diabetes. The purpose is to have a sufficiently rich but not too complicated structure to facilitate the creation of an *in silico* population of subjects with Type 1 diabetes with a wide spectrum of behaviour. Such a population is described in the next chapter.

The simulated subjects are designed to be used in the development of an extracorporeal pancreas. Therefore the simulated subjects must represent the input-output relationship anticipated with the artificial pancreas. In particular, this includes sensing of the subcutaneous glucose and the subcutaneous delivery of fast acting insulin. The model should also include physiological variables such as plasma glucose and plasma insulin for monitoring purposes.

4.2 General Overview

The model of subjects with Type 1 diabetes consists of a glucose kinetics subsystem (glucose absorption, distribution, and disposal), an insulin kinetics subsystem (insulin absorption, distribution, disposal), and an insulin action subsystem (insulin action on glucose transport, disposal, and endogenous production). As the model represents subject with Type 1 diabetes, a model of endogenous insulin secretion is omitted.

The core of the model contains a published description of glucose kinetics and insulin action (42) building on recent experimental and modelling work, which employed glucose tracers to determine structure and parameter values of glucose kinetics in normal subjects during basal conditions and during the intravenous glucose tolerance test .

The overall model structure is represented in *Figure 4.1*.

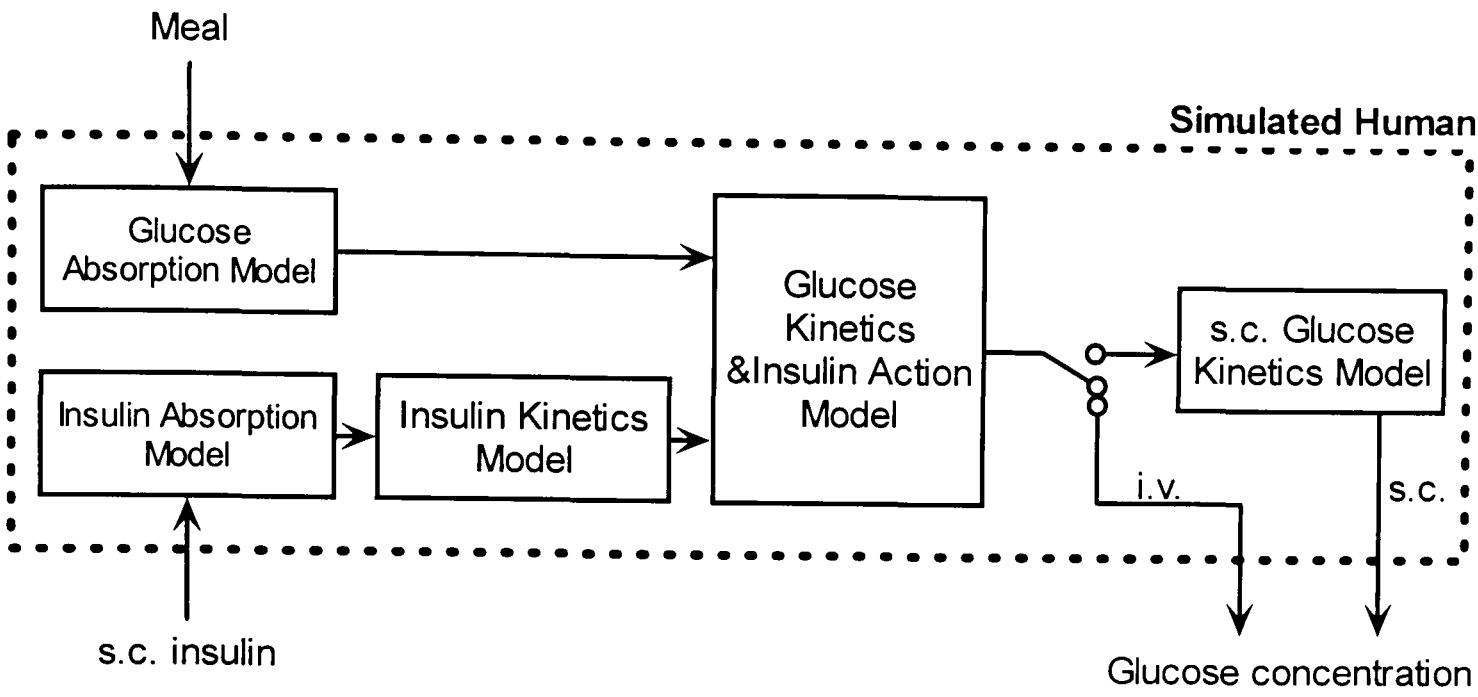

Figure 4.1: Model structure of a simulated subject with Type 1 diabetes.

4.3 Glucose Kinetics Subsystem

At the heart of the model is a two-compartment representation of glucose kinetics described as

$$\frac{dQ_1(t)}{dt} = -\left[\frac{F_{01}^c}{V_G G(t)} + x_1(t)\right]Q_1(t) + k_{12}Q_2(t) - F_R(t) + U_G(t) + EGP_0\left[1 - x_3(t)\right] \quad (4.1)$$

$$\frac{dQ_2(t)}{dt} = x_1(t)Q_1(t) - [k_{12} + x_2(t)]Q_2(t) \quad (4.2)$$

$$G(t) = \frac{Q_1(t)}{V_G} \quad (4.3)$$

where Q_1 (mmol kg^{-1}) and Q_2 (mmol kg^{-1}) represent the masses of glucose in the accessible (where measurements are made) and non-accessible compartments, k_{12} (min^{-1}) represents the transfer rate constant from the non-accessible to the accessible compartment, V_G (l kg^{-1}) represents the distribution volume of the accessible compartment, G (mmol l^{-1}) is the (measurable) glucose concentration, EGP_0 (μmol kg^{-1} min^{-1}) represents endogenous glucose production (EGP) extrapolated to the zero insulin concentration. $U_G(t)$ (mmol kg^{-1} min^{-1}) represents gut absorption and F_{01}^c (μmol kg^{-1} min^{-1}) is the total non-insulin dependent glucose flux corrected for the ambient glucose concentration where

$$F_{01}^{c} = \begin{cases} F_{01} & \text{if } G \geq 4.5\text{mmol l}^{-1} \\ \dfrac{F_{01}G}{4.5} & \text{otherwise} \end{cases} \qquad (4.4)$$

F_R (mmol kg^{-1} min^{-1}) is the renal glucose clearance above the glucose threshold G_{RT} (mmol l^{-1})

$$F_R = \begin{cases} k_{RT}(G - G_{RT})V_G & \text{if } G \geq G_{RT} \\ 0 & \text{otherwise} \end{cases} \qquad (4.5)$$

where k_{RT} (min^{-1}) is the renal clearance rate.

The variables x_1, x_2, and x_3 relate to the model of insulin action and are described in section 4.4.

The glucose kinetics subsystem, together with the insulin action subsystem is shown in *Figure 4.2*.

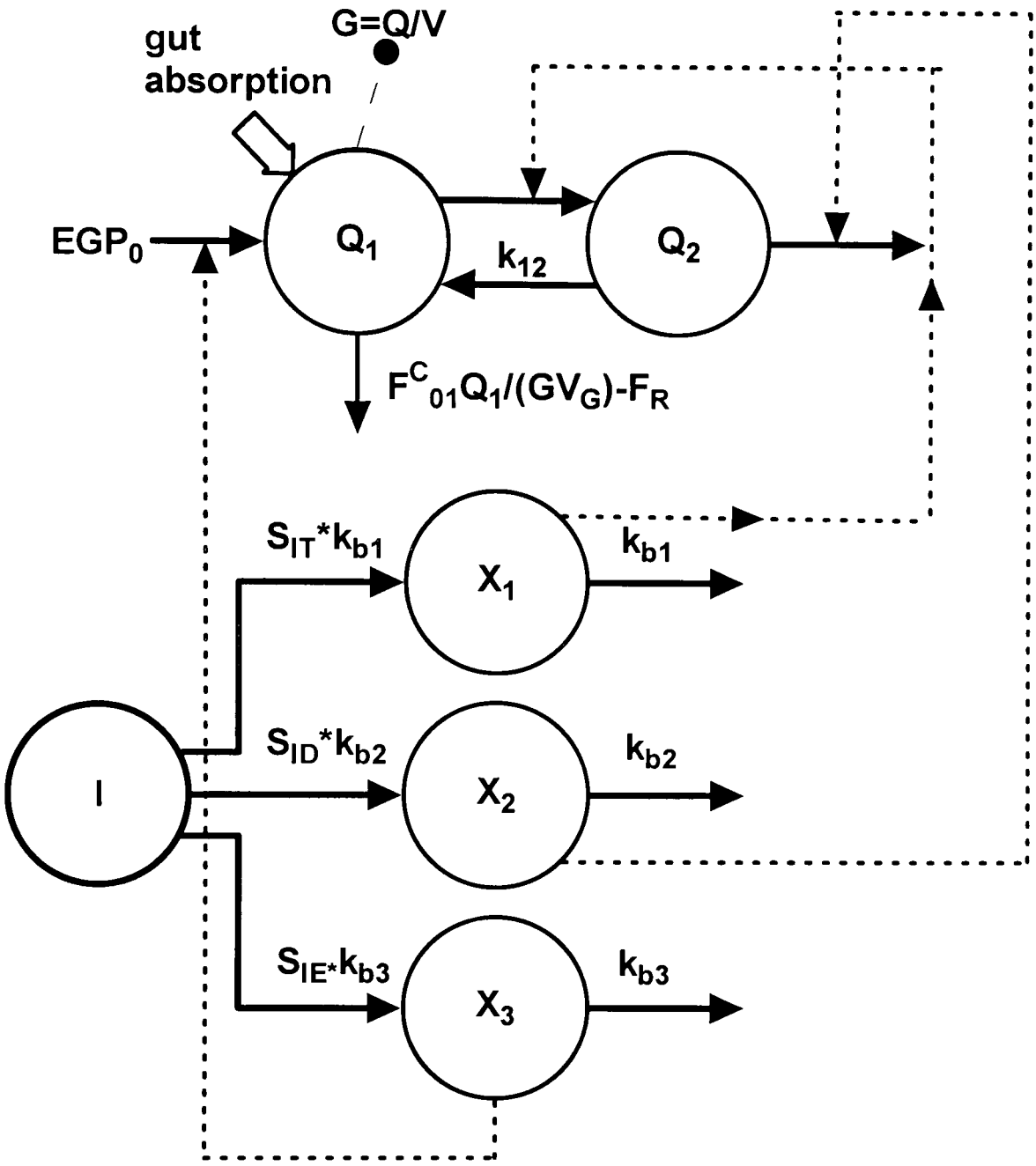

Figure 4.2: Compartmental model of glucose kinetics and insulin action. Q_1 and Q_2 represent masses in accessible (plasma) and non-accessible compartments, I represents plasma insulin, x_1, x_2, and x_3 represent insulin action on glucose transport, disposal, and endogenous glucose production, for more details, see section 4.3 and 4.4.

An example of model performance over one and a half days is shown in *Figure 4.3*, which includes plots of plasma glucose, renal clearance, endogenous glucose production (*EGP*), non-insulin dependent glucose flux (F_{01}^{c}), insulin dependent glucose disposal (F_{02}), and fluxes between the two compartments (F_{12} and F_{21}).

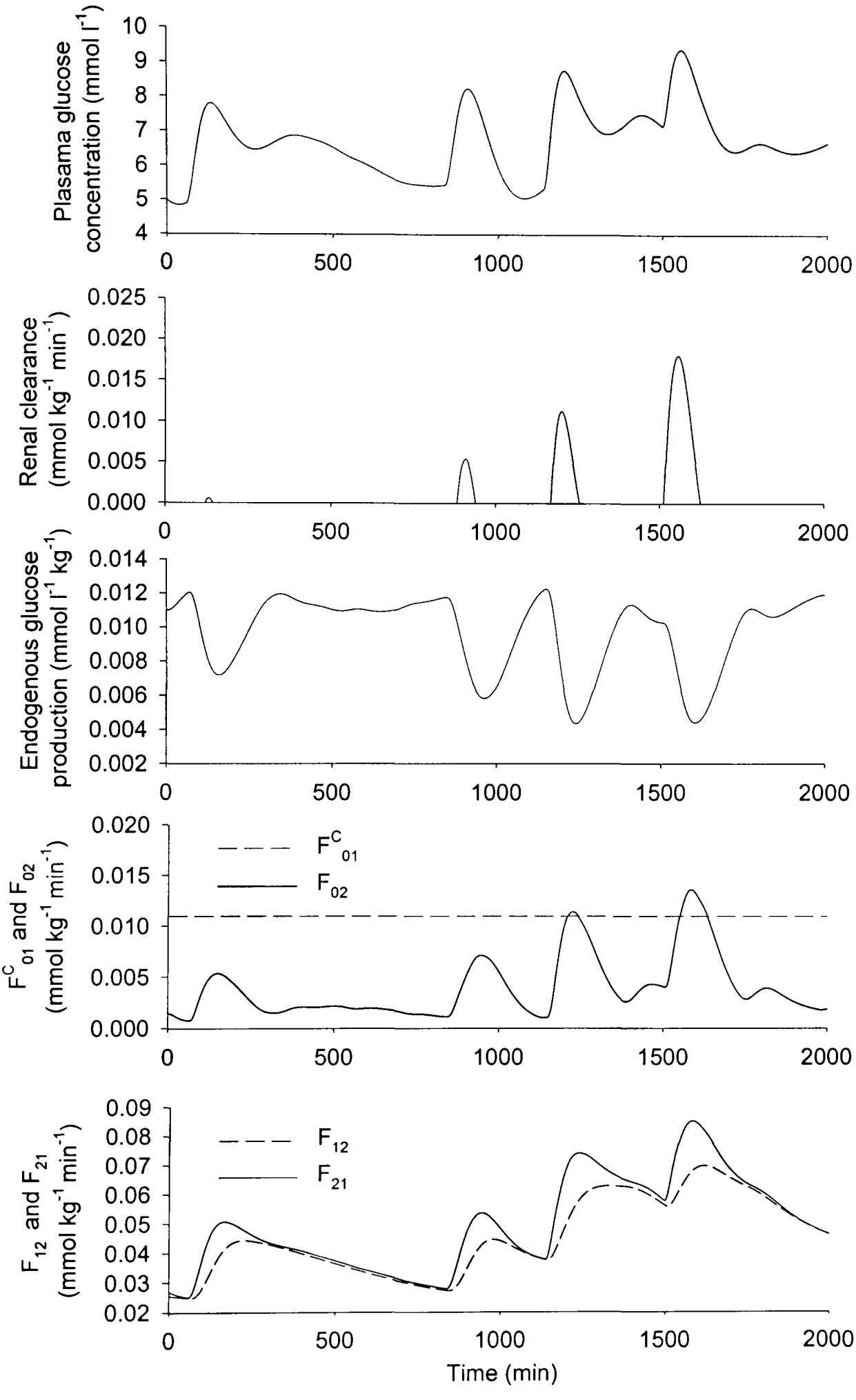

Figure 4.3: Sample simulation with the glucose kinetics subsystem over one and a half day. See text for details.

The simulation in *Figure 4.3* shows good glucose control during fasting but, in the post meal states (meals given at 840min, 1140min, and 1500min with 40, 70 and 60g carbohydrates (CHO), respectively), the plasma glucose concentration is high resulting in renal clearance of glucose.

The simulation shown in *Figure 4.3* employed parameters obtained from clinical experiments performed in 18 Type 1 subjects and generated from informed probability distributions. Further details about parameter estimation and generation are provided in Chapter 5 section 5.5.2. *Figure 4.3* employs parameters of subject 8.

The additional inputs to carry out the simulation include the provision of insulin action, see section 4.4, and the rate of gut absorption, see section 4.6. Parameter values of subject 8 were employed.

Table 4.1: Parameters of the glucose kinetics subsystem (subject 8) used to generate the simulation presented in Figure 4.3.

F_{01}‡ ($\mu mol\ kg^{-1}\ min^{-1}$)	EGP_0§ ($\mu mol\ kg^{-1}\ min^{-1}$)	k_{12}‖ ($10^{-2} \times min^{-1}$)	V_G¶ ($l\ kg^{-1}$)	G_{RT}# ($mmol\ l^{-1}$)	k_{RT}† (min^{-1})
11.04	14.07	2.93	0.18	7.8	0.011

‡ Non-insulin dependent glucose flux
§ Endogenous glucose production extrapolated to zero insulin concentration
‖ Transfer rate from non-accessible to accessible compartment
¶ Volume of distribution of the accessible glucose compartment
# Renal clearance threshold
† Renal clearance rate

4.4 Insulin Action Subsystem

The insulin action subsystem represents three actions of insulin on glucose kinetics (42) described as

$$\frac{dx_1}{dt} = -k_{b1}x_1(t) + k_{a1}\ I(t) \tag{4.6}$$

$$\frac{dx_2}{dt} = -k_{b2}x_2(t) + k_{a2}\ I(t) \tag{4.7}$$

$$\frac{dx_3}{dt} = -k_{b3}x_3(t) + k_{a3}\ I(t) \qquad (0.8)$$

where I is the plasma insulin concentration (mU l^{-1}), x_1 (min^{-1}) , x_2 (min^{-1}), and x_3 (unitless) represent the (remote) effect of insulin on glucose distribution/transport, glucose disposal, and endogenous glucose production; k_{bi} (min^{-1}), $i = 1..3$, represent deactivation rate constants, and k_{ai}, $i = 1..3$, represent activation rate constants.

The three insulin sensitivities, S_{IT}, S_{ID} and S_{IE},, given in *Table 4.2* represent the activities of insulin on the three glucose pathways. They are defined as the ratios of the activation and deactivation constants, i.e. $S_{IT} = k_{a1}/k_{b1}$, $S_{ID} = k_{a2}/k_{b2}$, and $S_{IE} = k_{a3}/k_{b3}$. In combination with the activation constants, the insulin sensitivities provide an alternative and presumably more robust parameterisation than that obtained with the activation and deactivation constants. Furthermore, the use of insulin sensitivities facilitates a more natural and transparent description and comparison of the insulin action system.

An example simulation with the insulin action subsystem is shown in *Figure 4.4*. The driving function, plasma insulin, is taken from section 4.5 (*Figure 4.6*). The model parameters used to carry out the simulation are given in *Table 4.2*.

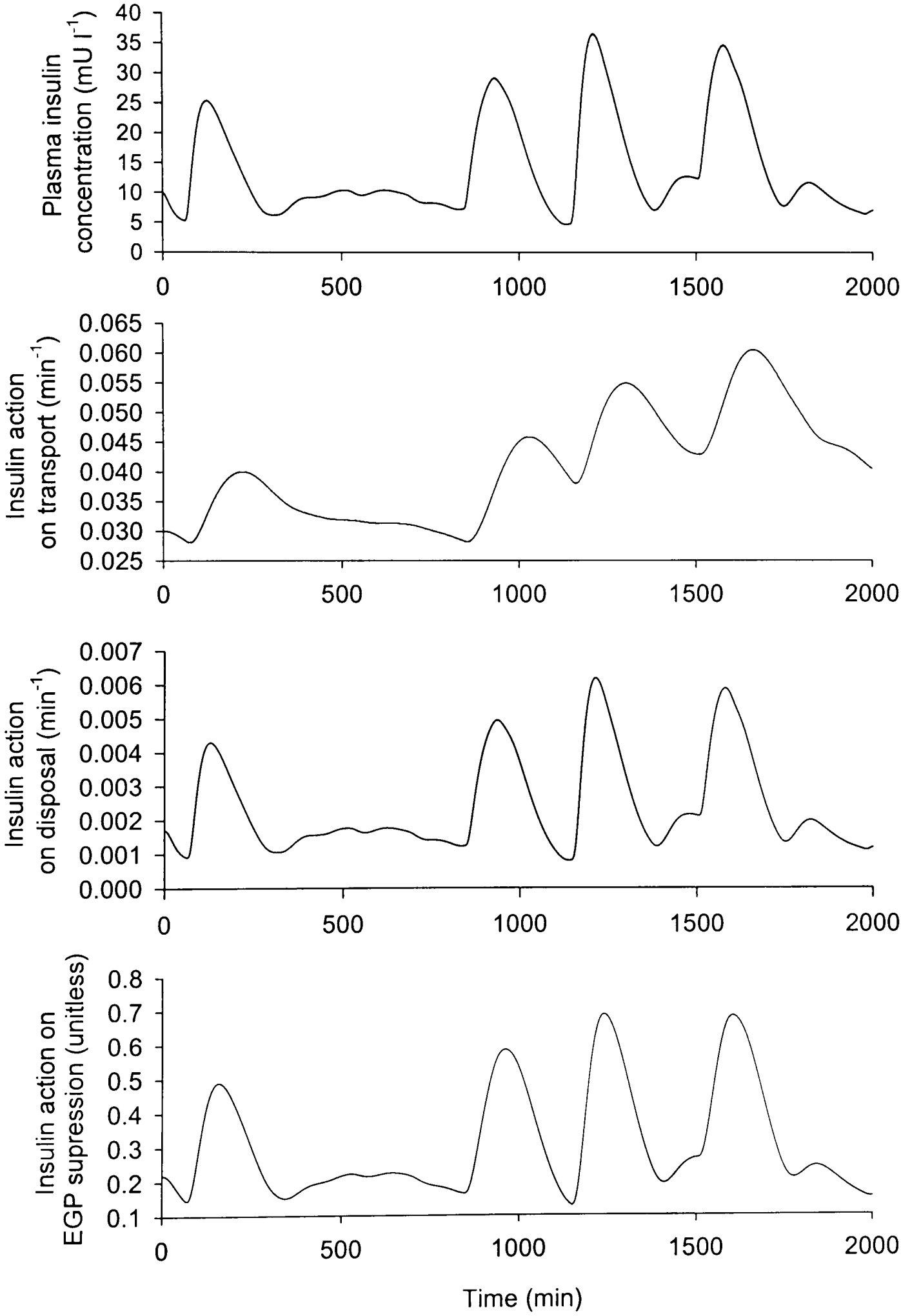

Figure 4.4: Sample simulation with the insulin action subsystem over one and a half day. See text for details.

Table 4.2: Parameters of the insulin action subsystem (subject 8) used to generate simulation presented in Figure 4.4

S_{IT}*	S_{ID}*	S_{IE}*	k_{b1}†	k_{b2}†	k_{b3}†
(10^{-4} x min^{-1} per mU l^{-1})		(10^{-4} x per mU l^{-1})		(10^{-2} x min^{-1})	
30.0	1.70	219	0.32	21.95	3.23

* $S_{IT}=k_{a1}/k_{b1}$, $S_{ID}=k_{a2}/k_{b2}$, $S_{IE}=k_{a3}/k_{b3}$ used as an alternative parameterisation
† Deactivation rate parameters

Figure 4.4 shows the activation and the deactivation of the insulin action compartments. In particular, it shows that the dynamics of the insulin action on glucose transport are slower compared to those associated with the other two insulin actions.

4.5 Insulin Kinetics Subsystem

The model represents the kinetics of subcutaneously delivered fast acting insulin such as Lispro. The model is shown in *Figure 4.5*.

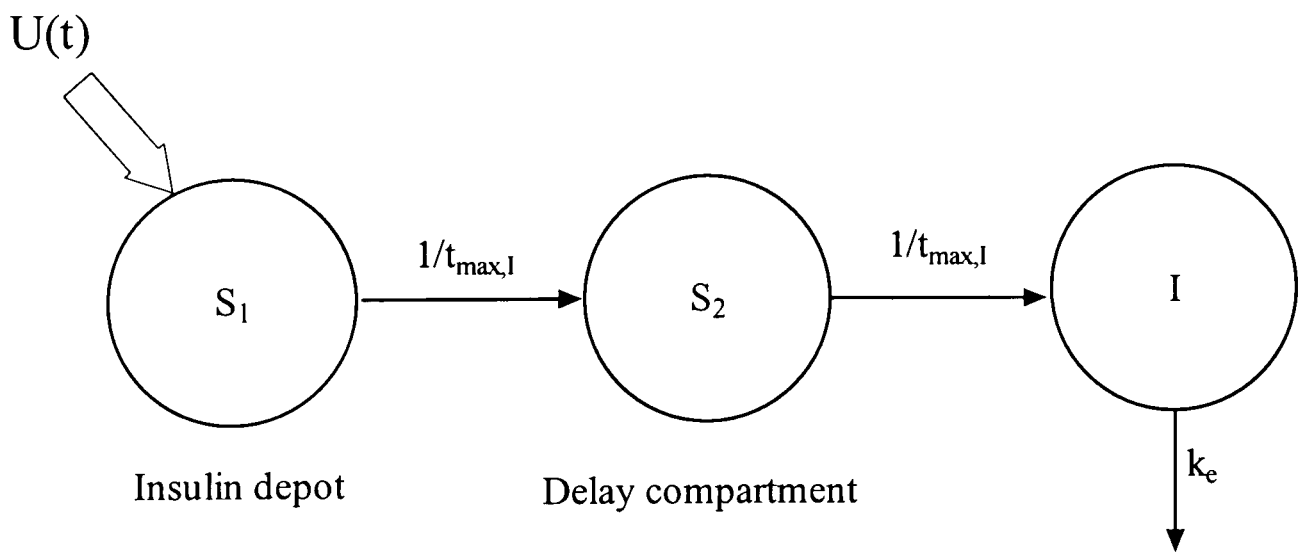

Figure 4.5: Subcutaneous insulin absorption model, see text for details.

The insulin kinetics subsystem is described as

$$\frac{dS_1(t)}{dt} = U(t) - \frac{S_1(t)}{t_{max,I}} \tag{4.9}$$

$$\frac{dS_2(t)}{dt} = \frac{S_1(t)}{t_{max,I}} - \frac{S_2(t)}{t_{max,I}} \tag{4.10}$$

$$\frac{dI(t)}{dt} = \frac{S_2(t)}{V_I t_{max,I}} - k_e I(t) \tag{4.11}$$

where S_1 (mU) and S_2 (mU) is a two-compartment chain representing absorption of subcutaneously administered fast-acting insulin, $U(t)$ represents administration (mU min^{-1}) of insulin given as a series of micro boluses every three minutes and/or as big boluses at meal time. The constant $t_{max,I}$ (min) corresponds to the time-to-maximum insulin absorption following an administration of a single bolus. I(t) (mU l^{-1}) is the plasma insulin concentration, k_e (min^{-1}) is the fractional elimination rate, and V_I (l kg^{-1}) is the distribution volume of insulin.

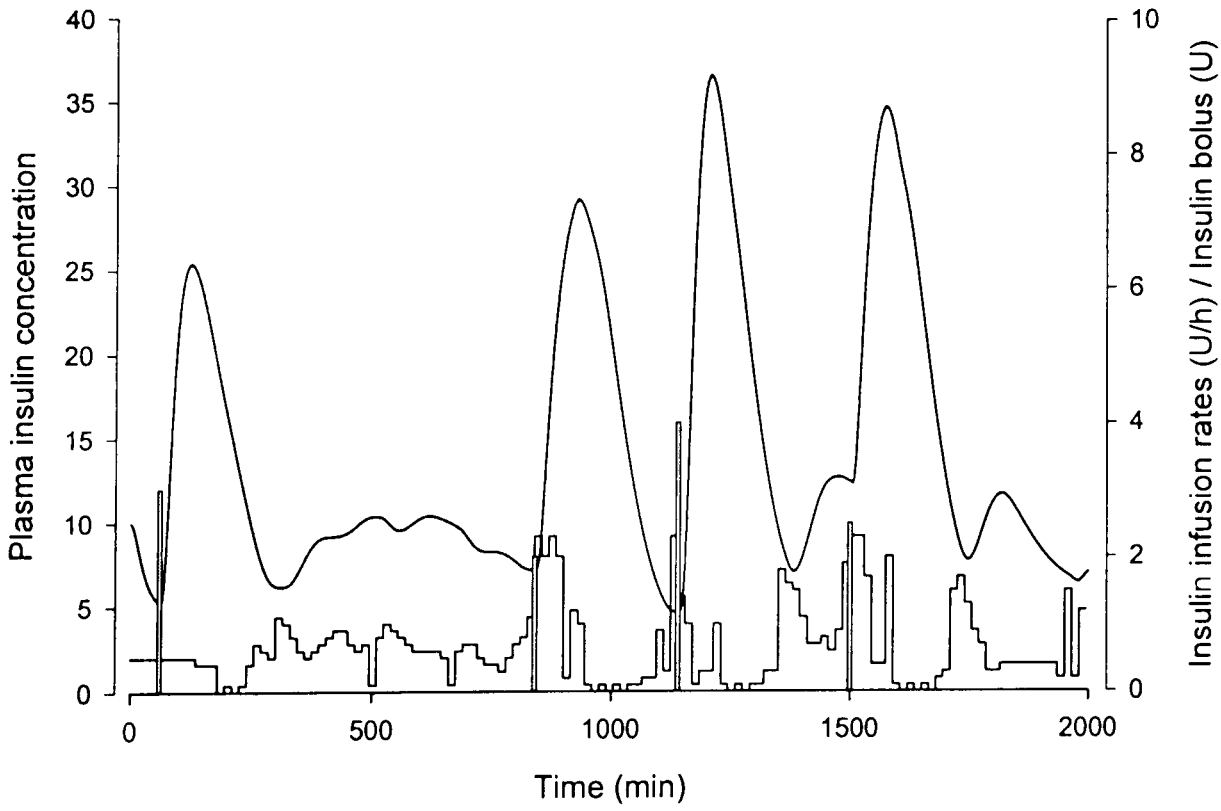

Figure 4.6: Insulin infusion rates (piecewise constant function), insulin bolus (vertical bars at 60, 840, 1140, and 1500) and the resulting plasma insulin profile.

An example of plasma insulin concentration resulting from insulin infusion and boluses over one and a half day is presented in *Figure 4.6*. The simulation employed parameters given in *Table 4.3*.

Table 4.3. Parameter values for the insulin kinetics subsystem (subject 8) employed to generate the simulation shown in Figure 4.6.

$t_{max,I}$ (min)*	k_e (10^{-2} x min^{-1})†	V_I (10^{-2} x l kg^{-1})‡
35	12.0	12.8

* Time-to-maximum of absorption of subcutaneously injected fast acting insulin
† Insulin elimination from plasma
‡ Insulin distribution volume

4.6 Gut Absorption Subsystem

Glucose absorption entering the accessible glucose compartment is a fundamental process affecting postprandial glucose excursions. The subsystem is shown in *Figure 4.7*.

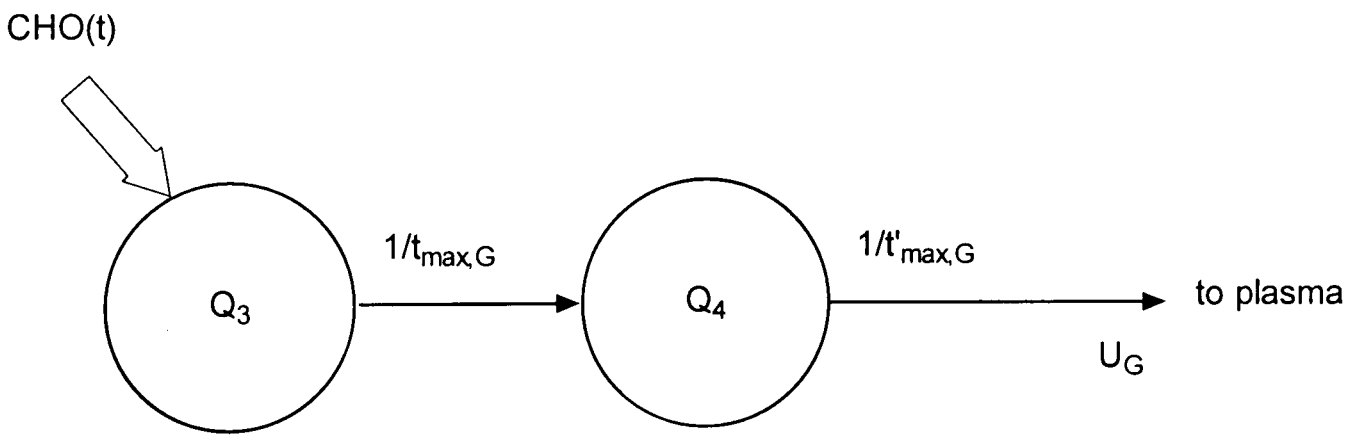

Figure 4.7: Glucose absorption subsystem

The model is described as

$$\frac{dQ_3}{dt} = -\frac{Q_3}{t_{max,G}} + CHO(t)B \tag{4.12}$$

$$\frac{dQ_4}{dt} = -\frac{Q_4}{t'_{max,G}} + \frac{1}{t_{max,G}}Q_3 \tag{4.13}$$

$$U_G = \frac{Q_4}{t'_{max,G}} \tag{4.14}$$

where Q_3 (mmol) and Q_4 (mmol) is a two-compartment chain representing absorption of carbohydrates from meals, CHO(t) (mmol) represents meal ingestion, B(%) is carbohydrate bioavailability, $t_{max,G}$ (min) is the time-of-maximum of the appearance of glucose in the accessible glucose compartment, and $t'_{max,G}$ is defined such as to limit the glucose appearance rate to a maximum of 0.025 mmol kg^{-1} min^{-1}.

$$t'_{max,G}\begin{cases} t_{max,G} & \text{if } \frac{Q_4}{t_{max,G}} \le 0.025 \text{ mmol kg}^{-1} \text{ min}^{-1} \\ \frac{0.025}{Q_4} & \text{otherwise} \end{cases} \tag{4.15}$$

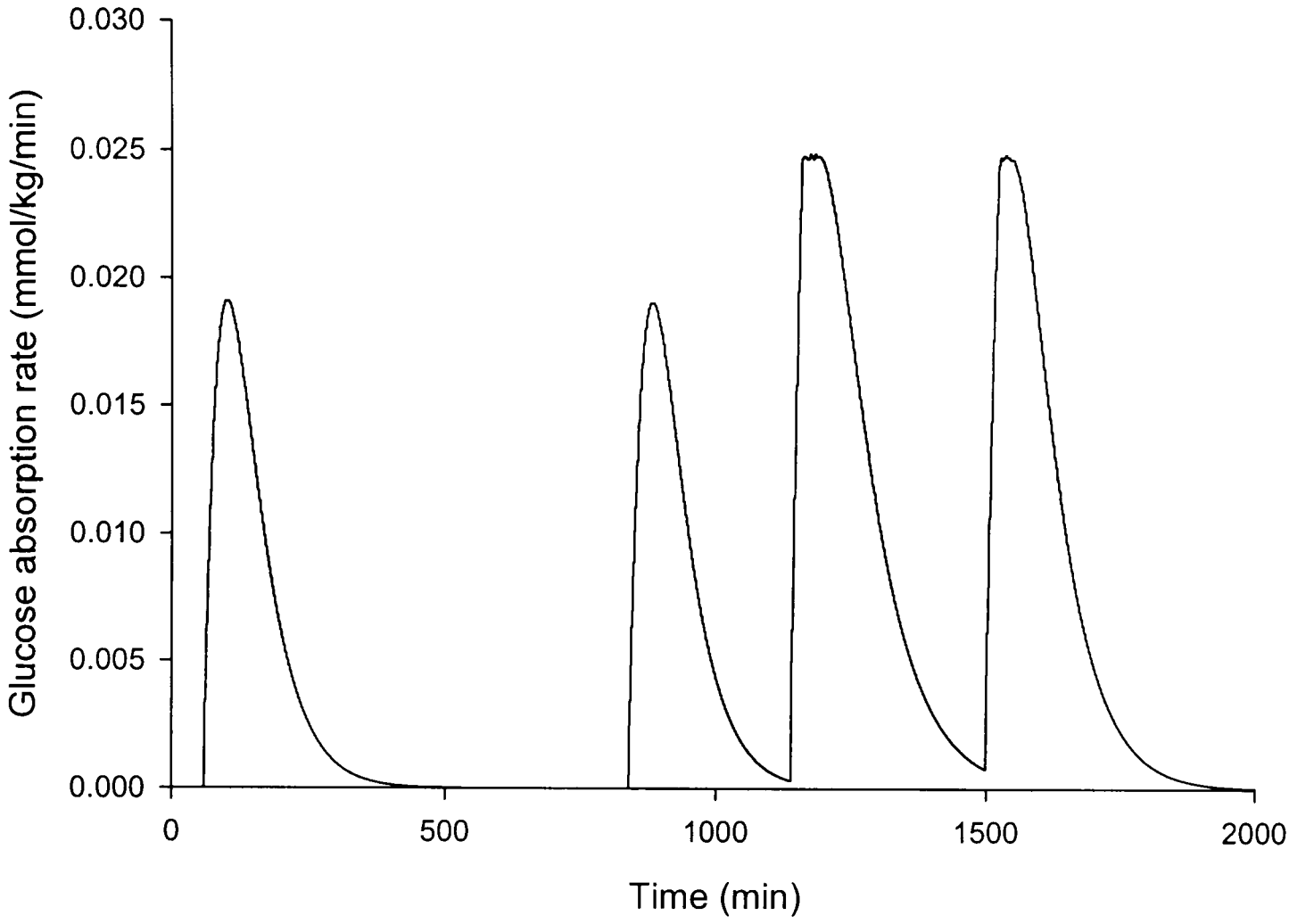

Figure 4.8: Sample simulation with the gut absorption subsystem with meals of 40, 40, 70, and 60g CHO digested at 60, 840, 1140, and 1500min, respectively.

A sample simulation using parameters given in *Table 4.4* is shown in *Figure 4.8* demonstrating the absorption profiles of four meals of various sizes. The attainment of the limit in the absorption rate of 0.025 mmol kg^{-1} min^{-1} is not well marked but can be observed in the last two meals.

Table 4.4: Parameters of the gut absorption subsystem (subject 8) used to generate Figure 4.8.

B* (%)	$t_{max,G}$† (min)
78	42

*CHO bioavailability
†Time-to-maximum of CHO absorption subject to 25% variation

4.7 Interstitial Glucose Kinetics Subsystem

The subcutaneous glucose kinetics subsystem is presented in *Figure 4.9*.

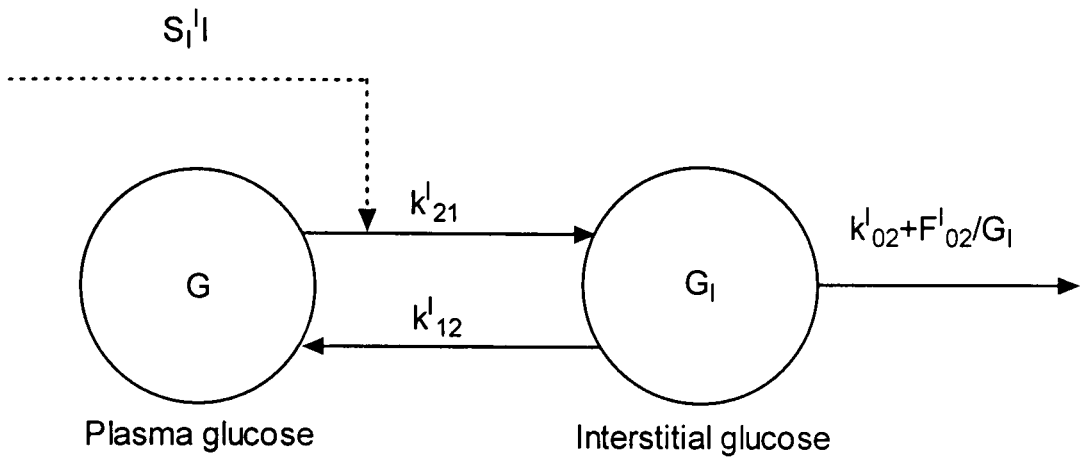

Figure 4.9: Interstitial glucose kinetics subsystem.

The model equation is given as

$$\frac{dG_I}{dt} = (k^I_{21} + S^I_I I)G - k^{II}_{02}G_I - F^I_{02} \qquad (4.16)$$

where G and G_I (mmol l^{-1}) represent plasma glucose and interstitial glucose concentrations, respectively k^I_{12}, k^I_{21}, and k^I_{02} (min^{-1}) are transfer rate constants, $k^{II}_{02}=k^I_{02}+k^I_{12}$ (min^{-1}) is an aggregated constant, I is the plasma insulin concentration (mU l^{-1}), $S^I_I I$ is insulin sensitivity associated with plasma-to-interstitial-fluid transfer (min^{-1} per mmol L^{-1}), and F^I_{02} (10^{-2} mmol l^{-1} min^{-1}) is the zero order glucose disposal. A sample simulation with the interstitial glucose kinetics subsystem is given in *Figure 4.10*. The simulation uses plasma glucose from an example in section 4.3 and plasma insulin from an example in section 4.5 as the forcing functions. The simulation example employs parameters given in *Table 4.5*.

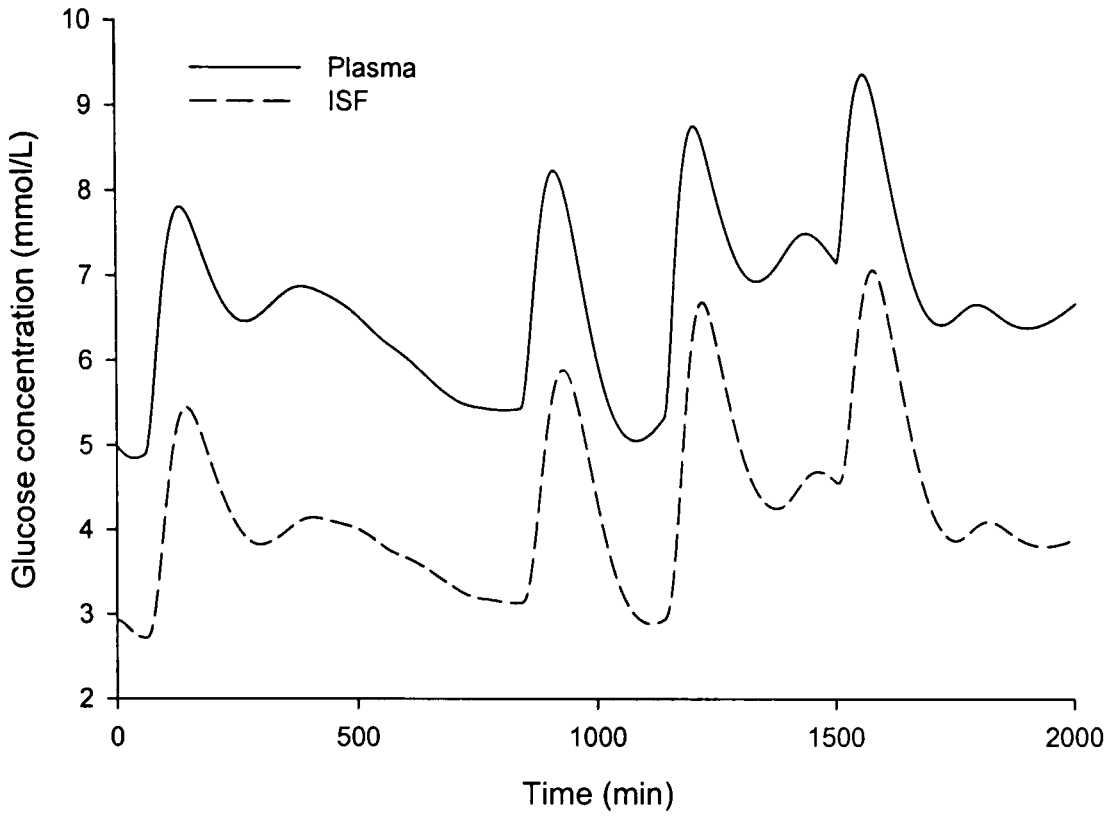

Figure 4.10: Sample simulation with the interstitial glucose kinetics subsystem.

Table 4.5: Parameters of the interstitial glucose kinetics subsystem (subject 8) used to generate simulation in Figure 4.10

K^{II}_{02}*	k^{I}_{21}†	F^{I}_{02}‡	S^{I}_{I}§
(10^{-2} x min^{-1})	(10^{-2} x mmol l^{-1} min^{-1})	(10^{-4} x min^{-1} per mU l^{-1})	
44.95	21.13	3.02	3.52

* Transfer rate between the interstitial and plasma glucose compartment
†Transfer rate between plasma glucose and interstitial glucose compartment
‡ Zero-order glucose disposal
§ Insulin sensitivity of glucose transfer from the plasma to interstitial compartment

4.8 Simulation Example

This section combines all the subsystems to exemplify the input-output relationship.

Figure 4.11 shows a simulation example containing some of the variables presented in earlier sections. The plot shows the forcing function for the model, the insulin input (insulin infusion and insulin boluses), the other forcing function represented by meal intake, and the resulting profiles of plasma glucose and interstitial glucose.

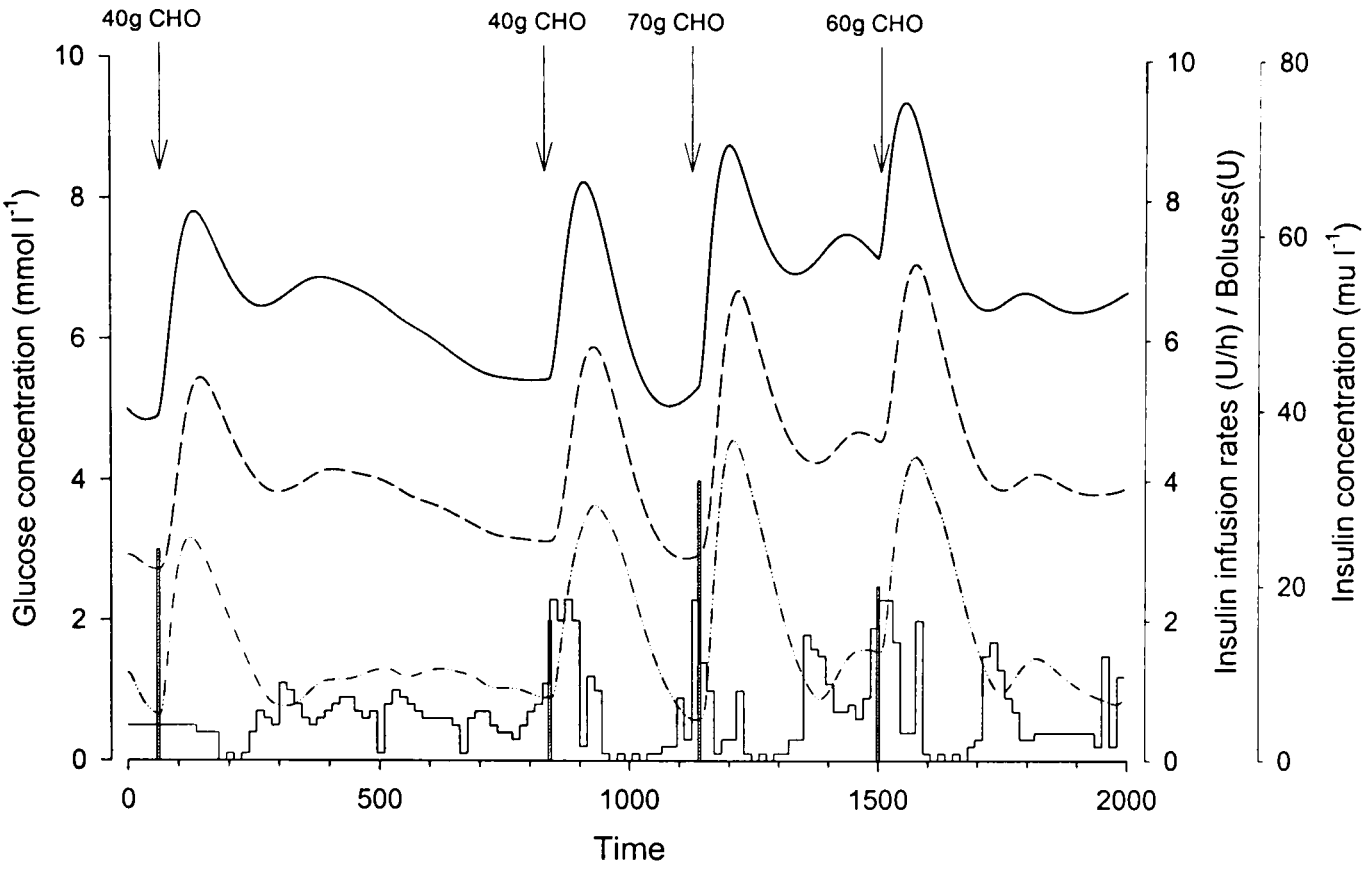

Figure 4.11: Simulation example over one and a half day. See text for details.

The simulation covers approximately one and a half days. It represents an evening meal (60min), and an overnight fasting period followed by three meals at 840min (breakfast), 1140min (lunch), and 1500min (dinner). The solid line is plasma glucose and the long dashed line represents interstitial glucose. The basal insulin delivery is represented by the piecewise constant function while boluses given at meal times are represented by vertical bars. The insulin profile is represented by the dash-double-dot line.

4.9 Implementation

The model is implemented in Matlab and its extension Simulink (The MathWork, Inc, Mass, USA). Matlab is a well-known package used to develop models and to perform system simulations. In association with Simulink, it is an ideal environment to facilitate symbolic system specification, visualisation, and programming.

The Simulink block diagrams of the model and subsystems are presented in Appendix B

4.10 Discussion

The purpose of this chapter was to present the overall model of a subject with Type 1 diabetes. A model of insulin secretion was excluded. The idea was to create a model which is simple enough to represent the physiology while retaining richness to represent various types of patients and settings. The model contains five interlinked submodels.

The glucose kinetics and insulin action submodels have been developed resorting to a tracer study and the classical methodology of model development (186). The novelty of the submodels is in the partitioning of insulin action on distribution/transport, disposal, and endogenous production. However, the model was developed employing data collected in healthy subjects during fasting and the intravenous glucose tolerance test (IVGTT). In addition to absent insulin secretion, subject with Type 1 diabetes differ from healthy subjects, for example by presenting a deficient suppression of the endogenous glucose production (187). However, by adjusting model parameters, differences can be represented.

The insulin absorption subsystem represents absorption of subcutaneous infused fast-acting insulin. Two absorption kinetics studies (57) provided the background for our two compartment chain model. The simulation results showed that the model adequately mimicked the absorption characteristics of the fast acting insulin.

A model of subcutaneous glucose kinetics is essential for the development of a subcutaneous-subcutaneous glucose controller. The transfer of glucose from plasma to the interstitial fluid introduces delays and a variable ratio between intravenous and interstitial glucose has been reported. This outlines the difficulties when using interstitial glucose for monitoring plasma glucose. Alongside this work, a modelling study was performed as part of another PhD thesis (188). Among several model structures, the best model, i.e. the model which best represented the experimental data, was selected by comparing the model fit error and by using the principle of parsimony as implemented by the

Akaike criterion (186). The measurement process employing interstitial glucose is described in details in the next chapter.

Gut absorption is a complex process which has been studied extensively. However, to our knowledge, no viable complex model is available and results are inconsistent. It follows that employing a very complex model was not justified. We therefore resorted to a structure using a two compartment chain. Tracer studies (187,189,190) evaluated the rate of absorption and our simulations are consistent with the experimental data. The studies included the oral glucose tolerance test (189,190) and the ingestion of mixed meals (187,191).

4.11 Conclusion

This chapter has presented a model of carbohydrate metabolism in subjects with Type 1 diabetes. Several subsystems have been combined in a modular way to simulate plasma and interstitial glucose kinetics based on subcutaneous delivery of fast acting insulin and the digestion of meals.

Supplied with appropriate parameters, the model has the potential to simulate a range of subjects. The generation of virtual subjects is described in the following chapter.

5 Simulation Environment

5.1 Introduction

In Chapter 4 a model of fundamental glucoregulatory processes in a subject with Type 1 diabetes was presented. The model includes submodels corresponding to physiological subsystems. Each submodel is defined by its structure and its behaviour is determined by associated parameter values.

An important aspect in testing glucose controllers is an evaluation of their performance in a range of subjects and not just in an "average" representative of a population with Type 1 diabetes. The controller has to be able to cope with a variety of behaviour ranging from insulin sensitive to insulin insensitive subjects, a delayed absorption of insulin, a faster absorption of carbohydrates following meal ingestion etc. This can be achieved by creating a virtual population of subjects. This representation of inter-subject variability should also be complemented by representing intra-subject variability, i.e. representing changes in metabolic settings during a day.

The present chapter describes the generation of a virtual population consisting of 18 subjects with Type 1 diabetes. This is achieved by assigning different parameter values to the common model structure. The chapter also includes the description of two additional submodels, a model of a glucose sensor and a model of an insulin pump, which together facilitate the establishment of the simulator, a complete environment for *in silico* testing of glucose controllers.

5.2 General Overview of Simulation Environment

The overall layout of the simulator environment is shown in *Figure 5.1*. It includes two main blocks, the simulator and the controller block. In the thesis, the control action is every 15 minutes. Therefore the simulator block will send historical data needed by the MPC controller every 15 minutes allowing the generation of a new insulin infusion rate.

The simulator includes the virtual subject represented by a physiologically-based compartmental glucoregulatory model described by a set of first order differential equations based on work by Hovorka *et al* (42) and presented in greater detail in Chapter 4. The measurement model block represents the measurement process and includes the properties of the glucose sensor such as the measurement error. The insulin pump delivers the insulin into the subcutaneous tissue of the virtual subject and can also be parameterised to include an error in the insulin delivery due to technical limitations and tissue properties. The simulation environment is implemented in Matlab and Simulink®.

The glucose controller is "outside" the environment in the sense that it is a separate computer program, which is started from within the Matlab code. The data exchange between the Matlab code and the controller is via ASCII files. This facilitates the testing of various controllers, which implement a specific format for the data exchange.

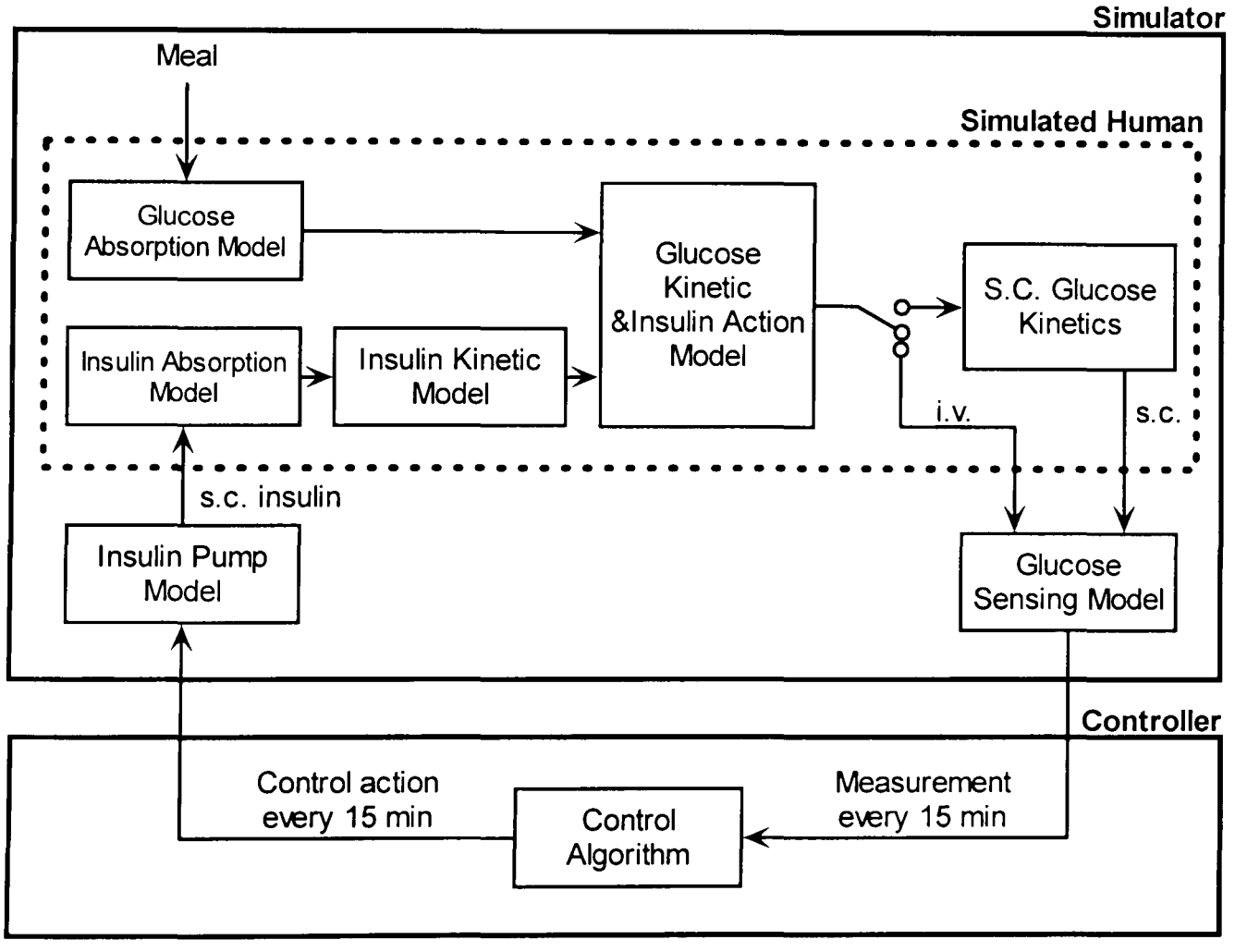

Figure 5.1: An overall layout of the simulation environment which include a simulated subject with Type 1 diabetes within the closed-loop control framework with measurement and insulin pump models and control algorithm to close the loop.

5.3 Insulin Pump Model

Discrepancies occur between the pump commands and the amount of insulin actually delivered. *Figure 5.2* presents the approach employed to represent the inclusion of errors in the delivery of insulin due to mechanical imprecision associated with the Disetronic D-Tron pump, which was used in clinical trials. Following the technical description of the pump, the simulated insulin delivery was represented by mini boluses three minutes apart.

The inaccuracies in the insulin infusion rate were represented by a normally distributed error with a zero mean and a coefficient of variation of 15%. The bolus was excluded from this process as flow rates are higher and the delivery error is likely to be negligible.

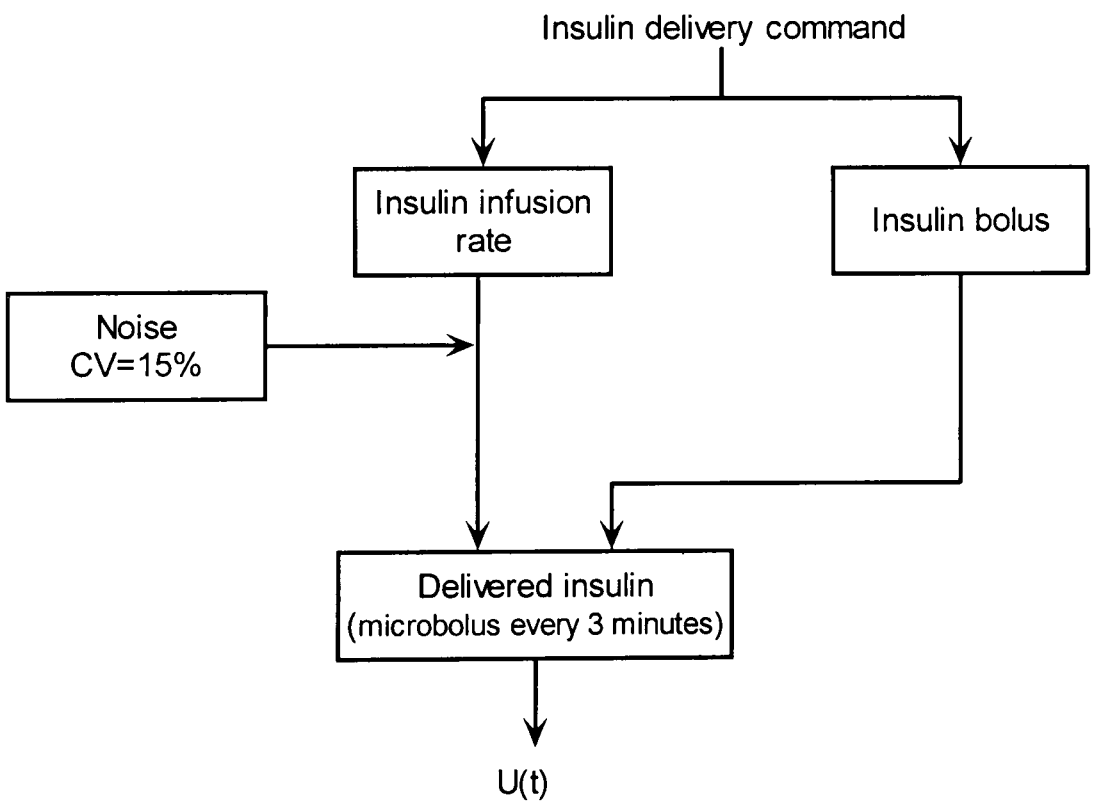

Figure 5.2: Model of insulin pump. U(t) represents insulin actually delivered by the pump. The noise is only associated with the insulin infusion rate because of the very small flow rates involved.

Figure 5.3 shows the actually delivered insulin infusion rate delivered in the form of microboluses at a 3 minutes interval. The intended, commanded insulin infusion rate is also shown.

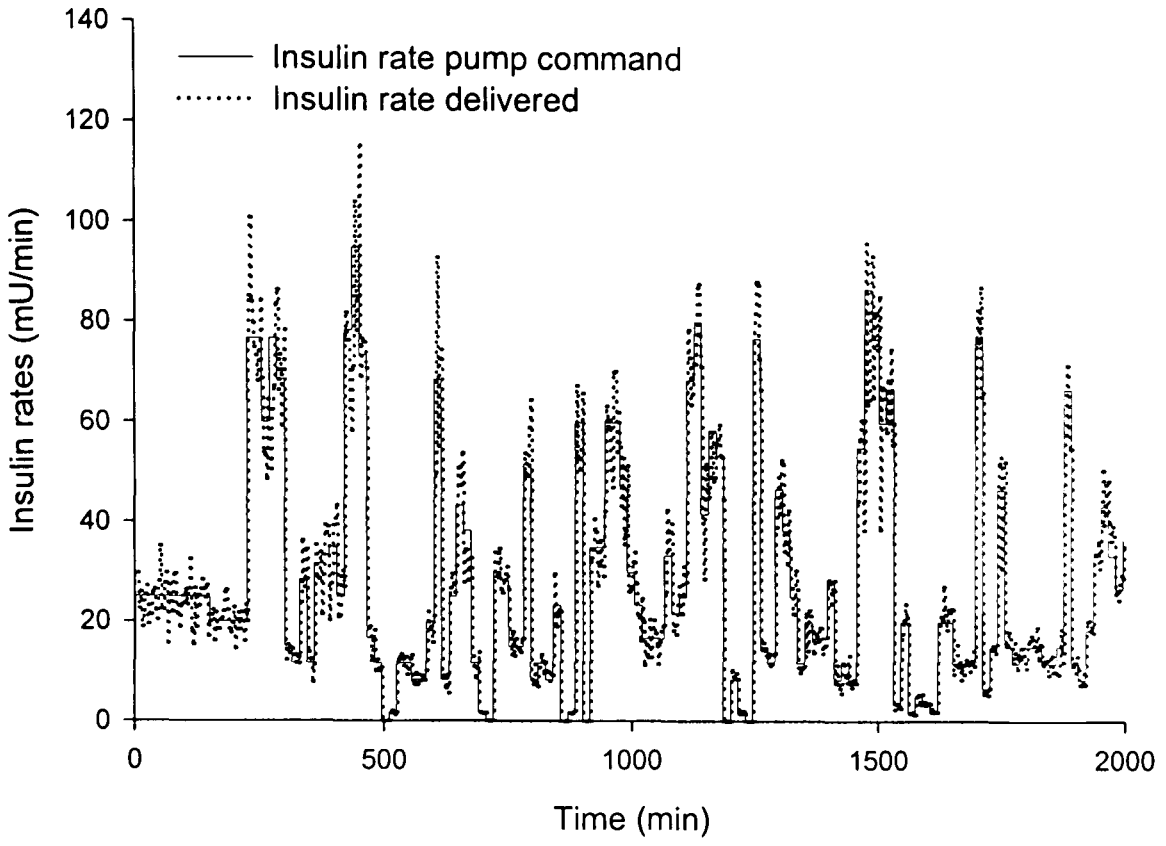

Figure 5.3: The commanded and the actually delivered insulin during a simulated trial with a model predictive controller. The actual infusion rate was delivered in the form of microboluses 3 min apart and a delivery error with a 15% CV.

5.4 Glucose Measurement Model

Within the framework of a minimally invasive artificial pancreas, the measurement of glucose employs subcutaneous sensing. Subcutaneous glucose measurements require calibration as there exist individual differences between plasma and interstitial glucose concentrations. Sensing is also corrupted by measurement error. *Figure 5.4* depicts the steps associated with determining the glucose measurement from the interstitial glucose concentration. These two processes, the calibration and the measurement error, were implemented in the simulator.

5.4.1 Calibration Model

Ideally, the subcutaneous glucose model presented in Chapter 4, section 4.7, could be employed to simulate the calibration procedure. However, the model relies on the knowledge of the plasma insulin concentration which is not available in real time. Therefore, to reproduce the experimental conditions, a simpler subcutaneous

glucose model which is not dependent on insulin level was employed, see *Figure 5.5*.

The former model was shown to be only marginally better in explaining experimental data (188) than its insulin free counterpart. Although, the model used for the calibration did not include the insulin effect on the glucose transfer from the plasma to the subcutaneous compartment, the data showed that IG/PG ratio increased by only 0.03 per 10mU/L. The consequence of removing the insulin effect from the simulations is therefore small.

Due to the lack of knowledge of individual subcutaneous model parameters, population parameter estimates were used as calibration constants (135,188,192).

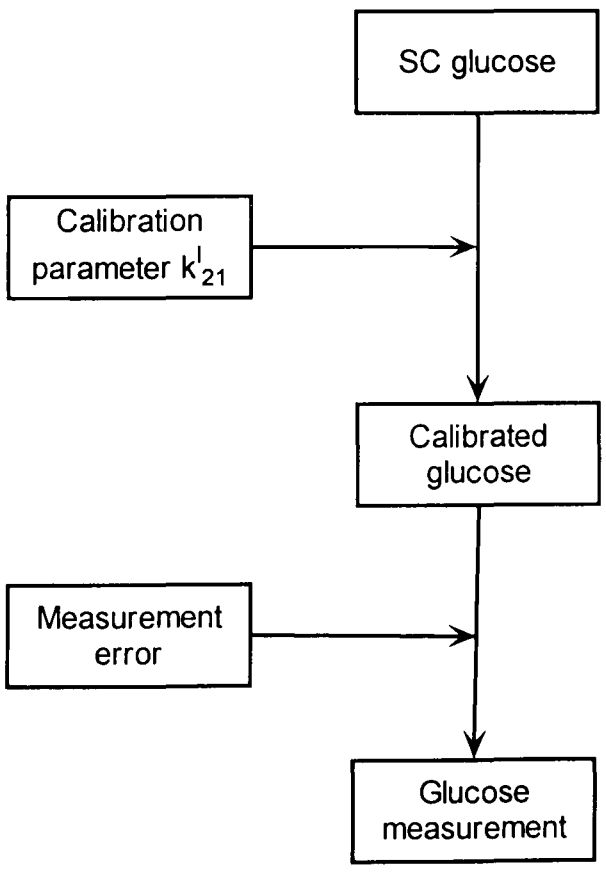

Figure 5.4: The sequence of determining glucose measurement from the subcutaneous glucose concentration.

The calibration consists of determining the parameter k'_{21} from the simulated plasma glucose and interstitial glucose measurements.

In particular, simulated plasma glucose G_0 is taken at time t_0. A patient specific parameter k_{21}^I is then derived from the steady state solution of equation (5.3) where:

$$k_{21}^I = \frac{(k_{12P}^I G_I + F_{02P}^I)}{G_0} \tag{5.1}$$

where G_I is the simulated interstitial glucose concentration obtained from the interstitial glucose subsystem presented in section 4.7, k_{12P}^I is the transfer rate from the interstitial glucose to plasma glucose compartment, F_{02P}^I is the zero order disposal from the interstitial glucose compartment. Population values of parameters k_{12P}^I and F_{02P}^I are used in these calculations, k_{12P}^I=0.0476min^{-1} and $F_{02P}^I = 0.0404$ mM^{-1} min^{-1} (135,188).

Plasma glucose is then calculated from interstitial glucose using the individually determined value of k_{21}^I as

$$G = \frac{(k_{12P}^I G_I + F_{02P}^I)}{k_{21}^I} \tag{5.2}$$

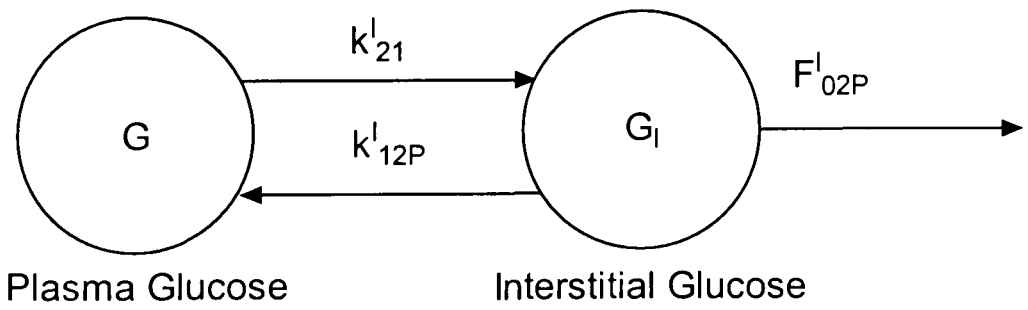

Figure 5.5: Model of subcutaneous glucose kinetics used for the calibration.

The model of the subcutaneous glucose kinetics employed for the calibration is shown in *Figure 5.5*. The model is represented by equation *(5.3)*

$$\frac{dG_I}{dt} = k_{21}^I G - k_{12P}^I G_I - F_{02P}^I \tag{5.3}$$

5.4.2 Measurement Error

A measurement error can be set to a specific value reflecting the performance of the measurement device. Throughout the investigations, a normally distributed measurement error was employed with a zero mean and a constant coefficient of variation. Unless stated otherwise, the CV was set at a level of 5%.

5.5 Inter-Subject Variability

5.5.1 Introduction

A characteristic of human physiology is the presence of differences between and within subjects. The aim of this section is two fold. First to present the approach employed by the simulator to account for inter-subject variability and, secondly, the method employed to introduce intra-subject variability.

18 synthetic subjects have been generated employing clinical data and probability distributions. The number of subjects was dictated by the availability of clinical data to determine the core of the model, i.e. the submodel of glucose kinetics and insulin action.

5.5.2 Glucose Kinetics Subsystem

The glucose kinetics subsystem was described in section 4.3, Chapter 4. It has six parameters. In conjunction with the model of insulin action it establishes the core of the model.

The determination of model parameters for an individual synthetic subject followed a two stage process. In the first stage, a subset of parameters was estimated from experimental data while other parameters were fixed at expected population values. In the second stage, the previously fixed parameters were sampled from univariate informed distributions.

Data for the first stage came from a clinical trial carried out in 18 subjects with Type 1 diabetes (data not shown). The experiment involved intravenous insulin infusion to maintain euglycaemia and lasted from 2200 until 0700 the following morning. Plasma glucose was sampled every 10 minutes and plasma insulin was sampled every 30 minutes.

The glucose kinetics and the insulin action submodels represent the relationship present in the experiment. Plasma insulin is the input and plasma glucose is the output. The experiment excluded subcutaneous insulin delivery and gut absorption. Due to identifiability issues (186) it was not however possible to estimate all 12 parameters of the two submodels. Therefore, parameters which were deemed not a posteriori identifiable from the experimental data were fixed at population values as obtained in Hovorka *et al* (42). This left five parameters to be estimated from the experimental data: the non insulin dependent glucose flux F_{01}, endogenous glucose production extrapolated to the zero insulin concentration EGP_0, and the three insulin sensitivities S_{IT}, S_{ID}, *and* S_{IE}.

These five parameters were successfully estimated from the data using Bayesian parameter estimation implemented in SAAM II (SAAM Institute, Seattle, USA). The resulting values are shown in *Table 5.1* and *Table 5.2*.

The second stage involved the generation of parameters values fixed during the first stage. The process was carried out to expand the inter-subject variability obtained during the first stage.

The generated parameter values are also shown in *Table 5.1* and *Table 5.2* . The tables include information about the generating distributions, its values, bracketing information, and where possible the literature source justifying the choice.

Regarding the choice of the generating distributions, the log-normal distribution was used for all parameters except the renal clearance threshold to represent skewed distribution and to guarantee non-negativity.

Table 5.1: Parameters of the glucose kinetics subsystem for the 18 synthetic subjects.

Subject	F_{01}‡ ($\mu mol\ kg^{-1}\ min^{-1}$)	EGP_0§	k_{12}‖ ($10^{-2} \times min^{-1}$)	V_G¶ ($10^{-2} \times l\ kg^{-1}$)	G_{RT}# ($mmol\ l^{-1}$)	k_{RT}† (min^{-1})
1	11.01	19.62	10.95	17.9	11.7	0.012
2	8.31	9.10	5.09	14.5	9.2	0.013
3	4.40	6.42	7.67	17.4	8.1	0.006
4	6.88	8.25	6.35	17.8	10.1	0.011
5	5.09	11.92	2.90	12.5	12.4	0.012
6	8.74	10.49	3.07	14.6	7.7	0.010
7	5.25	17.09	5.46	16.8	9.3	0.006
8	11.04	14.07	2.93	18.0	7.8	0.011
9	6.61	7.16	6.72	9.3	8.2	0.007
10	3.37	4.35	5.37	13.2	7.5	0.011
11	10.19	12.19	6.70	14.2	10.3	0.013
12	2.37	17.54	9.06	14.0	11.6	0.013
13	12.03	13.89	5.09	16.4	8.6	0.011
14	10.08	11.81	5.78	10.6	8.2	0.008
15	4.09	12.26	7.39	11.9	8.5	0.012
16	5.00	7.09	3.20	14.7	13.0	0.012
17	8.23	14.74	3.07	16.5	10.3	0.007
18	4.01	11.94	4.79	16.5	11.3	0.007

‡ Non-insulin dependent glucose flux; derived from clinical data
§ Endogenous glucose production extrapolated to zero insulin concentration; derived from clinical data
‖ Transfer rate constant from the non-accessible to accessible compartment; log transformed parameter was drawn from $N(-2.813, 0.43^2)$ bracketed by [0.01-0.2] (42)
¶ The glucose volume of distribution; log transformed parameter was drawn from $N(-1.897, 0.23^2)$ bracketed by [0.09-0.25] (42)
# The renal clearance threshold; drawn from $N(9,1.5^2)$ bracketed by [7.5-15.0]
† The renal clearance rate $N(0.01,0.025^2)$ bracketed by [0.003-0.03]

5.5.3 Insulin Action Subsystem Parameters

Table 5.2 shows parameters of the insulin action subsystem. With the provision of the plasma insulin concentration they quantify insulin action on the glucose kinetics as presented in Chapter 4 section 4.4. Insulin sensitivities S_{IT}, S_{ID}, *and* S_{IE} were generated from experimental data, the deactivation rate constants were generated employing random selection from log normal distributions.

Table 5.2: Parameters of the insulin action submodel

Subject	S_{IT}* (10^{-4} x min^{-1} per mU l^{-1})	S_{ID}*	S_{IE}* (10^{-4} x mU l^{-1})	k_{b1}†	k_{b2}†† (10^{-2} x min^{-1})	k_{b3}#
1	77.1	3.14	377	0.21	39.56	8.03
2	11.0	1.58	73	0.06	1.36	2.02
3	8.5	12.32	71	0.34	5.34	2.09
4	11.9	6.64	116	0.14	13.77	2.10
5	11.6	7.39	222	0.80	9.19	4.26
6	12.4	1.53	114	0.07	3.69	3.39
7	7.7	3.13	404	0.11	6.07	4.52
8	30.0	1.70	219	0.32	21.95	3.23
9	8.6	3.84	75	0.46	2.85	5.02
10	5.4	12.00	53	0.48	4.42	1.66
11	23.5	1.84	129	0.14	15.92	2.22
12	7.4	2.37	472	0.40	5.76	3.39
13	35.2	1.26	163	0.10	8.05	1.59
14	18.3	1.56	161	0.26	11.56	2.76
15	12.4	16.52	346	0.14	3.73	8.53
16	9.9	17.60	137	1.11	1.19	4.24
17	27.9	3.94	197	0.25	7.84	1.52
18	12.6	11.31	169	0.51	4.17	5.49

*$S_{IT} = k_{a1}/k_{b1}$, $S_{ID} = k_{a2}/k_{b2}$, $S_{IE} = k_{a3}/k_{b3}$ used as an alternative parameterisation; for more information see text; derived from clinical data

† Log transformed deactivation rate parameter was drawn from N(-5.684, 1.00^2) bracketed by [0.0002-0.0500] (42).

†† Log transformed deactivation rate parameter was drawn from N(-2.882, 0.75^2) bracketed by [0.0050-0.4000] (42).

Log transformed deactivation rate parameter was drawn from N(-3.730, 0.75^2) bracketed by [0.0030-0.1000] (42).

5.5.4 Insulin Kinetics Subsystem

The insulin kinetics subsystem has three parameters which determine the plasma insulin concentration profile from the subcutaneous insulin delivery by the pump. The parameters of the insulin absorption subsystem are presented in *Table 5.3*. The generation of the parameters involved a random selection from informed univariate normal distributions.

Table 5.3: Parameter of the insulin absorption submodel

Subject	$t_{max,I}$ (min)*	k_e (10^{-2} x min^{-1})†	V_I (10^{-2} x l kg^{-1})‡
1	50	13.2	11.3
2	63	10.1	13.1
3	70	15.2	12.2
4	40	14.0	13.0
5	58	11.5	12.8
6	39	17.7	11.5
7	40	14.4	12.3
8	35	12.0	12.8
9	93	17.4	9.8
10	41	16.7	12.9
11	42	26.3	12.4
12	42	11.2	12.7
13	41	16.6	11.4
14	49	15.6	12.2
15	50	15.9	11.1
16	29	10.5	8.6
17	36	12.5	12.4
18	45	12.8	13.0

*Time-to-maximum of absorption of subcutaneously injected fast acting insulin $t_{maxI}=1/k_a$; where k_a is drawn from $N(0.018, 0.0045^2)$ bracketed by [0.005 - 0.060] (46)

† Insulin elimination from plasma; drawn from $N(0.14, 0.0345^2)$ bracketed by [0.050 - 0.300] (42)

‡ Insulin distribution volume; drawn from $N(0.12, 0.012^2)$ bracketed by [0.080 - 0.180] (42)

5.5.5 Gut Absorption Subsystem

Meal responses are known to vary greatly between and within subjects. Meal composition, the time of day, and the nature of carbohydrates are some of the numerous factors that influence the meal effect on the plasma glucose concentration.

The model of gut absorption includes two parameters, the bioavailability B and the time to peak of gut absorption $t_{max,G}$. The bioavailability comprises two types of information. First, it is the true physiological bioavailability of digested carbohydrates in a mixed meal. Second, it is the mis-specification of the actual carbohydrates (CHO) content in the meal. Due to the latter, the bioavailability can exceed 100% representing underestimation of CHO in the meal.

The two parameters of the gut absorption subsystem were generated employing random selection from a uniform distribution for the bioavailability and a log normal distribution for the absorption rate parameter, see *Table 5.4*.

Table 5.4: Parameters of the glucose absorption model

Subject	B* (%)	$t_{max,G}$† (min)
1	71	43
2	90	55
3	113	38
4	77	29
5	82	30
6	72	54
7	72	69
8	78	42
9	81	30
10	71	52
11	84	48
12	87	61
13	98	63
14	88	51
15	89	49
16	88	68
17	116	46
18	79	44

* CHO bioavailability; drawn from U(70; 120)
†Time-to-maximum of CHO absorption, $t_{max,G}=1/a$, where a is log transformed parameter drawn from $N(-3.689, 0.25^2)$ bracketed by [0.010 - 0.040] (189)

5.5.6 Interstitial Glucose Kinetics

The model of the interstitial glucose kinetics includes four parameters. The parameters were generated using information about their distributions as described by Wilinska et al (135). In particular the parameters k_{21}^I and k_{12}^I were found strongly correlated.

The parameters of the subcutaneous glucose kinetics are shown in Table 5.5. Parameters were drawn from a log normal distribution with the exception of k_{21}^I which was correlated with k_{12}^I. The mean and the standard deviation of the ratio k_{21}^I / k_{12}^I were employed to generate a random ratio to derive k_{21}^I using a random draw of k_{12}^I.

Table 5.5: *Parameters of the model of subcutaneous glucose kinetics*

Subject	k^{I}_{12}* (10^{-2} x min^{-1})	k^{I}_{21}†	F^{I}_{02}‡ (10^{-2} x $mmol^{-1}$ l^{-1} min^{-1})	S^{I}_{I}§ (10^{-4} x min^{-1} per mU l^{-1})
1	16.12	10.55	3.37	0.70
2	2.27	1.61	1.18	0.21
3	25.25	20.06	6.05	5.36
4	13.01	28.03	18.34	0.32
5	8.68	12.12	16.86	1.49
6	3.35	4.70	29.95	0.86
7	17.00	15.13	0.45	0.25
8	7.88	6.53	3.62	4.72
9	2.33	3.89	4.97	6.84
10	2.87	2.08	1.45	0.43
11	3.16	2.73	2.22	1.05
12	10.39	11.65	0.76	0.31
13	28.68	16.56	0.64	3.33
14	21.55	12.94	1.63	0.21
15	5.58	2.24	2.03	2.21
16	9.20	4.35	0.48	2.48
17	17.12	9.90	2.53	0.88
18	44.95	21.13	3.02	3.52

*Transfer rate parameter between interstitial and plasma glucose compartment; log transformed parameter drawn from $N(-2.372, 1.09^2)$ (135)
†Transfer rate between the plasma glucose and interstitial glucose compartment; derived from $k^{I}_{21} = r^{*}k^{I}_{12}$, where r although not normally distributed was drawn from a normal distribution $N(0.630, 0.15^2)$ bracketed by [-1.00 -1.00] (135)
‡ Zero-order glucose disposal parameter; log transformed parameter drawn from $N(-3.066, 1.07^2)$ (135)
§ Insulin sensitivity of glucose transfer from the plasma to interstitial compartment; log transformed parameter drawn from $N(-8.517, 1.45^2)$ (135)

5.6 Intra-Subject Variability

5.6.1 Introduction

The inter-subject variability was introduced by assigning a unique set of parameters to each synthetic subject. In order to increase the realism and to represent more closely the physiology it is necessary to introduce the intra-subject variability representing diurnal variations and unmodelled effects.

The intra-subject variability was introduced employing two methods. First, oscillations were superimposed upon parameters values, i.e. certain model parameters were made time-variant. Second, an inter-occasion variability in gut absorption was used

to represent the variability in the meal absorption due to the meal composition and other effects causing a lower reproducibility of postprandial glucose excursions (193,194).

5.6.2 Parameter Variation

The primary route to include the intra-subject variability involved introducing oscillations in model parameters. Sinusoidal oscillations were superimposed on nominal values of most parameters, see *Table 5.6*. The variability in gut absorption was represented in a different fashion, see section 5.6.3.

The superimposed oscillations had a five percent amplitude and a three hour period. These characteristics were the same for all time variant parameters. However, each parameter had a different phase generated randomly from a uniform distribution U[0,3h].

Oscillatory parameters with different phases influence the unique behaviour of the synthetic subjects. The parameters can be in-phase or out-of-phase, increasing, for example, the oscillations in overall insulin sensitivity.

Table 5.6: Model parameters can be time-variant (oscillatory) or time-invariant (stationary).

Parameter	Variability
$t_{max,I}$	Oscillatory*
k_e	Oscillatory
V_I	Stationary
B	Stationary
$t_{max,G}$	Stationary†
k_{b1}	Oscillatory
k_{b2}	Oscillatory
k_{b3}	Oscillatory
S_{IT}	Oscillatory
S_{ID}	Oscillatory
S_{IE}	Oscillatory
F_{01}	Oscillatory
EGP_0	Oscillatory
k_{12}	Oscillatory
V_G	Stationary
G_{RT}	Stationary
K_{RT}	Stationary
K^I_{12}	Oscillatory
K^I_{21}	Oscillatory
F^I_{02}	Oscillatory
S^I_I	Oscillatory

*Sinusoidal oscillations; for details see text
†Subject to an additional 25% variability at each meal intake

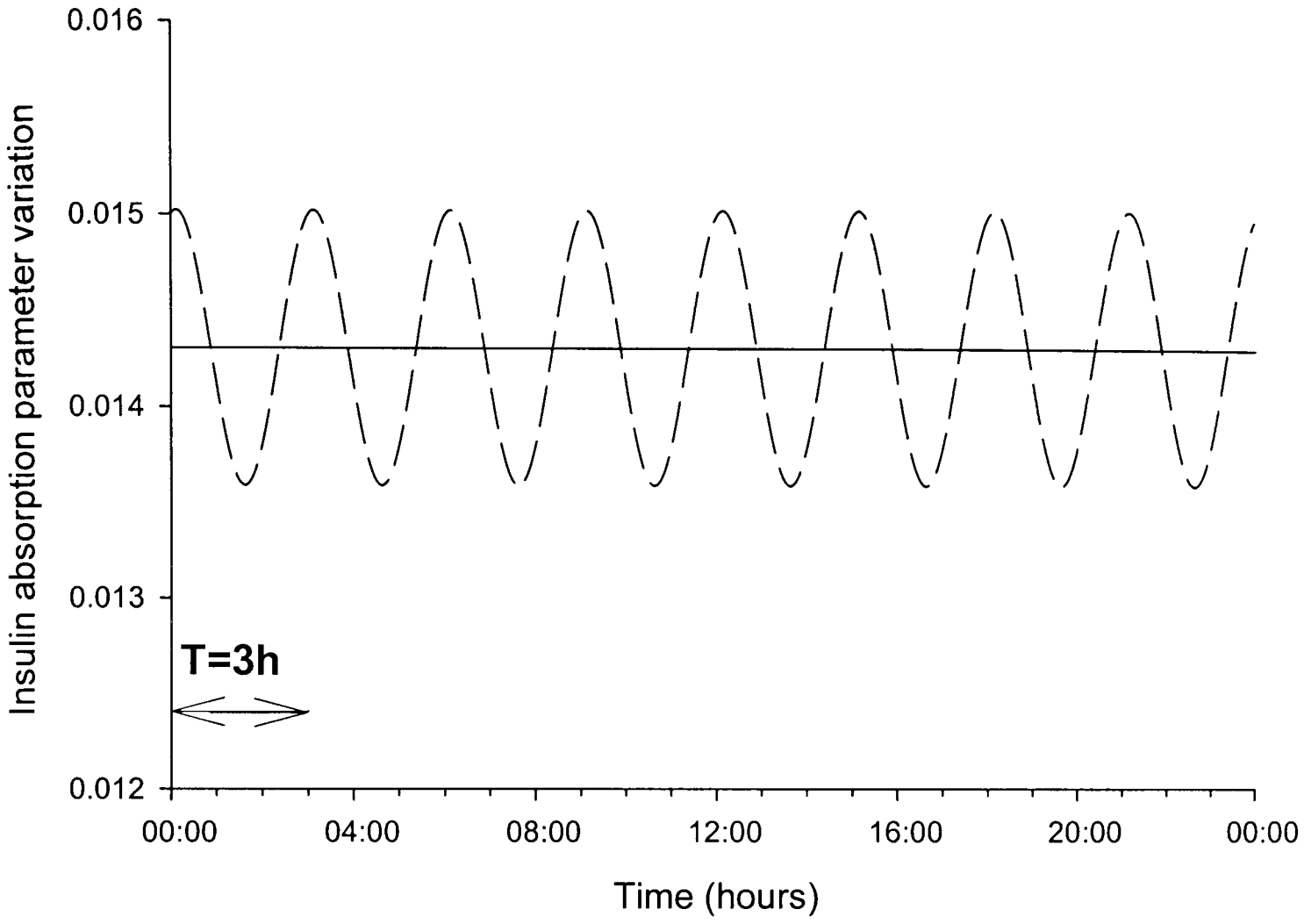

Figure 5.6: An example of parameter variation with the nominal value shown as a solid horizontal line and the varying profile as a dashed line.

The amplitude of oscillation influences the ability of the glucose controller to achieve normoglycaemia. This is exemplified in *Figure 5.7* and *Figure 5.8*. The former figure shows control with a 5% amplitude in parameter oscillations in subject 14, the latter figure shows control with a 30% amplitude.

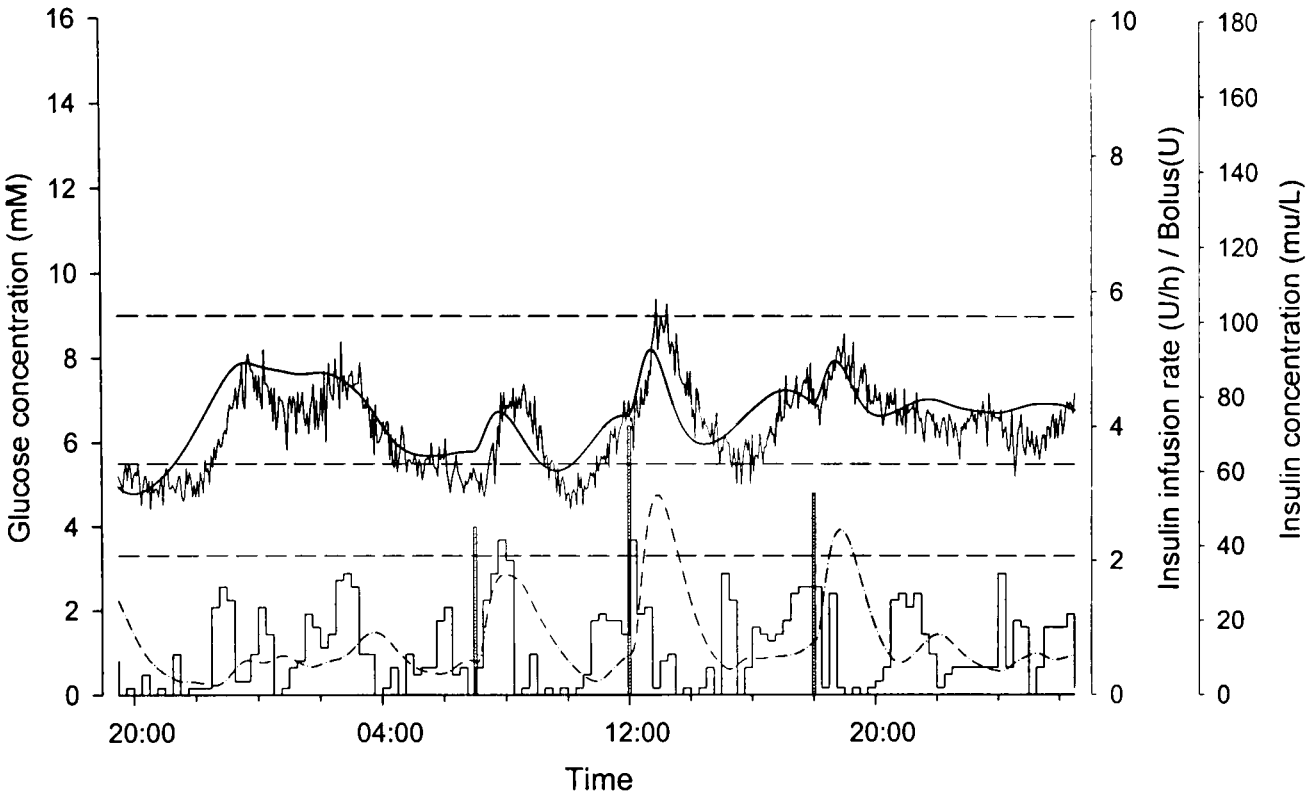

Figure 5.7: A sample simulation of subject 14 with a 5% sinusoidal oscillation superimposed upon time-variant parameters.

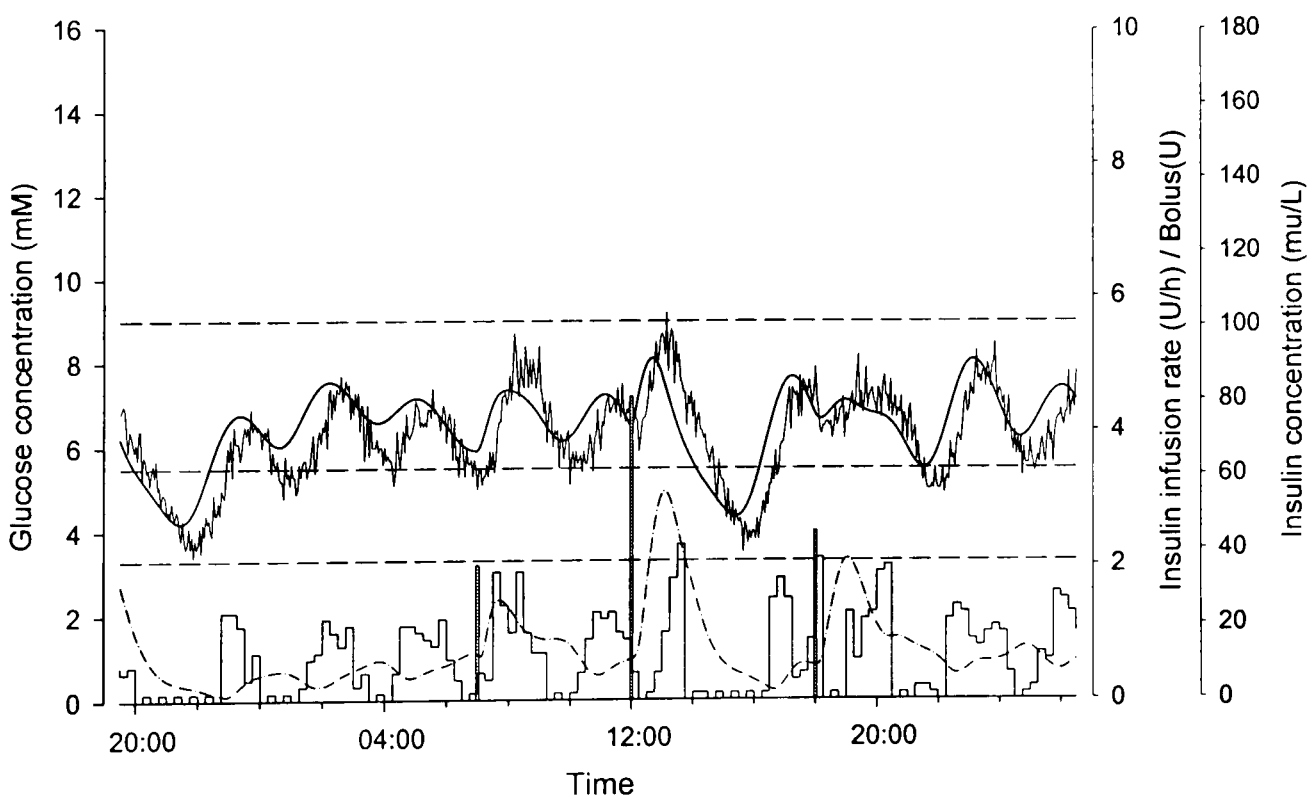

Figure 5.8: A sample simulation of subject 14 with a 30% sinusoidal oscillation superimposed upon time-variant parameters except parameters of the subcutaneous glucose kinetics left at the 5% amplitude.

It is evident that glucose excursion in subject 14 becomes more oscillatory with a 30% amplitude.

5.6.3 Variability in Glucose Absorption Rate

Due to a complex range of processes involved in meal digestion, similar meals or even the same meal can result in different gut absorption profiles (46). It is therefore important to include some variability in the absorption rate.

In the simulator, the bioavailability is not subjected to an inter-occasion variability but the absorption rate is associated with a 25% inter-occasion variability.

The effect of the inter-occasion variability is shown in *Figure 5.9*, which presents simulation runs with identical conditions up to the last meal at 1500min. The fixed absorption rate is then relaxed to include the 25% variability, normally included for all meals.

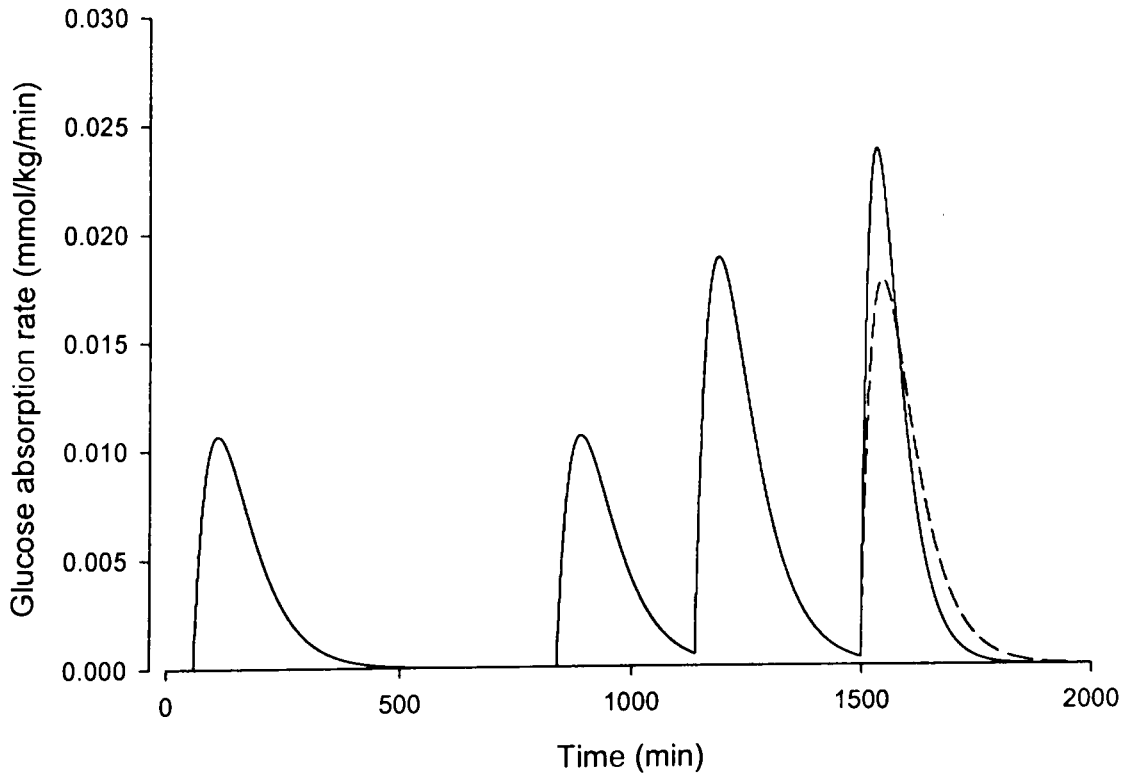

Figure 5.9: Simulations of the glucose absorption profile including a random variation in the absorption rate for the last meal (meals of 40, 40, 70, and 60g CHO at 60, 840, 1140, and 1500min).

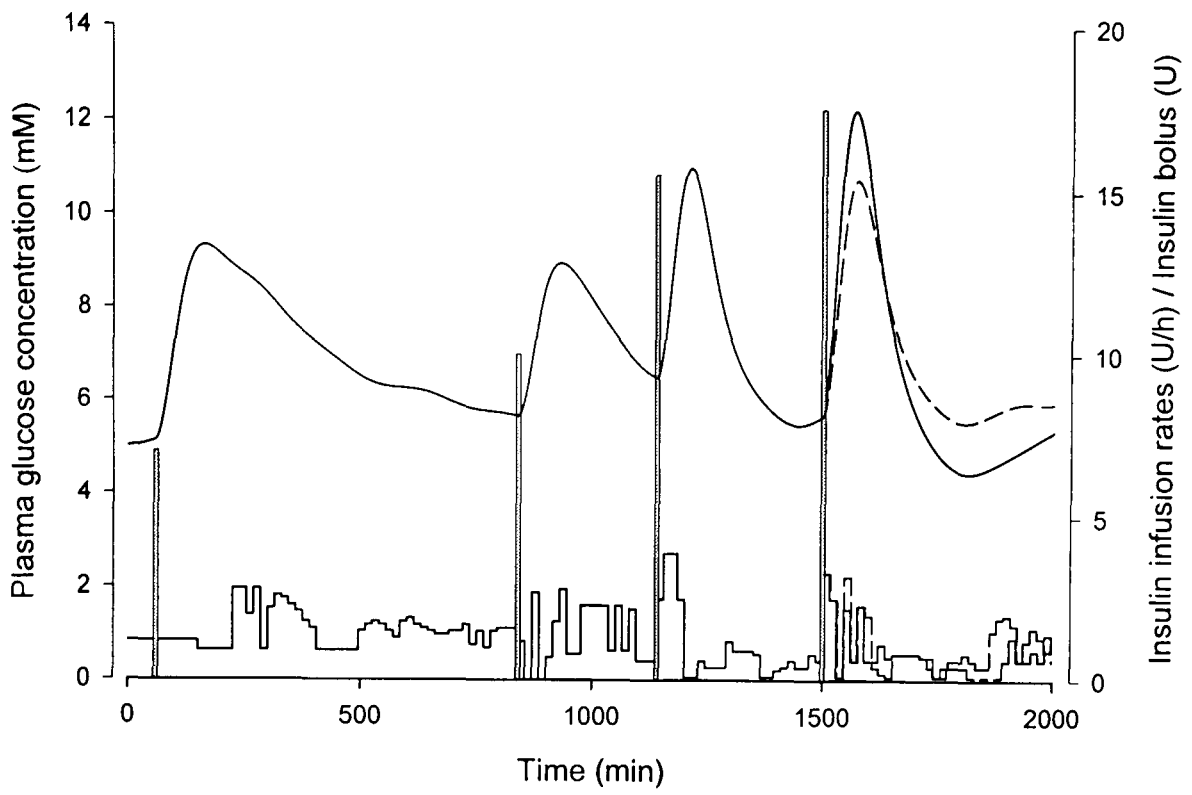

Figure 5.10: Simulations with a glucose controller using the glucose absorption profiles of Figure 5.9 as the forcing functions.

The absorption rates profiles in *Figure 5.9* show the effect of the variation in the speed of absorption of two meals of 60g of CHO. *Figure 5.10* shows the resulting glucose profiles with a higher peak followed by a minor undershoot with the faster gut absorption profile.

5.7 Characteristics of Synthetic Subjects

The generation process described in the previous section produced 18 distinct synthetic subjects. *Table 5.7* summarises the subjects by weight, insulin needs, and controllability employing a model predictive controller described in section Chapter 3, section 3.4.4. *Table 5.7* demonstrates a wide spectrum of insulin sensitivities represented by the group of synthetic subjects. The classification of controllability follows an assessment of control with regards to avoiding hypoglycaemia while achieving normoglycaemia and is based on an overall experience with the behaviour of the synthetic subjects under various conditions. The controllability ranges from 1 (easy to control) to 5 (difficult to control) where the latter represent cases unlikely to

be seen in clinical practice. The number of cases in categories 1 to 5 was 2, 7, 6, 1 and 2.

Table 5.7: Overall characteristics of 18 synthetic subjects

Subject	Weight (kg)	Basal needs (mU/kg/h)	Prandial needs (U/10g CHO)	Comments	Subjective controllability*
1	69	7	0.7	Very insulin sensitive and prone to hypoglycaemia	5
2	90	14	2.3	High postprandial glucose amplitude; insulin resistant; PG/IG lag	4
3	62	15	1.6	High postmeal excursions	3
4	87	11	1.6	Tendency to long lasting post meal excursions	2
5	75	9	0.5	High glucose amplitude; very insulin sensitive	3
6	107	16	3.4	Very insulin resistant; higher glucose values even during fasting	3

**Rating 1 to 5; 1 represents an easy to control subject, 5 represents a difficult to control subject.*

Table 5.8: Cont

Subject	Weight (kg)	Basal needs (mU/kg/h)	Prandial needs (U/10g CHO)	Comments	Subjective controllability*
7	51	22	1.4	Oscillatory glucose excursions; marked postmeal excursions; insulin resistant	3
8	76	9	0.5	Insulin sensitive; very easy to control	1
9	80	15	1.9	Extremely large postprandial glucose excursions; insulin sensitive Post meal resistant	5
10	101	13	3.0	Insulin resistant; relative moderation in the postmeal phase	2
11	73	26	3.1	The most resistant subject	2
12	60	25	2.1	Insulin resistant; tendency to stay in the above target glucose levels	2

**Rating 1 to 5. 1 represents an easy to control subject, 5 represents a difficult to control subject.*

Table 5.9: Cont

Subject	Weight (kg)	Basal needs (mU/kg/h)	Prandial needs (U/10g CHO)	Comments	Subjective controllability*
13	75	12	1.6	Stable control; tendency to stay at the above target glucose levels	2
14	60	20	1.6	Insulin resistant; prolonged postprandial glucose excursions	3
15	63	13	1.0	Oscillatory glucose excursions; insulin sensitive; a large PG/IG mismatch	3
16	79	5	0.5	Very insulin sensitive; good control	1
17	72	11	0.9	Insulin sensitive particularly to insulin bolus	2
18	65	14	0.8	Insulin sensitive; stable glucose control	2

**Rating 1 to 5. 1 represents an easy to control subject, 5 represents a difficult to control subject.*

The following three examples demonstrate differences among the subjects. *Figure 5.11* shows simulation with subject 5, who is difficult to control.

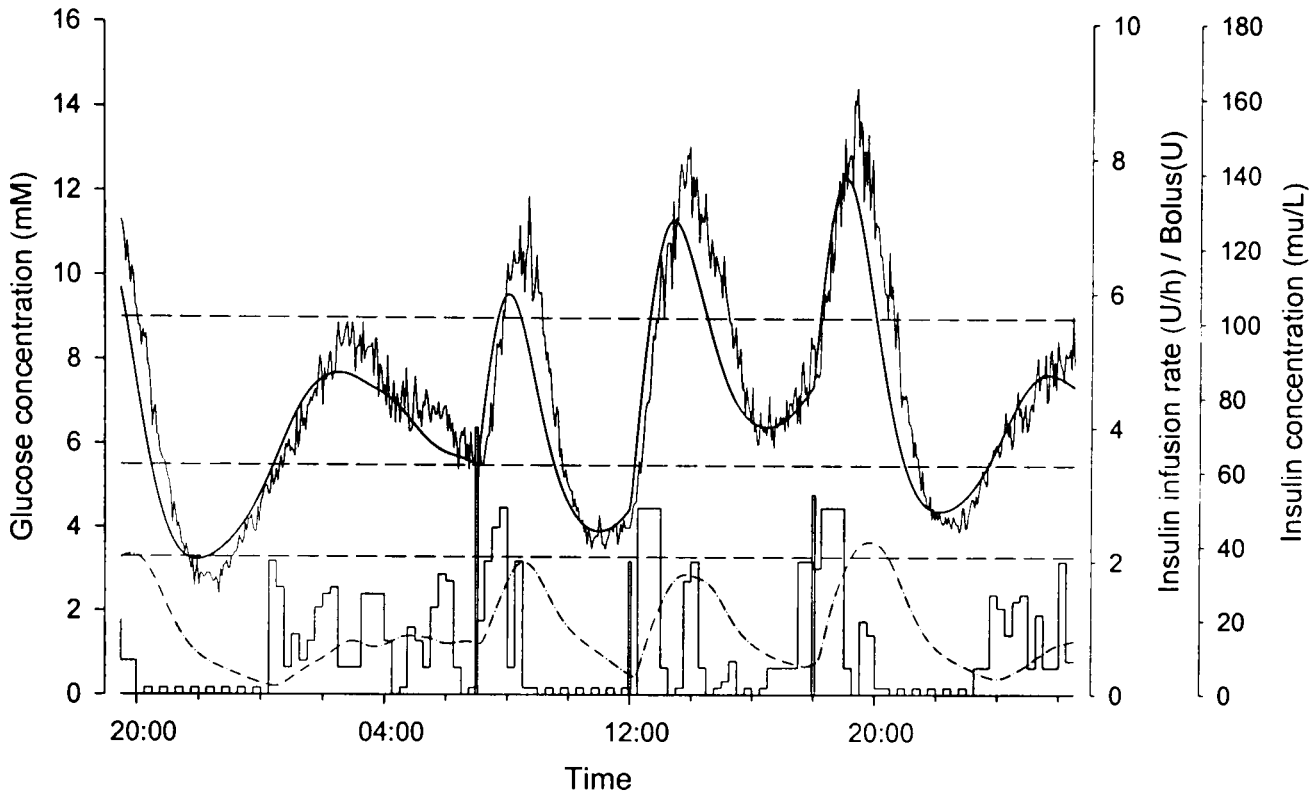

Figure 5.11: A sample simulation of a subject difficult to control (subject 5). See text for details of the experiment.

The plot shows plasma glucose (solid smooth line), the interstitial glucose measurements sampled every three minutes (5% measurement error; solid ragged line), the insulin infusion rate (piecewise constant solid line) and insulin boluses (open bars) delivered by the controller, and the plasma insulin concentration (dash-dot line). During the MPC controlled period, the subject ingested three meals at 840, 1140 and 1500 of 40, 70 and 60g CHO respectively. The insulin infusion rate was generated by the MPC described in section 3.4.3.

Subject 5 is characterised by large glucose fluctuations with steep glucose changes. The glucose profile presents both low and high glucose levels, the latter following meal digestion. The insulin sensitivity of the subject prevents large amount of insulin to be administrated to correct for glucose peaks.

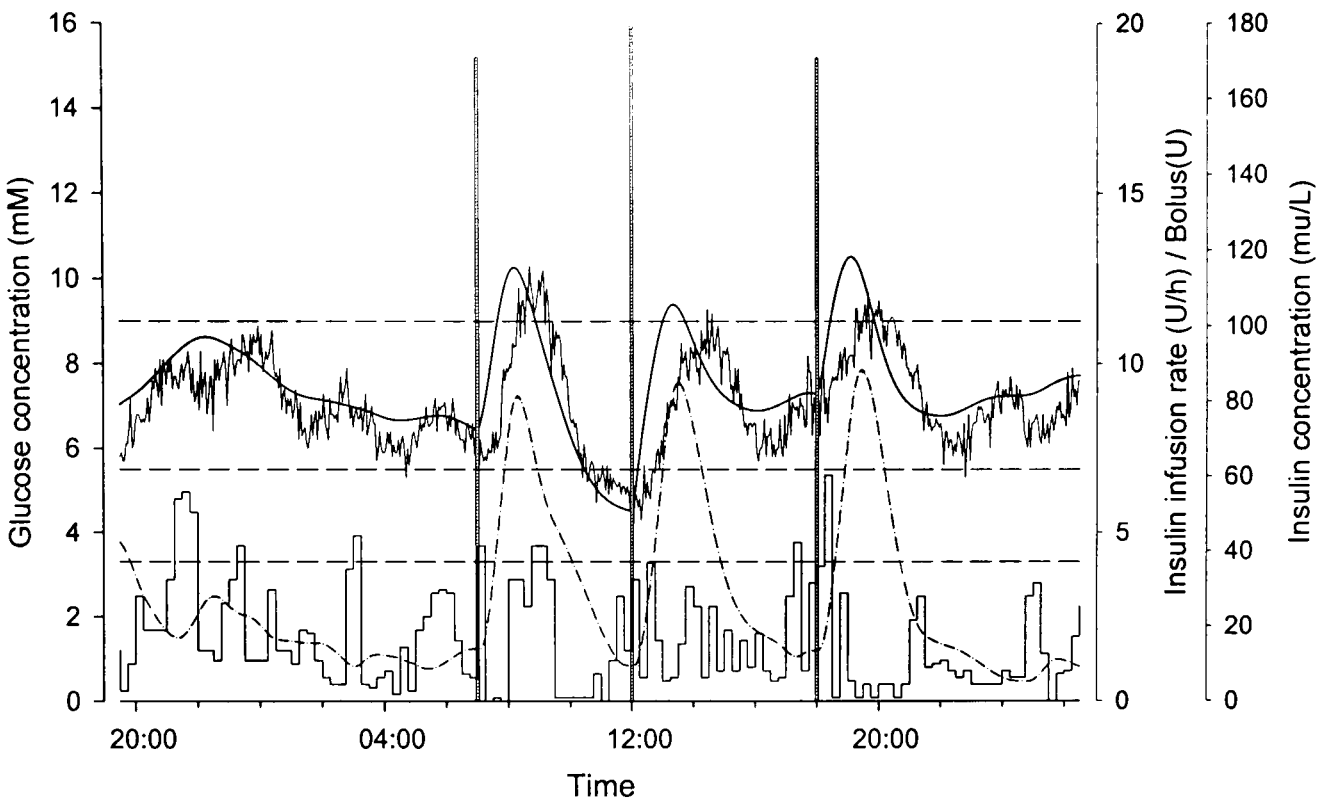

Figure 5.12: A sample simulation of a subject with high insulin requirements (subject 11). For details of the simulated experiment, see Figure 5.11.

Figure 5.12 shows a simulation with subject 11 also presenting considerable fluctuations in glucose levels. However, the hypoglycaemic range is not approached. This subject is characterised by high insulin requirements.

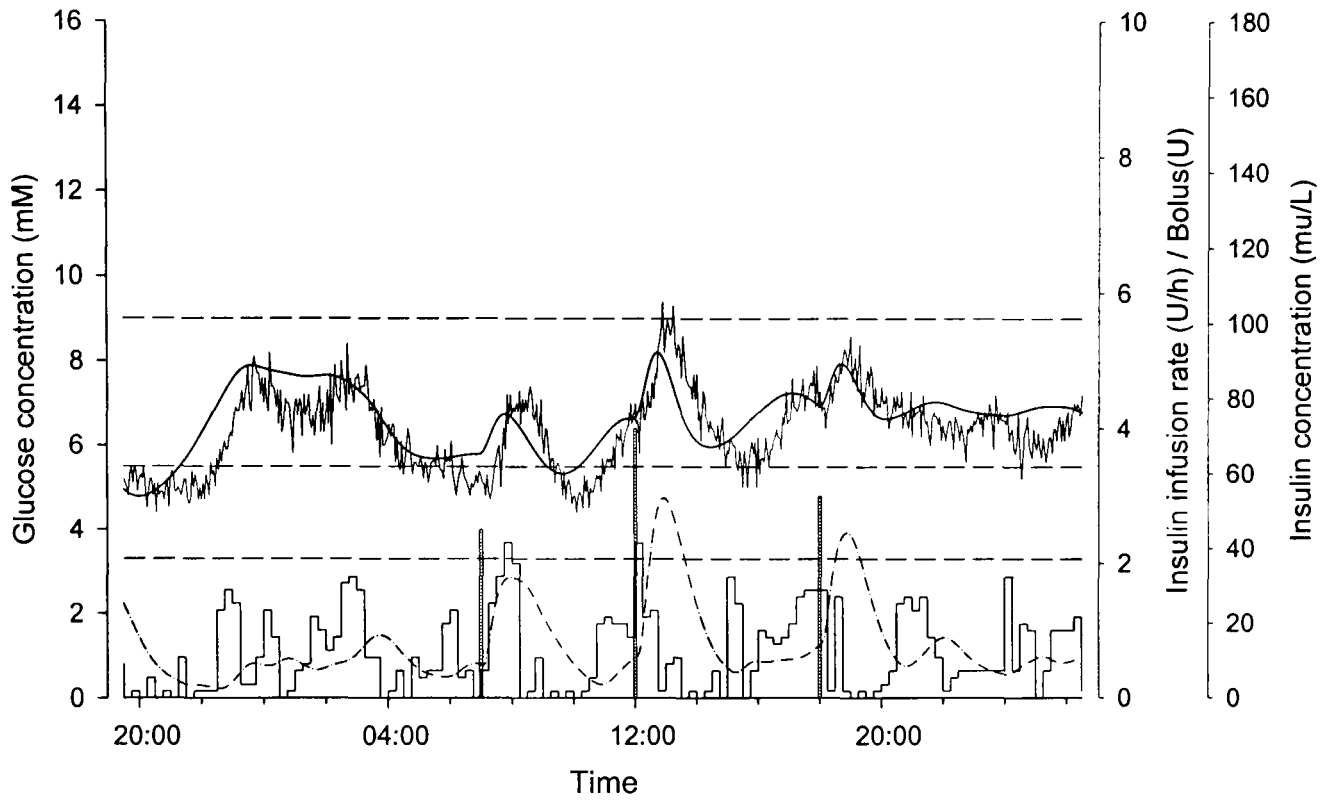

Figure 5.13: A sample simulation of a subject easy to control easy control case (subject 8). See Text for details of the experiment.

Figure 5.13 shows a simulation with subject 8 who, despite the presence of some oscillations, is easy to control. The glucose is never in the proximity of the hypoglycaemic threshold of 3.3mM. Elevated glucose levels either in the fasting or fed states are absent.

Appendix A shows simulations with all 18 subjects.

5.8 Discussion

The model of the glucoreglatory system in subjects with Type 1 diabetes was discussed in Chapter 3. Utilising the model, the purpose of the present chapter is to describe a simulation environment, which would enable glucose controllers to be tested.

To evaluate systematically a glucose controller, the simulation environment needs to represent a wide spectrum of subjects and include noise in the

insulin delivery and in glucose measurements. In our approach both inter-subject and intra-subjects variability were represented.

The sensing unit needs to represent certain characteristics for successful use with a closed-loop control system. It has been the focus of research for decades. The availability of a reliable subcutaneous glucose sensor is often considered the main obstacle for the development of an extracorporeal artificial pancreas (AP).

It is currently unclear what the real performance of a glucose sensor with a closed-loop system should be. A choice of a 5% measurement error presents an informed guess based on the data available with existing prototypes.

Insulin pumps are very reliable and versatile. However insulin delivery is not error-free especially at very low rates. It was therefore necessary to represent these pump errors. The delivery error was set at the level of 15% following an assessment of technical information provided for the Disetronic D-Tron pump.

The pump delivery error is not thought to pose a problem because of the relatively long time constant of the subcutaneous insulin absorption with a peak concentration at 71±17min (6) and 61±12min (195).

From the random generation and clinically derived 18 sets of parameters 18 synthetic subjects were obtained with Type 1 diabetes treated by continuous infusion of insulin lispro.

The variation in the subcutaneous insulin absorption is likely to generate large inter- and intra-subject variability (196). The absorption is a complex process affected by factors such as catheter insertion, skin sickness, or the duration of catheter placement (197).

Over and above oscillatory variations, other types of variations could have been included such as variation due to the dawn phenomenon. However, it is

unclear which parameters are affected. This could be insulin sensitivity (198) or hepatic glucose output (199).

In addition to representing a major disturbance, the meal intake is introducing variability into the glucoregulatory system. As gut absorption is an extremely complex process, the experimental results are conflicting (200). Meal timing appears to influence insulin requirements (201). Studies with meals with high fat (34), high protein (202), or different types of carbohydrates have shown to affect the glucose response. Other factors like circadian rhythmicity are also known to introduce variability in the response to meals (203,204).

Another aspect justifying the integration of variability in bioavailability is of a practical origin. The total carbohydrate content can be over- or under-estimated by the subject. A controller will have to use this information and should therefore demonstrate a certain level of insensitivity to those variations.

5.9 Conclusion

The parameter generation process resulted in a wide spectrum of subjects with large differences in fasting and prandial insulin requirements and with different levels of controllability. By combining a model of glucose measurements and a model of insulin delivery with a model of Type 1 diabetes, a closed-loop system can be simulated to test insulin infusion strategies.

The generation of 18 synthetic subjects facilitated the creation of a rich testing environment which will be employed in the development of a testing strategy presented in Chapter 6.

The validation of the simulator is the central topic of Chapter 7, where clinical validity and limitations are assessed using a comparative study with real clinical data obtained in subjects treated by a model predictive controller.

6 Evaluation of Glucose Controllers in Virtual Environment: Methodology and Sample Application

6.1 Introduction

As demonstrated in Chapter 2, glucoregulation is a complex process and adjusting insulin treatment to maintain normoglycaemia in Type 1 diabetes is highly desirable, not easily achieved, and particularly safety-critical.

In this chapter, an evaluation methodology is presented for testing glucose controllers in *in silico* simulation environment. The methodology includes two dimensions with the objective to promote the development of satisfactory controllers. The testing is first in relation to specific life style conditions (fasting and postprandial, for example), and, second, in relation to operating conditions such as expected or adverse operating conditions. This provides a coherent framework to carry out systematic evaluation proceeding from simple (most common) to more complex (less common) scenarios under which the system is expected to perform. The methodology helps to identify factors affecting the performance measures providing feedback for the development of the controller.

The use of the methodology is exemplified by tuning and evaluating the MPC controller presented in section 3.4.4 focusing on testing under fasting conditions.

6.2 Methods

6.2.1 Simulation Environment

The simulation environment shown in *Figure 6.1* was described in details in Chapter 5 and represents the interaction between the closed-loop components.

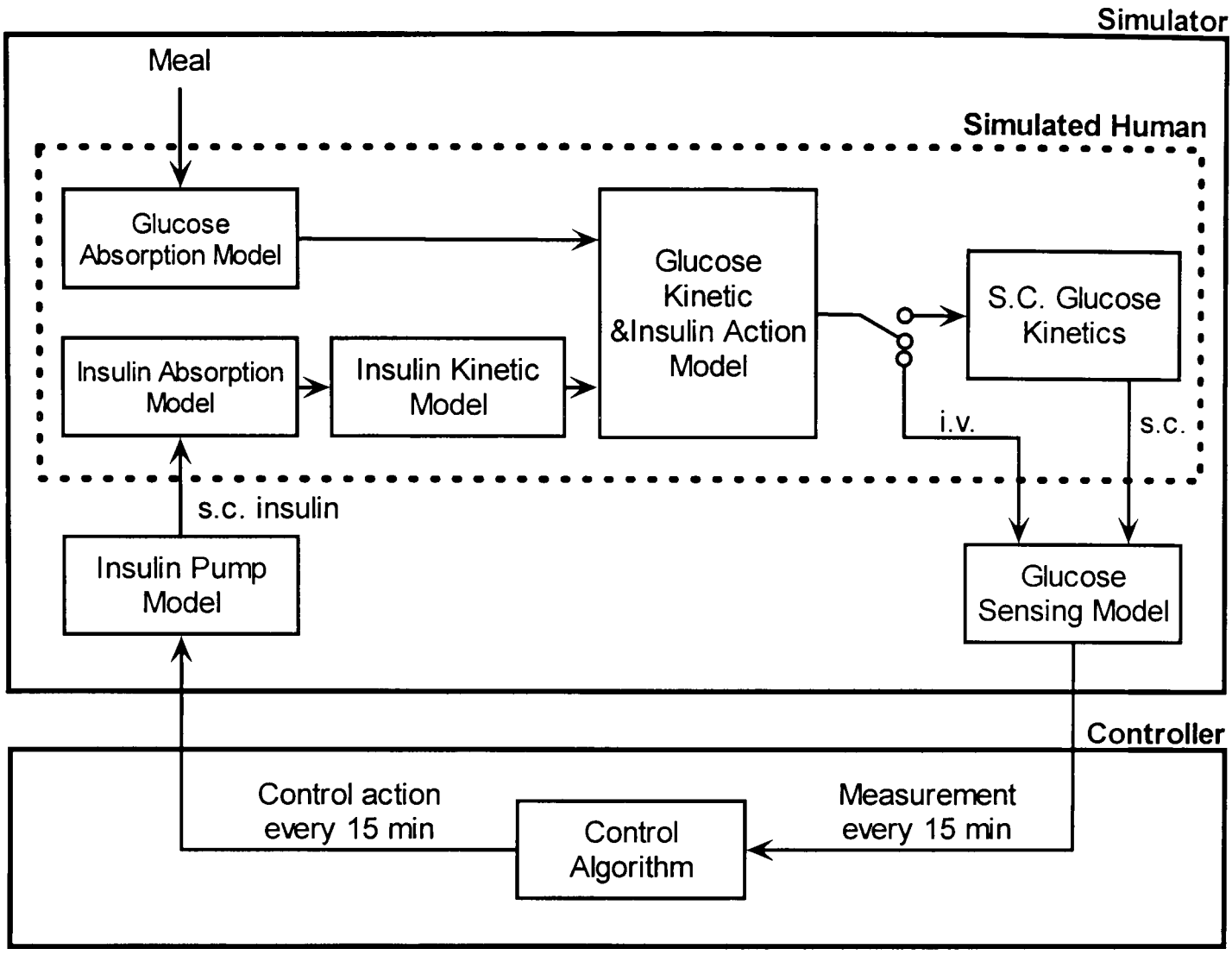

Figure 6.1: Overview of a simulation (virtual) environment to facilitate tuning and testing of glucose controllers.

The glucose measurement process consisted of a pure technical delay and a specific degree of measurement error.

The environment includes 18 virtual subjects with Type 1 diabetes. Differentiation among virtual subjects is achieved by assigning a unique set of parameters to the glucoregulatory model as explained in Chapter 5.

For this evaluation, the intra-individual variability of the glucoregulatory system is implemented in the virtual patients by superimposing sinusoidal oscillations on model parameters. These include fast oscillations (3h period) and slow oscillations (24h period) in combination with a low amplitude (5% of parameter value) and a high amplitude (30%). The phase is also drawn from a random (uniform) distribution for each parameter. This provides for virtual subjects with widely ranging behaviour characteristics.

6.2.2 Model Predictive Controller of Glucose Concentration

The model predictive control (MPC) (178) is an emerging methodology to facilitate control of systems with long time delays and open loop characteristics. When combined with adaptive capabilities, it promises to tackle successfully problems related to the difficulties encountered in the artificial pancreas (AP) development.

In this study, an MPC-based glucose controller (185) described in detail in Chapter 3 is evaluated. The controller has been designed to be used with an intravenous and subcutaneous glucose measurement, in combination with a subcutaneous insulin infusion of fast acting insulin such as Lispro.

The "aggressiveness" is a parameter of the MPC controller, which quantifies the penalty associated with large changes in the insulin infusion rate (the objective function of the dose optimiser contains two factors, one representing adherence to target glucose profile and the other is the norm of first differences in the sequence of insulin infusion rates). A large value of the aggressiveness increases the risk of hypoglycaemia whereas a low level results in a too slow normalisation of glucose levels.

6.2.3 System Tuning

The simulation environment represents an ideal tool to tune the controller and also to investigate the effect of various system set-ups. This is exemplified by finding an optimal value for the aggressiveness parameter of the controller and by assessing the effect of constraints in insulin infusion particularly the maximum infusion rate, see *Figure 6.2*.

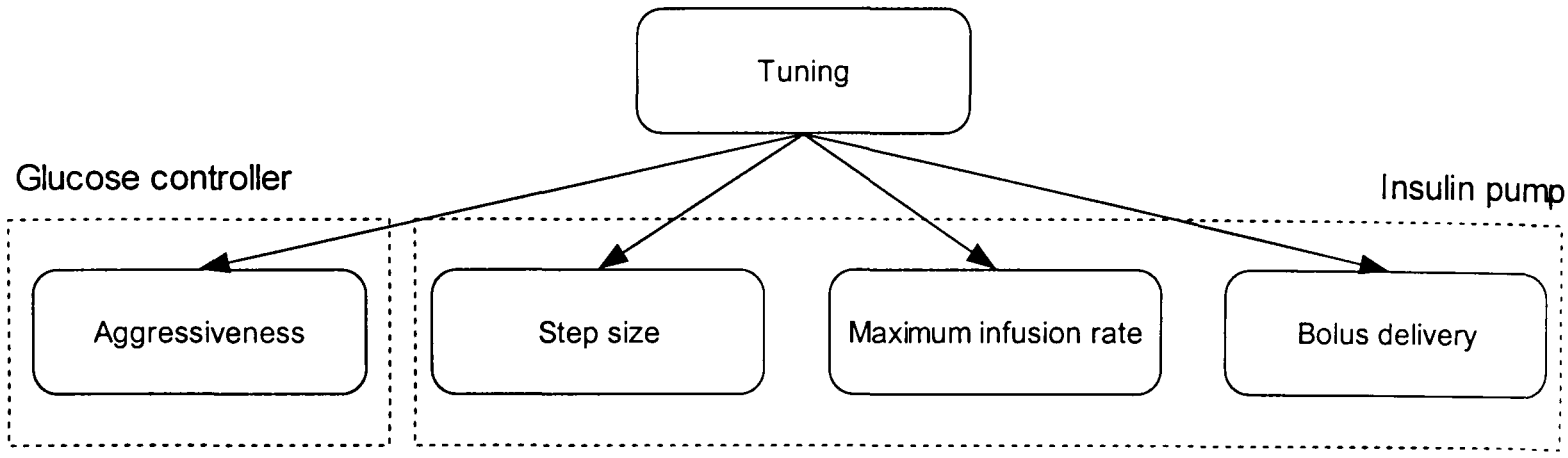

Figure 6.2: Simulation environment is instrumental in tuning the controller and assisting in the evaluation of settings of other system components such as the insulin pump.

6.2.4 Methodology to Test Blood Glucose Controllers Employing Simulator of Glucose Metabolism

6.2.4.1 Overview

The methodology evaluates the glucose controller in three (simulated) physiological conditions: fasting, postprandial, and life-style (metabolic) disturbances such as exercise, see *Figure 6.3*.

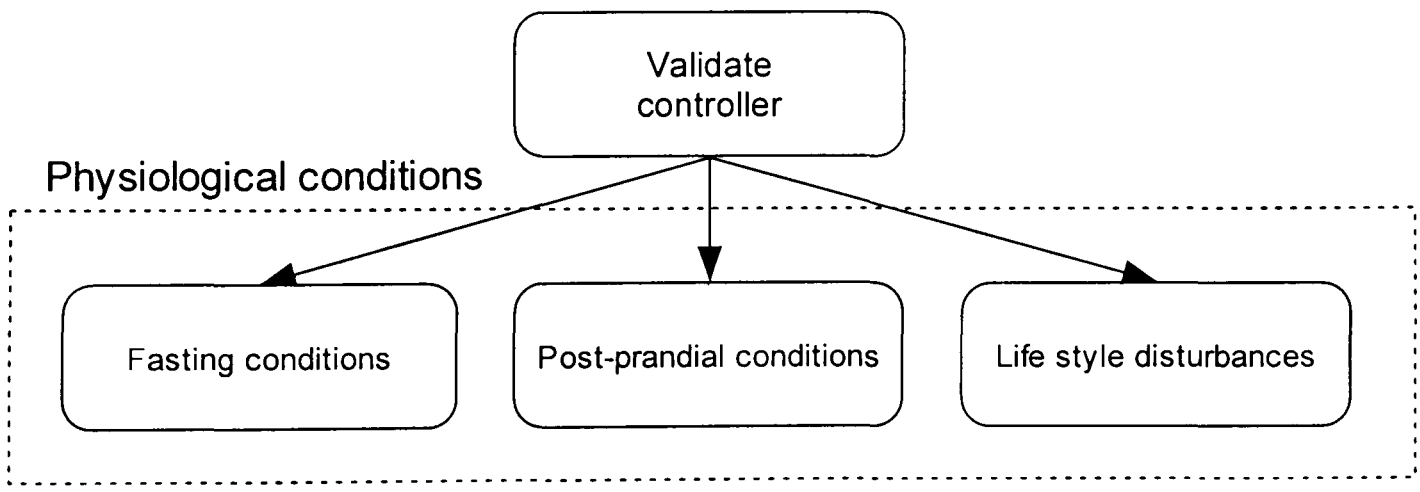

Figure 6.3: Glucose controller must be evaluated under different physiological conditions.

In each physiological condition, the concern is with the performance of the glucose controller under three operating conditions, expected operating conditions (EOC), adverse operating conditions, and system failure, see *Figure 6.4*.

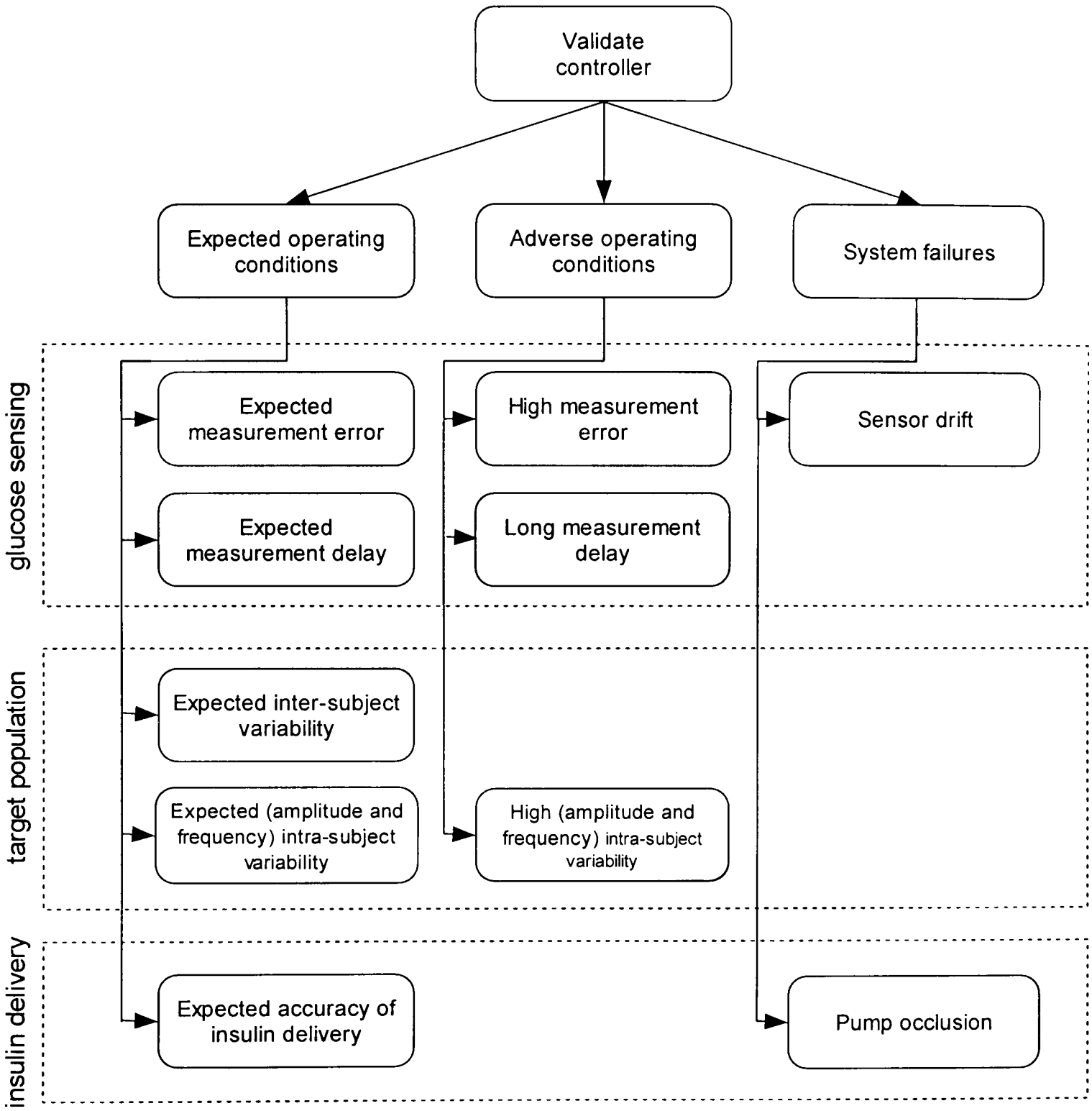

Figure 6.4: Overview of the validation methodology for blood glucose controllers (see text for details).

The EOC represents the typical conditions in which the controller is expected to work. These include the expected properties of the sensing device, properties of the target population, and properties of the insulin delivery device.

The glucose sensor is characterised by its measurement error, a measurement delay associated with subcutaneous glucose sensing (the delay is due to, for example, the kinetic properties of the glucose transport between

plasma and the interstitial fluid) (205,206). In the thesis, the model employed is by Wilinska *et al* (135,207), which is presented in detail in Chapter 4.

The target population is characterised by its inter-subject and intra-subject variability. Subjects differ in how much insulin they need (an inter-subject variability) which reflects their insulin sensitivity and other parameters of the glucoregulatory system. Second, insulin needs vary throughout the day due to, for example, diurnal changes in insulin sensitivity (an intra-subject variability).

As mentioned in Chapter 5, the insulin pump delivers insulin according to its technical specification (a step-by-step motor) and subject to constraints such as the maximum delivery rate and the step resolution.

The set-up for early clinical testing included intravenous glucose sampling and subcutaneous insulin delivery. A 3-5% coefficient of variation (CV) of the measurement error was expected, a 3min measurement delay (representing time needed to analyse plasma glucose on a bed-side analyser), a intra-subject variability (oscillations) of the parameters of the glucoregulatory system with a 5% CV and a 3h or 24h period, a 3min step delivery of insulin with a resolution 0.1U/h and a maximum infusion rate 4U/h, and a 15% CV of the error associated with insulin delivery.

Properties of the system components/environment can temporarily deteriorate and it is essential to assess the performance of glucose controllers under adverse operating conditions.

In particular, the measurement error associated with the glucose sensor can increase or the measurement delay can be prolonged. This also includes an increased amplitude of the intra-subject variability of the parameters of the glucoregulatory system.

Our implementation of the adverse operating conditions increased the CV of measurement error to 8% and 15%, the measurement delay from 30 to 40

min, and the amplitude of the intra-subject variability to 30% with an unaltered period of 3h or 24h. The measurement delay in the adverse operating conditions assumes subcutaneous glucose sampling via extracorporeal open flow microperfusion (208) and consists of a 10min physiological delay, a 20min dead space of the sampling cannula, and an additional adverse conditions related 10min delay.

System failure may have catastrophic consequences. Glucose controllers need to have a built-in safety (protection) scheme to deal with exceptional circumstances (209) with the objective of minimising the risk of insulin overdose and subsequent hypoglycaemia.

The tests proposed are related to a sensor drift and to an insulin pump occlusion. The sensor drift represents the situation where there is a progressively increasing bias between glucose measurements and the actual glucose levels. If the sensor overestimates actual glucose levels this may lead to insulin overdosing. A pump/tissue occlusion lasting several hours may lead to the creation of an insulin reservoir in the pump/tissue, which can abruptly enter the system. This problem can be exacerbated by the glucose controller increasing the insulin infusion during the occlusion period to "counteract" increasing glucose concentration.

6.2.4.2 Assessing Glucose Control

The glucose control is evaluated using two criteria, see *Table 6.1*. The primary criterion is the safety of glucose control. The secondary criterion is the efficacy of glucose control. The safety criterion is concerned with the avoidance of low plasma glucose (hypoglycaemia), the efficacy criterion with the avoidance of high plasma glucose (hyperglycaemia). The rationale behind the definitions of the two criteria is that of an acute danger such as unconsciousness or coma associated with hypoglycaemia, and that of the development and progression of microvascular and macrovascular complications of diabetes (limb amputations, blindness, renal failure etc), which is associated with a prolonged elevation of plasma glucose. From a clinical viewpoint, the

classification adopted in the current chapter is valid but crude, ignoring some of the physiological knowledge of the effect of impaired control on short and long term complications. It is technically oriented but retains the high level assessment of clinical safety and efficacy. The aim is to eliminate algorithm with insufficient performance from further testing and to benefit from simple criteria to improve iteratively the control strategy.

Table 6.1: Definition of safety and efficacy criteria for glucose controllers.

	Grade	Fasting conditions	Post-prandial state	Metabolic disturbances such as physical exercise, alcohol intake, etc
Safety	Excellent	No hypo* AND no serious hypo**	as for fasting conditions	as for fasting conditions
	Good	≤ 5% subjects with hypo AND no subject with serious hypo	as for fasting conditions	as for fasting conditions
	Satisfactory	≤ 20% subjects with hypo AND no subject with serious hypo	as for fasting conditions	as for fasting conditions
	Unsatisfactory	> 20% subjects with hypo OR at least one subject with serious hypo	as for fasting conditions	as for fasting conditions
Efficacy	Excellent	PG ≤ 6 mM	2 hour PG ≤ 8 mM	as for fasting conditions
	Good	PG ≤ 7 mM	2 hour PG ≤ 9 mM	as for fasting conditions
	Satisfactory	PG ≤ 8 mM	2 hour PG ≤ 11 mM	as for fasting conditions
	Unsatisfactory	PG > 8 mM	2 hour PG > 11 mM	as for fasting conditions

*hypo is defined as 2.0mM < PG ≤ 3.3mM; **serious hypo as PG ≤ 2.0mM

6.2.4.3 Safety Criteria

The safety criterion assesses the safety of the glucose control. This is achieved by evaluating the number of virtual subjects who present hypoglycaemia (2.0mM < plasma glucose ≤ 3.3mM) and serious hypoglycaemia (plasma glucose ≤ 2.0mM) during a relatively short duration (≤ 24h) of virtual tests.

"Excellent" safety is achieved by avoiding hypoglycaemia and severe hypoglycaemia in all subjects. "Good" safety is characterised by a very low risk of hypoglycaemia (≤ 5% of subjects with hypoglycaemia) without the presence of severe hypoglycaemia. "Satisfactory" safety is aimed to reflect incidence of hypoglycaemia with continuous subcutaneous insulin infusion (CSII), the current "gold" standard; there are limited comparable data and we set the limits (≤ 20% of subjects with hypoglycaemia; no severe hypoglycaemia) more stringently than those reported in a study by Renner *et al* (210) (about 40% subjects experienced hypoglycaemia in a day). "Unsatisfactory" safety is characterised by levels of hypoglycaemia in more than 20% subjects or by the presence of severe hypoglycaemia in one or more subjects.

The safety criterion is identical for all three "physiological" conditions, i.e. fasting, postprandial, and metabolic disturbances.

It is important to stress that simulated clinical trials are run for 8 to 24 hours and thus the safety criterion is defined taking into account the relatively short duration of the trials quantifying % of subjects with hypoglycaemia rather than incidence of hypoglycaemia per patient year as is standard in longitudinal studies such as the Diabetes Control and Complications Trial (DCCT) (210).

6.2.4.4 Efficacy criterion

The efficacy criterion evaluates the ability of glucose controllers to achieve glucose levels, which are known to avoid diabetes complications.

In the fasting state, "excellent" efficacy gives glucose levels (≤ 6mM) similar to those observed in healthy subjects. "Good" efficacy (plasma glucose ≤ 7mM)

was set to resemble the World Health Organisation (WHO) limit for the diagnosis of impaired glucose tolerance (211). The "satisfactory" efficacy (plasma glucose ≤ 8mM) corresponds approximately to the best currently available management practice as documented by intensive insulin therapy in the DCCT (210). "Unsatisfactory" efficacy is that which is less satisfactory, i.e. worse than the current best management practice.

In the postprandial state, the focus is on 2h postprandial glucose, which is widely used for the diagnosis of diabetes and in the assessment of postprandial glucose control. "Excellent" efficacy (2h plasma glucose ≤ 8mM/) was adopted to be similar to the WHO diagnostic limit of diabetes (211). "Satisfactory" efficacy (2h plasma glucose ≤ 11mM/) represents a slightly worse control than that observed with the best currently available management practice as exemplified by the intensive therapy during the DCCT (62). "Unsatisfactory" efficacy represents control worse than what is currently available.

In the conditions of life style disturbances, the efficacy criterion is the same as during the fasting conditions.

6.3 Results and Discussion

6.3.1 Simulation Environment

A sample outcome of a simulated clinical trial in a virtual subject is shown in *Figure 6.5*. The test included the digestion of a meal with co-administration of a "manually" determined insulin bolus. The closed-loop control commenced 3h after the meal.

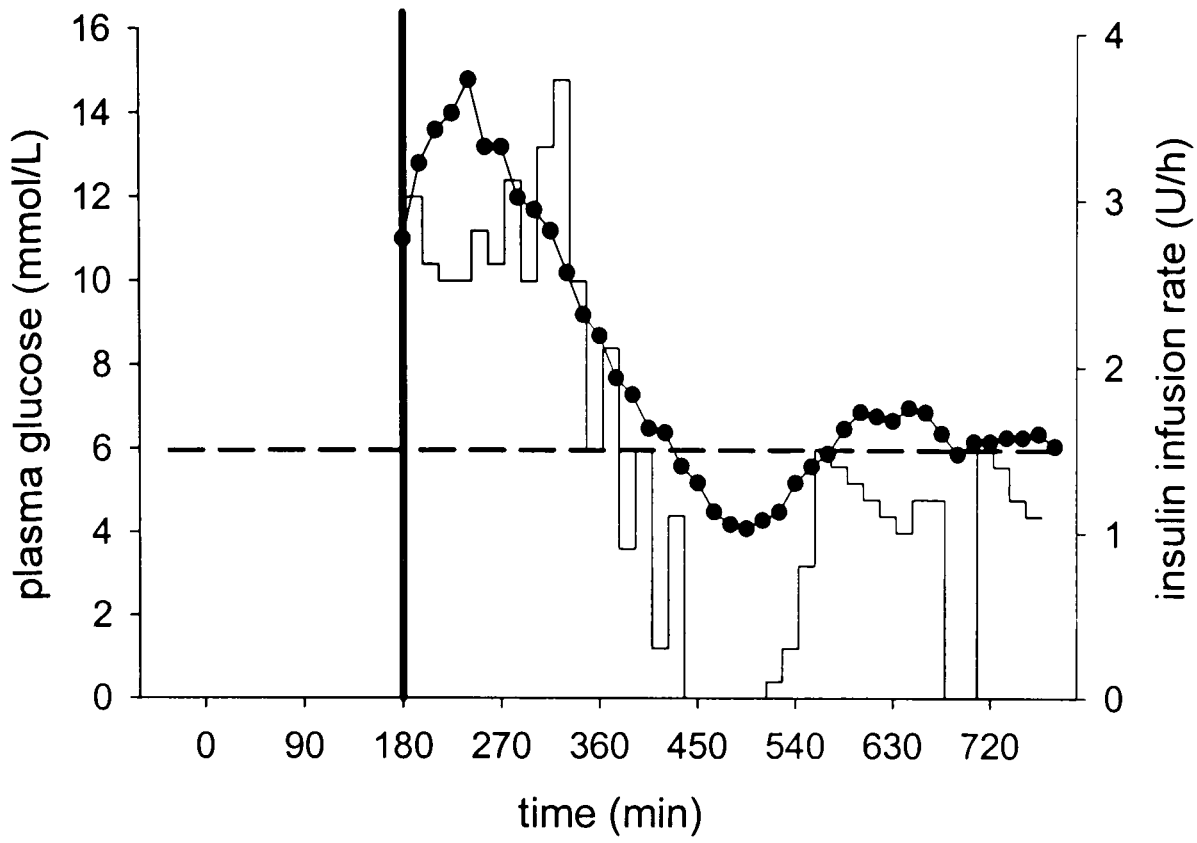

Figure 6.5: Example of glucose control using the simulator. At time 0min, a synthetic Type 1 diabetes subject had a meal and received insulin bolus. At 180min (vertical bar), glucose was artificially raised to 11mM and the subcutaneous insulin infusion was initiated. A model based glucose controller calculated the infusion rate every 15 min using intravenous glucose measurements also taken every 15 min.

6.3.2 System Tuning

The results of the system tuning are shown in *Table 6.2*.

Table 6.2: Tuning controller and insulin pump settings

	Set-up	Safety	Efficacy
Aggressiveness	1	Good	Good
	3	Good	Good
	5	Good	Excellent
	7	Satisfactory	Excellent
	1000	Satisfactory	Excellent
Maximum infusion rate 4U/h with step size 0.2 U/h		Good	Excellent
Maximum infusion rate 2U/h with step size 0.1 U/h		Excellent	Good
Bolus delivery		Excellent	Good

In the first instance, the effect of "aggressiveness" was investigated on the performance of the controller. The best trade-off was with aggressiveness 5 (unitless) which gave good safety and excellent efficacy. Higher values of aggressiveness maintained excellent efficacy but safety was compromised. Lower values of aggressiveness reduced efficacy.

All future runs with the controller were therefore run with the aggressiveness set to 5 (unitless).

A close inspection of the data collected during the "aggressiveness" tests indicated that some virtual subjects were temporarily infused with insulin rates above the upper limit currently employed during the CSII. Clinical considerations suggested employing an upper limit of 4U/h and technical considerations of an insulin pump to be employed in real clinical trials (to facilitate a fast manual change of the insulin pump rate) implied that a 2U/h limit should also be considered. The former limit was tested with a reduced step size of 0.2U/h (in all other tests a step size resolution was 0.1U/h) again considering a fast manual alteration of the pump rate.

The limit of 4U/h lead to the same results as the limit-free testing. The 2U/h limit improved safety. However, efficacy was reduced due to several insulin resistant subjects receiving too little insulin. It was decided to adopt the 4U/h and not the 2U/h limit for future testing. The step size was set at 0.1U/h as this was subsequently found technically feasible.

Insulin pumps deliver insulin in microboluses 0.5 to 3 min apart. This quantum insulin delivery may introduce a discrepancy between the expected and truly infused insulin at times when infusion rates change considerably. The discrepancy can be avoided by administering insulin not as a continuous insulin infusion but as boluses given at the start of the control cycle (in our system, insulin rate changes every 15min). The performance of bolus delivery was evaluated and gave excellent safety and good efficacy. The efficacy just failed to reach the excellent grade. Thus, in purely performance terms, bolus delivery of insulin every 15 min appears to be a preferable mode of insulin delivery. This feature was not retained as it was considered that a zero fluid flow for 15min at the tip of the cannula might increase the risk of an occlusion.

6.4 Application of the Methodology to Test Blood Glucose Controllers on Simulator

To exemplify the use of the methodology the performance of the model predictive controller was evaluated under fasting conditions. The results are shown in *Table 6.3*.

Table 6.3: Summary of validation results for model predictive controller during fasting conditions.

	Set-up	Fasting conditions	
		Safety	Efficacy
Expected operating conditions		Excellent	Good
Adverse operating conditions	High measurement error	Satisfactory	Good
	Long measurement delay	Excellent	Satisfactory
	High intra-subject variability	Unsatisfactory	Excellent
System failure	Sensor drift	ND*	ND*
	Pump occlusion	Satisfactory	Good

*Not done

Under expected operating conditions, the controller achieved excellent safety and good efficacy. No hypoglycaemia events were observed.

This provided the reassurance for subsequent real clinical testing which involved nine CSII treated subjects with type 1 diabetes (six females and three males) with basal insulin needs of 22.5±7.0 U/day. Subjects received a 40g breakfast at 8:00 after an overnight fast. From 11:30 the MPC took control until 19:30 employing IV glucose measurement and SC insulin Lispro infusion (212). The clinical study gave similar results to those obtained in the simulation study. The similarity of the two sets of results provides support for the validity of the virtual environment. This early stage clinical trial employed a simplified setting compared to that presented in Chapter 7, section 7.2.4.

Under adverse operating conditions, the high measurement error reduced safety while maintaining efficacy. The reduction in safety can be at least in part

attributed to "false-positive" hypoglycaemia events, i.e. plasma glucose above the hypoglycaemia threshold can be "measured" below the threshold after adding the measurement error and this situation will be exacerbated with an increased measurement error. The long measurement delay reduced efficacy but still achieved the satisfactory grade. The high intra-subject variability was the only set of conditions with unsatisfactory safety. This was due to the presence of one severe hypoglycaemia (out of 36 virtual tests). This indicates that large variations (30% of nominal values) in individual parameters are difficult to deal with by the glucose controller.

Of the two types of the system failure, only the pump occlusion was tested. The 2h occlusion gave satisfactory safety and good efficacy as assessed by post-occlusion plasma glucose over a period of 5h. This was an important observation as the pump occlusion is not a rare event. Modern insulin pumps are equipped with pressure sensors to detect the occlusion but an additional safety margin is beneficial. The sensor drift has not been tested as limited information is known about the glucose sensor being developed for this particular version of the artificial pancreas.

6.5 General Discussion

The development and testing in a simulation environment is an appealing and worthwhile strategy to lower costs and to reduce the development time. The validity of the approach lies in the creation of a virtual environment faithfully representing real world conditions. In the medical field, the richness of the environment has to reflect the variability between individuals, variability within individuals, and characteristics of the technical components such as the measurement error. The simulation environment was presented in detail in Chapter 4 and Chapter 5 and designed in such a way that the different methodological components can easily be addressed.

In this chapter, the concern is with the development of a testing methodology for glucose controllers. Several notes related to the development and validation of the virtual environment apply. First, the virtual development should be based on

real data. It is clear, however, that there will be components for which our knowledge is incomplete and/or inconsistent. For example, the pump characteristics may change and alleviate some of its limitations and new knowledge may support some amendments in the methodology describe here. This requires qualified guesses to be made about underlying probability distributions of some parameters and properties. Second, the validation of the virtual environment is an important issue but this can normally be resolved only after real clinical tests have been conducted.

The methodology presented in this chapter holds general applicability for other medical systems where the need for adaptive techniques in a varying environment is applicable. The evaluation is divided first according to the life style conditions starting with simple to more complex (or most common to less common) under which the application is planned to be used. This reflects that these conditions may require different definition of evaluative criteria. The second dimension of the evaluation is related to the settings of physiological and technical parameters of the system (stressing that the human is part of system) proceeding from the normal (expected) operating conditions to those which can be classified as the system failure. An important part of the methodology is a definition of the evaluative criteria. In the medical domain these neatly divide into safety (is the system safe to use) and efficacy (does the system achieves its primary goal).

6.6 Conclusion

A methodology has been developed to test glucose controllers in a simulated (virtual) environment. The methodology is instrumental in anticipating the results of real clinical tests for different physiological conditions and for different operating conditions. The thorough testing in the virtual environment reduces costs and speeds up the development process. The following chapter is presenting a methodology to assess glucose control from a clinical point of view and its use for the simulator validation.

7 Clinical Assessment of Control and Simulator Validity

7.1 Introduction

Chapter 6 described an evaluation strategy to support *in silico* development of glucose controllers. The strategy provided a framework for systematic classification of the performance of glucose controllers for a range of physiological conditions and different types of the operating environment. The objective of the evaluation strategy was to prevent the deployment or even clinical testing of substandard controllers.

From a clinical view point, the classification adopted in Chapter 6 is inevitably crude and ignores some of the physiological knowledge of the effect of impaired control on short and long term complications.

National and international bodies have compiled such knowledge and have provided guidelines suggesting threshold values. This includes organisations such as the America Diabetes Association (ADA), Diabetes U.K, the American Association of Clinical Endocrinology, and the World Health Organisation (WHO).

First new criteria are defined to assess the performance of glucose controllers. In this case, a purely clinical viewpoint is adopted and the criteria are based on therapeutic guidelines. As there are minor inconsistencies among guidelines from different organisations, suggestions proposed by the ADA are adopted.

The system introduces six grade values A to F to describe the level of control and the required therapeutic action during fasting and postprandial conditions. The outcome of grading is the quantification of time spent in each grade and is illustrated through individual examples.

Secondly, the grading system is used to compare the synthetic subjects and real subjects with Type 1 diabetes with main characteristics shown in *Table 7.1*.

Table 7.1: Characteristics of real and synthetic subject groups

	Real subjects	Data used to generate synthetic subjects
Number of males	8	11
Number of females	4	7
Age (years)	41±11	35±7
BMI (kg/m^2)	24±2	25±3
Duration of diabetes (years)	24±12	16±9

Both subject groups had similar basal insulin needs with a wider variability in the synthetic subject group (14.7±3.9 vs 14.2±6.0 mU/kg/h; real subjects vs synthetic subjects; mean±SD; range 9.3-20.9 vs 5.0-26.0 mU/kg/h). The prandial needs were lower in the synthetic subject group (0.7±0.3 U/10g CHO; range 0.3-1.1) than in the real subject group (1.6±0.9/10g CHO; range 0.5-3.4 /10g CHO). Both subject groups underwent a similar trial and were controlled over 24h by the MPC described in section 3.4.4.

Although examples of individual control are provided, the comparison among the two subject groups is based on population rather than individual basis and serves to demonstrate the validity of the simulation environment. We employed the average glucose profile and average indices of glucose control in the comparison.

The primary aim of *in silico* testing is to replace, where possible, clinical testing. Similarity of the level of control would support the clinical notion of validity.

Apart from clinical validation, other validation modalities could be considered. This includes the validation of model subsystems, intra-subject variability, and inter-subject variability. These validation modalities are not considered here.

7.2 Methodology

7.2.1 Clinical Criteria and Setting

Controlling glucose profile is the essential goal of insulin therapy. The focus is to limit glucose excursions while avoiding hypoglycaemia. Ideally, a glucose profile should be reproduced by limiting postprandial glucose excursions and achieving fasting glucose levels within a narrow range to avoid and/or reduce the long term complications.

By employing clinical criteria to assess the control of the glucose profile it is possible to demonstrate the strengths and weaknesses of a glucose controller and its ability to achieve glucose control.

7.2.2 Definition of the Clinical Criteria

A grading system with grades A,B,C,D,E, and F, see table *Table 7.2*, was introduced following the approach broadly adopted by Clarke *et al* (213) to assess clinical utility of alternative sites/devices for glucose measurements. The grades describe, in a quantitative fashion, the level of ambient glucose reflecting the need or lack or need of a therapeutic intervention. Grade A corresponds to the glucose level within the tight physiological range without the need for a corrective action. Grade F corresponds to life threatening control with the need for an immediate action.

Grading of ambient glucose levels depends on physiological status. At present we considered two, postprandial and fasting conditions. For each condition, grading is based on threshold glucose values, see *Table 7.3*. The postprandial condition is defined from 15 min to 180 min following meal ingestion. The fasting condition is that outside the postrandial condition.

Table 7.2: Qualitative grading of glucose control

Qualitative grade	Control efficacy level / Action recommendation
A	Excellent control / No action required
B	Good control / No action required
C	Sub optimal control / Action recommended
D	Poor control / Action required
E	Very poor control / Immediate action required
F	Life threatening control / Require assistance

Table 7.3: Grading for fasting and postprandial conditions.

Plasma glucose (mM)	Fasting Conditions	Postprandial Conditions
≤2.8	F	F
≤3.3	E	E
≤4.4	C	D
≤6.1	A	B
≤7.2	B	A
≤7.8	C	A
≤10.0	D	B
≤13.9	D	C
≤25	E	D
>25	F	F

7.2.3 Explanatory Notes

This section justifies the selection of threshold values adopted in *Table 7.3*.

7.2.3.1 Fasting Conditions

The plasma glucose value at 2.8mM or below represents severe hypoglycaemia (16) which is likely to require an external assistance (214) and is potentially life threatening. The plasma glucose level 3.3mM represents a hypoglycaemia

threshold (16) , see for example a study comparing the multiple daily injections and the continuous subcutaneous insulin infusion (76). A subject should still be able to counteract the hypoglycaemia by an immediate glucose intake.

Below the plasma level of 4.4mM, hypoglycaemia threshold is close and although the subject may not feel any discomfort (215), an action from the patient may be required as a prevention.

In the fasting conditions, the target plasma glucose for very good control is between 4.4 and 6.1mM. The lower bound has been used, for example, by pregnant women with Type 1 diabetes (216). The upper bound has been chosen as a limit of normality by the ADA (30) and the WHO.

In fasting conditions, plasma glucose level up to 7.2mM is outside the normal range in a healthy subject but still low enough to be considered good and is the preprandial maximum plasma glucose concentration recommended for adults (217).

Plasma glucose above 7.8mM increases the risk of complications. The threshold is employed by the WHO and is also often associated with the elevated glucose in the postprandial condition (30). Therefore, adjustment should take place to optimise the glucose control.

Glucose above 10mM represents poor control which requires a control action. Glucose above 13.9mM increases further the risk of complications and an immediate action is required to prevent the appearance of ketones. However, the life of the subject is not in an immediate danger. Plasma glucose of 25mM is a diagnostic criterion for diabetes ketoacidosis which can lead to a diabetic coma if not treated.

At plasma glucose of 25mM and above an external assistance may be required such as hospitalisation due to the diabetic coma.

7.2.3.2 Postprandial Conditions

Threshold employed for the postprandial conditions require a slightly different approach as glucose values can be elevated even in healthy subjects.

The two lower thresholds are similar to those adopted for the fasting conditions.

Plasma glucose below a threshold of 4.4mM in the postprandial conditions is likely to result in insulin overdosing which could lead to an accelerated downward trend when glucose appearance from the gut is completed.

To a lesser extent, a similar consideration applies to a glucose level below 6.1mM explaining the choice for its B grading.

In the postprandial conditions, plasma glucose in healthy subjects is elevated and glucose levels up to 7.8mM can be observed but the endogenous surge in insulin secretion at the meal time limits the transient glucose excursions. The plasma glucose level of 7.8mM represents the threshold separating normal and impaired glucose tolerance (30) but represents an excellent control. Insulin dosing is preventing the large glucose excursion while allowing glucose to rise providing a safety margin to protect from a potential hypoglycaemia.

Plasma glucose of 10mM is recommended by the ADA as the peak postmeal glucose excursion and is therefore graded as a good control. Above the threshold of 10mM, plasma glucose is referred to as suboptimally controlled.

For the same reasons but to a larger extent, plasma glucose above 13.9mM is classified as poorly controlled. Above this level, the ketones start to be present and a control action from the subject is required.

Above plasma glucose of 25mM, the risk of diabetic coma is greatly increased.

7.2.4 Clinical Trial Setting

The single centre clinical trial (University Hospital, University of Graz, Austria) studied 12 subjects with Type 1 diabetes (duration of diabetes 24±11 years) aged 21 to 64 years; BMI 24±2 kg/m^2. The subjects were well controlled (HbA_{1c} 7.3±0.9%) and were treated by continuous subcutaneous insulin infusion (CSII) with fast acting insulin. Their insulin needs were 20±6 U/day for the basal infusion and 22±6 U/day for the prandial bolus.

The subjects arrived at the clinic at 14:00 and left at 22:00 the next day. After arrival, subjects were normalised to a target plasma glucose level of 5.5-6.6mM with intravenous insulin and glucose until 17:00. Then the intravenous-intravenous route was discontinued and subjects were switched onto the usual insulin pump administrating fast acting insulin lispro (Humalog, Eli Lilly). At 18:00 dinner was ingested and a standard prandial bolus was administrated. At 19:30 an automated insulin delivery driven by the Model Predictive Control (MPC) was initiated and lasted overnight followed by a breakfast at 7:00 (60, 72, or 84g carbohydrates (CHO)), lunch (60, 72, or 84g CHO) at 12:00 and dinner (48, 60, or 72g CHO) at 18:00. The meal choice was based on the usual daily caloric intake of a subject.

The insulin infusion was driven by the MPC over a 26.5 hour period with intravenous plasma glucose measurements and insulin pump rates adjusted every 15 minutes. At the time of a meal, the algorithm was provided with the subject's estimated carbohydrate intake and an insulin bolus generated by the MPC was administrated at the time of meal ingestion. A 10g oral glucose would be given in case of hypoglycaemia defined as a plasma glucose measurement at or below 3.3mM. To simulate subcutaneous glucose measurements, the plasma glucose measurements were presented to the MPC with a 30min delay.

One subject presented abnormal insulin needs and was removed from the comparison.

7.2.5 Simulated Trial

During the simulation, the automated control covers the same time span (26.5 hours) as during the clinical trial. The simulation started at 17:00. Similarly to the clinical trial, at 18:00 a dinner and in individually determined bolus were given. At 19:30, the MPC took over the insulin administration. Breakfast, lunch, and dinner were taken at the same time as during the clinical trial (7:00, 12:00 and 18:00); the CHO quantities were 40, 70, and 60g CHO, respectively. Plasma glucose measurements were obtained every 15 minutes and were made available to the MPC with a 30 minutes delay. Insulin boluses at the meal times were also generated by the MPC.

The average insulin needs were 25±10 U/day for the basal insulin and 27±15 U/day for prandial boluses, see Chapter 5.

Due to abnormal insulin needs and the kinetics of glucose after meal ingestion, subject 9 was excluded from the comparison. The remaining 17 synthetic subjects were compared against 11 real subjects with Type 1 diabetes.

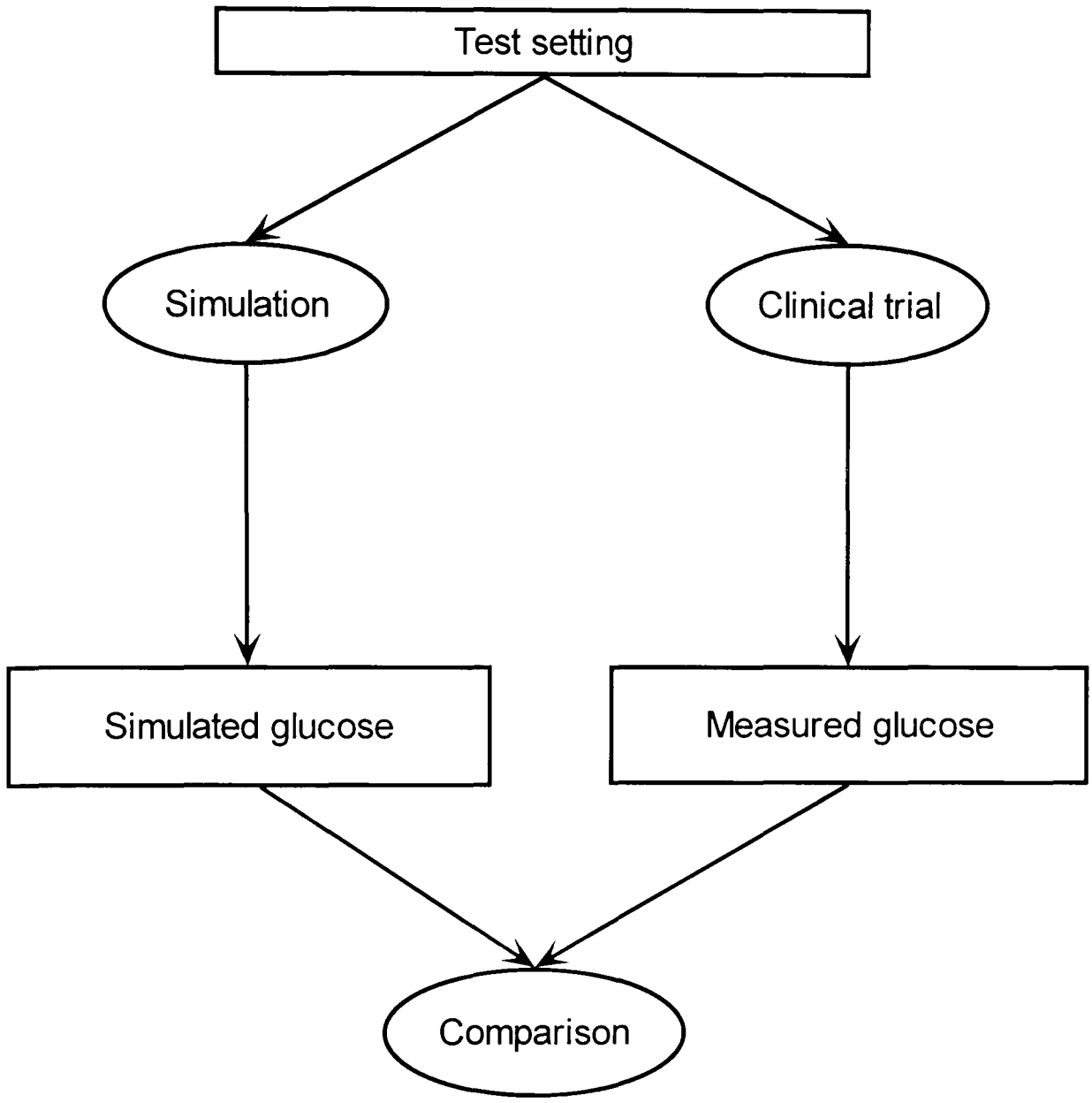

Figure 7.1: The approach to compare the simulator with data collected during a real clinical trial.

7.3 Results

7.3.1 An Example Use of the Criteria

Glucose controls in two synthetic subjects are presented in *Figure 7.2* and *Figure 7.3*. The former figure presents a profile of a well controlled subject and the latter figure a profile of a suboptimally controlled subject. The qualitative criteria for the two profiles are shown in *Table 7.4* and *Table 7.5*.

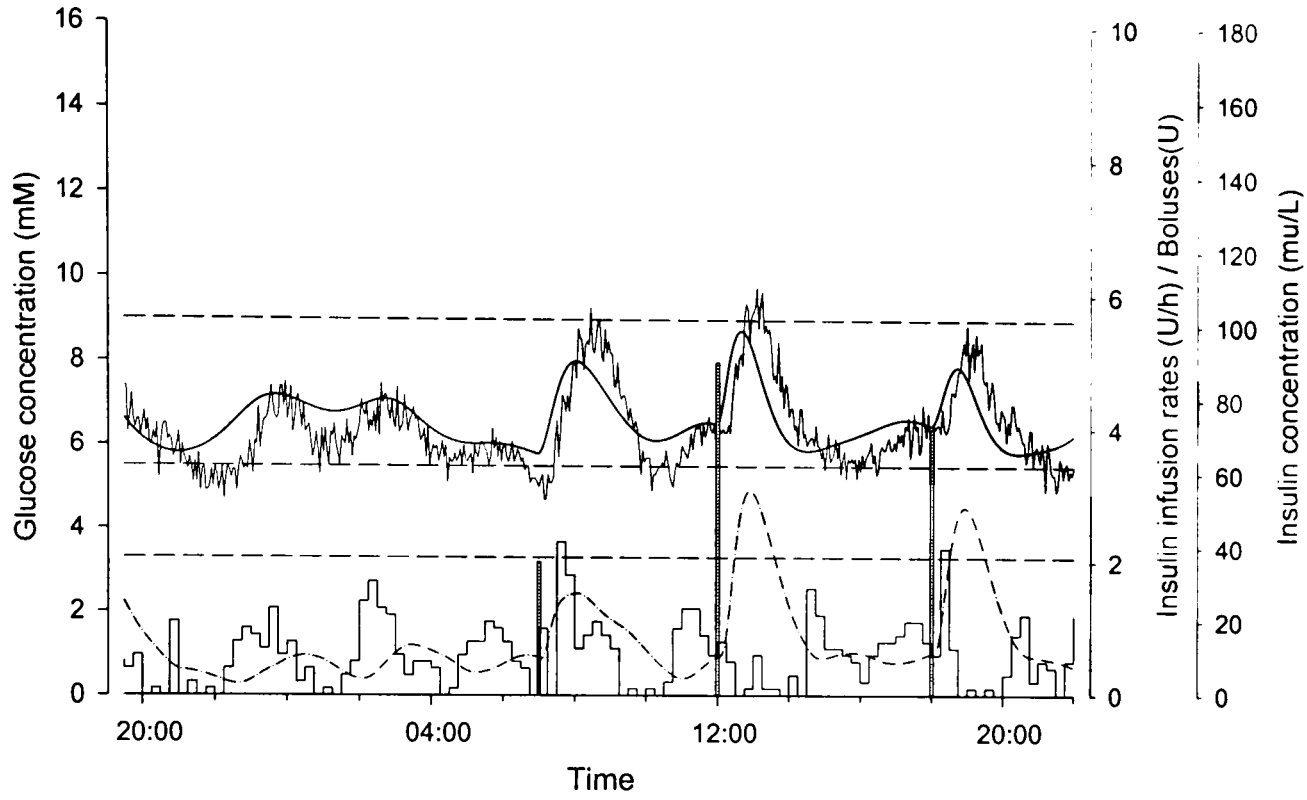

Figure 7.2: Plasma glucose profile (smooth solid line) as an example of good control in synthetic subject 14.

Table 7.4: Percentage time spent in grade A to F for fasting and postprandial conditions, and both conditions for a well controlled subject 14.

Conditions	A	B	C	D	E	F
Fasting	28.0	71.8	0.2	0.0	0.0	0.0
Postprandial	49.9	50.1	0.0	0.0	0.0	0.0
Fasting and Postprandial	36.1	63.8	0.1	0.0	0.0	0.0

Subject 14 is representative of very well controlled subjects with almost 100% of the plasma glucose levels falling into A and B grades. Such a subject is less likely to develop complications due to elevated glucose. Postmeal glucose excursions are within the normal range while the risk of hypoglycaemia is limited by maintaining glucose levels above 4.1mM. The performance in this case is excellent.

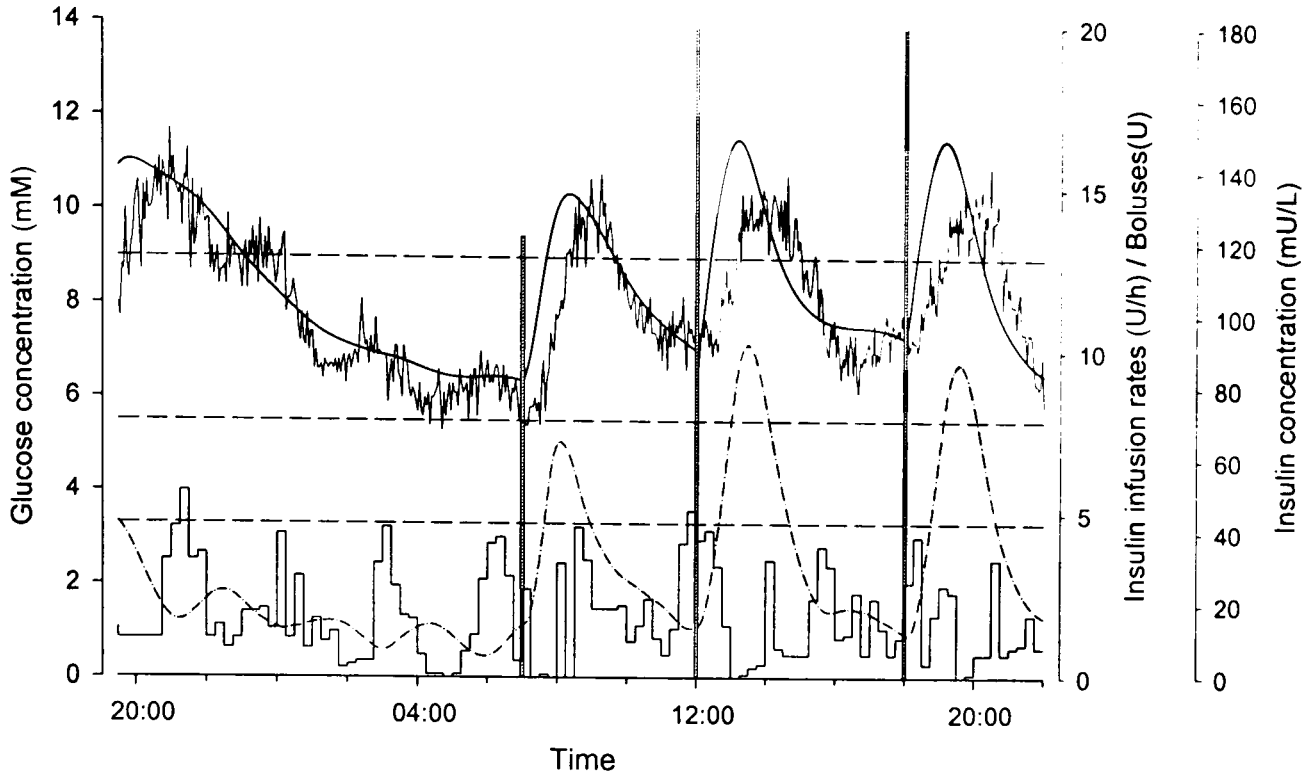

Figure 7.3: Plasma glucose profile (smooth solid line) as an example of poor control in synthetic subject 17.

Table 7.5: Percentage time spent in grade A to F for fasting and postprandial conditions and both conditions for a suboptimally controlled subject 17.

Conditions	A	B	C	D	E	F
Fasting	0	40.2	30.4	29.4	0	0
Postprandial	4.9	42.7	52.4	0	0	0
Fasting and Postprandial	1.8	41.3	38.7	18.7	0	0

The second example illustrates the difficulties encountered with an insulin resistant subject. The glucose profile never falls in Grade A in the fasting period and less than a half of the time it falls in the Grade B leaving about 60% of the fasting time in Grade C and D. In the postprandial conditions, a considerable amount of time is spent above the ADA peak limit of 10mM. Consequently, more than 50% of the postprandial time is spent in Grade C. Reflecting the clinical implications of the elevated glucose levels this subject is clearly at the risk of developing long term complications. The MCP did not control this subject well.

The previous examples suggest that more insulin resistant subjects attain poorer control. *Table 5.7* shows the fasting and meal related insulin needs for each subject. These values were correlated with the percentage of time spent in very good and good bands (A+B), see *Table 7.6*.

Table 7.6: Correlations between basal and prandial needs with time spent in (A+B) bands during fasting, prandial and combined conditions.

	Basal needs	Prandial needs
A+B in fasting state	-0.76	-0.43
A+B in postprandial state	-0.51	-0.31
A+B in Fasting and Postprandial combined	-0.75	-0.44

There is a clear association in the level of basal insulin needs and the level of control. The higher the basal needs, the less time is spent in the (A+B) bands. Thus the controller achieves less favourable control in more insulin resistant subjects.

7.3.2 Comparison Assessment

Employing the grading system presented in section 7.2.2, the glucose control was evaluated by calculating the time spent in each grade. Fasting and postprandial periods were considered separately. The overall performance was considered by combining the two periods.

Figure 7.4 shows the plasma glucose profiles during the clinical and simulated trials.

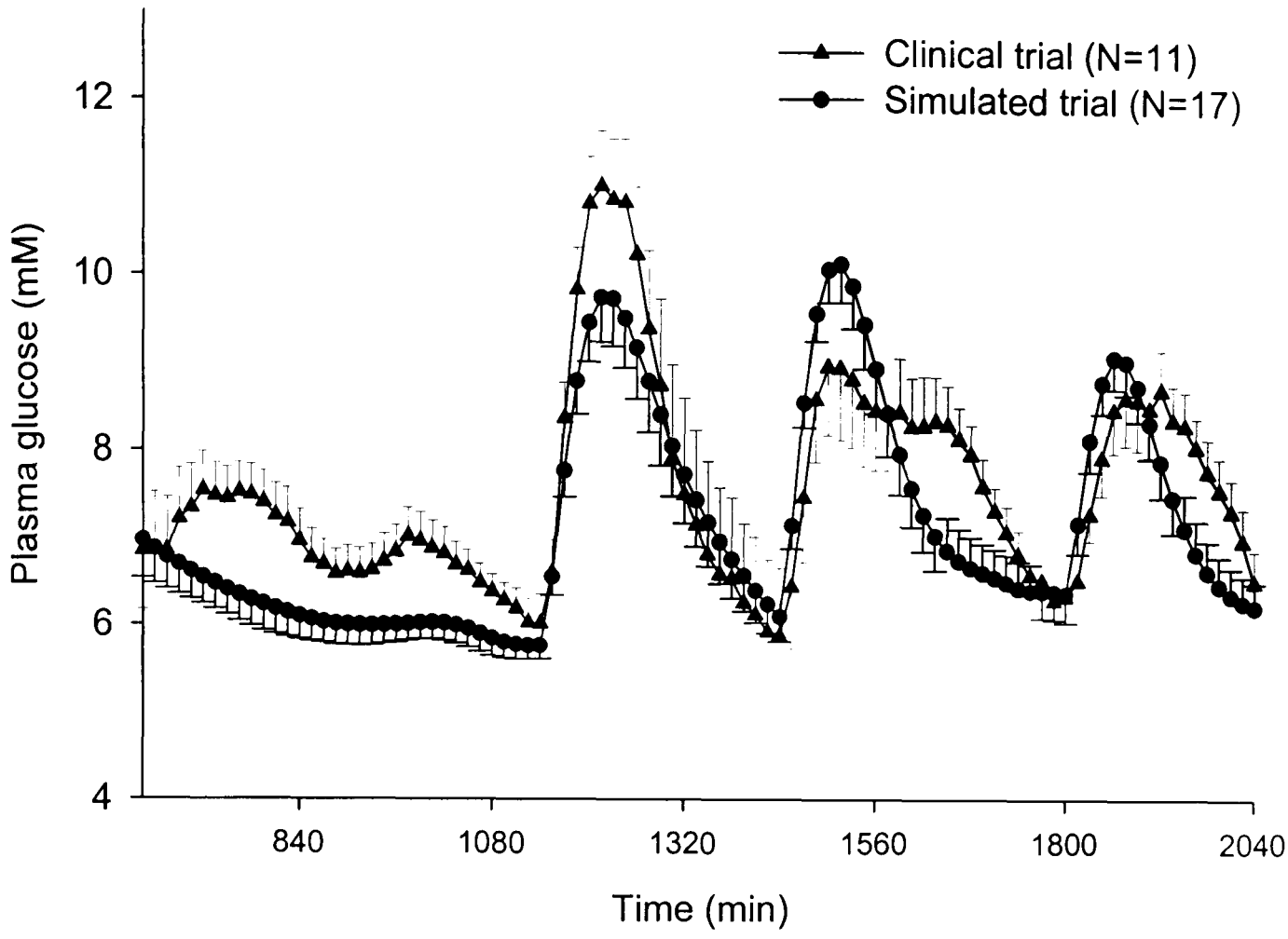

Figure 7.4: Plasma glucose profiles during the clinical and simulated trial (mean±SE).

The glucose profile can be divided into five periods, the first postmeal period, the overnight fast, and the following three postmeal periods.

A mismatch was present following the ingestion of the first meal (first dinner) due to initial conditions (data not shown). The start of the comparison between the simulated and clinical trial is at 645min (585min after the first dinner) when plasma glucose during the simulated trial was normalised. During the overnight fast, i.e. from 645 to 1140min, the simulated glucose profile is less oscillatory.

Following the breakfast at 1140min, the two glucose curves reach their maximum at a similar time. However, a peak difference of 1.5mM is present. This is greater than the difference of 0.5mM prior to the breakfast. Both curves are decaying in a similar fashion. Glucose profiles reach a fairly similar level prior to the lunch.

Following the lunch at 1500min a second glucose excursion is present. Compared to the breakfast, the plasma glucose excursion is less pronounced during the clinical trial and very similar during the simulated trial. The initial part of the excursions shows a very good level of comparability and again an identical time to peak. However, the simulated excursion has a slightly higher peak. A mismatch occurs during the decays. During the clinical trial a short term plateau is observed followed by a fast decay whereas during the simulation trial a monotonic decay is observed. Nevertheless, the glucose concentration prior the second dinner is identical in both trials.

The second-dinner postprandial profiles have a similar nadir but the time-to-peak is delayed during the clinical trial and is followed by a fast decay.

The grading system described in the present Chapter was used to classify the level of control during the fasting and postprandial periods, see *Figure 7.5*.

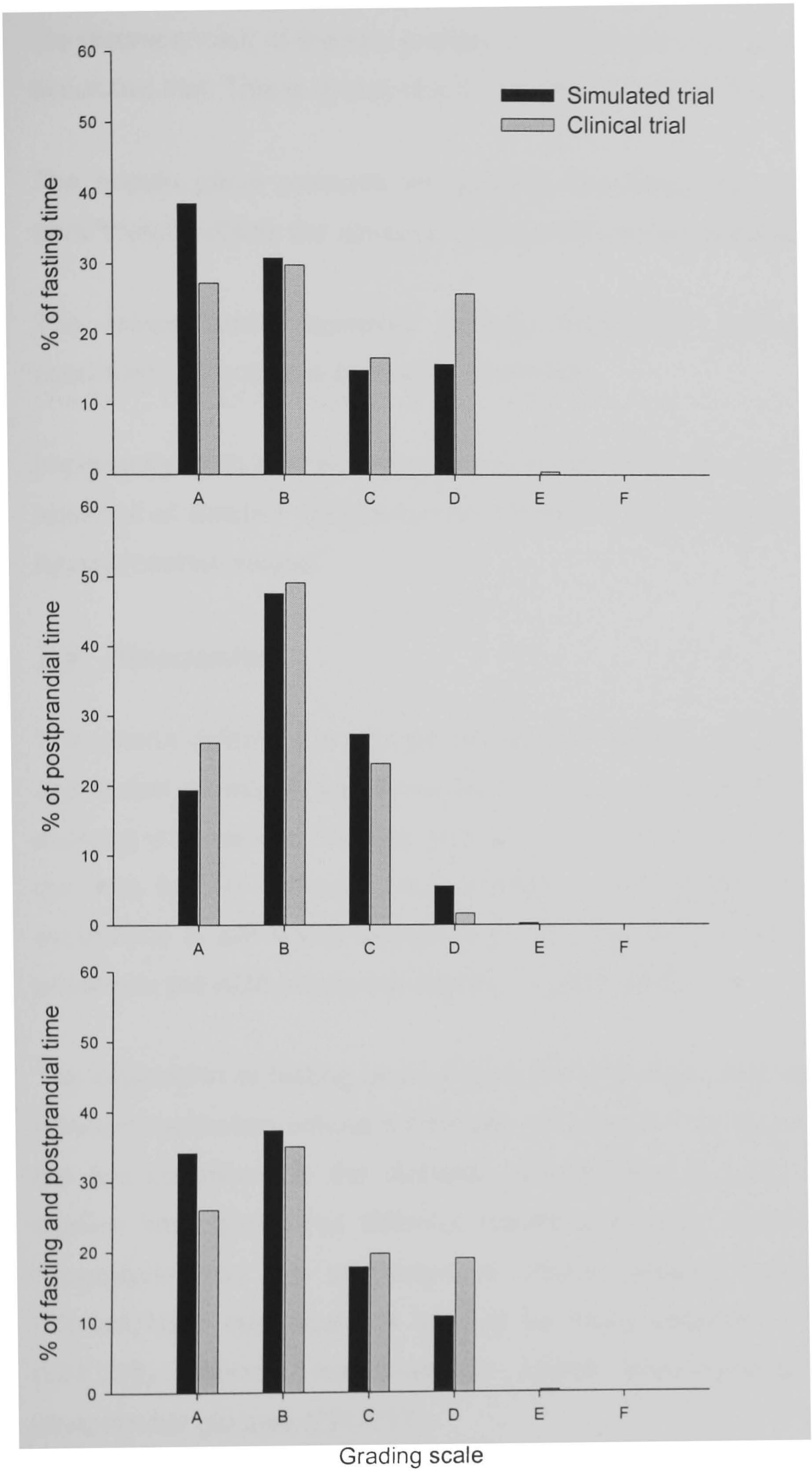

Figure 7.5: Grading of glucose profiles observed during the simulated and clinical trial.

The upper panel of *Figure 7.5* compares the fasting periods. The results reflect the discrepancies of the two profiles characterised by a better control during the simulated trial. This is mainly due to the differences in the overnight period.

The middle panel presents the grading describing the postprandial period. A good match reflects the absence of large differences between the two trials.

The lowest panel compiles grading from both fasting and postprandial conditions. A good match is again observed.

Importantly, both studies show a near to zero time spent in Grade E and a total absence of Grade F indicating the absence of extreme high glucose or serious hypoglycaemia values.

7.4 Discussion

The criteria defining the various grades are based on present recommendations and recent criteria of hypoglycaemia. However, the recommendations have been evolving with new knowledge and should therefore be seen as a valuable but dynamic tool. In particular, the question of the utility of controlling postmeal excursions is still under debate and the peak limit of the ADA (218) was not present in the ADA recommendations for 2002 (219).

The separation of fasting and postprandial conditions has resulted in the use of different evaluation criteria for the two conditions. The respective contribution of the two conditions to the diabetes complications is under debate as various studies have presented different results (220-223). Fasting and postprandial hyperglycaemias are suspected to induce different types of complications. Microvascular complications tend to be more associated with elevated FPG (224,225) whereas macrovascular seems predominantly linked to high postprandial glucose (225-227).

A major obstacle to limit elevated glucose concentrations is an increased risk of hypoglycaemia events as evidenced by the Diabetes Control and Complications

Trial (DCCT) (228) and other studies (229). Hypoglycaemia is an acute life threatening condition and the use of continuous glucose sensing have evidenced that a good $HbA1_c$ accompanied by near normal premeal plasma glucose concentrations are not enough as shown by the prevalence of prolonged hypoglycaemia in children (16). Moreover hypoglycaemia is a major cause of death among subject with Type 1 diabetes.

Another critical aspect of glucose control is an individual adaptation of treatment goals which is included in the ADA recommendations (230). This limits our approach to the evaluation. In order to be in line with the recommendations, a comparison of the personalised goals and actual glucose profile would have to be performed.

A real system is more complex compared to a model. The question which emerges is whether the approximation by the model retains enough of the system characteristics so that it can be used for its intended purposes.

The aim of the evaluation in the present chapter is to demonstrate the usefulness of the simulator to assess the performances of glucose controllers As opposed to validation principles (186), which are employed in model development, the concern here is the clinical validity of simulations.

The early part of the glucose profile is excluded from the evaluation. The clinical protocol allowed corrective actions to provide a "clean" start. The corrections were based on the intravenous route. This resulted in well controlled glucose levels compared to the simulation which was characterised by large excursions. The insulin was individually chosen and aimed at avoiding hypoglycaemia. Intravenous corrective actions were not executed. It is important to note that 6 out of the 11 real subjects experienced hypoglycaemia following the first dinner. Therefore, additional oral glucose had to be given suggesting an over delivery of insulin. The ensuing fasting period which is characterised by a more elevated and oscillatory glucose pattern during the clinical trial could be explained by the oral glucose input which represents another disturbance to the system and also by hypoglycaemia counteregulation causing a rebound in the glucose trajectory.

However, the hypoglycaemia occurrence did not affect the glucose profile. Following hypoglycaemia, the average glucose was virtually identical over the post dinner to pre breakfast period, see *Table 7.7*. Glucose variability as measured by J-index (231) did not differ among the two groups, see *Table 7.7*.

Table 7.7: Plasma glucose level and oscillation characteristics following first dinner and preceding first breakfast (mean±SD).

	Plasma glucose (mmol l^{-1})	J-Index (unitless)
Subjects who did not experience hypoglycaemia (N=5)	6.95±0.89	20.12±4.10
Subjects who experienced hypoglycaemia (N=6)	6.79±1.21	20.98±5.33

Another important factor is related to the data accessible to the MPC. During the clinical trial subjects came several hours prior to the start of the automated control. This provided ample data for the controller which has been designed to use up to 6 hour of the past data. During the simulated set-up, the data are available only for 150min prior to the start of the automated control as the simulation started 60min prior to the first dinner.

Because of the difference in the initial conditions, the comparison during the fasting conditions presented differences. Nevertheless, plasma glucose prior to the breakfast was similar with about 0.5mM difference. The underestimation of the peak following breakfast ingestion is likely to be due to the smaller CHO content during the simulated trial. Glucose excursions during lunch and dinner are also similar.

During the simulation, the characteristics of the glucose excursions are identical for the three meals. During the clinical trial, lunch and dinner resulted in delayed and lower glucose peaks. This can be explained by differences in meal composition among the breakfast, lunch, and dinner. The breakfast was usually hyperglucidic and therefore likely to be quickly absorbed.

7.5 Conclusion

Clinically relevant criteria have been designed and employed to assess glucose profiles in the fasting and postabsorbative states. The criteria can be used to evaluate the glucose control by glucose controllers. The criteria were used to compare the control in synthetic subjects and in subjects undergoing clinical testing with the MPC controller. This served two purposes. First, the ability of the MPC to control glucose was evaluated from the clinical viewpoint. Second, the comparison between *in silico* and clinical testing has facilitated the validation of the simulator.

Although the glucose profiles exhibit some differences especially during the overnight fast, the simulated profile is of clinical validity. The differences can be explained by the differences in the initial conditions and the difference in meal intake.

8 General Discussion and Conclusions

8.1 General Discussion

The thesis has two major objectives. The technical objective consist of creating a simulation environment representing a model of a subject with Type 1 diabetes treated by continuous subcutaneous insulin infusion (CSII) and incorporating models of the subcutaneous measurement process and the insulin pump. To represent a variety of metabolic profiles a group of 18 virtual subjects was generated with the aim to provide a tool, which combined with an appropriate methodology, can facilitate the development of an extracorporeal artificial pancreas (AP). The clinical objective was to employ the simulating environment to evaluate the performance of a specific glucose controller resorting to clinically motivated safety and efficacy criteria.

In the last decade, the treatment of Type 1 diabetes has made a tremendous progress, but the problem of optimising insulin therapy remains. The Diabetes Control and Complications Trial (DCCT) (1) has demonstrated benefits of tight control through intensive therapy. This required large resources limiting its large scale application. An automated insulin delivery system, the so called "artificial pancreas", could provide means to improve glucose control in a spectrum of subjects with Type 1 diabetes.

The approaches to the AP can be divided into two main categories. An implantable AP provides several advantages by avoiding delivery and sensing delays and retaining a more physiological insulin profile. However, considering the long term safety aspects, it is more appropriate to focus on an extracorporeal AP. Implantable insulin pumps still await wider use.

External insulin pump systems are now mature and represent an excellent minimally invasive insulin delivery (76,79,232) but are associated with a delay in insulin appearance. Moreover the subcutaneous route demands the availability of an accurate and long term subcutaneous glucose sensor. Such a device is still

not commercially available but the existing products and the extensive research in this field give a real hope for the near future.

Medical treatment delivery systems are subject to rigorous safety evaluation. As clinical safety and efficacy need to be clearly demonstrated there is a need for extensive clinical trialling at considerable financial, human, and time costs.

Simulations and *in silico* testing have already been adopted by the pharmaceutical industry to optimise and predict the outcome of clinical trials to reduce financial burden involved in the development of new drugs. Similarly, the approach can be employed in the development of medical devices.

As seen in Chapter 3, the concept of a simulated clinical trial to evaluate an automated insulin delivery is not new. Many studies have been conducted but usually did not include the subcutaneous route resorting to simpler setting using the intravenous route or did not adopt a systematic and extensive evaluation strategy.

This fuelled the need to develop a complete testing platform for a subcutaneous-subcutaneous system. During the development of a simulation environment described in Chapter 5 representing the closed-loop system, in which the patient has a central role, the importance of the sources of uncertainty and the noise from the measurement process were reflected on, together with the pump inaccuracies, and most importantly the between and within subject variability.

The *in silico* testing phase for the development of an AP requires an evaluation strategy. This was defined in Chapter 6, where a systematic approach to test control algorithms is presented. The approach offers a clear map of the different issues to be tested. However, its universal application is limited. These limitations are related to technical properties of the pump or the sensor. They also relate to the assumptions employed to generate parameters of synthetic subjects.

In Chapter 7, clinical criteria were defined to assess the performance of glucose controllers taking into account fasting and postprandial conditions. The grading offers a qualitative assessment of the overall performance of glucose control and employs six grades ranging from Grade A (best control) to Grade F (worst control).

The mapping of levels of glucose to the grades is different for the fasting and postprandial conditions. This is justified by the fact that transient elevated glucose levels during the postmeal phase are acceptable as elevated glucose is also present following meals in healthy subjects.

The cut-off plasma glucose values defining the mapping procedure were chosen to reflect the current standards of glucose control suggested by the American Diabetes Association ADA and employed in a number of studies for evaluation of glucose control. This underpins the acceptance and credibility of the grading by health care professionals as opposed to the criteria presented in Chapter 6, which were aimed to provide information for the technical development.

In Chapter 7, the validity of the simulator is assessed comparing results from a simulated trial to these obtained during a real clinical study employing the grading system. The simulated trial shows the ability of the MPC to achieve safe glucose levels throughout the trial as demonstrated by the absence of the time spent in Grade F and virtually no time spent in Grade E. This has been confirmed by the clinical study.

The origin of the discrepancies between the simulated and clinical trials is due to the differences in the initial conditions and the differences in meals contents. Nevertheless glucose levels prior to each meal intake are comparable.

The glucose monitor needs to present certain characteristics to be used successfully in a closed-loop glucose control system by providing frequent measurements with a sufficient accuracy and stability over time. It has been the focus of extensive research for decades and represents a major obstacle for the

development of an extracorporeal AP (233). An increasing number of research approaches and results indicate a significant progress toward its realisation.

8.2 Achievements of Objectives

This section outlines the achieved objectives. The structure echoes the objectives and is therefore divided into technical and clinical objectives.

The technical achievements are:

- Models have been successfully developed to achieve a representation of a subcutaneous-subcutaneous controlled system which can be used as a simulating environment to test algorithm to control glucose in Type 1 diabetes subjects;

- 18 subjects were generated on the base of real clinical data and informed probability distribution. The virtual subjects represent a population with wide metabolic profile;

- The subcutaneous-subcutaneous system was scrutinised and a methodology to test performance of glucose controllers in terms of safety and efficacy was defined;

- The simulator validity was evaluated using clinical trial employing subcutaneous glucose measurements and subcutaneous insulin infusion. It was shown to be useful for the development of a model predictive controller.

The clinical achievements are:

- Simulation runs have demonstrated the wide range of metabolic profile of the virtual subjects reflecting the actual variability of insulin needs;

- Suggested guidelines from the ADA were compiled and organised and

criteria used in various studies to establish qualitative criteria to evaluate glucose control during trials with the AP;

- The defined criteria were employed to appraise the simulator's validity.

8.3 Future Work

Certain parameters were drawn from probability distribution. Models and/or methods could be developed to estimate parameters from data collected during clinical tests with the AP to provide means to generate additional subjects.

The parameter variation is partly based on informed probability distributions and designed to represent a variety of metabolic profiles and behaviour. However the variation does not represent some of the known patterns of the metabolism found in humans. For example, the dawn phenomenon was not specifically reproduced.

The methodology was adopted and comparisons were made employing a single algorithm, the MPC. Others algorithms could benefit from our testing approach.

Subjects with Type 2 diabetes are mostly treated by diet and oral agents. However, some studies have suggested to use CSII to treat the disease (14). An extension to Type 2 diabetes by incorporating a model of insulin secretion could facilitate testing of controllers in Type 2 diabetes.

Finally the benefits of tight glucose control in critically ill patients have been clearly demonstrated and the extension of the simulation environment to encompass subjects in the intensive care units could facilitate the evaluation of different treatment strategies.

References

1. Diabetic Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin-dependent diabetes mellitus. *N.Engl.J.Med.* 329:977-986, 1993

2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352:837-853, 1998

3. Dorchy H, Roggemans MP: Improvement of the compliance with blood glucose monitoring in young insulin-dependent diabetes mellitus patients by the Sensorlink system. *Diabetes Res.Clin.Pract.* 36:77-82, 1997

4. Tubiana-Rufi N, Levy-Marchal C, Mugnier E, Czernichow P: Long term feasibility of multiple daily injections with insulin pens in children and adolescents with diabetes. *Eur.J Pediatr.* 149:80-83, 1989

5. Houtzagers CM, Berntzen PA, van der SH, Van Maarschalkerweerd WW, Lanting P, Boen-Tan I, Heine RJ, Van der Veen EA: Efficacy and acceptance of two intensified conventional insulin therapy regimens: a long-term cross-over comparison. *Diabet.Med.* 6:416-421, 1989

6. Heise T, Weyer C, Serwas A, Heinrichs S, Osinga J, Roach P, Woodworth J, Gudat U, Heinemann L: Time-action profiles of novel premixed preparations of insulin lispro and NPL insulin. *Diabetes Care* 21:800-803, 1998

7. Hoffman A, Ziv E: Pharmacokinetic considerations of new insulin formulations and routes of administration. *Clin Pharmacokinet.* 33:285-301, 1997

8. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142-2148, 2000

9. Bolli GB: Physiological insulin replacement in type 1 diabetes mellitus. *Exp.Clin.Endocrinol.Diabetes* 109 Suppl 2:S317-S332, 2001

10. Lemozy-Cadroy S, Crognier S, Gourdy P, Chauchard MC, Chale JP, Tauber Dagger JP, Hanaire-Broutin H: Intensified treatment of type 1 diabetes: prospective evaluation at one year of a therapeutic patient education programme. *Diabetes Metab.* 28:287-294, 2002

11. Bak JF, Nielsen OH, Pedersen O, Beck-Nielsen H: Multiple insulin injections using a pen injector versus insulin pump treatment in young diabetic patients. *Diabetes Res.* 6:155-158, 1987

12. Pernet A: [Intensified insulin therapy by multiple injections or by pump]. *Schweiz.Med.Wochenschr.* 116:77-82, 1986

13. Boland EA, Grey M, Oesterle A, Fredrickson L, Tamborlane WV: Continuous subcutaneous insulin infusion. A new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes [see comments]. *Diabetes Care* 22:1779-1784, 1999

14. Bode BW, Sabbah HT, Gross TM, Fredrickson LP, Davidson PC: Diabetes management in the new millennium using insulin pump therapy. *Diabetes Metab Res.Rev.* 18 Suppl 1:S14-S20, 2002

15. Lenhard MJ, Reeves GD: Continuous subcutaneous insulin infusion: a comprehensive review of insulin pump therapy. *Arch.Intern.Med.* 161:2293-2300, 2001

16. Boland E, Monsod T, Delucia M, Brandt CA, Fernando S, Tamborlane WV: Limitations of conventional methods of self-monitoring of blood glucose - Lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. *Diabetes Care* 24:1858-1862, 2001

17. Shichiri M, Kawamori R, Hakui N, Yamasaki Y, Abe H: Closed-loop glycemic control with a wearable artificial endocrine pancreas. Variations in daily insulin requirements to glycemic response. *Diabetes* 33:1200-1202, 1984

18. Kraegen EW, Chisholm DJ: Closure of the loop by glucose sensing. Physiological and practical considerations. *Horm.Metab.Res.Suppl.* 20:1-4, 1988

19. Chassin LJ, Hovorka R: Closed-loop glucose control with IV glucose sampling and SC insulin infusion: Evaluation by simulation studies. *Diabetologia* 44 (Suppl 1):221, 2001

20. Chassin LJ, Haueter U, Hovorka R, Massi-Benedetti M, Orsini-Federici M, Pieber TR, Schaller HC, Schaupp L, Vering T, Wilinska M: Closed-loop glucose control algorithm: Evaluation methodology by simulation (Abstract). *Diabetes Technology & Therapeutics* 4:212, 2002

21. Shichiri M: *Artificial Endocrine Pancreas. Development and Clinical Applications*. Kumamoto, Japan, Kamome Press Co., 2000

22. Thennadil SN, Rennert JL, Wenzel BJ, Hazen KH, Ruchti TL, Block MB: Comparison of Glucose Concentration in Interstitial Fluid, and Capillary and Venous Blood During Rapid Changes in Blood Glucose Levels. *Diabetes.Technol.Ther.* 3:357-365, 2001

23. Summers LKM, Clark ML, Humphreys SM, Bugler J, Frayn KN: The use of microdialysis to monitor rapid changes in glucose concentration. *Horm.Metab.Res.* 31:424-428, 1999

24. Sternberg F, Meyerhoff C, Mennel FJ, Bischof F, Pfeiffer EF: Subcutaneous glucose concentration in humans. Real estimation and continuous monitoring. *Diabetes Care* 18:1266-1269, 1995

25. Selby JV, Ray GT, Zhang D, Colby CJ: Excess costs of medical care for patients with diabetes in a managed care population. *Diabetes Care* 20:1396-1402, 1997

26. Bjork S: The cost of diabetes and diabetes care. *Diabetes Res.Clin.Pract.* 54 Suppl 1:S13-S18, 2001

27. Jacobs J, Sena M, Fox N: The cost of hospitalization for the late complications of diabetes in the United States. *Diabet.Med.* 8:S23-S29, 1991

28. Boyle JP, Honeycutt AA, Narayan KMV, Hoerger TJ, Geiss LS, Chen H, Thompson TJ: Projection of Diabetes Burden Through 2050: Impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 24:1936-1940, 2001

29. Amos AF, McCarty DJ, Zimmet P: The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet.Med.* 14 Suppl 5:S1-85, 1997

30. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 26 Suppl 1:S5-20, 2003

31. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 26 Suppl 1:S33-S50, 2003

32. Macdonald IA: Physiological regulation of gastric emptying and glucose absorption. *Diabet.Med.* 13:S11-S15, 1996

33. Gannon MC, Ercan N, Westphal SA, Nuttall FQ: Effect of added fat on plasma glucose and insulin response to ingested potato in individuals with NIDDM. *Diabetes Care* 16:874-880, 1993

34. Ercan N, Gannon MC, Nuttall FQ: Effect of added fat on the plasma glucose and insulin response to ingested potato given in various combinations as two meals in normal individuals. *Diabetes Care* 17:1453-1459, 1994

35. Torsdottir I, Alpsten M, Andersson H, Schweizer TF, Tolli J, Wursch P: Gastric emptying and glycemic response after ingestion of mashed bean or potato flakes in composite meals. *Am.J.Clin.Nutr.* 50:1415-1419, 1989

36. Thorens B: [Gluco-incretin hormones in insulin secretion and diabetes]. *Med.Sci.(Paris)* 19:860-863, 2003

37. Thorens B: Glucagon-like peptide-1 and control of insulin secretion. *Diabete Metab.* 21:311-318, 1995

38. Blat S, Malbert CH: The vagus is inhibitory of insulin secretion under fasting conditions. *Am.J.Physiol.* 281:E782-E788, 2001

39. Meyer C, Dostou JM, Welle SL, Gerich JE: Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis. *Am.J.Physiol.* 282:E419-E427, 2002

40. Ferrannini E, Wahren J, Felig P, DeFronzo RA: The role of fractional glucose extraction in the regulation of splanchnic glucose metabolism in normal and diabetic man. *Metabolism* 29:28-35, 1980

41. Tortora GH, Anagnostakos NP: *Principles of Anatomy and Physiology*. New York, Harper and Row Publishers, 1987

42. Hovorka R, Shojaee-Moradie F, Carroll PV, Chassin LJ, Gowrie IJ, Jackson NC, Tudor RS, Umpleby AM, Jones RH: Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *Am.J.Physiol.* 282:E992-1007, 2002

43. Hachiya HL, Treves ST, Kahn CR, Sodoyez JC, Sodoyez-Goffaux F: Altered insulin distribution and metabolism in type I diabetics assessed by [123I]insulin scanning. *J.Clin.Endocrinol.Metab.* 64:801-808, 1987

44. Baba H, Zhang XJ, Wolfe RR: Glycerol gluconeogenesis in fasting humans. *Nutrition* 11:149-153, 1995

45. Williams G, Pickup JC: *Handbook of Diabetes*. London, Blackwell Science, 1999

46. Silink M: Childhood diabetes: a global perspective. *Horm.Res.* 57 Suppl 1:1-5, 2002

47. Tessari P, Inchiostro S, Barazzoni R, Zanetti M, Orlando R, Biolo G, Sergi G, Pino A, Tiengo A: Fasting and postprandial phenylalanine and leucine kinetics in liver- cirrhosis. *Am.J.Physiol.* 267:E 140-E 149, 1994

48. Prevention of diabetes mellitus. Report of a WHO Study Group. *World Health Organ.Tech.Rep.Ser.* 844:1-100, 1994

49. Weiss PA, Scholz HS, Haas J, Tamussino KF, Seissler J, Borkenstein MH: Long-term follow-up of infants of mothers with type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. *Diabetes Care* 23:905-911, 2000

50. Gerstein HC, VanderMeulen J: The relationship between cow's milk exposure and type 1 diabetes. *Diabet.Med.* 13:23-29, 1996

51. Pozzilli P, Di Mario U: Autoimmune Diabetes Not Requiring Insulin at Diagnosis (Latent Autoimmune Diabetes of the Adult): Definition, characterization, and potential prevention. *Diabetes Care* 24:1460-1467, 2001

52. Kaila B, Taback SP: The effect of day care exposure on the risk of developing type 1 diabetes: a meta-analysis of case-control studies. *Diabetes Care* 24:1353-1358, 2001

53. Cryer PE: Hypoglycemia-associated autonomic failure in diabetes. *Am J Physiol Endocrinol Metab* 281:E1115-E1121, 2001

54. Bolli GB: How to ameliorate the problem of hypoglycemia in intensive as well as nonintensive treatment of type 1 diabetes. *Diabetes Care* 22 Suppl 2:B43-B52, 1999

55. Hubinger A, Weber W, Jung W, Wehmeyer K, Gries FA: The pharmacokinetics of two different concentrations of short-acting insulin, intermediate-acting insulin, and an insulin mixture following subcutaneous injection. *Clin.Investig.* 70:621-626, 1992

56. Holman RR, Steemson J, Darling P, Reeves WG, Turner RC: Human ultralente insulin. *Br.Med.J.* 288:665-668, 1984

57. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR: [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. *Diabetes* 43:396-402, 1994

58. Beyer J, Krause U, Dobronz A, Fuchs B, Delver JR, Wagner R: Assessment of insulin needs in insulin-dependent diabetics and healthy

volunteers under fasting conditions. *Horm.Metab.Res.Suppl.* 24:71-77, 1990

59. Campbell RK, White JR, Levien T, Baker D: Insulin glargine. *Clin.Ther.* 23:1938-1957, 2001

60. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T: Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 23:644-649, 2000

61. Heinemann L, Heise T, Jorgensen LN, Starke AA: Action profile of the rapid acting insulin analogue: human insulin B28Asp. *Diabet.Med.* 10:535-539, 1993

62. Service FJ, O'Brien PC: The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic Control and Complications Trial. *Diabetologia* 44:1215-1220, 2001

63. DAFNE Study Group: Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *Br.Med.J.* 325:746, 2002

64. Wilinska ME, Schaller H, Schaupp L, Pieber TR, Chassin LJ, Hovorka R: Relationship between interstitial and plasma glucose during physiological conditions (Abstract). *Diabet.Med.* 19 (Suppl. 2):71, 2002

65. Bohannon NJ: Insulin delivery using pen devices. Simple-to-use tools may help young and old alike. *Postgrad.Med* 106:57-4, 68, 1999

66. Pickup JC, White MC, Keen H, Parsons JA, Alberti KG: Long-term continuous subcutaneous insulin infusion in diabetics at home. *Lancet* 2:870-873, 1979

67. Bode BW, Sabbah HT, Gross TM, Fredrickson LP, Davidson PC: Diabetes management in the new millennium using insulin pump therapy. *Diabetes Metab.Res.Rev.* 18:S14-S20, 2002

68. Reichel A, Rietzsch H, Kohler HJ, Pfutzner A, Gudat U, Schulze J: Cessation of insulin infusion at night-time during CSII-therapy: comparison of regular human insulin and insulin lispro. *Exp.Clin.Endocrinol.Diabetes* 106:168-172, 1998

69. Guerci B, Meyer L, Salle A, Charrie A, Dousset B, Ziegler O, Drouin P: Comparison of metabolic deterioration between insulin analog and regular insulin after a 5-hour interruption of a continuous subcutaneous insulin infusion in type 1 diabetic patients. *J.Clin.Endocrinol.Metab.* 84:2673-2678, 1999

70. Piwernetz K, Benedetti MM, Vermeij D, Deleiva A, Kock CM, Landgraf R: Diabcare thinkshop - quality network diabetes - under the auspices of the regional offices for europe of who and idf grassau, germany, 24- 26 september 1992. *Diab.Nutr.Metab.* 6:107-122, 1993

71. Renner R, Pfutzner A, Trautmann M, Harzer O, Sauter K, Landgraf R: Use of insulin lispro in continuous subcutaneous insulin infusion treatment - Results of a multicenter trial. *Diabetes Care* 22:784-788, 1999

72. Stegall MD, Larson TS, Kudva YC, Grande JP, Nyberg SL, Prieto M, Velosa JA, Rizza RA: Pancreas transplantation for the prevention of diabetic nephropathy. *Mayo Clin.Proc.* 75:49-56, 2000

73. Kishikawa H, Taguchi T, Matsumoto K, Shichiri M: [Indication of intensive insulin therapy and its practice]. *Nippon Rinsho* 57:681-687, 1999

74. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients

with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res.Clin.Pract.* 28:103-117, 1995

75. The Diabetes Control and Complications Trial Research Group: The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N.Engl.J.Med.* 329:977-986, 1993

76. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. *Diabetes Care* 23:1232-1235, 2000

77. De Beaufort CE, Houtzagers CM, Bruining GJ, Aarsen RS, den Boer NC, Grose WF, Van Strik R, De Visser JJ: Continuous subcutaneous insulin infusion (CSII) versus conventional injection therapy in newly diagnosed diabetic children: two-year follow- up of a randomized, prospective trial. *Diabet.Med.* 6:766-771, 1989

78. Yki-Jarvinen H, Koivisto VA: Continuous subcutaneous insulin infusion therapy decreases insulin resistance in type 1 diabetes. *J.Clin.Endocrinol.Metab.* 58:659-666, 1984

79. Bode BW, Steed RD, Davidson PC: Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. *Diabetes Care* 19:324-327, 1996

80. Hovorka R, Andreassen S, Benn JJ, Olessen KG, Carson ER: Causal probabilistic network modelling - An illustration of its role in the management of chronic diseases. *IBM Syst.J.* 31:635-648, 1992

81. Schifferdecker E, Schmidt K, Boehm BO, Schatz H: Long-term compliance of intensified insulin therapy. *Diabetes Res.Clin.Pract.* 23:17-23, 1994

82. Kanakis SJ, Watts C, Leichter SB: The Business of Insulin Pumps in Diabetes Care: Clinical and Economic Considerations. *Clin.Diabetes* 20:214-216, 2002

83. Zakzewski CA, Wasilewski J, Cawley P, Ford W: Transdermal delivery of regular insulin to chronic diabetic rats: effect of skin preparation and electrical enhancement. *J Control Release* 50:267-272, 1998

84. Kari B: Control of blood glucose levels in alloxan-diabetic rabbits by iontophoresis of insulin. *Diabetes* 35:217-221, 1986

85. Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA: Treatment Satisfaction With Inhaled Insulin in Patients With Type 1 Diabetes: A randomized controlled trial. *Diabetes Care* 24:1556-1559, 2001

86. Heinemann L, Klappoth W, Rave K, Hompesch B, Linkeschowa R, Heise T: Intra-individual variability of the metabolic effect of inhaled insulin together with an absorption enhancer. *Diabetes Care* 23:1343-1347, 2000

87. Heinemann L, Pfutzner A, Heise T: Alternative routes of administration as an approach to improve insulin therapy: update on dermal, oral, nasal and pulmonary insulin delivery. *Curr.Pharm.Des.* 7:1327-1351, 2001

88. Steiner S, Pfutzner A, Wilson BR, Harzer O, Heinemann L, Rave K: Technosphere/Insulin--proof of concept study with a new insulin formulation for pulmonary delivery. *Exp.Clin.Endocrinol.Diabetes* 110:17-21, 2002

89. Dorkoosh FA, Verhoef JC, Borchard G, Rafiee-Tehrani M, Verheijden JH, Junginger HE: Intestinal absorption of human insulin in pigs using delivery

systems based on superporous hydrogel polymers. *Int.J Pharm.* 247:47-55, 2002

90. Moriyama K, Ooya T, Yui N: Pulsatile peptide release from multi-layered hydrogel formulations consisting of poly(ethylene glycol)-grafted and ungrafted dextrans. *J Biomater.Sci.Polym.Ed* 10:1251-1264, 1999

91. Jerry N, Anitha Y, Sharma CP, Sony P: In vivo absorption studies of insulin from an oral delivery system. *Drug Deliv.* 8:19-23, 2001

92. Ramdas M, Dileep KJ, Anitha Y, Paul W, Sharma CP: Alginate encapsulated bioadhesive chitosan microspheres for intestinal drug delivery. *J Biomater.Appl.* 13:290-296, 1999

93. Saslawski O, Weingarten C, Benoit JP, Couvreur P: Magnetically responsive microspheres for the pulsed delivery of insulin. *Life Sci.* 42:1521-1528, 1988

94. Rossetti L, Papachristou D, Shulman G, Smith D, Defronzo R: Insulin resistance in partially pancreatectomized rats (Px) - Reversal with phlorizin therapy. *Diabetes* 35:A38, 1986

95. Kendall DM, Robertson RP: Pancreas and islet transplantation - Challenges for the twenty-first century. *Endocrinology And Metabolism Clinics Of North America* 26:611, 1997

96. Madsbad S, Christiansen E, Tibell A, Tyden G, Rasmussen K, Burcharth F, Christensen NJ, Kirkegaard P, Olgaard K, Falholt K, Groth CG, Pedersen O, Tronier B, Volund A: Beta-cell dysfunction following successful segmental pancreas transplantation. *Transplantation Proceedings* 26:469-470, 1994

97. Redmon JB, Teuscher AU, Robertson RP: Hypoglycemia after pancreas transplantation. *Diabetes Care* 21:1944-1950, 1998

98. Kendall DM, Robertson RP: Pancreas and islet transplantation. *Endocrinologist* 5:28-35, 1995

99. Cobelli C, Toffolo G: Compartmental vs. noncompartmental modeling for two accessible pools. *Am J Physiol* 247:R488-R496, 1984

100. Cobelli C, Bier DM, Ferrannini E: Modeling glucose metabolism in man: theory and practice. *Horm.Metab.Res.Suppl.* 24:1-10, 1990

101. Cobelli C, Toffolo G, Ferrannini E: A model of glucose kinetics and their control by insulin, compartmental and noncompartmental approaches. *Math.Biosc.* 72:291-315, 1984

102. BOLIE VW: Coefficients of normal blood glucose regulation. *J Appl.Physiol* 16:783-788, 1961

103. Ackerman E, Gatewood LC, Rosevear JW, Molnar GD: Model studies of blood-glucose regulation. *Bull.Math.Biophys.* 27:Suppl-37, 1965

104. Cerasi E, Fick G, Rudemo M: A mathematical model for the glucose induced insulin release in man. *Eur.J Clin Invest* 4:267-278, 1974

105. Insel PA, Liljenquist JE, Tobin JD, Sherwin RS, Watkins P, Andres R, Berman M: Insulin control of glucose metabolism in man. *J.Clin.Invest.* 55:1057-1066, 1975

106. Ferrannini E, Smith JD, Cobelli C, Toffolo G, Pilo A, DeFronzo RA: Effect of insulin on the distribution and disposition of glucose in man. *J Clin Invest* 76:357-364, 1985

107. Salzsieder E, Fischer U, Stoewhas H, Thierbach U, Rutscher A, Menzel R, Albrecht G: A model-based system for the individual prediction of metabolic responses to improve therapy in type I diabetes. *Horm.Metab.Res.Suppl.* 24:10-19, 1990

108. Boroujerdi MA, Umpleby AM, Jones RH, Sonksen PH: A simulation model for glucose kinetics and estimates of glucose utilization rate in type 1 diabetic patients. *Am.J.Physiol.* 268:E766-E774, 1995

109. Cobelli C, Saccomani MP, Ferrannini E, DeFronzo RA, Gelfand R, Bonadonna R: A compartmental model to quantitate in vivo glucose transport in the human forearm. *Am J Physiol* 257:E943-E958, 1989

110. Guyton JR, Foster RO, Soeldner JS, Tan MH, Kahn CB, Koncz L, Gleason RE: A model of glucose-insulin homeostasis in man that incorporates the heterogeneous fast pool theory of pancreatic insulin release. *Diabetes* 27:1027-1042, 1978

111. Sorensen, J. T. A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes. 1985.

112. Bergman RN, Ider YZ, Bowden CR, Cobelli C: Quantitative estimation of insulin sensitivity. *Am J Physiol* 236:E667-E677, 1979

113. Cobelli C, Pacini G, Toffolo G, Sacca L: Estimation of insulin sensitivity and glucose clearance from minimal model: new insights from labeled IVGTT. *Am.J.Physiol.* 250:E591-E598, 1986

114. Cobelli C, Ruggeri A: A reduced sampling schedule for estimating the parameters of the glucose minimal model from a labeled IVGTT. *IEEE Trans.Biomed.Eng.* 38:1023-1029, 1991

115. Vicini P, Caumo A, Cobelli C: The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity. *Am.J.Physiol.* 273:E1024-E1032, 1997

116. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C: Oral glucose tolerance test minimal model indexes of beta-cell function and insulin sensitivity. *Diabetes* 50:150-158, 2001

117. Hovorka R, Chassin L, Luzio SD, Playle R, Owens DR: Pancreatic beta-cell responsiveness during meal tolerance test: model assessment in normal subjects and subjects with newly diagnosed noninsulin-dependent diabetes mellitus. *J.Clin.Endocrinol.Metab.* 83:744-750, 1998

118. Cobelli C, Mari A: Validation of mathematical models of complex endocrine-metabolic systems. A case study on a model of glucose regulation. *Med.Biol.Eng Comput.* 21:390-399, 1983

119. Trajanoski Z, Wach P: Fuzzy filter for state estimation of a glucoregulatory system. *Comput.Methods Programs Biomed.* 50:265-273, 1996

120. Kienitz KH, Yoneyama T: A robust controller for insulin pumps based on H-infinity theory. *IEEE Trans.Biomed.Eng.* 40:1133-1137, 1993

121. Brunetti P, Cobelli C, Cruciani P, Fabietti PG, Filippucci F, Santeusanio F, Sarti E: A simulation study on a self-tuning portable controller of blood glucose. *Int.J.Artif.Organs* 16:51-57, 1993

122. Parker RS, Doyle FJ, III, Peppas NA: A model-based algorithm for blood glucose control in type I diabetic patients. *IEEE Trans.Biomed.Eng.* 46:148-157, 1999

123. Trajanoski Z, Wach P: Neural predictive controller for insulin delivery using the subcutaneous route. *IEEE Trans.Biomed.Eng.* 45:1122-1134, 1998

124. Trajanoski Z, Regittnig W, Wach P: Simulation studies on neural predictive control of glucose using the subcutaneous route. *Comput.Methods Programs Biomed.* 56:133-139, 1998

125. Salzsieder E, Albrecht G, Fischer U, Freyse EJ: Kinetic modeling of the glucoregulatory system to improve insulin therapy. *IEEE Trans.Biomed.Eng.* 32:846-855, 1985

126. Boroujerdi MA, Williams CD, Piwernetz K, Carson ER, Hepp KD, Sonksen PH: Simulation approach for planning insulin regimes. In Int. Symp. on Advanced Models for Therapy of Insulin-Dependent Diabetes. 1 ed. Brunetti P, Waldhurst WK, Eds. New York, Raven Press, 1987, p. 41-46

127. Fisher ME, Teo KL: Optimal insulin infusion resulting from a mathematical model of blood glucose dynamics. *IEEE Trans.Biomed.Eng.* 36:479-486, 1989

128. Fischer U, Schenk W, Salzsieder E, Albrecht G, Abel P, Freyse EJ: Does physiological blood glucose control require an adaptive control strategy? [published erratum appears in IEEE Trans Biomed Eng 1988 Apr;35(4):282]. *IEEE Trans.Biomed.Eng.* 34:575-582, 1987

129. Candas B, Radziuk J: An adaptive plasma glucose controller based on a nonlinear insulin/glucose model. *IEEE Trans.Biomed.Eng.* 41:116-124, 1994

130. Berger M, Rodbard D: Computer-simulation of plasma-insulin and glucose dynamics after subcutaneous insulin injection. *Diabetes Care* 12:725-736, 1989

131. Lehmann ED, Deutsch T: A physiological model of glucose interaction in Type 1 Diabetes Mellitus. *Journal of Biomedical Engineering* 14:235-242, 1992

132. Monsod TP, Flanagan DE, Rife F, Saenz R, Caprio S, Sherwin R, Tamborlane W: Do sensor glucose levels accurately predict plasma glucose concentrations during hypoglycemia and hypoinsulinemia. *Diabetes Care* 25:889-893, 2002

133. Moberg E, HagstromToft E, Arner P, Bolinder J: Protracted glucose fall in subcutaneous adipose tissue and skeletal muscle compared with blood during insulin-induced hypoglycaemia. *Diabetologia* 40:1320-1326, 1997

134. Schmidt FJ, Slatter WJ, Schooner AJM: Glucose concentration in subcutaneous extracellural space. *Diabetes Care* 16:695-700, 1993

135. Wilinska ME, Schaller HC, Schaupp L, Pieber TR, Hovorka R: Modelling interstitial glucose kinetics in subjects with type 1 diabetes during physiological conditions. In Proceedings of the Second Joint EMBS-BMES Conference. Ghorbel FH, Ed. Houston, IEEE, 2002, p. 228-229

136. Wilinska ME, Schaller HC, Schaupp L, Pieber TR, Chassin LJ, Hovorka R: Hypoglycaemia reduces and insulin increases interstitial to plasma glucose ratio during physiological conditions in subjects with Type 1 diabetes. *Diabetologia* 45 (Suppl 2):A310, 2002

137. Cobelli C, Ruggeri A: Evaluation of portal/peripheral route and of algorithms for insulin delivery in the closed-loop control of glucose in diabetes--a modeling study. *IEEE Trans.Biomed.Eng.* 30:93-103, 1983

138. Cobelli C, Mari A: Control of diabetes with artificial systems for insulin delivery - algorithm independent limitations revealed by a modeling study. *IEEE Trans.Biomed.Eng.* 32:840-845, 1985

139. Kobayashi T, Sawano S, Itoh T, Kosaka K, Hirayama H, Kasuya Y: The pharmacokinetics of insulin after continuous subcutaneous infusion or bolus subcutaneous injection in diabetic patients. *Diabetes* 32:331-336, 1983

140. Puckett WR, LIGHTFOOT M: A model for multiple subcutaneous insulin injections developed from individual diabetic patient data. *Am J Physiol* 269:E1115-E1124, 1995

141. Kraegen EW, Chisholm DJ: Insulin responses to varying profiles of subcutaneous insulin infusion: kinetic modelling studies. *Diabetologia* 26:208-213, 1984

142. Shimoda S, Nishida K, Sakakida M, Konno Y, Ichinose K, Uehara M, Nowak T, Shichiri M: Closed-loop subcutaneous insulin infusion algorithm with a short-acting insulin analog for long-term clinical application of a wearable artificial endocrine pancreas. *Front Med.Biol.Eng.* 8:197-211, 1997

143. Trajanoski Z, Wach P, Kotanko P, Ott A, Skraba F: Pharmacokinetic model for the absorption of subcutaneously injected soluble insulin and monomeric insulin analogs. *Biomedizinische Technik* 38:224-231, 1993

144. Hauser T, Campbell LV, Kraegen EW, Chisholm DJ: Application of physicians predictions of meal and exercise effects on blood-glucose control to a computer-simulation. *Diabetic Med.* 10:744-750, 1993

145. Lehmann ED, Deutsch T, Carson ER, Sonksen PH: AIDA: an interactive diabetes advisor. *Comput.Methods Programs Biomed.* 41:183-203, 1994

146. Lehmann ED: Interactive educational diabetes simulators: Future possibilities. *Diab.Nutr.Metab.* 12:380-387, 1999

147. Lehmann ED: Preliminary experience with the Internet release of AIDA - an interactive educational diabetes simulator. *Comput.Methods Programs Biomed.* 56:109-132, 1998

148. Sano A: Adaptive and optimal schemes for control of blood glucose levels. *Biomed.Meas.Infor.Contr.* 1:16-22, 1986

149. Deutsch T, Roudsari AV, Leicester HJ, Theodorou T, Carson ER, Sonksen PH: UTOPIA: a consultation system for visit-by-visit diabetes management. *Med Inform.(Lond)* 21:345-358, 1996

150. Deutsch T, Lehmann ED, Carson ER, Roudsari AV, Hopkins KD, Sonksen PH: Time-series analysis and control of blood-glucose levels in diabetic-patients. *Comput.Methods Programs Biomed.* 41:167-182, 1994

151. Dazzi D, Taddei F, Gavarini A, Uggeri E, Negro R, Pezzarossa A: The control of blood glucose in the critical diabetic patient: a neuro-fuzzy method. *J Diabetes Complications* 15:80-87, 2001

152. Bellazzi R, Ironi L, Guglielmann R, Stefanelli M: Qualitative models and fuzzy systems: an integrated approach for learning from data. *Artif.Intell.Med* 14:5-28, 1998

153. Arita S, Yoneda M, Hori Y: [Quantitative analysis of glucose tolerance tests, responses using fuzzy inference]. *Nippon Rinsho* 54:2807-2811, 1996

154. Hejlesen OK, Andreassen S, Hovorka R, Cavan DA: DIAS - the diabetes advisory system: an outline of the system and the evaluation results obtained so far. *Comput.Methods Programs Biomed.* 54:49-58, 1997

155. Hovorka R, Tudor RS, Southerden D, Meeking DR, Andreassen S, Hejlesen OK, Cavan DA: Dynamic updating in DIAS-NIDDM and DIAS causal probabilistic networks. *IEEE Trans.Biomed.Eng.* 46:158-168, 1999

156. Tudor RS, Hovorka R, Cavan DA, Meeking D: Insulin secretion model implemented in CPN. In Computers in Diabetes '96. Graz, University of Graz, 1996, p. 28

157. Tudor RS, Hovorka R, Cavan DA, Meeking D, Hejlesen OK, Andreassen S: DIAS-NIDDM - a model-based decision support system for insulin dose adjustment in insulin-treated subjects with NIDDM. *Comput.Methods Programs Biomed.* 56:175-191, 1998

158. Hovorka R, Svacina S, Carson ER, Williams CD: A consultation system to assist in insulin therapy for in-patients (Abstract). *Clinical Science* 78 (suppl):14p, 1990

159. Skyler JS, Skyler DL, Seigler DE, O'Sullivan MJ: Algorithms for adjustment of insulin dosage by patients who monitor blood glucose. *Diabetes Care* 4:311-318, 1981

160. Zahlmann G, Franczykova M, Henning G, Strube M, Huttl I, Hummel I, Bruns W: DIABETEX--a decision support system for therapy of type I diabetic patients. *Comput.Methods Programs Biomed.* 32:297-301, 1990

161. Stadelmann A, Abbas S, Zahlmann G, Bruns W, Hennig I: DIABETEX decision module 2--calculation of insulin dose proposals and situation recognition by means of classifiers. *Comput.Methods Programs Biomed.* 32:333-337, 1990

162. Rutscher A, Salzsieder E, Fischer U: KADIS: model-aided education in type I diabetes. Karlsburg Diabetes Management System. *Comput.Methods Programs Biomed.* 41:205-215, 1994

163. Pfeiffer EF, Thum C, Clemens AH: The artificial beta cell - A continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). *Horm.Metab.Res.* 6:339-342, 1974

164. Clemens AH, Chang PH, Myers RW: The development of Biostator, a Glucose Controlled Insulin Infusion System (GCIIS). *Horm.Metab.Res.* Suppl 7:23-33, 1977

165. Clemens AH: Feedback control dynamics for glucose controlled insulin infusion system. *Med.Prog.Technol.* 6:91-98, 1979

166. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W: An artificial endocrine pancreas. *Diabetes* 23:389-404, 1974

167. Botz CK: An improved control algorithm for an artificial beta-cell. *IEEE Trans.Biomed.Eng.* 23:252-255, 1974

168. Marliss EB, Murray FT, Stokes EF, Zinman B, Nakhooda AF, Denoga A, Leibel BS, Albisser AM: Normalization of glycemia in diabetics during meals with insulin and glucagon delivery by the artificial pancreas. *Diabetes* 26:663-672, 1977

169. Kraegen EW, Campbell LV, Chia YO, Meler H, Lazarus L: Control of blood glucose in diabetics using an artificial pancreas. *Aust.N.Z.J.Med.* 7:280-286, 1977

170. Broekhuyse HM, Nelson JD, Zinman B, Albisser AM: Comparison of algorithms for the closed-loop control of blood glucose using the artificial beta cell. *IEEE Trans.Biomed.Eng.* 28:678-687, 1981

171. White NH, Skor D, Santiago JV: Practical closed-loop insulin delivery. A system for the maintenance of overnight euglycemia and the calculation of basal insulin requirements in insulin-dependent diabetics. *Ann.Intern.Med.* 97:210-213, 1982

172. Shichiri M, Kawamori R, Goriya Y, Yamasaki Y, Nomura M, Hakui N, Abe H: Glycaemic control in pancreatectomized dogs with a wearable artificial endocrine pancreas. *Diabetologia* 24:179-184, 1983

173. Swan GW: An optimal control model of diabetes mellitus. *Bull.Math.Biol.* 44:793-808, 1982

174. Ollerton RL: Application of optimal control theory to diabetes mellitus. *Int.J.Control* 50:2503-2522, 1989

175. Parker RS, Doyle FJ, Ward JH, Peppas NA: Robust H-infinity glucose control in diabetes using a physiological model. *Aiche Journal* 46:2537-2549, 2000

176. Sarti E, Cruciani P, Fabietti PG: Self-tuning control algorithm for wearable artificial pancreas. *Proceedings of the 14th Annual International*

Conference of the IEEE Engineering in Medicine and Biology Society 6:2267-2269, 1992

177. Sano S: Adaptive and optimal schemes for control of blood glucose levels. *Biomed.Meas.Infor.contr* 1:16-22, 1986

178. Camacho EF, Bordons C: *Model Predictive Control*. Springer-Verlag, 1999

179. Roberts PD: A brief overview of model predictive control. *Comput.Control.Eng.J.* 10:186-188, 1999

180. Rave K, Heinemann L, Puhl L, Gudat U, Woodworth JR, Weyer C, Heise T: Premixed formulations of insulin lispro. Activity profiles in type 1 diabetic patients. *Diabetes Care* 22:865-866, 1999

181. Cobelli C, Federspil G, Pacini G, Salvan A, Scandellari C: An integrated mathematical model of the dynamics of blood glucose and its hormonal control. *Math.Biosc.* 58:27-60, 1982

182. Salzsieder E, Albrecht G, Fischer U, Freyse EJ: Kinetic modeling of the glucoregulatory system to improve insulin therapy. *IEEE Trans.Biomed.Eng.* 32:846-855, 1985

183. Lynch SM, Bequette BW: Estimation-based model predictive control of blood glucose in type I diabetics: A simulation study. *Proceedings of the Ieee 27Th Annual Northeast Bioengineering Conference*79-80, 2001

184. Hovorka R, Chassin LJ, Haueter U, Massi-Benedetti M, Orsini-Federici M, Pieber TR, Schaller HC, Schaupp L, Vering T, Wilinska M: Model predictive control algorithm for artificial pancreas (Abstract). *Diabetes Technology & Therapeutics* 4:221, 2002

185. Hovorka R, Chassin LJ, Haueter U, Massi-Benedetti M, Orsini-Federici M, Pieber TR, Schaller H, Schaupp L, Vering T, Wilinska M: Model predictive

control algorithm: using nonlinear model to control glucose excursions in subjects with type 1 diabetes. In Adaptive Systems and Hybrid Computational Intelligence in Medicine. Special Session Proceedings of the EUNITE - 2001 Symposium. Dounias GD, Linkens DA, Eds. Chios, University of Aegean, 2001, p. 44

186. Carson ER, Cobelli C, Finkelstein L: *The Mathematical Modeling of Metabolic and Endocrine Systems*. New York, Wiley, 1983

187. Pehling G, Tessari P, Gerich JE, Haymond MW, Service FJ, Rizza RA: Abnormal meal carbohydrate disposition in insulin-dependent diabetes. Relative contributions of endogenous glucose production and initial splanchnic uptake and effect of intensive insulin therapy. *J.Clin.Invest.* 74:985-991, 1984

188. Wilinska, M. E. Modelling of glucose and insulin kinetics to facilitate the development of a wearable artificial pancreas. 2004. London, City University.

189. Benn JJ, Bozzard SJ, Kelley D, Mitrakou A, Aoki T, Sorensen J, Gerich J, Sonksen PH: Persistent abnormalities of the metabolism of an oral glucose load in insulin-treated type I diabetics [see comments]. *Metabolism* 38:1047-1055, 1989

190. Darmaun D, Cirillo D, Koziet J, Chauvet D, Young VR, Robert JJ: Whole body glucose kinetics in type I diabetes studied with [6,6-2H] and [U-13C]-glucose and the artificial B-cell. *Metabolism* 37:491-498, 1988

191. Capaldo B, Gastaldelli A, Antoniello S, Auletta M, Pardo F, Ciociaro D, Guida R, Ferrannini E, Sacca L: Splanchnic and leg substrate exchanges after ingestion of a natural mixed meal in humans. *Diabetes* 47:1196, 1998

192. Wilinska ME, Chassin LJ, Schaller HC, Schaupp L, Pieber D, Hovorka R: Modelling insulin lispro kinetics during CSII in type 1 diabetes. *IEEE Trans.Biomed.Eng.* 2004

193. Gannon MC, Nuttall FQ: Factors affecting interpretation of postprandial glucose and insulin areas. *Diabetes Care* 10:759-763, 1987

194. Coulston AM, Hollenbeck CB, Swislocki AL, Reaven GM: Effect of source of dietary carbohydrate on plasma glucose and insulin responses to mixed meals in subjects with NIDDM. *Diabetes Care* 10:395-400, 1987

195. Jacobs MA, Keulen ET, Kanc K, Casteleijn S, Scheffer P, Deville W, Heine RJ: Metabolic efficacy of preprandial administration of Lys(B28), Pro(B29) human insulin analog in IDDM patients. A comparison with human regular insulin during a three-meal test period. *Diabetes Care* 20:1279-1286, 1997

196. Natarajan R, Mcculloch CE: A note on the existence of the posterior distribution for a class of mixed models for binomial responses. *Biometrika* 82:639-643, 1995

197. Liu D, Moberg E, Wredling R, Lins PE, Adamson U: Insulin Absorption Is Faster When Keeping the Infusion Site in Use for 3 Days During Continuous Subcutaneous Insulin Infusion. *Diabetes Research and Clinical Practice* 12:19-24, 1991

198. De Feo P, Perriello G, Ventura MM, Calcinaro F, Basta G, Lolli C, Cruciani C, Dell'Olio A, Santeusanio F, Brunetti P: Studies on overnight insulin requirements and metabolic clearance rate of insulin in normal and diabetic man: relevance to the pathogenesis of the dawn phenomenon. *Diabetologia* 29:475-480, 1986

199. Blackard WG, Barlascini CO, Clore JN, Nestler JE: Morning insulin requirements. Critique of dawn and meal phenomena. *Diabetes* 38:273-277, 1989

200. Parillo M, Riccardi G: Dietary carbohydrates and glucose metabolism in diabetic patients. *Diabete Metab.* 21:391-401, 1995

201. Service FJ, Rizza RA, Hall LD, Westland RE, O'Brien PC, Clemens AH, Haymond MW, Gerich JE: Prandial insulin requirements in insulin-dependent diabetics: effects of size, time of day, and sequence of meals. *J.Clin.Endocrinol.Metab* 57:931-936, 1983

202. Nuttall FQ, Gannon MC, Wald JL, Ahmed M: Plasma glucose and insulin profiles in normal subjects ingesting diets of varying carbohydrate, fat, and protein content. *J.Am.Coll.Nutr.* 4:437-450, 1985

203. Van Cauter EV, Polonsky KS, Scheen AJ: Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr.Rev.* 18:716-738, 1997

204. Van Cauter EV, Shapiro ET, Tillil H, Polonsky KS: Circadian modulation of glucose and insulin responses to meals - relationship to cortisol rhythm. *Am.J.Physiol.* 262:E467-E475, 1992

205. Sternberg F, Meyerhoff C, Mennel FJ, Mayer H, Bischof F, Pfeiffer EF: Does fall in tisue glucose precede fall in blood glucose? *Diabetologia* 39:609-612, 1996

206. Pfeiffer EF, Meyerhoff C, Bischof F, Keck FS, Kerner W: On line continuous monitoring of subcutaneous tissue glucose is feasible by combining portable glucosensor with microdialysis. *Horm.Metab.Res.* 25:121-124, 1993

207. Schaller HC, Schaupp LA, Bodenlenz M, Sommer R, Wutte A, Semlitsch B, Chassin LJ, Wilinska M, Hovorka R, Wach P, Pieber TR: Feasibility of

the SC-SC route for an extracorporeal artificial pancreas (Abstract). *Diabetes* 51 (Suppl. 2):462, 2002

208. Schaupp L, Ellmerer M, Brunner GA, Wutte A, Sendlhofer G, Trajanoski Z, Skrabal F, Pieber TR, Wach P: Direct access to interstitial fluid in adipose tissue in humans by use of open-flow microperfusion. *Am J Physiol* 276:E401-E408, 1999

209. Goriya Y, Ueda N, Nao K, Yamasaki Y, Kawamori R, Shichiri M, Kamada T: Fail-safe systems for the wearable artificial endocrine pancreas. *Int.J.Artif.Organs* 11:482-486, 1988

210. DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am.J.Med.* 90:450-459, 1991

211. World Health Consultation: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Organisation, 1999

212. Schaller HC, Bodenlenz M, Schaupp L, Plank J, Wach P, Pieber TR, Chassin LJ, Wilinska M, Hovorka R, Haueter U, Vering T, Orsini-Federici M, Celleno R, Akwe J, Canonico V, Massi-Benedetti M: MPC algorithm controls blood glucose in patients with type 1 diabetes mellitus under fasting conditions using the IV-SC route (Abstract). *Diabetes Technology & Therapeutics* 4:234, 2002

213. Clarke WL, Cox D, Gonderfrederick LA, Carter W, Pohl SL: Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* 10:622-628, 1987

214. Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. *Diabetes* 46:271-286, 1997

215. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV: Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes* 37:901-907, 1988

216. Preconception care of women with diabetes. *Diabetes Care* 26 Suppl 1:S91-S93, 2003

217. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 26 Suppl 1:S33-S50, 2003

218. Asbury AJ, Henderson PD, Brown BH, Turner DJ, Linkens DA: Effect of Diazepam on Pancuronium-Induced Neuromuscular Blockade Maintained by A Feedback-System. *British Journal Of Anaesthesia* 53:859-863, 1981

219. Standards of Medical Care for Patients With Diabetes Mellitus. *Diabetes Care* 25:33S-349, 2002

220. Bonora E, Calcaterra F, Lombardi S, Bonfante N, Formentini G, Bonadonna RC, Muggeo M: Plasma glucose levels throughout the day and HbA(1c) interrelationships in type 2 diabetes: implications for treatment and monitoring of metabolic control. *Diabetes Care* 24:2023-2029, 2001

221. Bouma M, Dekker JH, de Sonnaville JJ, van der Does FE, De Vries H, Kriegsman DM, Kostense PJ, Heine RJ, van Eijk JT: How valid is fasting plasma glucose as a parameter of glycemic control in non-insulin-using patients with type 2 diabetes? *Diabetes Care* 22:904-907, 1999

222. Avignon A, Radauceanu A, Monnier L: Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care* 20:1822-1826, 1997

223. Bastyr EJ, III, Stuart CA, Brodows RG, Schwartz S, Graf CJ, Zagar A, Robertson KE: Therapy focused on lowering postprandial glucose, not

fasting glucose, may be superior for lowering HbA1c. IOEZ Study Group. *Diabetes Care* 23:1236-1241, 2000

224. Tanne D, Koren-Morag N, Goldbourt U: Fasting plasma glucose and risk of incident ischemic stroke or transient ischemic attacks: a prospective cohort study. *Stroke* 35:2351-2355, 2004

225. Valeri C, Pozzilli P, Leslie D: Glucose control in diabetes. *Diabetes Metab Res.Rev.* 20 Suppl 2:S1-S8, 2004

226. Arcavi L, Behar S, Caspi A, Reshef N, Boyko V, Knobler H: High fasting glucose levels as a predictor of worse clinical outcome in patients with coronary artery disease: results from the Bezafibrate Infarction Prevention (BIP) study. *Am Heart J* 147:239-245, 2004

227. Singleton JR, Smith AG, Bromberg MB: Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care* 24:1448-1453, 2001

228. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal Of Medicine* 329:977-985, 1993

229. Cryer PE, Binder C, Bolli GB, Cherrington AD, Gale EA, Gerich JE, Sherwin RS: Hypoglycemia in IDDM. *Diabetes* 38:1193-1199, 1989

230. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 26 Suppl 1:S33-S50, 2003

231. Wojcicki JM: "J"-index. A new proposition of the assessment of current glucose control in diabetic patients. *Horm.Metab Res.* 27:41-42, 1995

232. Wolf FM, Jacober SJ, Wolf LL, Cornell RG, Floyd JC, Jr.: Quality of life activities associated with adherence to insulin infusion pump therapy in the treatment of insulin dependent diabetes mellitus. *J.Clin.Epidemiol.* 42:1129-1136, 1989

233. Jaremko J, Rorstad O: Advances toward the implantable artificial pancreas for treatment of diabetes. *Diabetes Care* 21:444-450, 1998

Personal Bibliography

Journal Papers

1. **Chassin LJ**, Wilinska ME, Hovorka R: Grading system to assess clinical performance of closed-loop glucose control. *Diabetes Technol.Ther.* 7:72-82, 2005

2. **Chassin LJ**, Wilinska ME, Hovorka R: Evaluation of glucose controllers in virtual environment: Methodology and sample application. *Artif.Intell.Med.* 32:171-181, 2004

3. Schaller HC, Schaupp L, Bodenlenz M, Wilinska ME, **Chassin LJ**, Wash P, Vering T, Hovorka R, Pieber TR: On-line adaptive algorithm with glucose prediction capacity for subcutaneous closed loop control of glucose: evaluation under fasting conditions in patients with type 1 diabetes. *Diab.Med.* In press, 2005

4. Wilinska ME, **Chassin LJ**, Schaller HC, Schaupp L, Pieber TR, Hovorka R: Insulin kinetics in type-I diabetes: continuous and bolus delivery of rapid acting insulin. *IEEE Trans.Biomed.Eng* 52:3-12, 2005

5. Hovorka R, Canonico V, **Chassin LJ**, Haueter U, Massi-Benedetti M, Orsini FM, Pieber TR, Schaller HC, Schaupp L, Vering T, Wilinska ME: Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas.* 25:905-920, 2004

6. Hovorka R, **Chassin, LJ**, Wiliska ME, Canonico V, Akwe J, Orsini-Federici M, Massi-Benedetti M, Zaugg C, Kaufmann H, Both M, Vering T, Schaller H, Schaupp L, Bodenlenz M, Pieber TR: Closing the Loop: The ADICOL Experience. *Diabetes Technol.Ther.* 6:307-318, 2004.

7. Wilinska ME, Bodenlenz M, **Chassin LJ**, Schaller HC, Schaupp L, Pieber TR, Hovorka R: Interstitial glucose kinetics in subjects with Type 1 diabetes under physiological conditions. *Metabolism.* 11:1484-91, 2004

8. Wilinska ME, **Chassin LJ**, Schaller HC, Schaupp L, Pieber D, Hovorka R: Modelling insulin lispro kinetics during CSII in Type 1 diabetes. *IEEE Trans.Biomed.Eng* in revision: 2004

9. Hovorka R, Shojaee-Moradie F, Carroll PV, **Chassin LJ**, Gowrie IJ, Jackson NC, Tudor RS, Umpleby AM, Jones RH: Partitioning glucose distribution/transport, disposal, and endogenous production during intravenous glucose tolerance test (IVGTT). *Am.J.Physiol.* 282:E992-E1007, 2002

Abstracts

10. **Chassin LJ**, Hovorka R: Closed-loop glucose control with IV glucose sampling and SC insulin infusion: Evaluation by simulation studies. *Diabetologia* 44 (Suppl 1):221, 2001

11. **Chassin LJ**, Haueter U, Hovorka R, Massi-Benedetti M, Orsini-Federici M, Pieber TR, Schaller H, Schaupp L, Vering T, Wilinska M: Simulating control of glucose concentration in subjects with Type 1 diabetes: example of control system with inter- and intra-individual variations. In Adaptive Systems and Hybrid Computational Intelligence in Medicine. Special Session Proceedings of the EUNITE - 2001 Symposium. Dounias GD, Linkens DA, Eds. Chios, University of Aegean, 2001, p. 68

12. **Chassin LJ**, Haueter U, Hovorka R, Massi-Benedetti M, Orsini-Federici M, Pieber TR, Schaller HC, Schaupp L, Vering T, Wilinska M: Closed-loop glucose control algorithm: Evaluation methodology by simulation (Abstract). *Diabetes Technol.Ther.* 4:212, 2002

13. **Chassin LJ**, Wilinska ME, Hovorka R: Assessing the effect of delay in glucose sampling on closed-loop glucose control: A simulation study (Abstract). *Diabet.Med.* 19 (Suppl. 2):69, 2002

14. **Chassin LJ**, Wilinska ME, Hovorka R: Simulating closed-loop glucose control: Effect of delay in glucose measurement (Abstract). *Diabetes* 51 (Suppl. 2):1606, 2002

15. **Chassin LJ**, Hovorka R, Wilinska ME: The effect of temporary loss of glucose readings on closed-loop glucose monitor: An evaluation study using simulations. In Diabetes Technology Meeting. San Francisco, 2003, p. A9

16. **Chassin LJ**, Wilinska ME, Hovorka R: Automated subcutaneous insulin infusion driven by subcutaneous glucose measurements presents clinically acceptable control over a 24-h study (Abstract). *Diabet.Med.* 20 (Suppl. 2):49, 2003

17. **Chassin, LJ**, Wilinska, M. E., and Hovorka, R. Virtual Type 1 'diabetic' treated by CSII: Model description. Allen, B. and Lowell, N. Proceedings of World Congress on Medical Physics and Biomedical Engineering. 2003. Sydney.

18. Canonico V, Orsini-Federici M, Ferolla P, Celleno R, Akwe J, Timi A, **Chassin LJ**, Wilinska ME, Vering T, Hovorka R, Massi Benedetti M: Evaluation of a feedback model based on simulated interstitial glucose for continuous insulin infusion. *Diabetologia* 45 (Suppl 2):A322, 2002

19. Hovorka R, **Chassin LJ**, Haueter U, Massi-Benedetti M, Orsini-Federici M, Pieber TR, Schaller HC, Schaupp L, Vering T, Wilinska M: Model predictive control algorithm for artificial pancreas (Abstract). *Diabetes Technol.Ther.* 4:221, 2002

20. Hovorka, R., Canonico, V., **Chassin, L. J.**, Massi-Benedetti, M., Orsini-Federici, M., Pieber, T. R., Schaller, H. C., Schaupp, L, Vering, T., and Wilinska, M. Control of glucose in Type 1 diabetes with subcutaneous insulin infusion: Non-linear model predictive control with Bayesian parameter estimation. Allen, B. and Lowell, N. 2003. Sydney. Proceedings of World Congress on Medical Physics and Biomedical Engineering. 2003.

21. Schaller HC, Bodenlenz M, Schaupp L, Wutte A, Wach P, Pieber TR, **Chassin LJ**, Wilinska M, Hovorka R, Haueter U, Vering T, Orsini-Federici M, Celleno R, Canonico V, Akwe J, Massi-Benedetti M: Regelung des Blutzuckerspiegels von Patienten mit Typ-1-Diabetes mellitus mit hilfe des MPC-Algorithmus. *Acta Med.Austriaca* Suppl. 55:19, 2001

22. Schaller HC, Schaupp LA, Bodenlenz M, Sommer R, Wutte A, Semlitsch B, **Chassin LJ**, Wilinska M, Hovorka R, Wach P, Pieber TR: Feasibility of the SC-SC route for an extracorporeal artificial pancreas (Abstract). *Diabetes* 51 (Suppl. 2):462, 2002

23. Schaller HC, Bodenlenz M, Schaupp L, Plank J, Wach P, Pieber TR, **Chassin LJ**, Wilinska M, Hovorka R, Haueter U, Vering T, Orsini-Federici M, Celleno R, Akwe J, Canonico V, Massi-Benedetti M: MPC algorithm controls blood glucose in patients with Type 1 diabetes mellitus under fasting conditions using the IV-SC route. *Diabetes Technol.Ther.* 4:234, 2002

Appendices

A. Glucose profile in 18 synthetic subjects controlled by MPC

B. Simulator simulink block diagrams

C. Publications

A. Glucose Profile in 18 Synthetic Subjects Controlled by MPC

Appendix A shows glucose control using the simulation environment in 18 synthetic subjects. Plasma glucose is represented by the solid smooth line, the interstitial glucose with a 5% measurement error sampled every three minutes is represented by the solid ragged line, the insulin infusion rate is represented by a piecewise constant solid line, and the insulin boluses are represented by solid bars at meal times ingested at 840, 1140 and 1500min and consisting of 40, 70, and 60g carbohydrates (CHO), respectively.

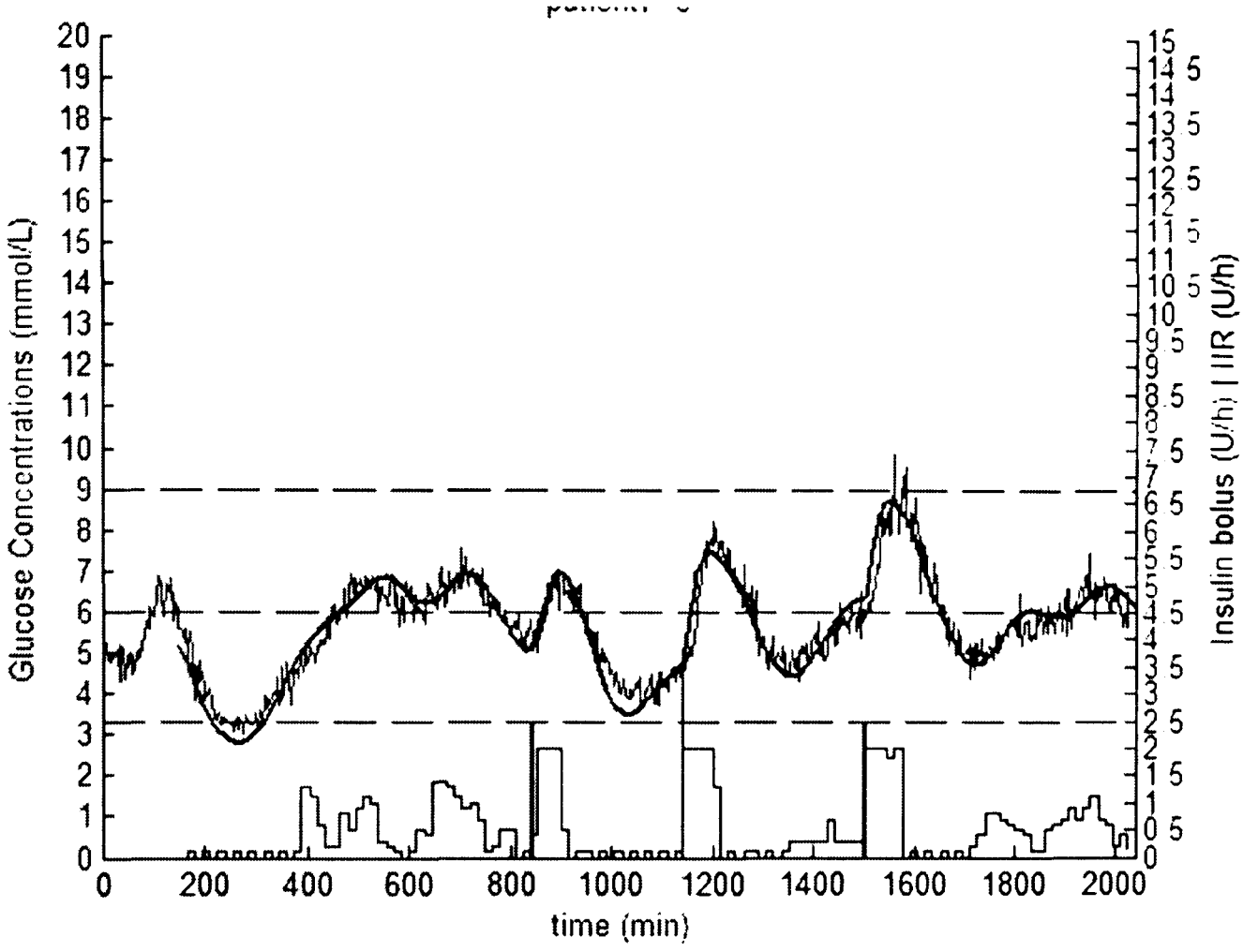

Figure A.1: Simulation of subject 1.

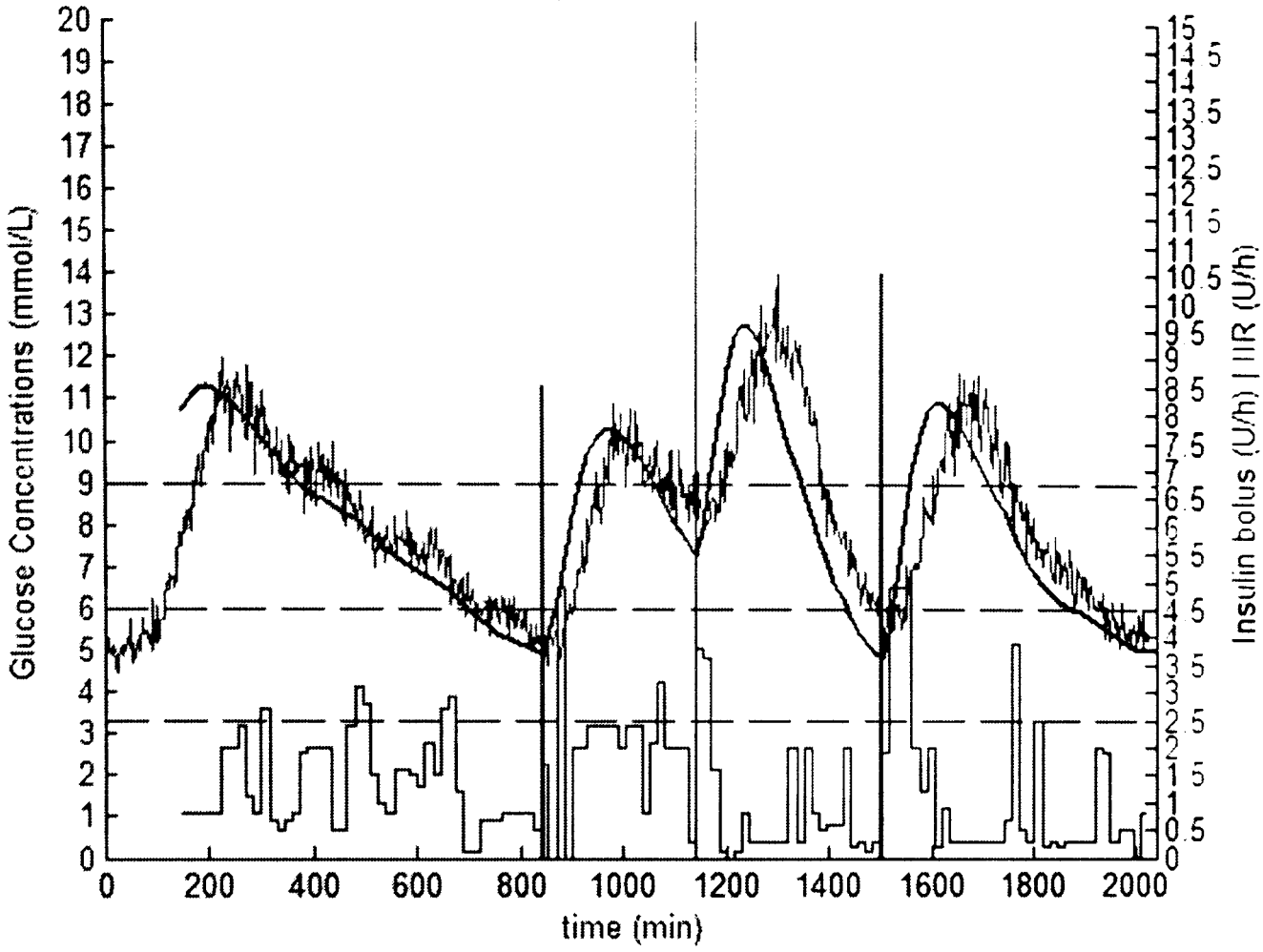

Figure A.2: Simulation of subject 2.

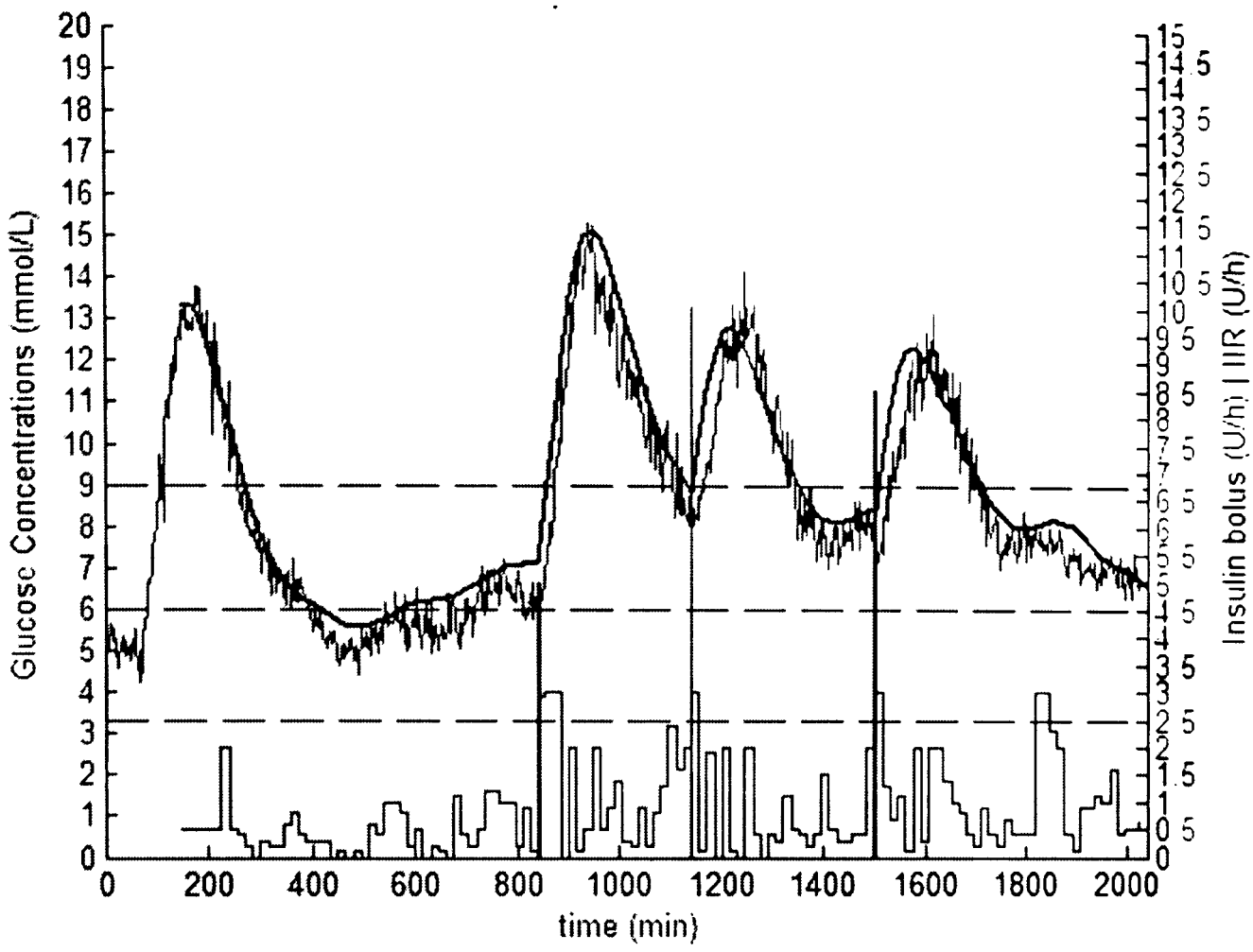

Figure A.3: Simulation of subject 3.

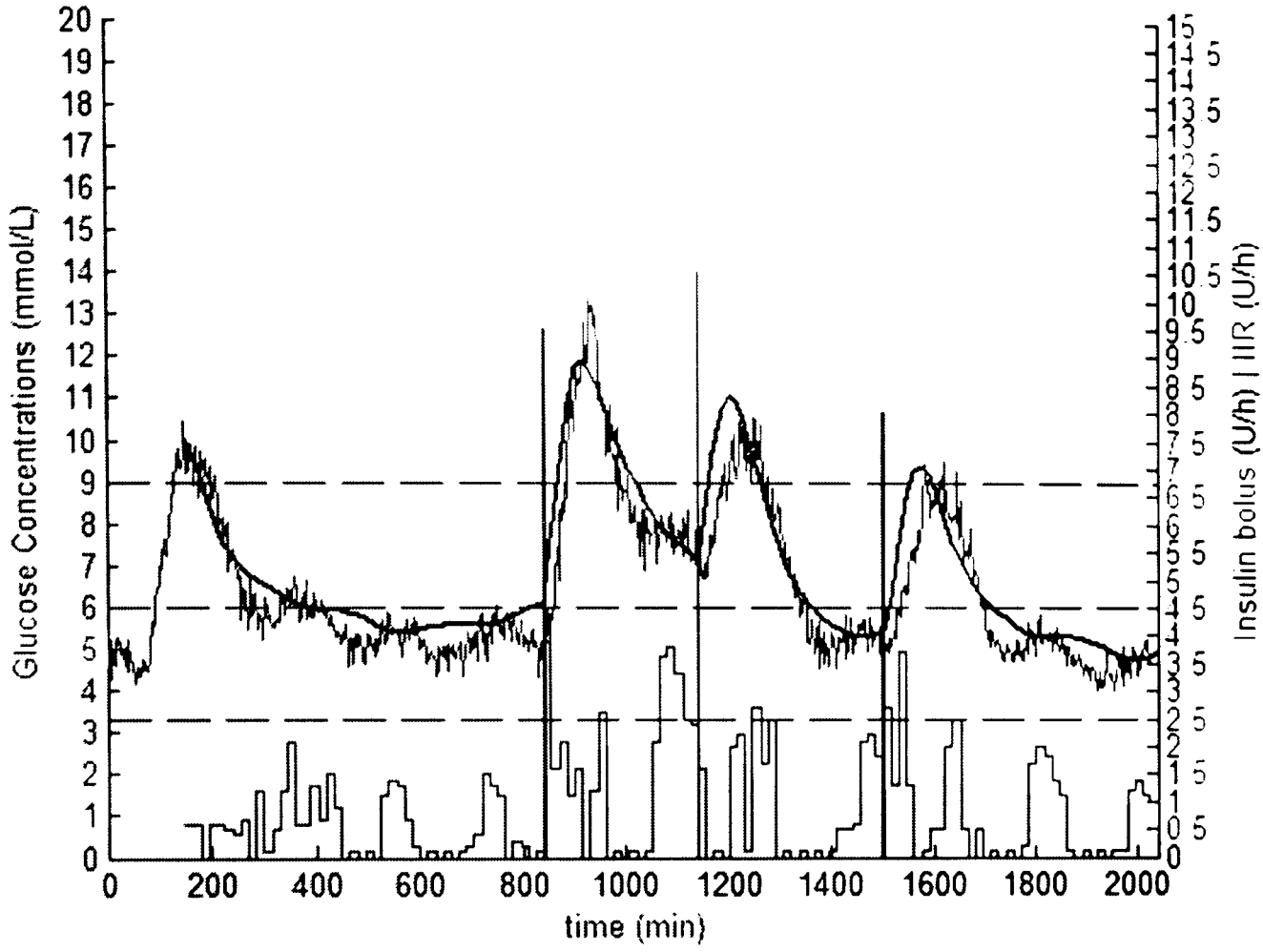

Figure A.4: Simulation of subject 4.

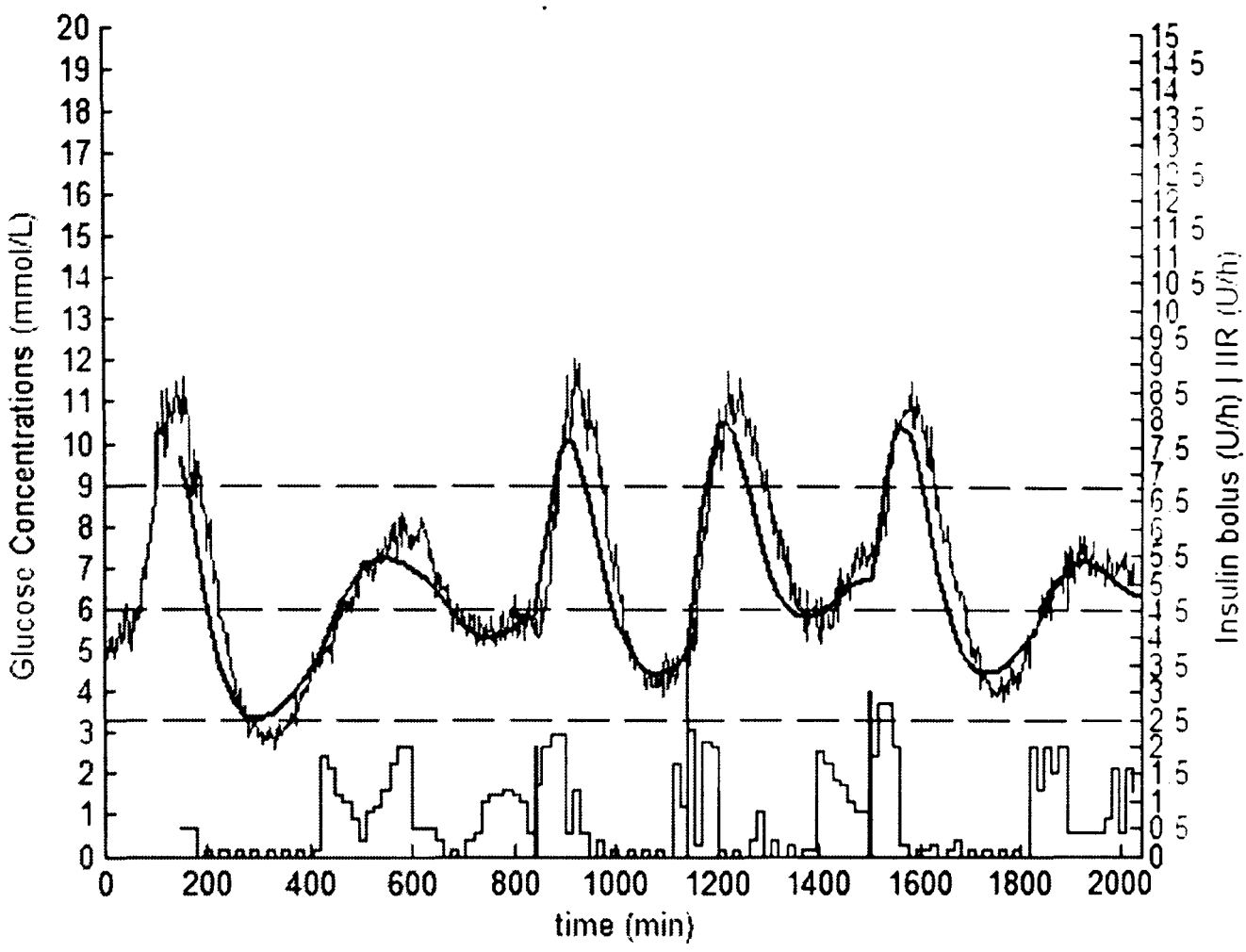

Figure A.5: Simulation of subject 5.

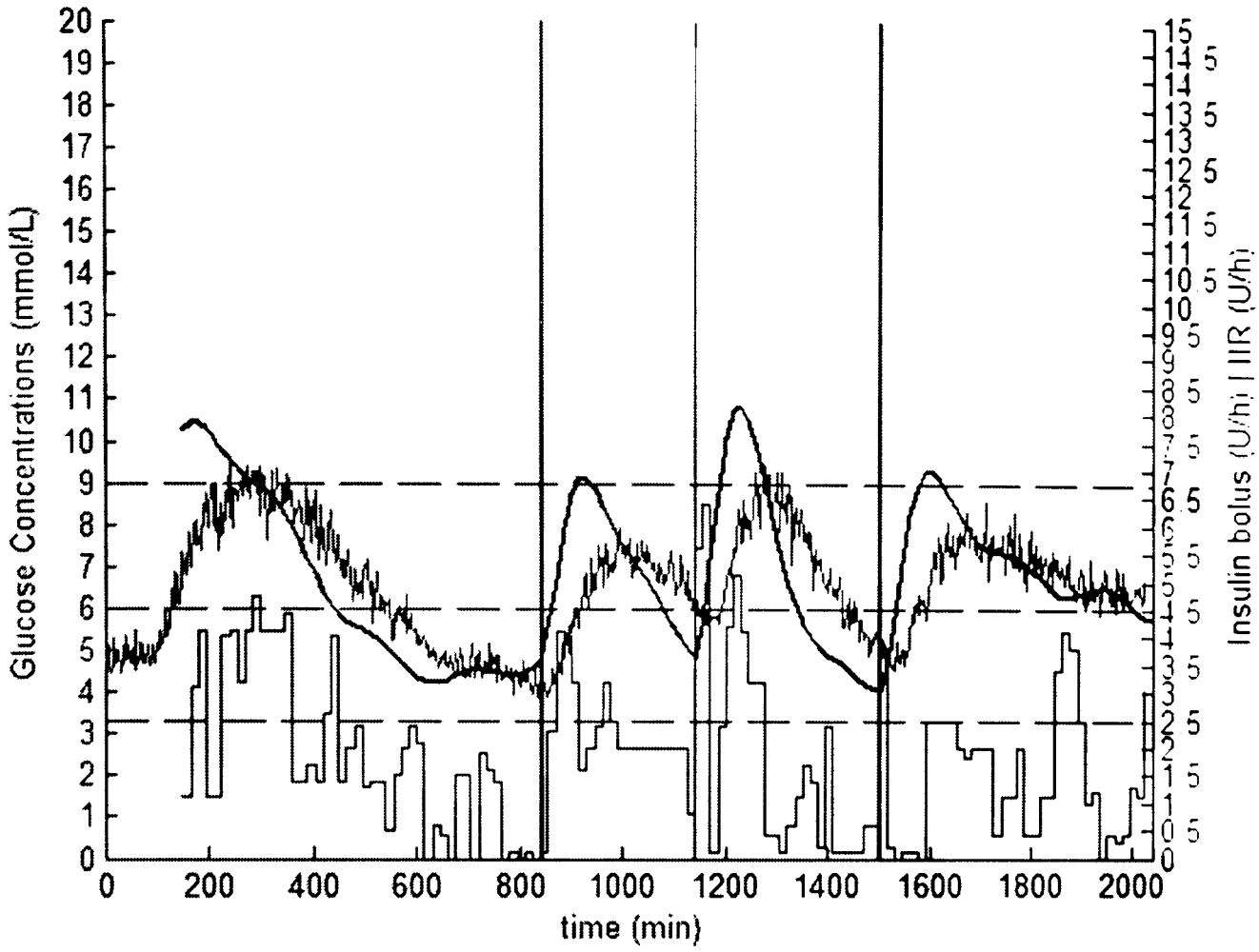

Figure A.6: Simulation of subject 6.

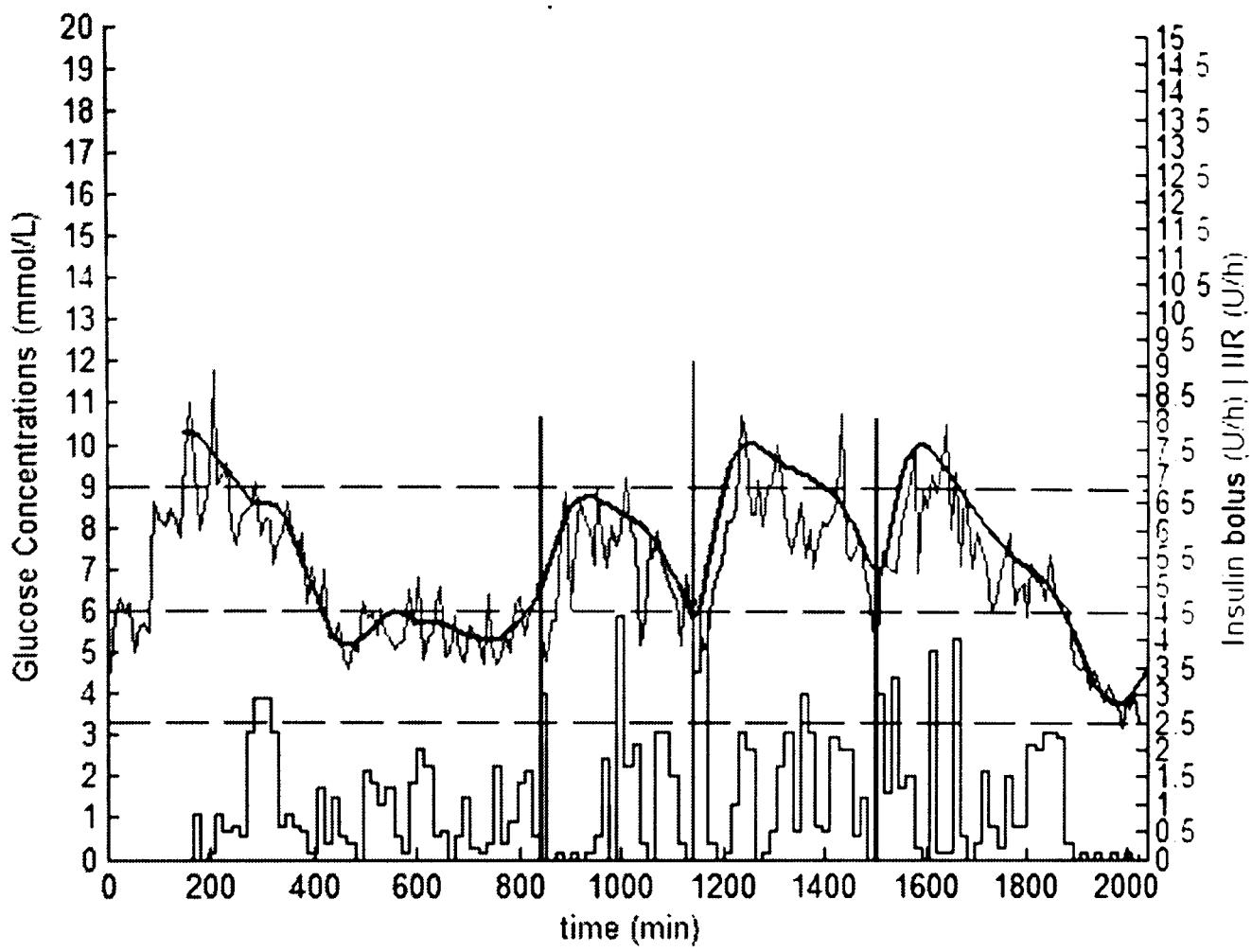

Figure A.7: Simulation of subject 7.

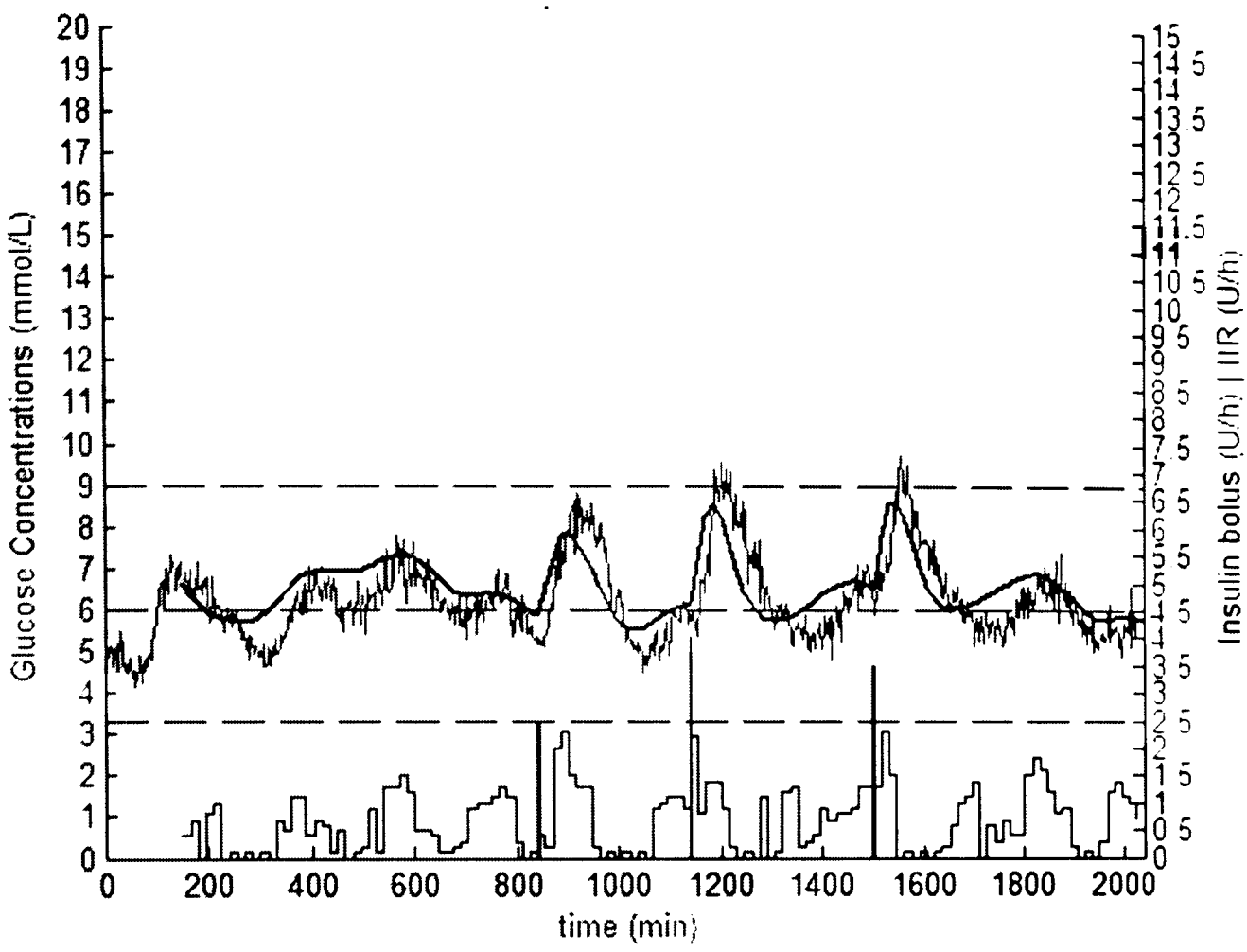

Figure A.8: Simulation of subject 8.

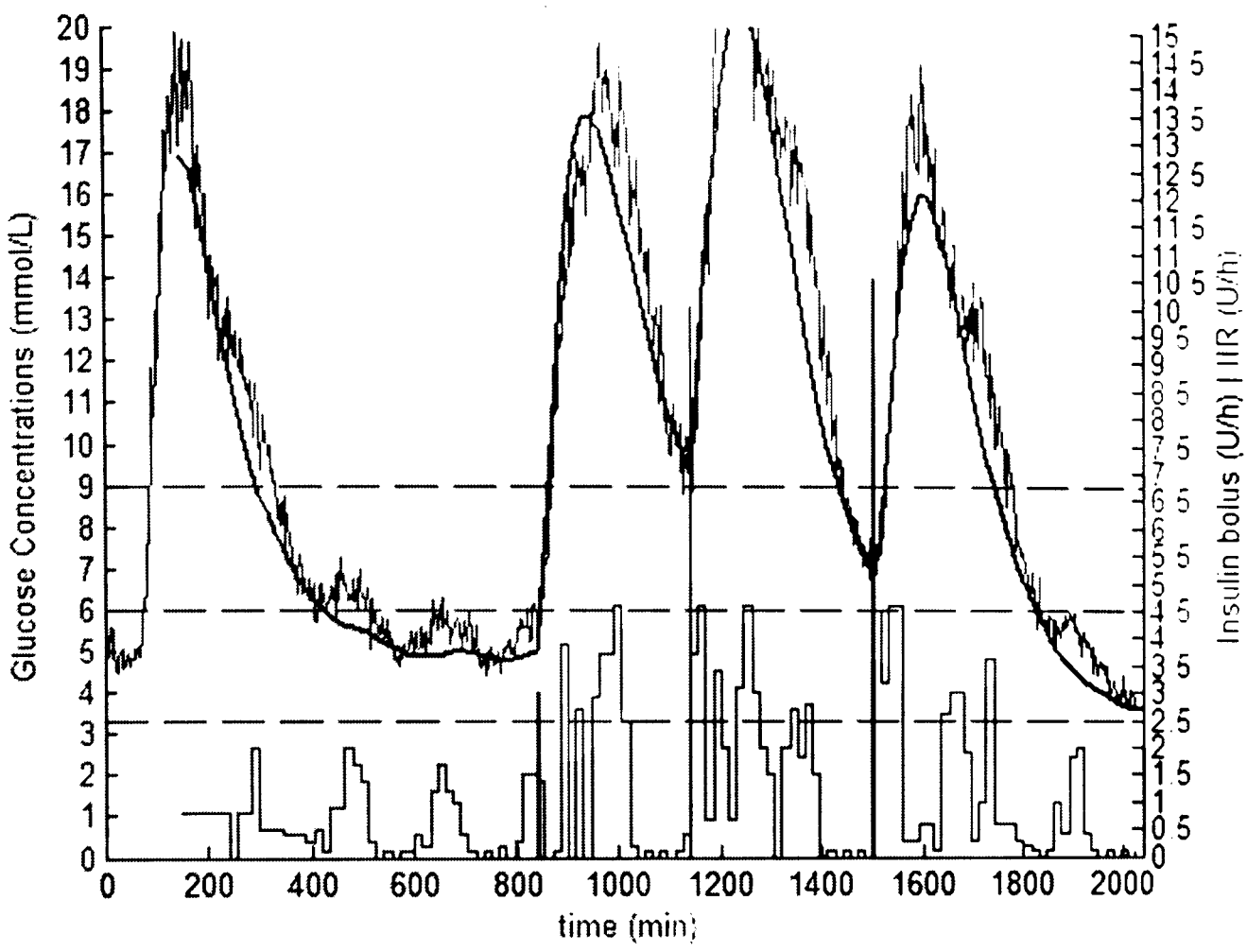

Figure A.9: Simulation of subject 9.

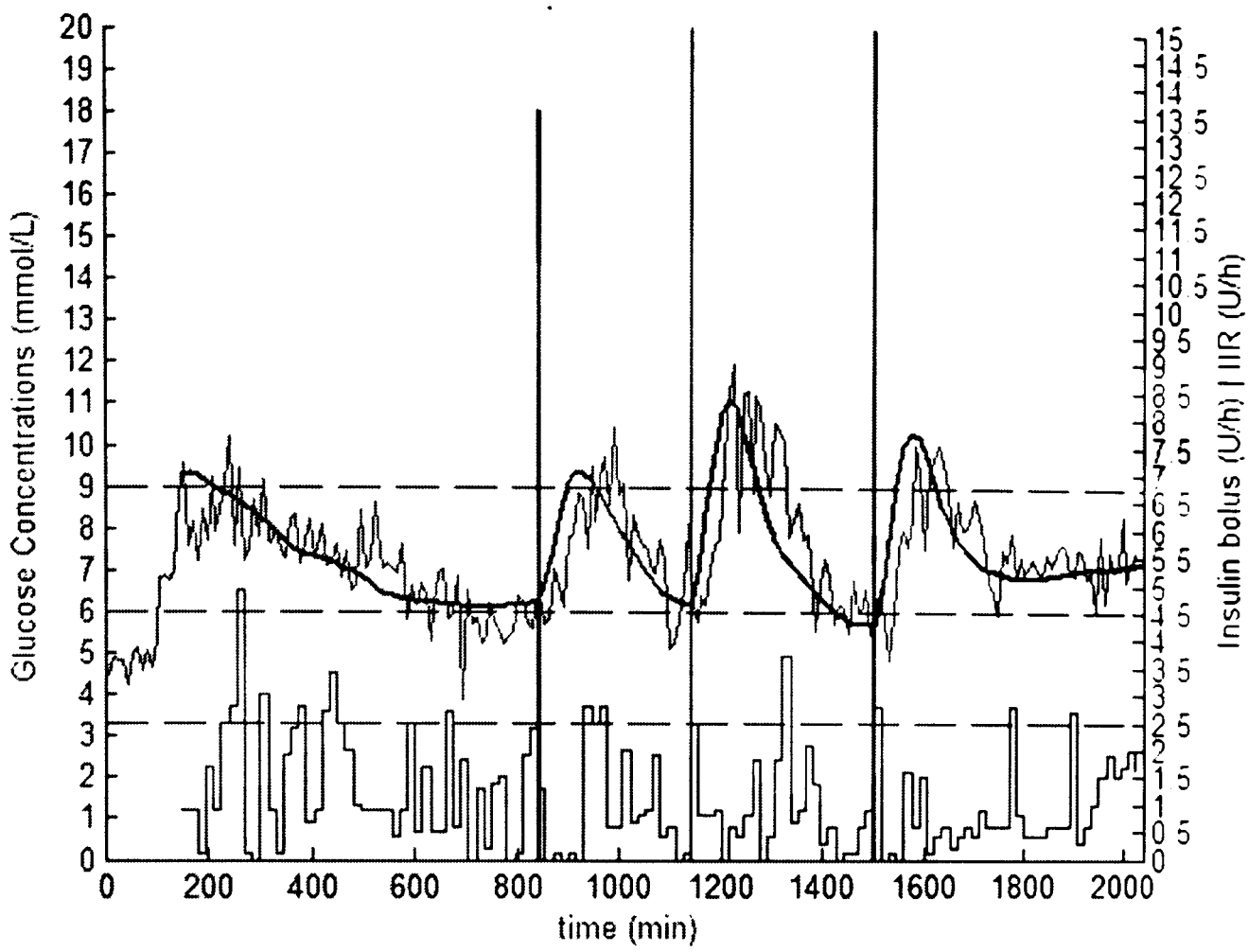

Figure A.10: Simulation of subject 10.

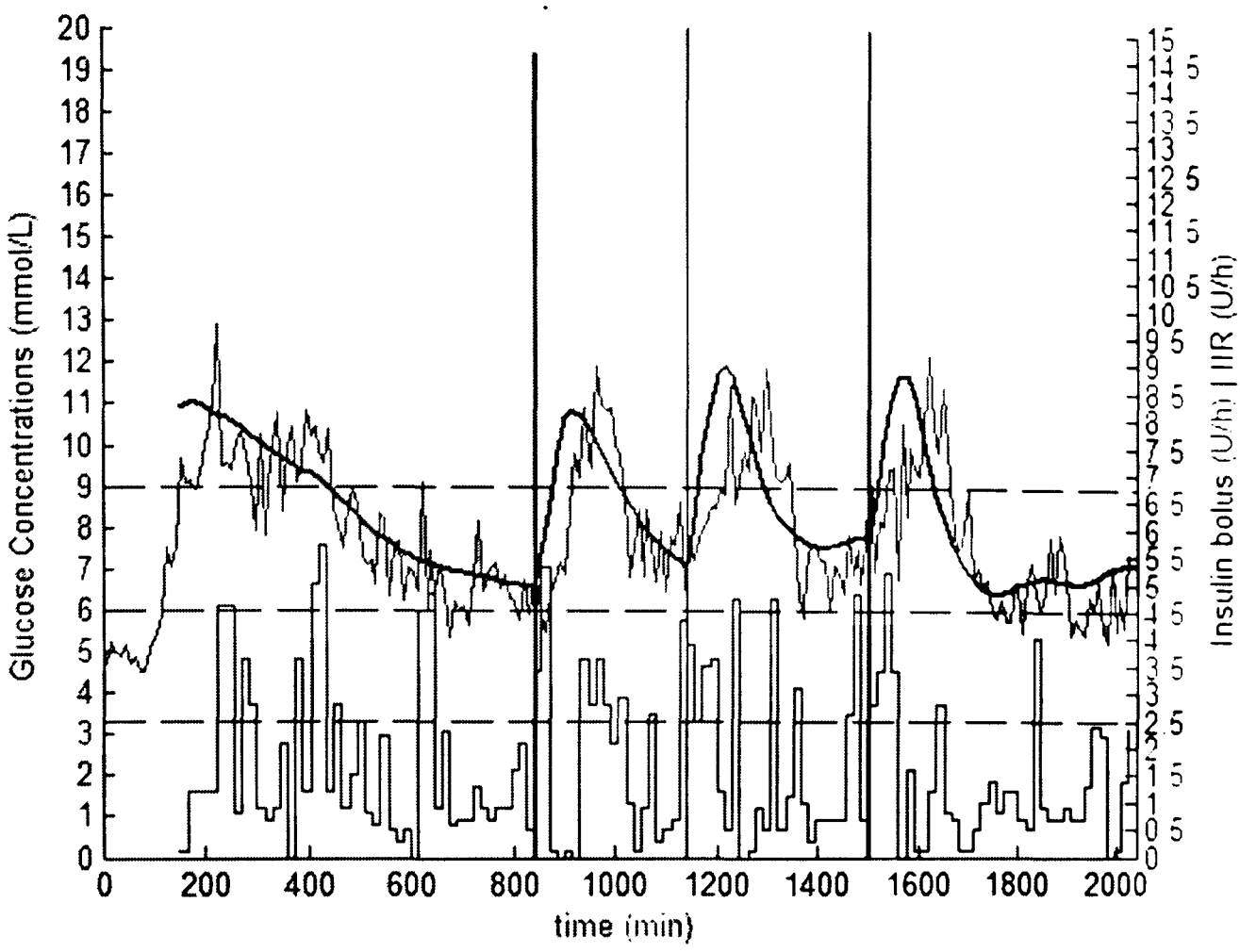

Figure A.11: Simulation of subject 11.

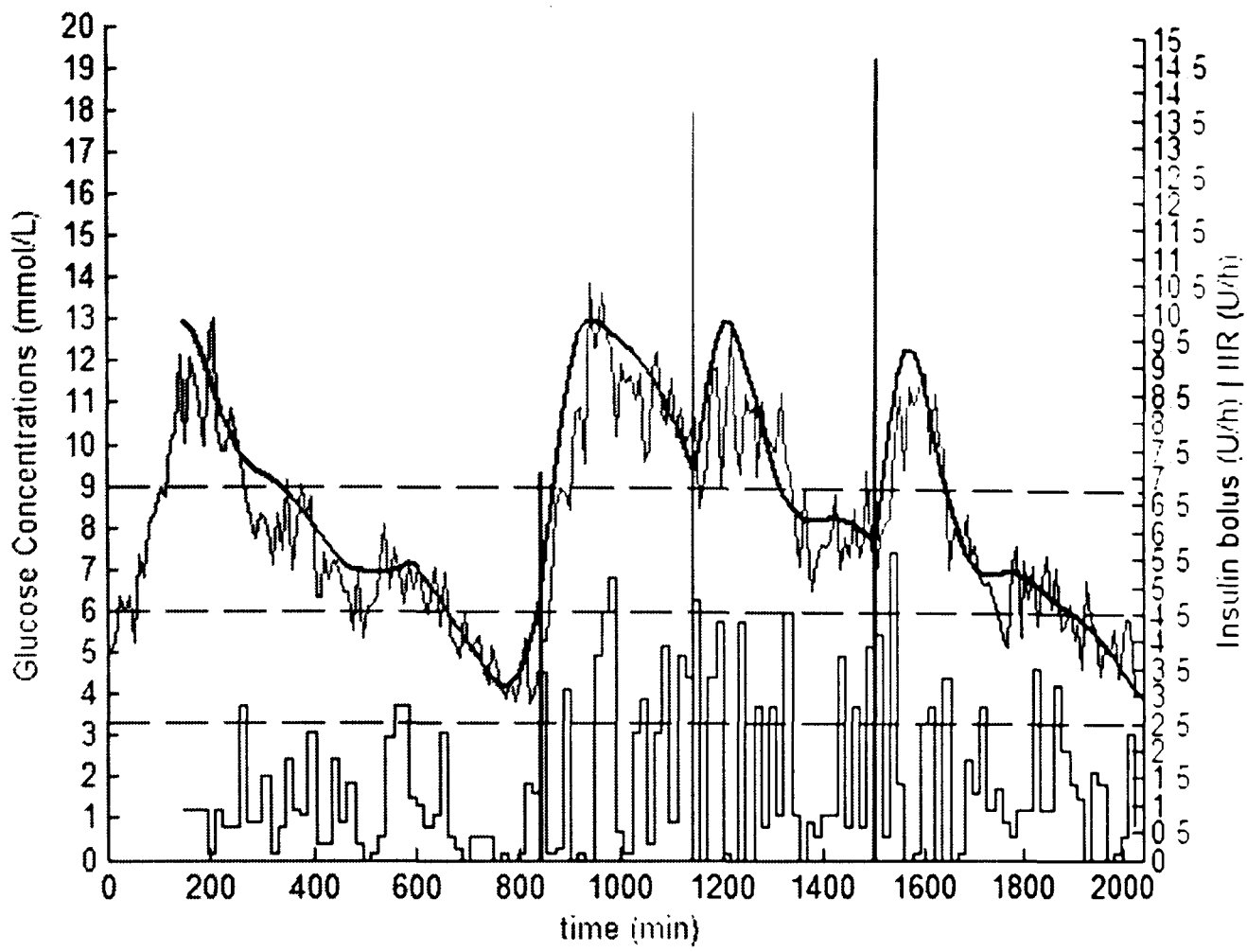

Figure A.12: Simulation of subject 12.

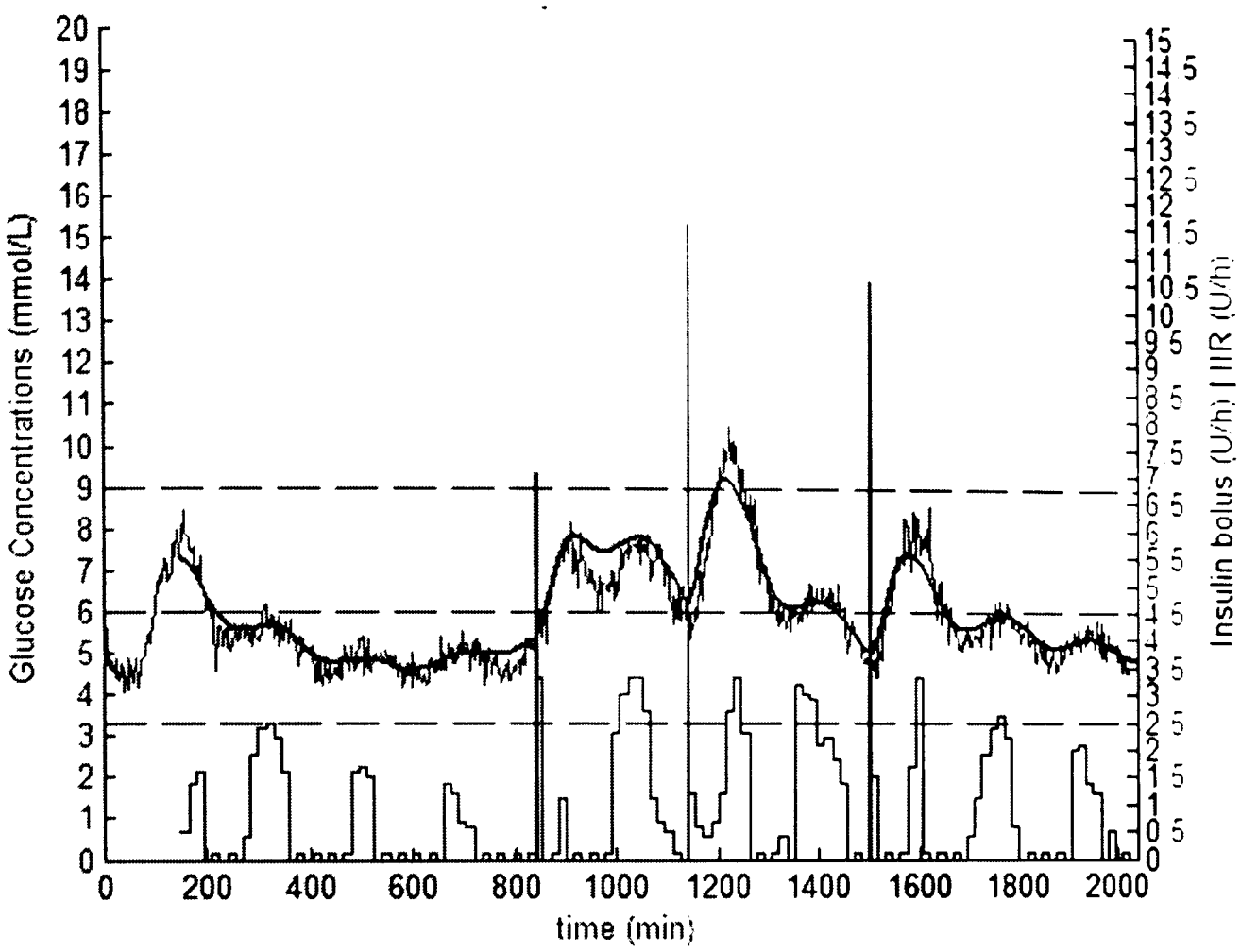

Figure A.13: Simulation of subject 13.

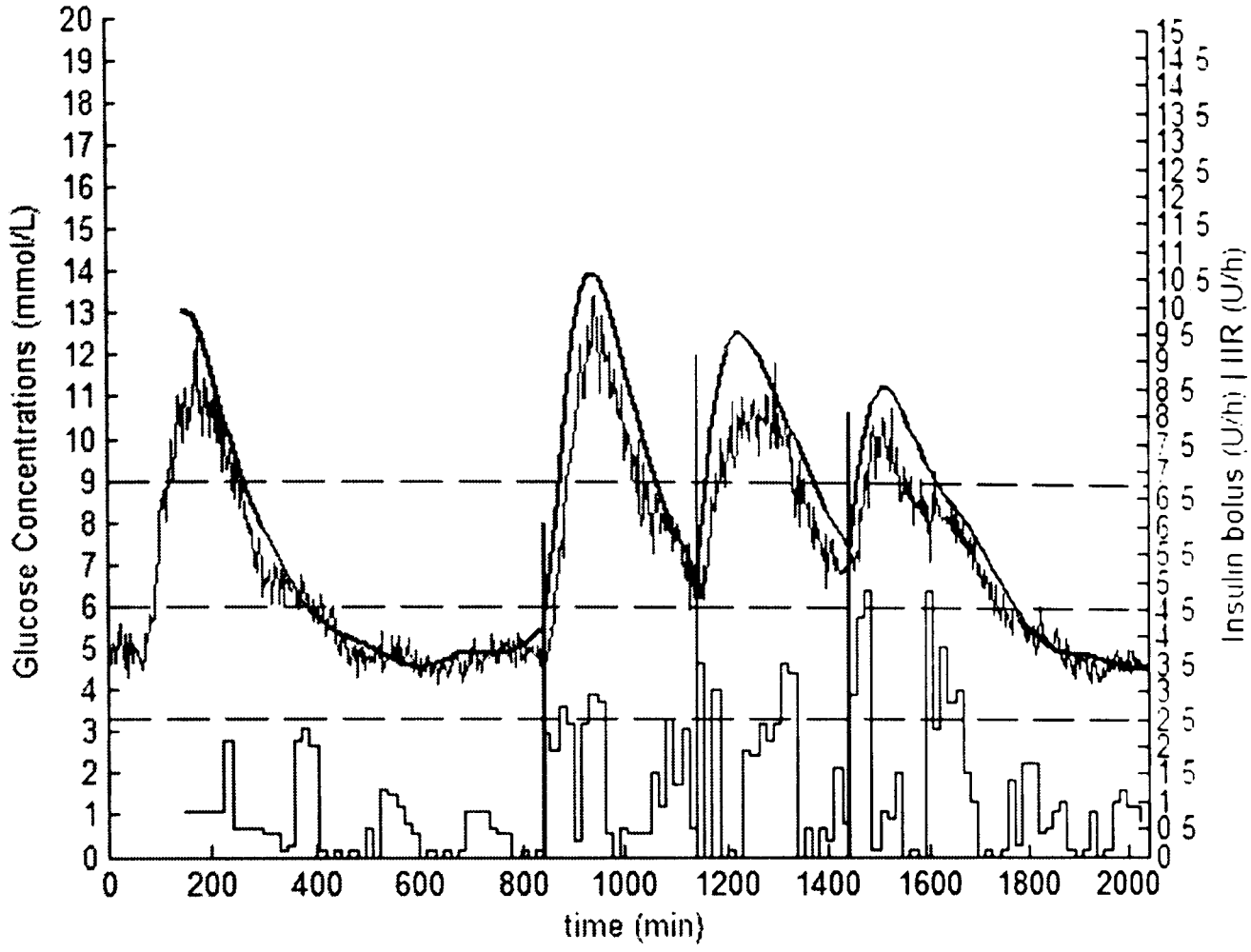

Figure A.14: Simulation of subject 14.

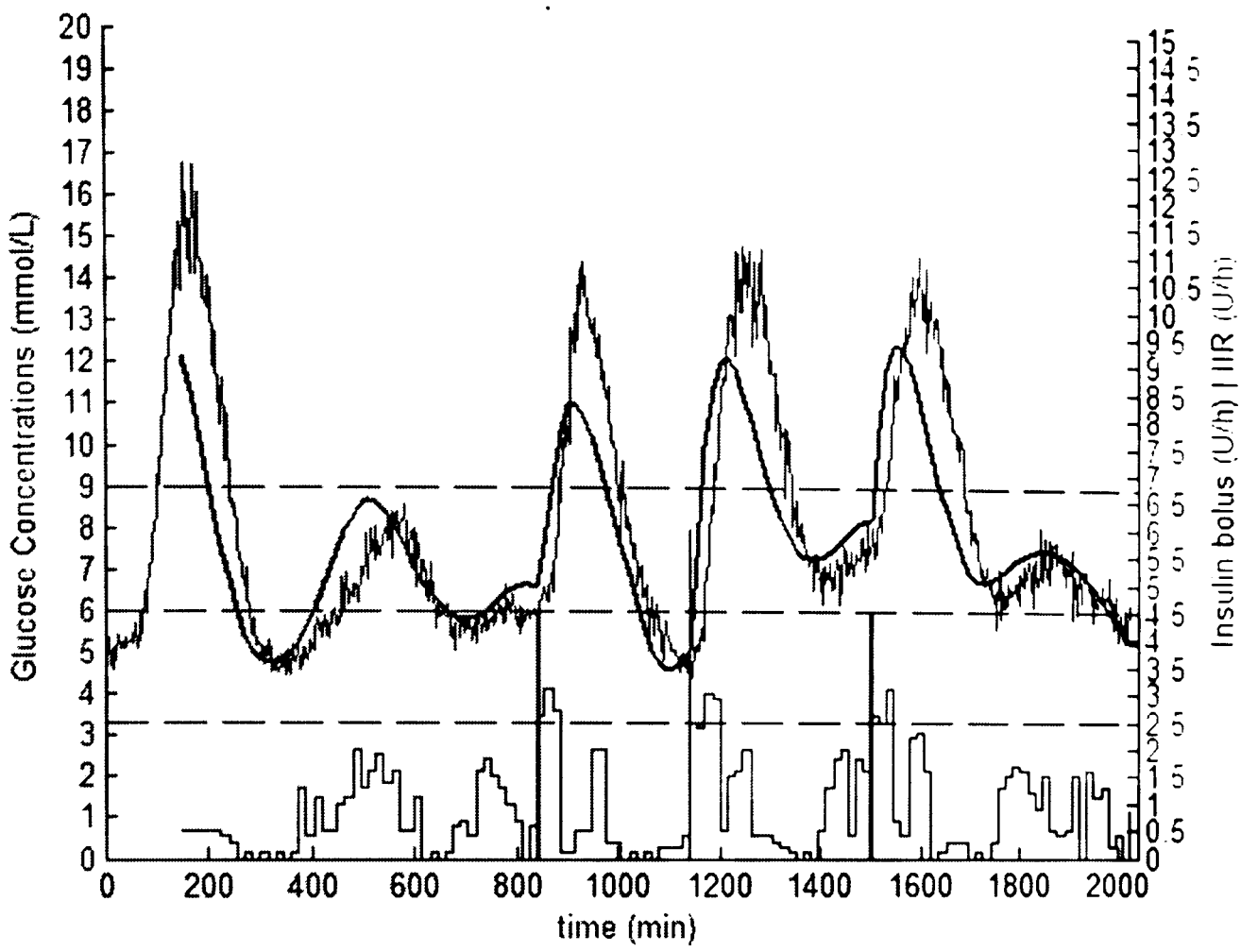

Figure A.15: Simulation of subject 15.

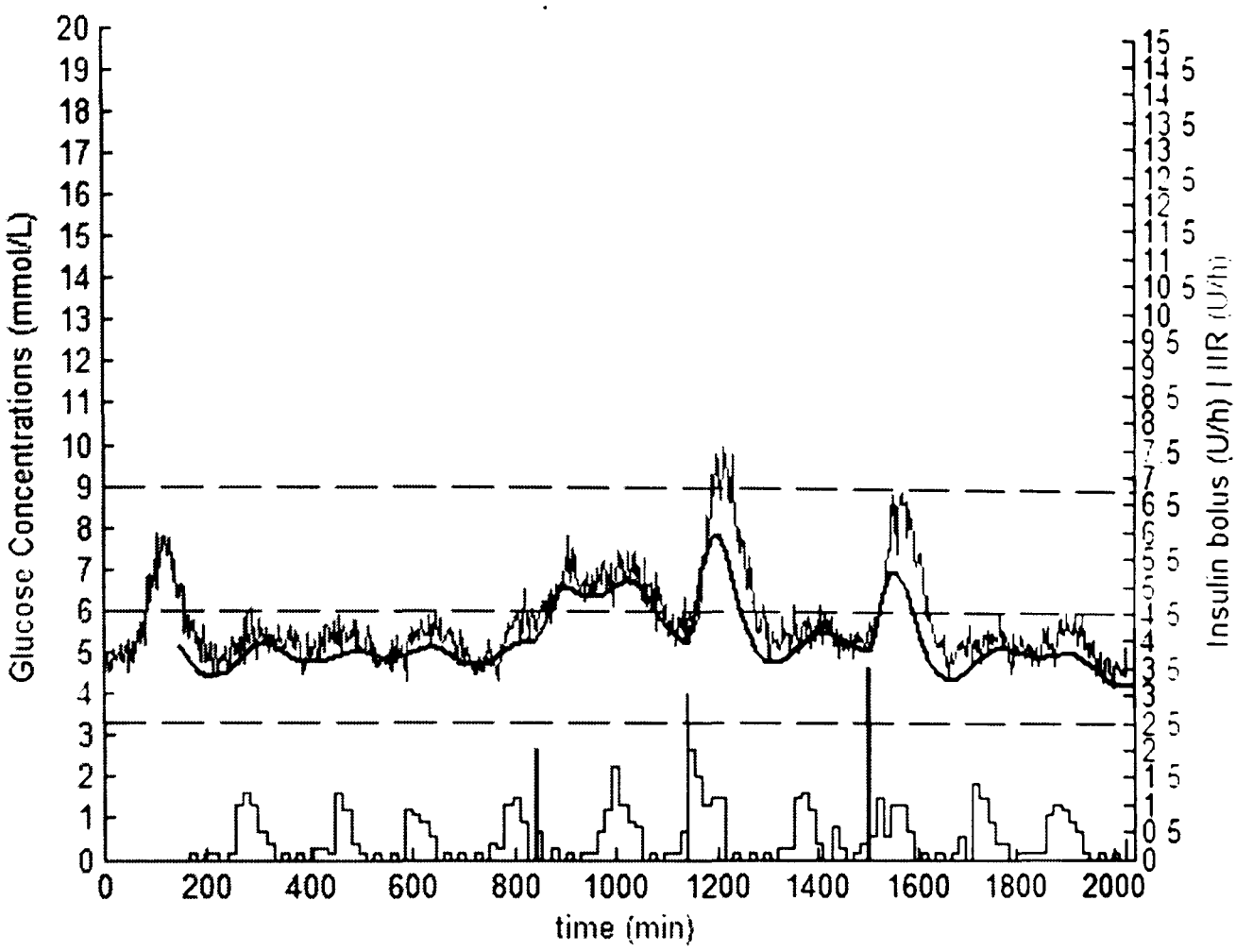

Figure A.16: Simulation of subject 16.

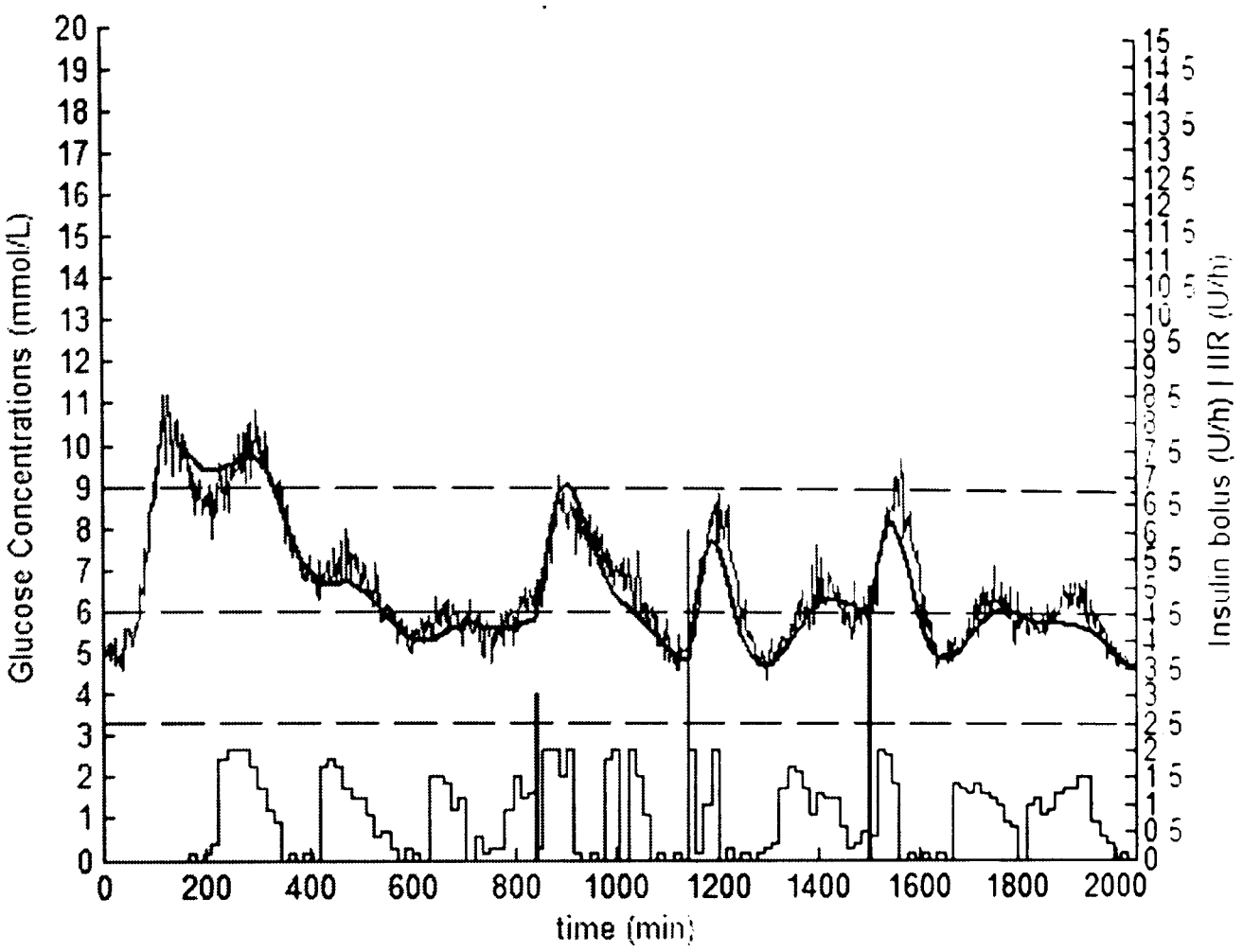

Figure A.17: Simulation of subject 17.

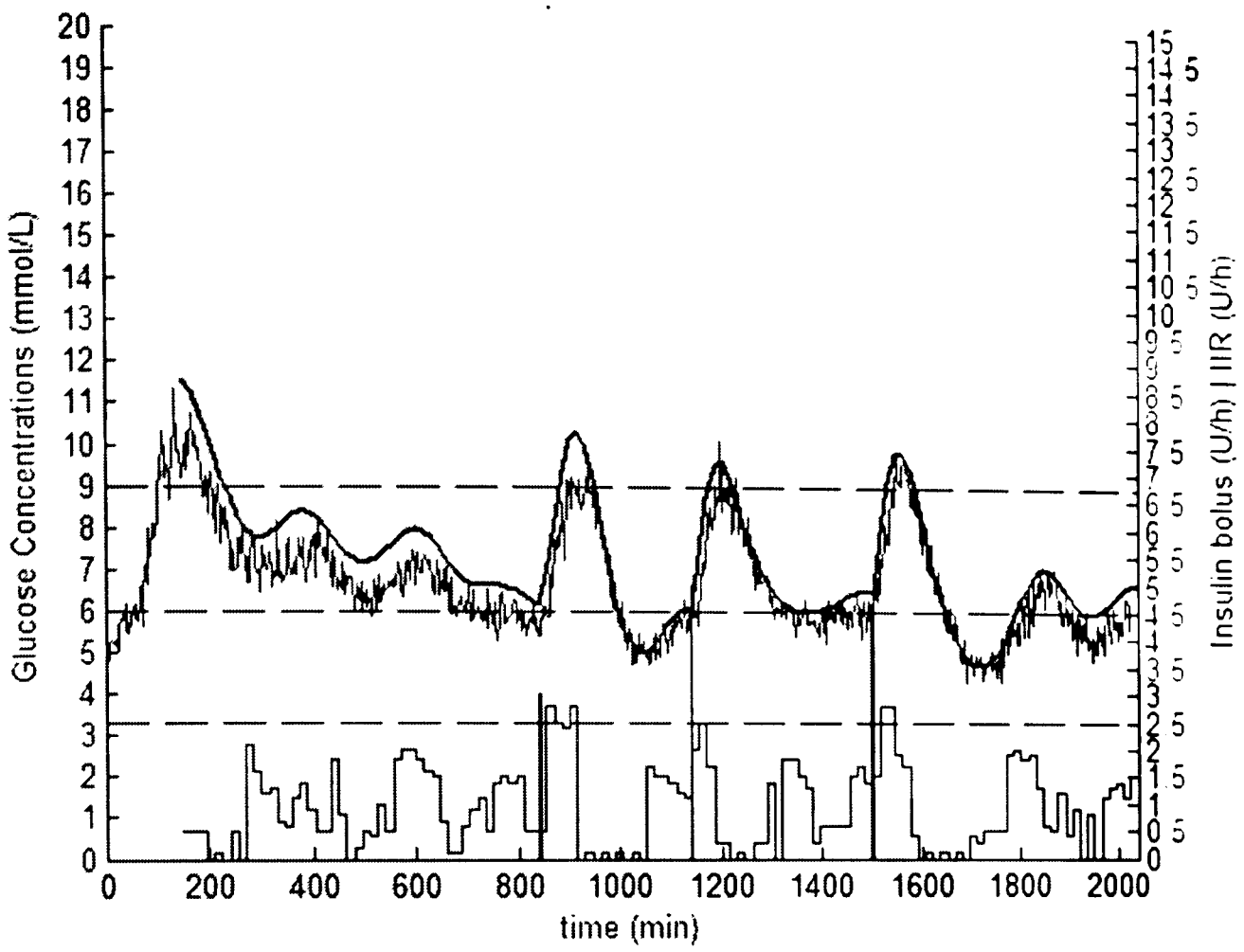

Figure A.18: Simulation of subject 18.

B. Simulator Simulink Block Diagrams

This Appendix contains the simulator Simulink schematic diagrams of a closed loop insulin delivery system employing subcutaneous measurements and subcutaneous insulin delivery.

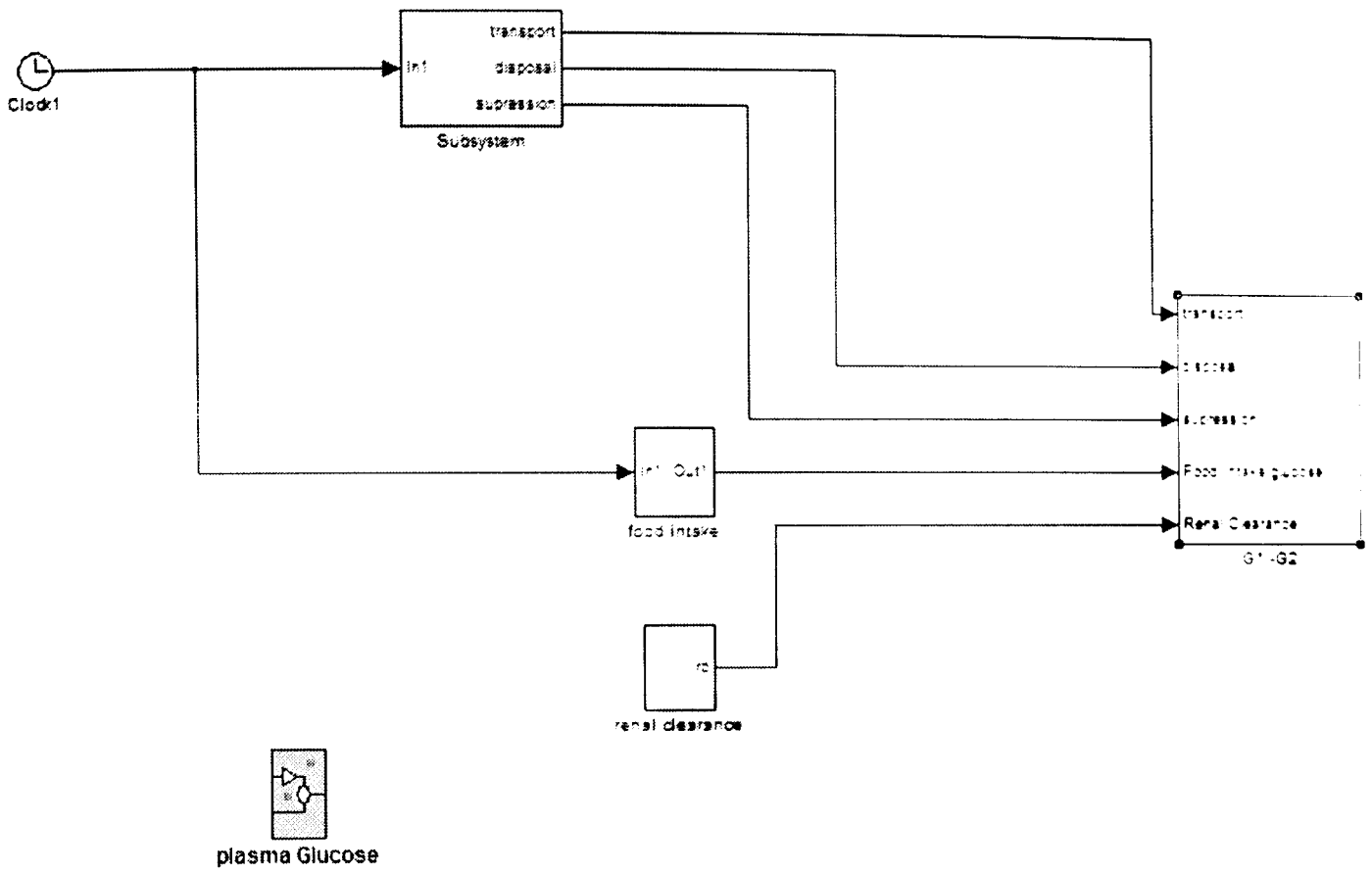

Figure B.1: Simulink schematic diagram showing the top level structure of the simulator

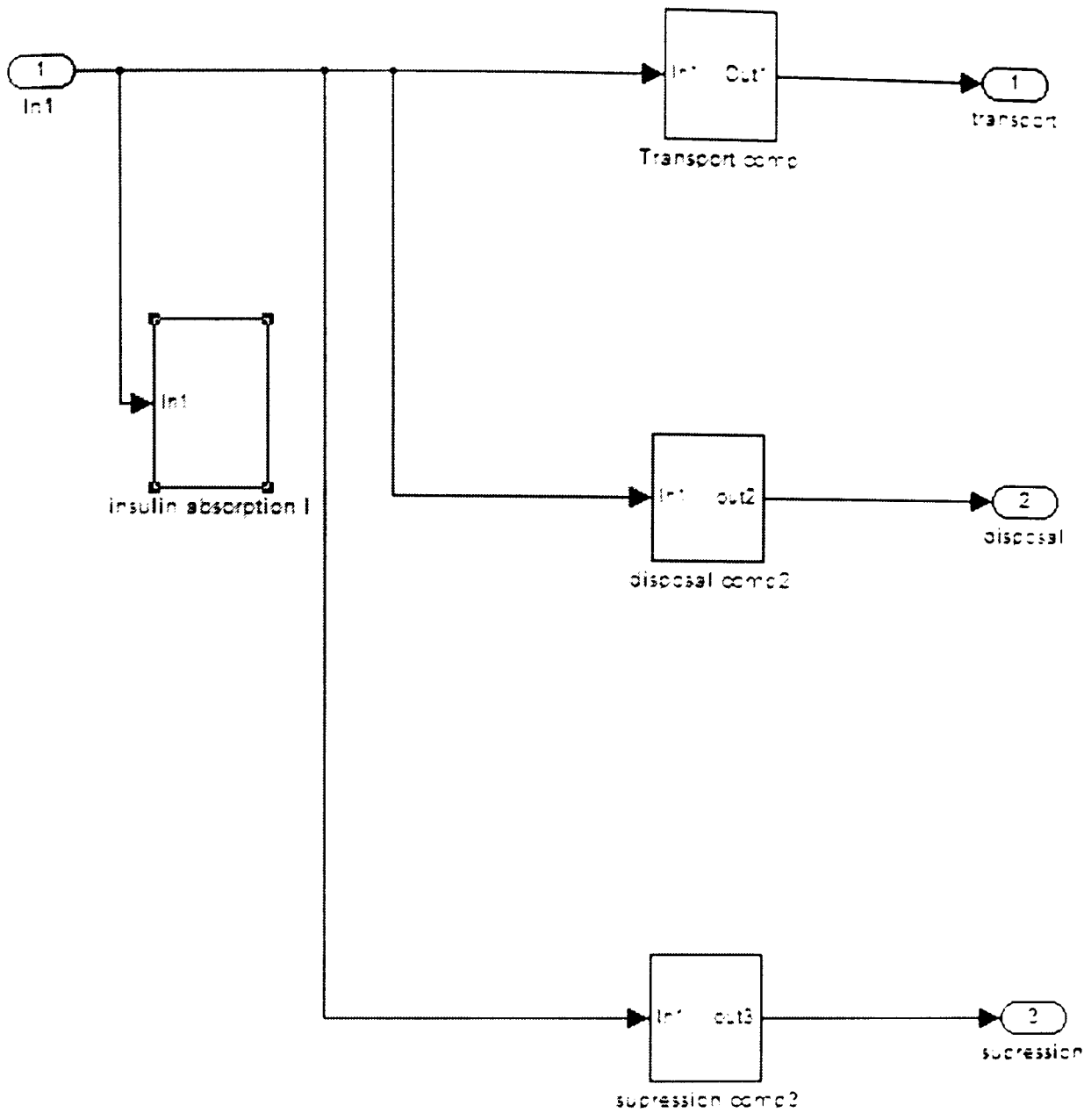

Figure B.2: Simulink schematic diagram showing the top level of the insulin absorption model and the three insulin actions on transport, disposal, and suppression.

Figure B.3: Simulink schematic diagram showing insulin absorption implemented as a function block.

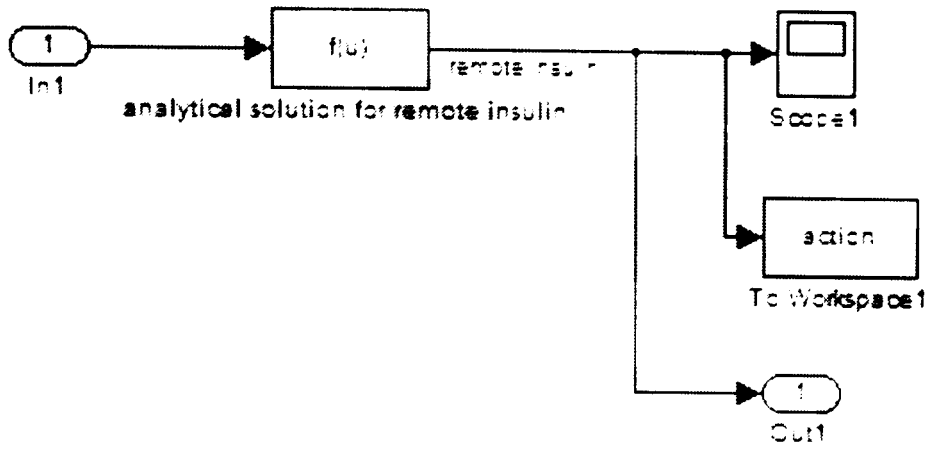

Figure B.4: Simulink schematic diagram showing insulin absorption implemented as a function block.

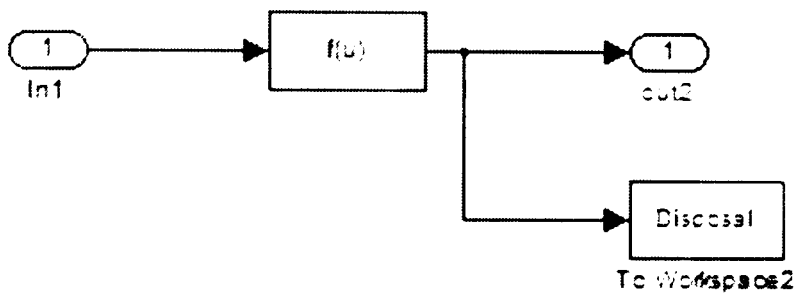

Figure B.5: Simulink schematic diagram showing insulin action on disposal implemented as a function block.

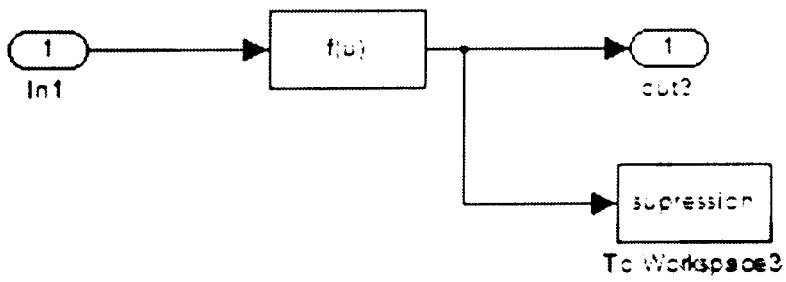

Figure B.6: Simulink schematic diagram showing insulin action on hepatic glucose production implemented as a function block.

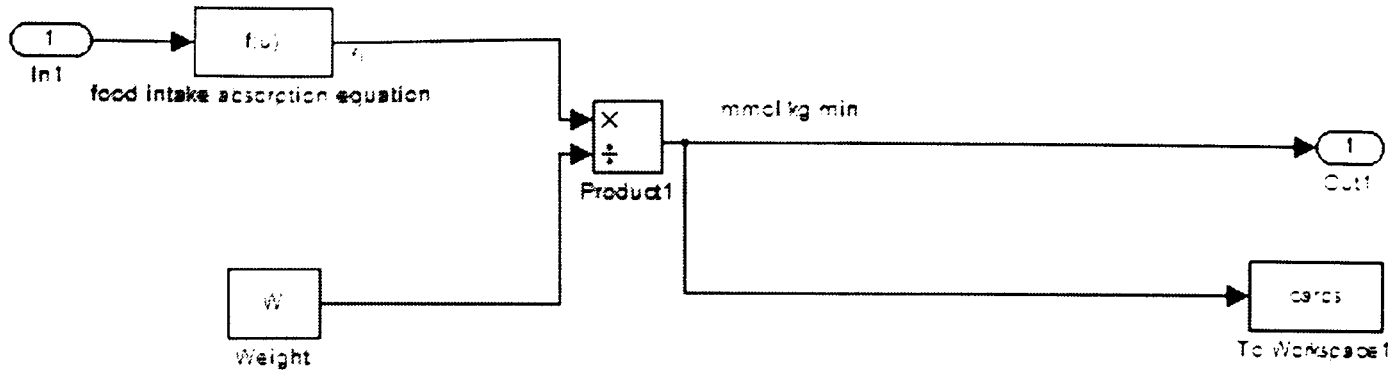

Figure B.7: Simulink schematic diagram showing gut absorption.

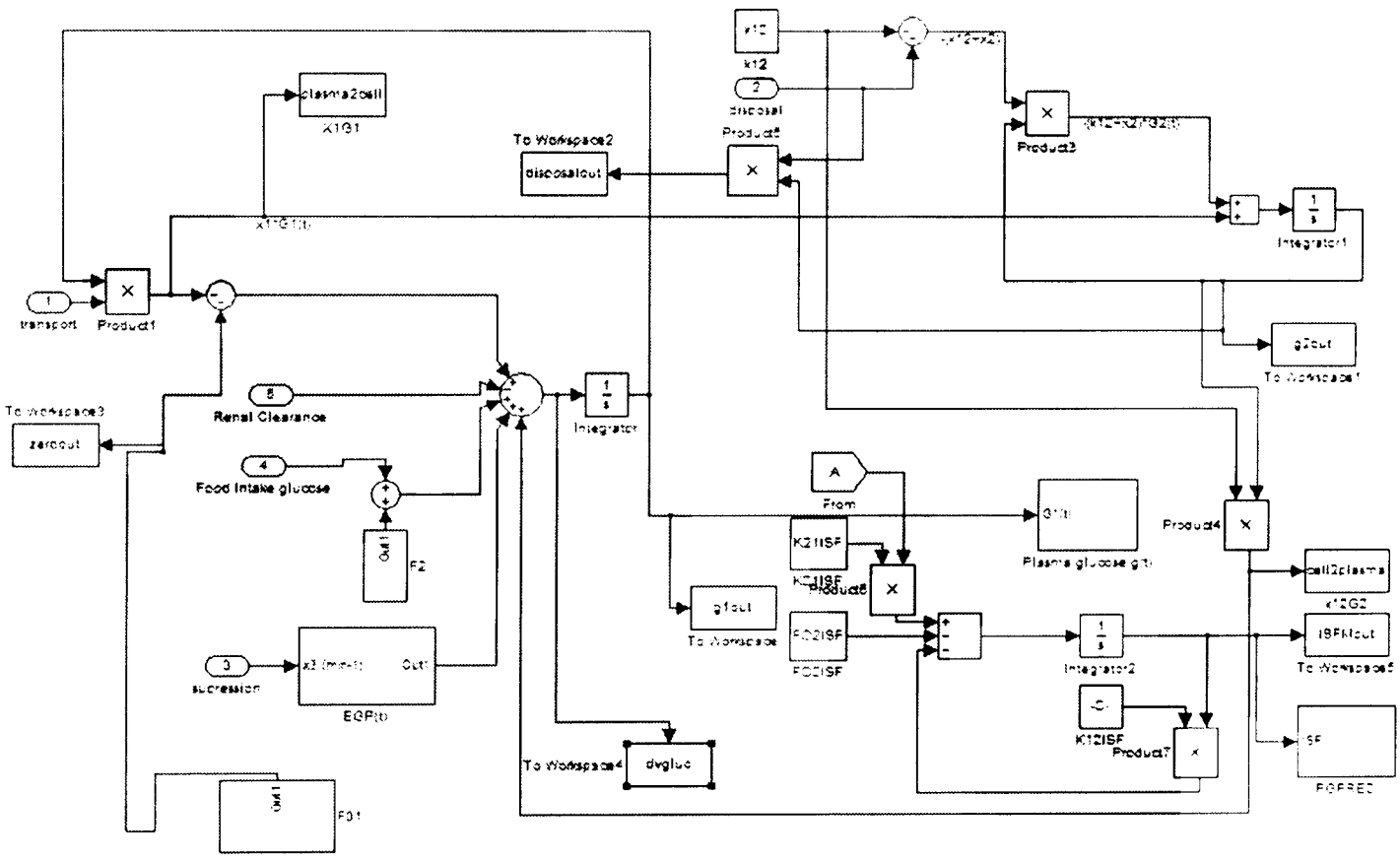

Figure B.8: Simulink schematic diagram showing fluxes associated with the glucose accessible compartment and the non accessible compartment G_1 and G_2.

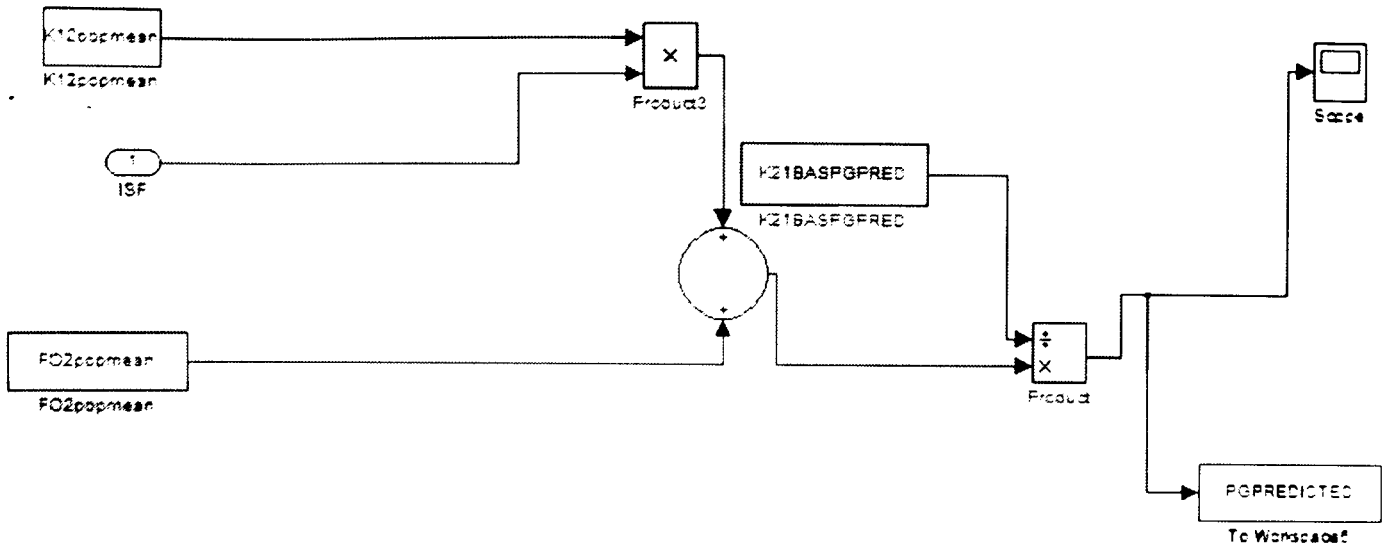

Figure B.9: Simulink schematic diagram showing the calibration procedure.

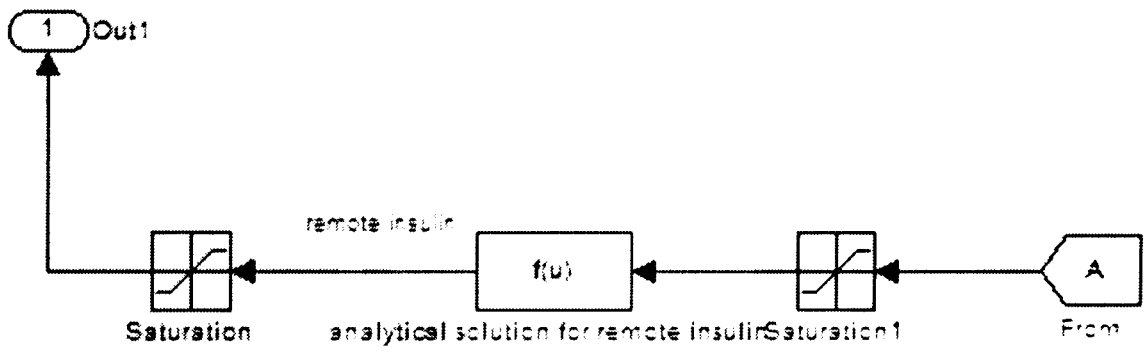

Figure B.10: Simulink schematic diagram showing saturation process of F_{01}

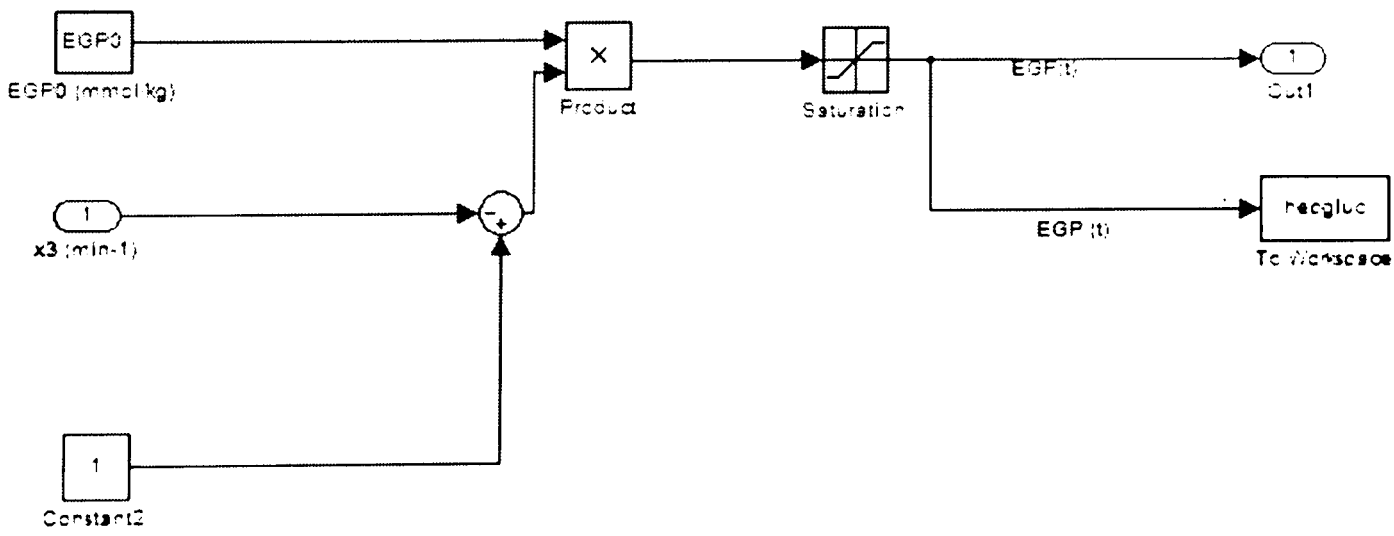

Figure B.11: Simulink schematic diagram showing hepatic glucose production.

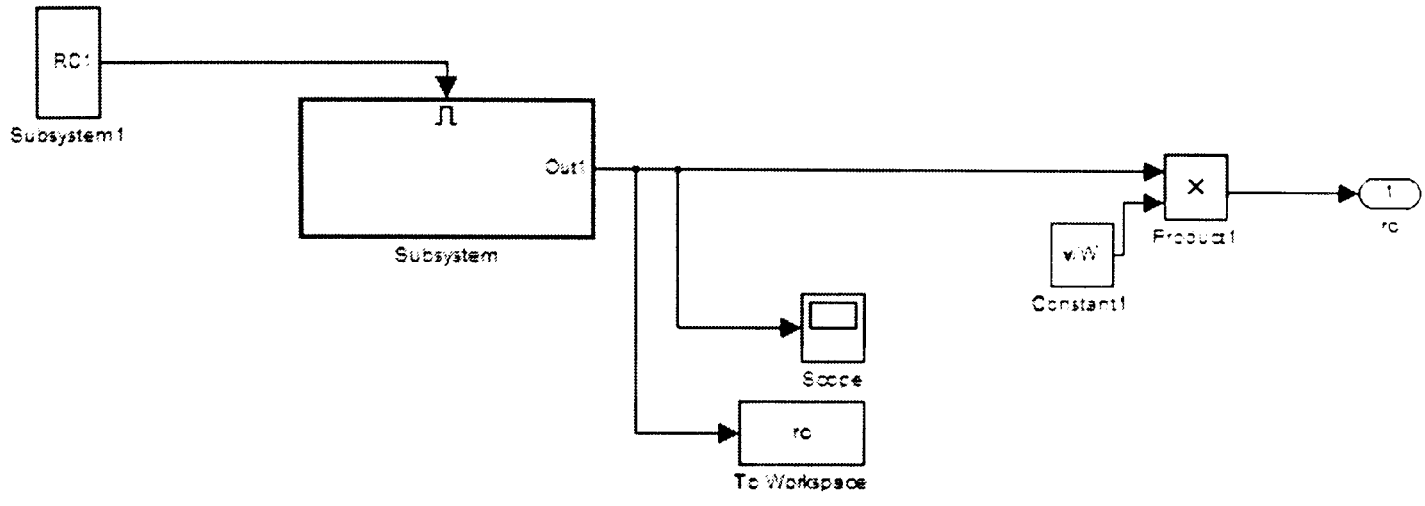

Figure B.12: Simulink schematic diagram showing the top level structure of the renal clearance model.

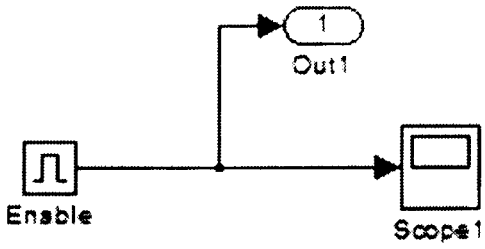

Figure B.13: Simulink schematic diagram showing the renal clearance threshold.

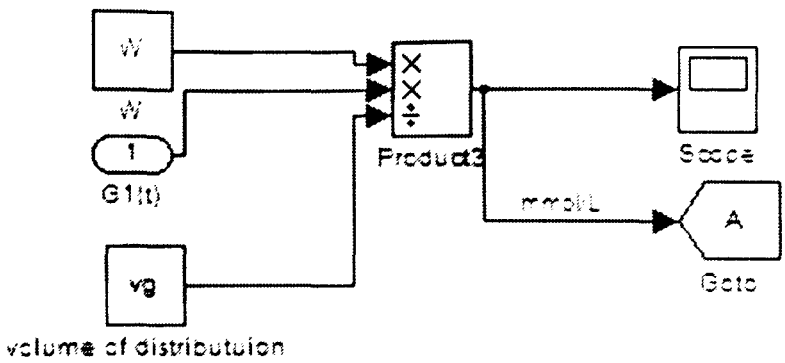

Figure B.14: Simulink schematic diagram showing conversion of amount to concentration.

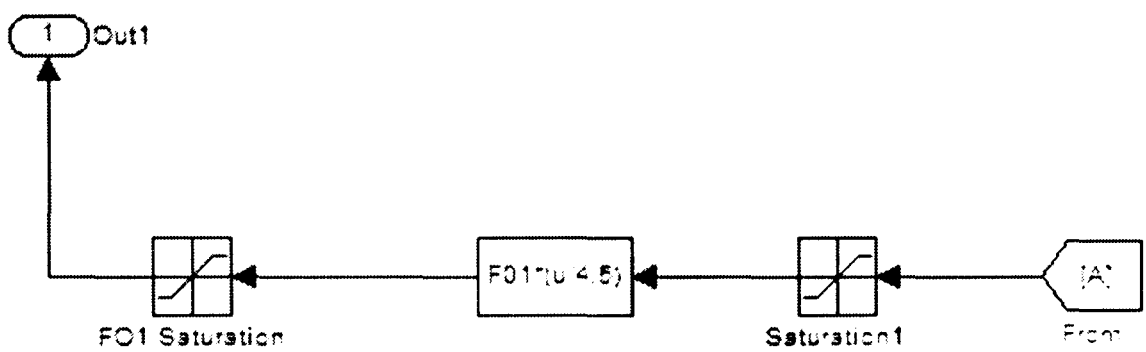

Figure B.15: Simulink schematic diagram showing F_{O1} saturation process.

C. Publications

This appendix contains, an article published in Artificial Intelligence in Medicine, Elsevier, and an article published in Diabetes Technology & Therapeutics.

SOME PARTS EXCLUDED UNDER INSTRUCTION FROM THE UNIVERSITY