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# Automatic Blood Glucose Control in Diabetes

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# Problem Description

Design a closed-loop control structure for automatic regulation of blood glucose concentration.

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# Abstract

In this thesis, a closed-loop control algorithm for regulating the blood glucose concentration in type 1 diabetic patients is developed. Two control criteria are imposed on the system, namely:

- Avoidance of hypoglycemia. (blood glucose concentrations should always be above $3\frac{mmol}{L}$)
- Reduction in the average blood glucose concentration compared to what is achieved with manual control. (average blood glucose concentrations should preferably be less than $7.0\frac{mmol}{L}$).

The developed control algorithm manages to fulfill both these control criteria. Hypoglycemia is avoided, and average blood glucose concentrations is reduced by 20% and 22% to a level of $7.0\frac{mmol}{L}$ and $6.9\frac{mmol}{L}$ in the two test subjects. However, further experiments should be carried out to test the robustness of the control algorithm, and a thorough investigation of safety issues for the user needs to performed.

As a basis for the implementation of closed-loop blood glucose control, data from three diabetic patients is used to identify the parameters of a proposed mathematical model of the human insulin-glucose regulatory system. The identification process reveals that there is large variations between individual patient's parameter values, and the difference in insulin sensitivity is found to be specially high, both between and within patients.

# Preface

This master thesis was carried out at Department of Engineering Cybernetics, Norwegian University of Science and Technology, under supervision of Professor Bjarne Foss. Chief Physician Kristian Fougner and PhD student Anders Fougner has functioned as co-advisors. I would like to thank all three for valuable input and guidance througout this semester.

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# 1 Introduction

## 1.1 Motivation

Insulin-depentent diabetes mellitus is a chronic metabolic disorder that is characterized by the disability of the body to maintain blood glucose levels within physiological ranges. Particularly, it is an autoimmune disease in which the beta cells of the pancreas are destroyed, resulting in the absence of insulin secretion. Long term complications from diabetes include heart disease, stroke, vascular disease, blindness, nerve damage, amputation and kidney disease. These long term complications are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society. The Diabetes Atlas claims that "Some 3.8 million men and women worldwide are expected to die from diabetes in the year 2007. This is more than 6% of total world mortality" [12].

In 1993 the Diabetes Control and Complications Trial published compelling evidence that "intensive therapy with the goal of maintaining blood glucose concentrations close to the normal range, effectively delays the onset and slows the progression of diabetic retinopathy[1], nephropathy[2], and neuropathy[3] in patients with insulin-dependent diabetes mellitus" [8]. The study proved a 50-70% reduction in the complications of diabetes with near-normalization of blood glucose concentrations. This result was confirmed by the U.K. Prospective Diabetes Study [15] in 1998, encouraging the search for ways to implement tighter blood glucose control in diabetes. One way of achieving this is to create a closed-loop artificial pancreas. Recent development in the areas of insulin pumps and continuous blood glucose monitors are introducing the possibility for a realization of such a diabetes management scheme in relatively near future.

This thesis will focus on the control algorithm, that is a necessary part of a closed-loop artificial pancreas. If implemented successfully, closed-loop blood glucose control could improve quality of life for people with type 1 diabetes mellitus and insulin-dependent type 2 diabetes mellitus. Ideally, one would be able to keep blood glucose levels close to those of a non-diabetic person, ensuring less long term medical complications, as well as avoiding hypoglycemic and hyperglycemic incidents.

[1] non-inflammatory damage to the retina of the eye
[2] damage to or disease of the kidney
[3] deranged function and structure of peripheral motor, sensory, and autonomic neurons

## 1.2 Aim of the Study

The aim of this study is to evaluate how well a closed loop control scheme could perform for type 1 diabetic patients. Research on long-term diabetic complications conclude that lowering the average blood glucose has a beneficial effect, and this will be the performance goal of the implemented control algorithm. However, reducing average blood glucose concentrations comes with the risk of increasing hypoglycemic incidents, so performance of the control algorithm will also be closely connected to its ability to avoid hypoglycemia.

A mathematical model of the human glucose homeostasis has been developed in an earlier project [32]. In this thesis, some of the model parameters will be identified by the use of measured data obtained during a study of a continuous blood glucose monitor [25]. The identified parameters will be used to analyze how constants related to insulin absorption and glucose sensitivity vary between patients and through time within each individual subject. The results of the parameter identification will give an indication of to what extent off-line and online adaptive model parameter estimaion is necessary in closed-loop blood glucose regulation.

A discussion of safety issues regarding the closed loop glucose control scheme is also included in this thesis, and much emphasis is put on the importance of robust and secure control.

# 2 Theory

## 2.1 Diabetes

**The Human insulin-glucose homeostasis** makes sure that the concentration of glucose in the blood stream stays at healthy levels at all times.

Two of the hormones secreted in the pancreas, namely insulin and glucagon, have important functions in the regulation of blood glucose concentration. Insulin increases transportation of glucose from the blood into insulin-sensitive cells. Glucagon mobilizes glucose from stores in the liver into the bloodstream. Figure 1 illustrates the role of the two hormones in human glucose regulation.

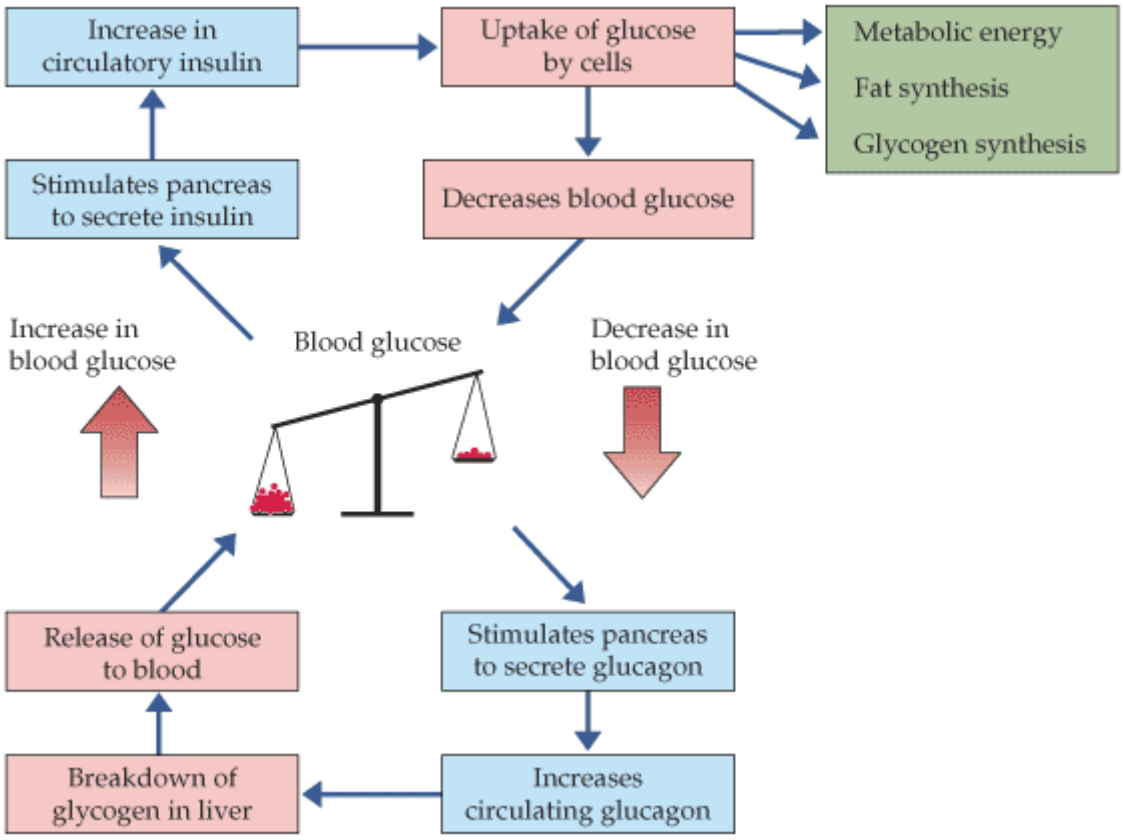



**Figure 1:** Insulin and glucose regulation model. The illustration is used with permission from [19]

In the absence of insulin, the entry of glucose into skeletal, cardiac, smooth muscle and other tissues is decreased, as shown in figure 2. Intestinal absorption of glucose is unaffected by insulin, as is glucose uptake by most of the brain and the red blood cells. When insulin is lacking for a longer period of time, the muscle and tissue cells will start using fat as energy source, instead of glucose from the blood stream. Oxidation of the resulting free fatty acids leads

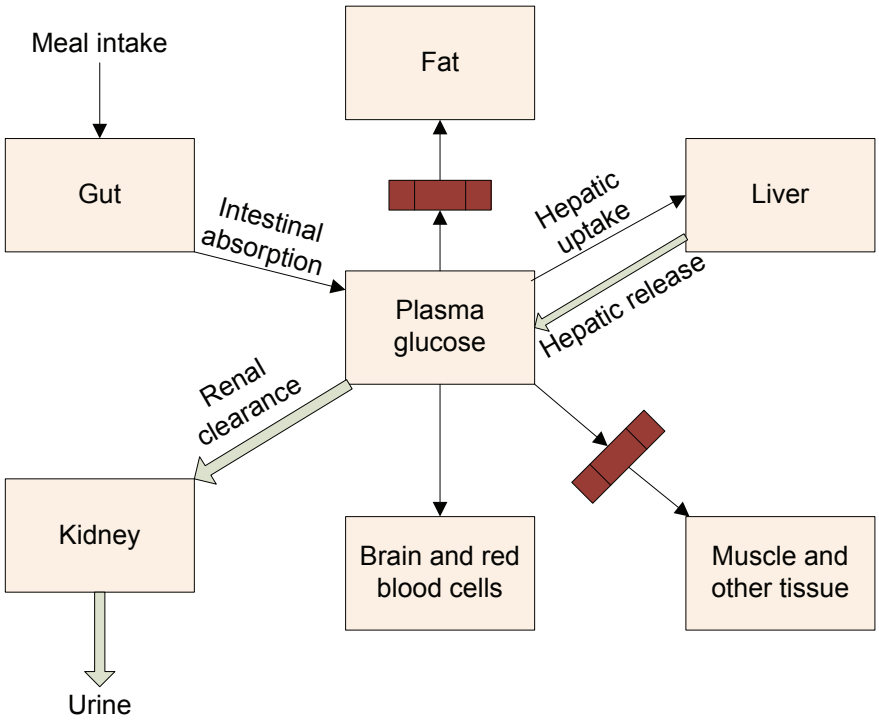



**Figure 2:** Plasma glucose homeostasis in insulin deficiency. The heavy arrows indicate reactions that are accentuated. The red rectangles across arrows indicate reactions that are blocked. Inspired from figure 19-9 in the textbook "Review of Medical Physiology" [49]

to production of ketone bodies, that upset the chemical balance of the blood. This life threatening condition is called diabetic ketoacidosis, and can only be treated by insulin injections.

**Diabetes** is recognized as a group of heterogeneous disorders with the common elements of high blood glucose concentration and glucose intolerance, due to insulin deficiency, impaired effectiveness of insulin action, or both [3]. The most common types of diabetes are diabetes mellitus type 1, sometimes referred to as insulin-dependent diabetes, and diabetes mellitus type 2, which does not necessarily require insulin injections. Type 2 constitutes about 85 to 95% of the approximately 246 million people worldwide with diabetes [12]. The number of type 1 diabetics is estimated to be $10 - 20$ million worldwide [2].

**Insulin** is a hormone needed to enable glucose to enter the cells in the body in order to provide energy. In response to high levels of glucose in the blood, the beta cells in the pancreas secrete insulin. Type 1 diabetes occurs when these beta cells are destroyed by the body's own immune system [50].

Untreated T1DM (Type 1 diabetes mellitus) will cause the fasting plasma glucose concentration to be permanently above 7 $\frac{mmol}{L}$, a state called **hyperglycemia** [50]. The blood glucose levels in diabetes can be a lot higher than the hyperglycemic limit, but concentrations of more than $10 - 20\frac{mmol}{L}$[4] will normally cause symptoms such as nausia, excessive thirst, excessive urination and fatigue. Concentrations above $30\frac{mmol}{L}$ usually require medical treatment and may be accompanied by diabetic ketoacidosis[5]. As mentioned in section 1, high average glucose concentration is believed to be an important factor in development of the long-term complications of diabetes.

**Hypoglycemia** is a complication that indirectly occurs from T1DM. This is an accute and life threatening condition, where the blood glucose concentration is too low (less than $2.0\frac{mmol}{L}$ [9]). This occurs in diabetic patients if the amount of injected insulin is too high compared to the the blood glucose concentration. Incidents of hypoglycemia is quite common for many diabetics, and is very dangerous if it is not rapidly treated with glucose intake. Since glucose is the predominant metabolic fuel for the brain, and the brain can not syntesize or store glucose, this fuel must be provided from the blood circulation. Thus, the prevention or correction of hypoglycemia is critical to survival [9].

**A normal blood glucose level** is set by the WHO to be a fasting plasma glucose concentration of less than $6.1\frac{mmol}{L}$ [50]. One should take special notice of the fact that blood glucose values below $2.0\frac{mmol}{L}$ is an accute and deadly condition, whereas concentrations up to $20\frac{mmol}{L}$ can be experienced without discomfort, at least for shorter periods of time. This results in a tight bound on the blood glucose concentration downwards, but some deviation can be tolerated for higher than normal blood glucose levels.

**The disturbance** of meal intake introduces large challenges to automatic blood glucose control. In normal functioning human glucose regulation, increased blood glucose concentration after a meal is stimulus for prompt release of insulin from the pancreas. The relatively large time constants involved in external blood glucose measurement and insulin injection[6], makes a response close to the normal-functioning one hard to achieve in automatic diabetic treatment. Complicating matters further is the fact that the composition of food affects intestinal absorption rates. Glucose from some foods is absorbed more rapidly than the same amount of glucose in other foods. Also, fats and proteins cause delays in absorption of glucose from carbohydrates eaten at the same time [13]. In addition to this, physical exercise affects the blood glucose regulation by

[4] the value differs for each individual

[5] A severe condition caused by lack of insulin. When the cells in the body cannot use glucose for fuel, the body breaks down fat for energy instead. A by-product of fat breakdown, is a chemical called ketones, which appear in the blood and urine, causing the blood to become more acidic than normal [21].

[6] See section 2.2

reducing the need for insulin during-, and for quite a long time after, work-out. This is partly because working muscle has the ability to absorb some glucose without the help of insulin. Other factors that are even harder to measure, such as stress, physical illness and many more, are involved in the blood glucose regulation process, making accurate models, prediction of parameters and satisfactory closed-loop control hard to achieve.

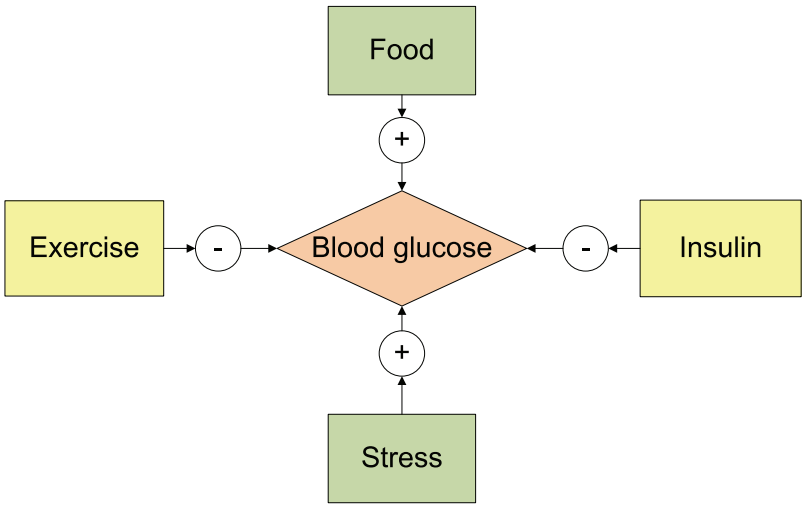



**Figure 3:** How blood glucose is affected by external factors.

**Today's glucose control schemes** for diabetic treatment involve non-continuous blood glucose measurements by taking blood samples[7]. This is done several times a day, usually by the patients themselves. Insulin is then injected through needles or insulin pumps. The size of the injections are based on the blood glucose measurements, knowledge about food intake and to a large part on the personal experience of the individual diabetic [5]. The metabolism of a non-diabetic person normally keeps blood glucose levels within the range of 4 to $8\frac{mmol}{L}$ at all times. For insulin-dependent diabetes therapy to capture the insulin-glucose dynamics of a healthy person, Takahashi [47] claims that "the designed algorithms and mathematical representations need to be complex and nonlinearly modeled in order to resemble the real hormone secretion". An attempt to identify such a mathematical representation will be made in section 3 of this thesis.

[7]Hereby referred to as "fingerprick measurement" because the glucose test is normally performed by piercing the skin (typically, on the finger tip) to draw blood, then placing the blood on a chemically active disposable strip which indicates the result either by changing the colour or an electrical characteristic (if an electric meter is used).

## 2.2 Equipment

Three components are essential for the implementation of a closed-loop artificial pancreas: an insulin injection device, a blood glucose sonsor and a control algorithm. This section gives a brief introduction to each of the three.

### 2.2.1 The Insulin Pump

Insulin pumps allow continuous subcutaneous infusion of insulin 24 hours a day at preset levels, and the ability to program bolus doses of insulin as needed at meal times. Subcutaneous injection is considered the safest way to infuse insulin to the body, because it is relatively simple and the risk of infection at the injection site is smaller than with an intravenous route [47]. Intravenous injection would, however, have been more optimal from a control technical point of view, because the time delays are smaller here. The study of [22] found the lag from subcutaneous injection to insulin concentrations in blood plasma to vary between $8 - 24$ minutes.

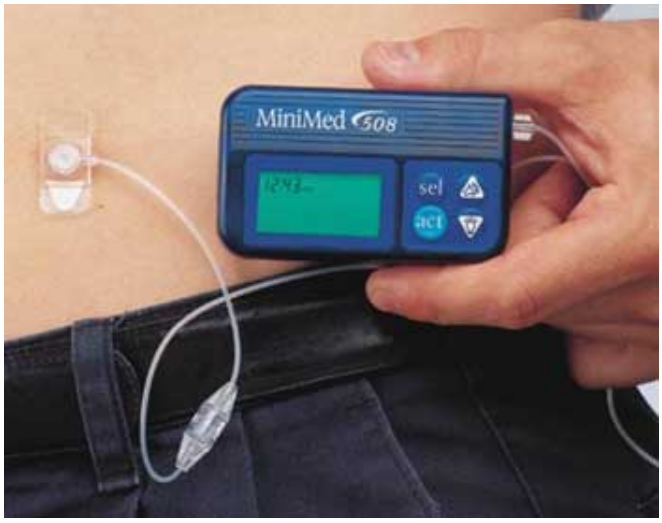



**Figure 4:** The MiniMed insulin pump from Medtronic. Insulin is injected through the syringe. A basal insulin infusion amount can be preprogrammed by the user, in addition to bolus doses before meals. The picture is taken from [**?** ].

There are several insulin pumps on the market today. Most of them are powered by batteries and consist of a small processing module with a display, a disposable insulin reservoir and an insulin syringe. In a closed-loop control scheme, the amount of insulin supplied from the pump would be set automatically, depending on blood glucose measurements and the control algorithm.

### 2.2.2 The Glucose Monitor

Subcutaneous glucose sensors are small electrode devices that can be inserted into the skin in the fatty tissues. When the sensors are placed correctly, a current proportional to the concentration of glucose in interstitial fluid can be detected [47]. An important advantage of subcutaneous glucose sensors over traditional fingerprick blood glucose measurement, is that monitoring can be performed continuously in a wearable fashion. Disadvantages of this measurement scheme include [7]:

- Continuous systems must be calibrated with a traditional blood glucose measurement, requiring a fingerprick blood measurement 2 to 4 times per day.
- Glucose levels in interstitial fluid, where the sensor is placed, lag temporally behind blood glucose values by a value of $5 - 15$ min.
- Depending on the glucose monitor model, the sensor has to be changed every 3 to 7 days.
- The accuracy of the measurements is variable and very much dependent on the calibration.
- Today's sensors are expensive.

R Hovorka states in [17](2005) that "The glucose monitor remains the main limiting factor in the development of a commercially viable closed-loop system, as presently available monitors fail to demonstrate satisfactory characteristics in terms of reliability and/or accuracy". Hopefully, this will be improved in the future, providing better and more reliable continuous blood glucose monitors than what is on the market today.

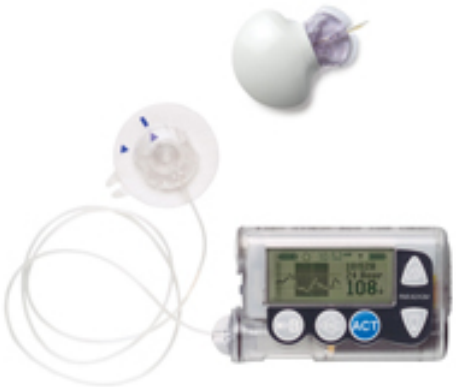


**Figure 5:** Combined continious glucose monitor and insulin pump from Medtronic. The sensor (located on the upper white device in the picture) is placed in the subcutaneous tissue, and measurement signals are transmitted wirelessly to the monitor.

### 2.2.3 The Control Algorithm

To be able to close the loop, and thus make the control scheme an automatic one, a set of decision rules for the insulin injection based on the measured glucose concentration is required. Several attempts have been made to design such a control algorithm using the theories of MPC, H-infinity, PID control and Fuzzy logic among others [8]. Some aspects of the human glucose regulation and todays available diabetes treatment equipment makes automatic control particularily challenging. These elements are identified as:

- **Time delay**. Since both insulin delivery and glucose measurement is done in the subcutaneous tissue, the controller would have to deal with time delays for the injected insulin to take effect and for the correct blood glucose value to be measured. Making things even more complicated, these time constants vary for each individual and also depends greatly on the blood glucose value and its rate of change.

- **Saturated input**. The system model is set to have two inputs: delivered insulin and meal intake. Insulin decreases blood glucose concentrations and meal intake increases them. But of the two inputs, only insulin injections are controlled by the algorithm, removing the posibility for agressive control action when blood glucose is too low. This could lead to dangerous incidents of hypoglycemia. Glucagon injection has been proposed as a solution to this problem [23], but has not yet been successfully implemented in human closed-loop glucose regulation.

- **Feed forward**. To reproduce the insulin secretion of the human glucose regulation, bolus injections of insulin would have to be administered before meals. This requires interference by the user, to let the controller know that a meal will be eaten some 10-20 minutes in advance. An assessment will have to be done on how detailed the meal information should be, considering control performance versus simplicity of use.

- **Safety issues**. Introducing automatic control to a process in the human body requires heavy focus on safety. A fatal outcome must be avoided by all means, and security alarms must be able to detect any critical state or event.

[8] See [46], [42], [43], [39] and [6].

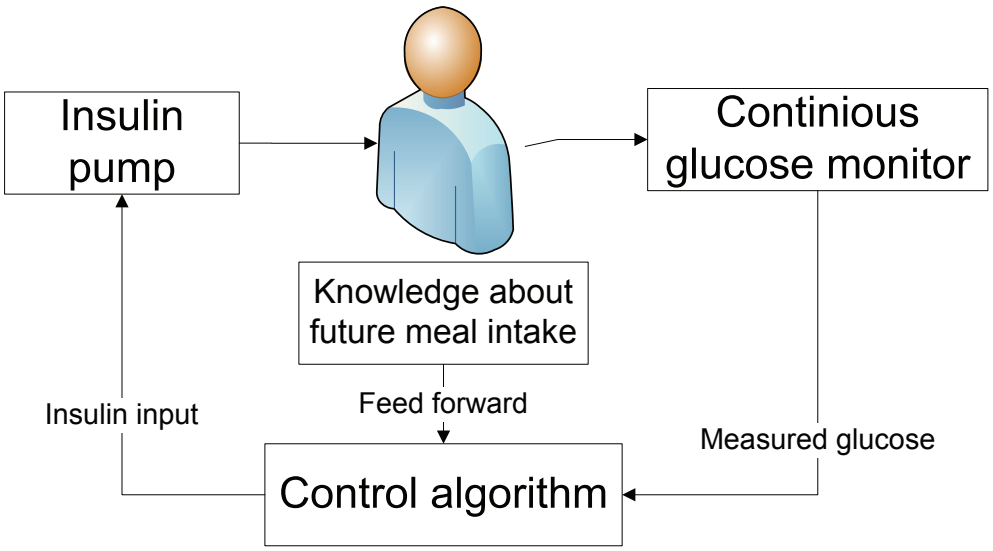



**Figure 6:** Illustration of the control algorithm.

## 2.3 The Mathematical Model

The model used in this thesis is an expanded version of the minimal model developed by Bergman [38]. For a detailed description of the exposition of the model, the reader is refered to [32]. The elements that added to the original minimal model equations are:

- The effect of meal intake $E_g$
  -Describes how different composition of meals affects blood glucose concentrations.
- Hepatic balance $E_b$
  -Describses how the liver both produces and utilizes glucose depending on the blood glucose and insulin levels.
- Renal clearance $E_r$
  -Describes how glucose is excreted through urine at high blood glucose levels.
- Subcutaneous compartment in insulin injection $S$
  -Describes the time delay from subcutaneous insulin to blood insulin concentration.
- Subcutaneous compartment in glucose measurement $Y$
  -Describes the time delay from blood glucose to measured subcutaneous glucose concentration.

The model equations are given as:

$$\frac{dI(t)}{dt} = \frac{1}{T_{xi}}[-I(t) + K_i \cdot S(t)] \tag{1}$$

$$\frac{dX(t)}{dt} = \frac{1}{T_m}[-X(t) + I(t)] \tag{2}$$

$$\frac{dS(t)}{dt} = \frac{1}{T_i}[-S(t) + U(t)] \tag{3}$$

$$\frac{dG(t)}{dt} = -\frac{G(t)}{T_{YG}} + \frac{Y(t)}{T_{GY}} + \frac{1}{V_G}[E_g(t) + E_b(t)] - E_r(t) \tag{4}$$

$$\frac{dY(t)}{dt} = K_{YG}[\frac{G(t)}{T_{YG}} - \frac{Y(t)}{T_{GY}}] - K_{is}X(t)Y(t) \tag{5}$$

As one can see from the equations above, the model includes an insulin kinetics subsystem (equation 1 - 3), featuring a third order, linear, compartmental model, and a glucose kinetics subsystem (equation 4 - 5), consisting of a second order, nonlinear, compartmental model. A simulink diagram representation of the model is given in figure 7.

The physical interpretation of the model parameters are given in table 1 and some are described mathematically in equation 6 - 12 below. For information about the numerical coefficients of the equations the reader is referred to sections 3.5 and 3.6.

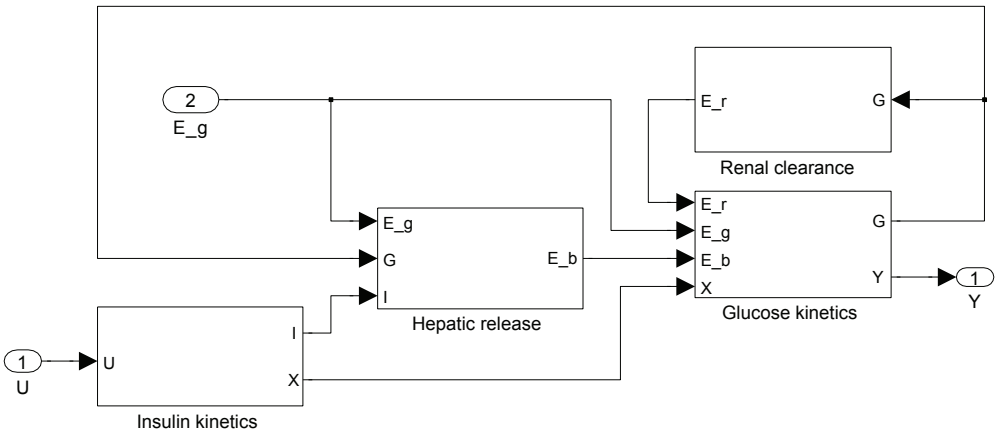



**Figure 7:** Model structure

$$E_b = Q_r - Q_c \tag{6}$$

$$Erel = \frac{14}{I} - 0.17 \tag{7}$$

$$Q_r = \begin{cases} 0.88 & if E_{rel} > 0.88 \\ E_{rel} & if 0.88 \geq E_{rel} \geq 0 \\ 0 & else \end{cases} \tag{8}$$

$$Q_g = \begin{cases} 0.061 \cdot G - 0.25 & if 0.061 \cdot G - 0.25 \geq 0.23 \\ 0.23 & else \end{cases} \tag{9}$$

$$Q_c = 0.25 \cdot E_g + Q_g \tag{10}$$

$$E_m = 0.117(0.87 + \tanh 0.0045(G - 175)) \tag{11}$$

$$E_r = \begin{cases} E_m & if E_m \geq 0 \\ 0 & else \end{cases} \tag{12}$$

**Table 1:** Model parameters

| Parameter | Unit | Description |
|---|---|---|
| $U(t)$ | $\frac{mU}{min}$ | Rate of insulin subutaneous infusion, input |
| $S(t)$ | $\frac{mU}{min}$ | Insulin flow from the subcutaneous to the plasma compartment |
| $I(t)$ | $\frac{mU}{mL}$ | Blood plasma insulin concentration |
| $X(t)$ | $\frac{mU}{mL}$ | Insulin-excitable tissue glucose activity |
| $G(t)$ | $\frac{mmol}{L}$ | Blood plasma glucose concentration |
| $Y(t)$ | $\frac{mmol}{L}$ | Subcutaneous glucose concentration, output |
| $T_i$ | $min$ | Time constant of insulin diffusion in the subcutaneous compartment |
| $T_m$ | $min$ | Time constant of insulin in the remote compartment |
| $T_{xi}$ | $min$ | Time constant of insulin in the plasma compartment |
| $K_i$ | $\frac{mL}{min}$ | Constant related to the plasma insulin distribution volume |
| $T_{GY}$ | $min$ | Time constant of glucose diffusion from interstitial to blood compartment |
| $T_{YG}$ | $min$ | Time constant of glucose diffusion from blood to interstitial compartment |
| $K_{is}$ | $\frac{\frac{mL}{mU}}{min}$ | Sensitivity coeffisient in the insulin-dependent glucose metabolism |
| $E_g(t)$ | $\frac{mmol}{min}$ | Rate of exogenous glucose input in blood (intestinal absorption) |
| $F_s$ | $-$ | Starch fraction in the total meal carbohydrate amount |
| $F_m$ | $-$ | Fraction of mixed meal in the starch absorption model |
| $R_i$ | $\frac{mmol}{min}$ | Rate of carbohydrate ingestion during meals |
| $A_g$ | $\frac{mmol}{min}$ | Rate of glucose apperance in blood from sugar |
| $A_s$ | $\frac{mmol}{min}$ | Rate of glucose apperance in blood from fast absorption starch |
| $A_m$ | $\frac{mmol}{min}$ | Rate of glucose apperance in blood from slow absorption starch |
| $E_b$ | $\frac{mmol}{min}$ | Rate of endogenous glucose input in blood from hepatic balance |
| $Q_r$ | $\frac{mmol}{min}$ | Rate of hepatic glucose release |
| $Q_c$ | $\frac{mmol}{min}$ | Rate of hepatic glucose uptake |
| $E_{rel}$ | $\frac{mmol}{min}$ | Auxiliary variable in the hepatic release description |
| $Q_g$ | $\frac{mmol}{min}$ | Auxiliary variable in the hepatic uptake description |
| $E_r$ | $\frac{mmol}{min}$ | Rate of renal glucose clearance |
| $E_m$ § | $\frac{mmol}{min}$ | Auxiliary variable in the renal clearance description |

# 3 System Identification

## 3.1 Collected Data

Throughout the work on this thesis, an attempt has been made to identify the parameters of the model described in section 2.3. To achieve this, data from 4 type 1 diabetics was collected during a time period of 4 days. The patients were wearing the Guardian REAL-Time, Medtronic Minimed glucose sensor, and insulin was injected through insulin pumps. Each of the patients kept a meal diary, where the time and content of every meal was written down. Information about physical activity, exercise and extraordinary events was also recorded. The meal diary sheets are included as attached files. For further details on the execution of the study, the reader is referred to the report of medical student Line Langeland [25].

Information about measured blood glucose and infused insulin was transferred to excel sheets by use of the Medtronic software "Carelink" [30]. The dietary accounting software "Mat på data 5.0" [29] was used to find the parameters connected to each specific meal; the rate of carbohydrate ingestion $R_i$, the fraction of slow acting starch $F_m$ and the fraction of fast acting starch $F_s$. This information was punched into an excel sheet together with information about measured blood glucose values and amount of injected insulin. The resulting sheets are given in the attached files Data_patient1.xls, Data_patient2.xls, Data_patient3.xls.

Due to the time comsuming task of identifying parameters for every meal and the poor quality of some of the measurement data, some of the collected data was not analysed to the full extent in this thesis. The three data sets that contained the longest continuous measurement time series and the most complete meal diaries, were chosen to be analyzed, and the patients whose data were used are hereby referred to as patient 1, 2 and 3. The included data of patient 3 is based on data collected throughout two days, -that is only half the time series of patient 1 and 2. The data obtained from patient 3 is also less complete than the other two data sets, because of a longer time period in which the glucose sensor did not function correctly. It was chosen to include patient 3 in the report, but because the data is insufficient, the main discussion of this thesis will focus on the results of patient 1 and 2.

The collected data was used to estimate the patient specific model parameters using the System Identification Toolbox in MATLAB. Some theory on the system identification method used is given in section 3.2, and the following sections will give a description of the specific model identification done in this thesis.

## 3.2 Gray box modeling

According to Ljung [26], the construction of a model from data involves three basic entities:

- A data set $Z^N$. In this experiment blood glucose measurements, records of insulin infusion and meal diaries from the three test subjects.
- A set of candidate models. In this experiment, the model described in section 2.3, with four of its parameters set as unknown.
- A rule by which candidate models can be assessed using the data. In this experiment the nonlinear least squares selection rule was implemented, by use of the System Identification Toolbox in MATLAB.

Model equations 1 - 5, section 2.3, are developed based on physical laws and experimental results through the theoretical work and experiments of several researchers. All though the model equations are set to be fixed in time, some of the model parameters are expected to vary within different people and at different times. Such model sets, where the equations have a physical interpretation and a set of adjustable parameters, are called gray box models.

The essence of gray box modeling is that the structure of a system is assumed known, but that some of the parameter values need to be identified. An illustration of the general idea can be seen in figure 8. The matlab code for the system identification used in this thesis is given in the attached $identify.m$-files.

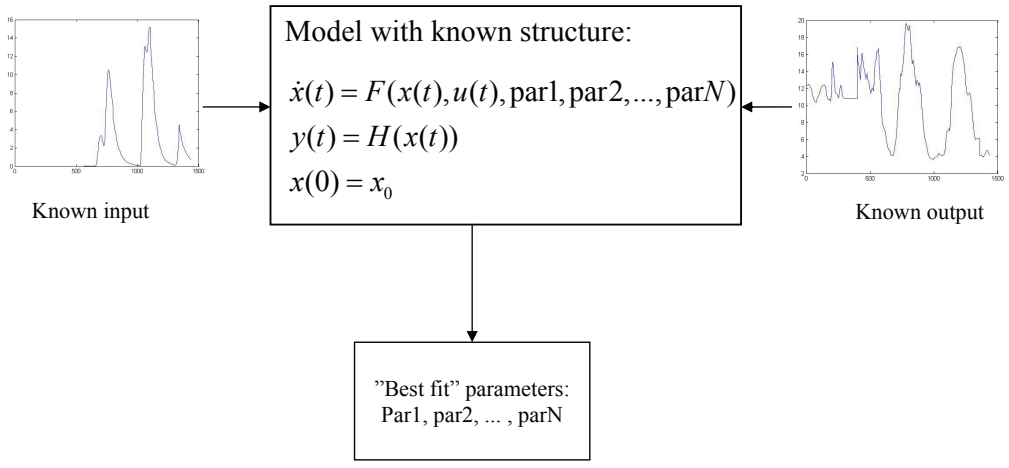



**Figure 8:** Gray box modeling. The known input and output data are used to find the optimal parameters of the model. In this thesis, this is done by minimizing the difference between measured values and model output, using a nonlinear least squares algorithm.

**Open-loop identification** An important factor for estimating model parameters is the informativeness of an experiment, meaning how much information about the system a data set contains. This issue will be addressed for the specific experiment of this thesis in section 3.5. Theorem 13.1 in [26] states that an input signal must be persistently exciting of the same order as the model, for an experiment to be informative enough. This theorem is valid for open-loop systems. When a satisfactory informativeness of the data set is established and a candidate model structure is found, it is time to start the actual parameter identification. A rule for estimating the parameters of the model with the goal of reproducing the measured data must be introduced. There are many different ways of organizing such a search and also different views of what one should search for. One view is set by Ljung [26] to be: A good model is one that produces small prediction errors when applied to the observed data. Identification methods based on this criteria are called prediction-error identification methods. A special case of these methods, namely the least squares method shown in equation 13, will be used in this thesis.

$$\theta_N^{LS} = argmin \frac{1}{N} \sum_{t=1}^{N} \frac{1}{2} [Y(t) - \phi(t)\theta]^2 \tag{13}$$

The identified parameter set $\theta^{LS}$ is the one that minimizes the prediction error $\epsilon = Y(t) - \phi(t)\theta$. This adaptive estimation algorithm is chosen because it is easy to understand and implement, it is robust and has good convergence properties [20]. Performance is evaluated by comparing the resulting identified model to the measured data.

Open loop parameter identification using the method above is done for three of the model parameters in section 3.5.

**Persistently exciting signals** A signal being persistently exciting with respect to a model set means that the signal contains sufficiently many distinct frequencies to uniquely identify any two different models in the set. More specifically, an input signal $u(t)$ is PE of order n if its power specter $\phi_u(\omega)$ is different from zero in at least n points. The PE properties for this specific experiment will be illustrated in figure 12a.

**Closed loop identification** Some fallacies are associated with closed loop identification, which is done for one of the model parameters in section 3.6 of this thesis. The basic problem of identification with closed loop data is that it typically contains less information about the open loop system, since an important purpose of feedback is to make the closed loop system less sensitive to changes in the open loop system.

One challenge is that the closed loop experiment may be non-informative even if the input $u$ in itself is persistently exciting. For closed loop systems, we instead

introduce the criteria from theorem 13.2 [26]: The closed loop experiment is informative if and only if the reference $r$ is persistently exciting.

A directly applied prediction error method will work well for closed loop systems if the true system can be described within the chosen model structure. Therefore, the identified model will give consistent estimates for closed loop data only if both the noise and dynamics model describes the true system well. The only modeled noise in the experiment of this thesis is meal intake. If any other noise or disturbances were to be present, convergence to the true model set is not guaranteed.

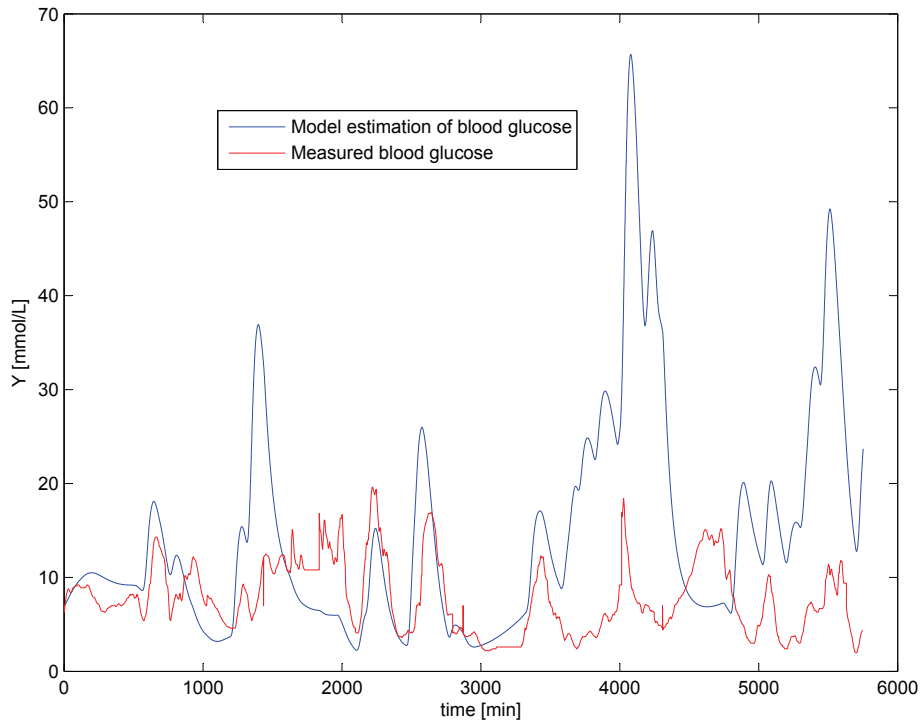
**Model validation** The testing of whether a given model is appropriate is called model validation. The quality of the estimated model in this thesis is measured by a mean-square error criterion, by comparing the estimated output to the measured one. An analysis of whether the model performs satisfactory for its intended purpose of regulator design will be carried out in section 6.1.

## 3.3 Performance of the original model

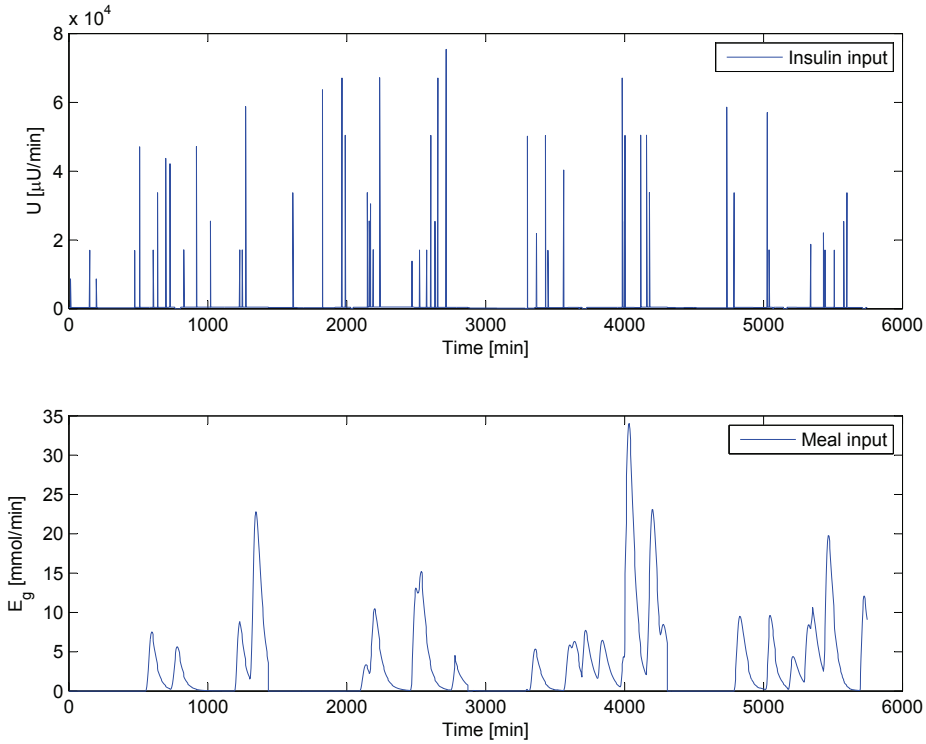
Before starting the parameter estimation process, let's take a closer look at the performance of the model with its original parameters. The real input values of patient 1 were set as input to the theoretical model, and a comparison between the model output and the measured values of the patient was done. This gives an indication of how realistic the model structure is, and the result is given in figure 9.

As one can see from the figure, the performance of the original model is not satisfactory. Several aspects contribute to this, and some of the most significant error factors are:

- **Time of meal.** There is reason to believe that some of the patients have used approximate values for the time of some of the meals written in the meal diary. This would result in the model graph being moved to the right or left compared to the measured data.
- **Insulin sensitivity.** The body's ability to respond to insulin in the blood plasma changes over time. This means that the same amount of insulin will give a lesser or larger effect depending on the time it is injected. A constant set of model parameters will not be able to describe this change in insulin sensitivity, and insulin response will sometimes be under- or overestimated.
- **Meal model accuracy.** The calculated amount of carbohydrates in each meal is based on the patient eating "standard sized" meals. Obviously, a piece of bread is not necessary exactly $30g$ as the "Mat På Data" - software claims. Wrong calculations of meal sizes and carbohydrate content will introduce errors in the estimated meal contribution on blood glucose.




9a: Measured blood glucose and model output.




9b: Meal and insulin input.

**Figure 9:** Comparison between the measured blood glucose and the model output with input from one specific patient and a fixed model parameter set obtained from [32].

- **Measurement error.** The continuous glucose sensors on the market today are not perfect, and all the patients in the test group had time intervals where the measurements failed, or were far out of range when calibrated. Earlier studies have shown [4] that the sensor is functioning best when blood glucose values are in the normal and hyperglycemic range, giving larger deviations when hypoglycemia occurs.
- **Active glucose/insulin at initial time.** Due to time delays in the intestinal meal absorption and subcutaneous insulin absorption processes, insulin and glucose that are not accounted for will be present at initial time. It is therefor impossible to get a good parameter prediction at the beginning of the model identification.

Most notisable when looking at figure 9 is the effect of increased insulin sensivity after exercise. The patient whose data is shown in the figure went cross country skiing for two hours after approximately 2560 minutes of the experiment period had passed. One sees that the following days (from approximately $t = 3000$ min and throughout the experiment period), less insulin is needed to keep blood glucose values in the normal range, even after intake of large meals. The theoretical model, however, does not take this increased insulin sensitivity into consideration, and the model output becomes as high as $65\frac{mmol}{L}$ (at $t = 4100$ min), and has an average value of $14.7\frac{mmol}{L}$ more than the real output throughout the post-exercise time period. To be able to deal with this element, the model parameters that describe insulin sensitivity would need to be estimated and updated in real time.

The online identification of insulin sensitivity will be handled in section 3.6, but no specific measure will be taken to eliminate the other error factors described above. This means that the identified model will contain uncertainties, and it is not expected to reproduce the exact course of real life diabetic blood glucose concentrations.

## 3.4 Model identification

To successfully use the model in feedback control, some of the model parameters need to be identified to achieve personalization to each single patient's requirements, and to follow changes in the patient's physiological responses over time. In normal glucose regulation, two biological variables of interest are easily accessible; namely blood glucose concentrations $G(t)$ and plasma insulin concentrations $I(t)$. When closing the loop outside the body, evaluation of insulin concentration requires lengthy laboratory analysis, which makes it unsuitable for feedback control. Therefore, control action must be performed on the basis of measured glucose values $Y(t)$ only.

Another limitation is the time required for online model identification, which increases with the number of parameters to be identified. This number should therefore be as low as possible, while still keeping the personalization of the model at a satisfactory level. The following two sections will explain the choices

**Table 2:** Parameters to be estimated

| Parameter | Description |
|---|---|
| $T_{xi}$ | Time constant of insulin diffusion in the plasma compartment |
| $T_m$ | Time constant of insulin diffusion in the remote compartment |
| $K_i$ | Constant related to the plasma insulin distribution volume |
| $K_{is}$ | Sensitivity coeffisient in the insulin-dependent glucose metabolism |

that have been made in the process towards making the model an easily identifiable one. Table 2 lists the four parameters that will be estimated for each patient in this thesis. Section 3.5 describes the off-line identification of the three parameters connected to the absorption of insulin in interstitial tissue, and section 3.6 gives a description of the online estimation of the insulin sensitivity parameter $K_{is}$. An analysis of the obtained parameters is done in section 3.7 and two criteria for model validation is given in section 3.8.

## 3.5 Insulin submodel - open loop identification

The insulin submodel consists of the subcutaneous, blood plasma and remote compartments. It is modeled to describe the delay of the insulin concentration from it is injected subcutaneously $S(t)$ until it reaches the blood $I(t)$, and after that is transported out to the cells and peripheral tissue $X(t)$. The time constant related to insulin diffusion in the subcutaneous compartment $T_i$ is obtained from litterature, and depends on the insulin type.

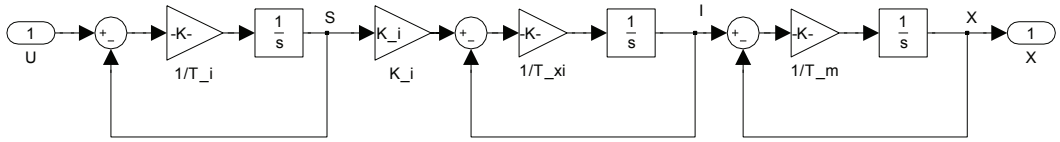



**Figure 10:** Insulin kinetics

The parameters that will be estimated here are the time constants $T_{xi}$ and $T_m$, related to insulin diffusion in the plasma and remote compartment, respectively, and the constant $K_i$, related to the plasma insulin distribution volume. The estimation is done in an off-line manner before closed-loop control is introduced. To be able to uniquely identify these parameters, the input has to be a percistently exciting signal. This means that the signal going into the system has to envoke a signal on the output that is rich enough for the parameter estimates to converge to their true values [26]. For each patient, a relatively short data time series right after a meal intake and its corresponding insulin boluses was used to identify the insulin submodel parameters. The time series that was used for estimation of the parameters in patient 1 is shown in figure 11, and the frequency spectra of the input signals are shown in figure 12.

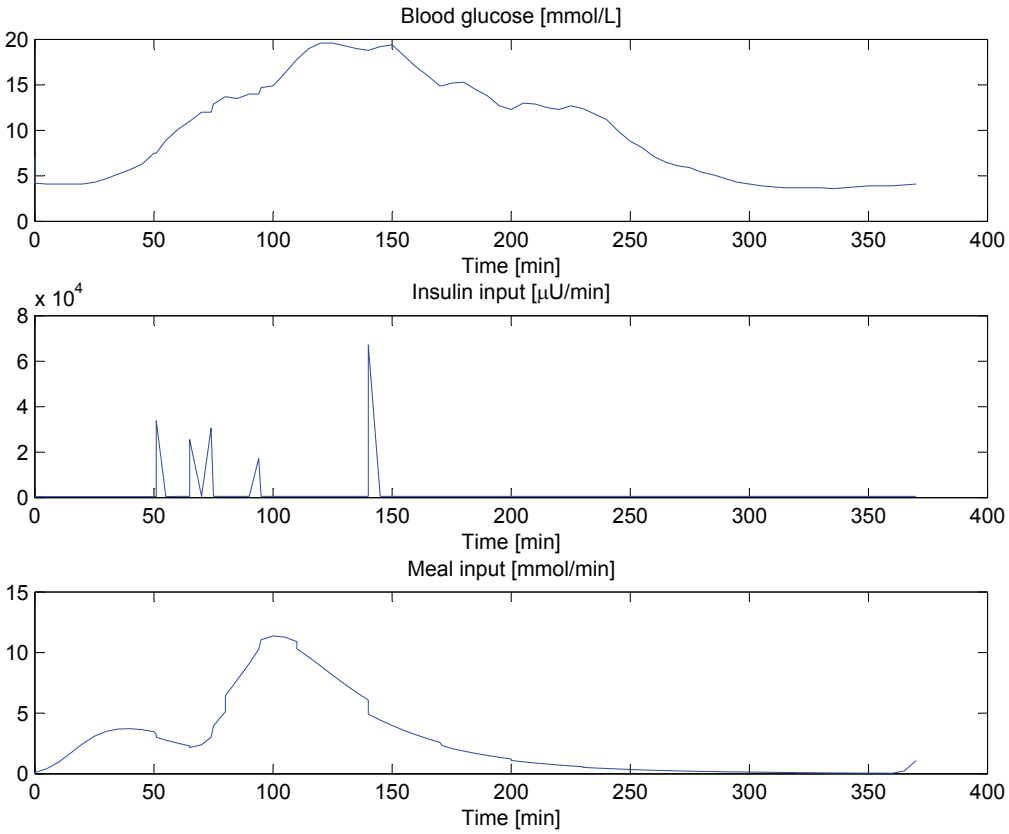
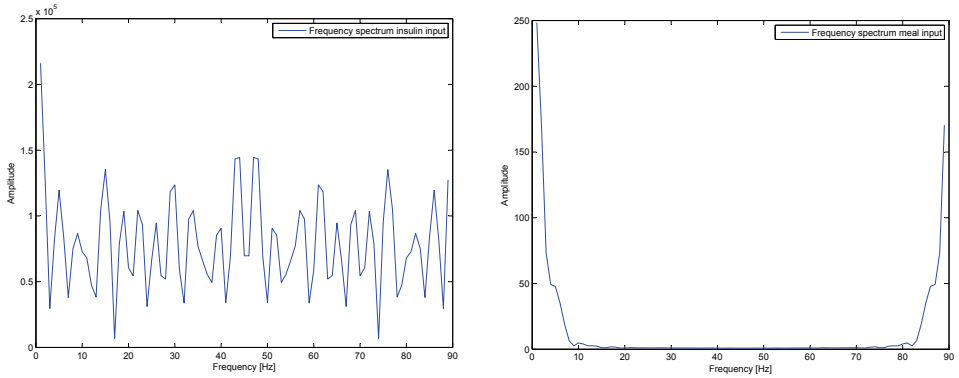



**Figure 11:** Inputs and output for the insulin submodel parameter estimation shown for patient 1.




12a: Insulin input.

12b: Meal input.

**Figure 12:** Frequency specter for the insulin submodel parameter identification input data series of patient 1.

**Table 3:** Estimated insulin submodel parameter values.

| Parameter | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| $T_{xi}[min]$ | 108.6 | 115.8 | 106.0 |
| $T_m[min]$ | 147.0 | 133.9 | 149.4 |
| $K_i[\frac{mL}{min}]$ | 0.0202 | 0.0233 | 0.3997 |

Figure 12a confirms that the input signal used in identifying the insulin submodel parameters is persistently exciting, since the power specter is non-zero for all frequencies. This is often the case for real life input signals, as they tend to contain several frequency components.

During the off-line insulin submodel parameter identification of this section, the parameter $K_{is}$, which is to be estimated online during blood glucose control, is set to a constant value. Its value is chosen as the average result of estimated $K_{is}$ from the experiments of [33].

### 3.5.1 Off-line estimation results

The estimated insulin parameters for each of the patients are given in table 3. The result of the model identification for the data set time series used is illustrated in figure 13. A model fit of 65.77% is achieved. Matlab code for the insulin submodel parameter identification is given in the attached file $identify\_insulin\_parameters.m$.

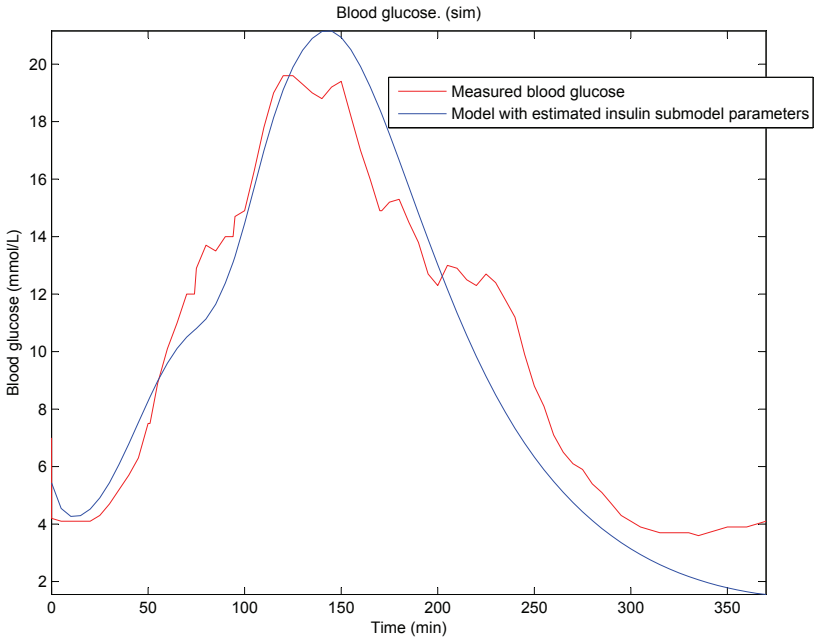



**Figure 13:** Comparison between the measured blood glucose and the model output with estimated insulin parameters for patient 1 during the time series used for the off-line identification.

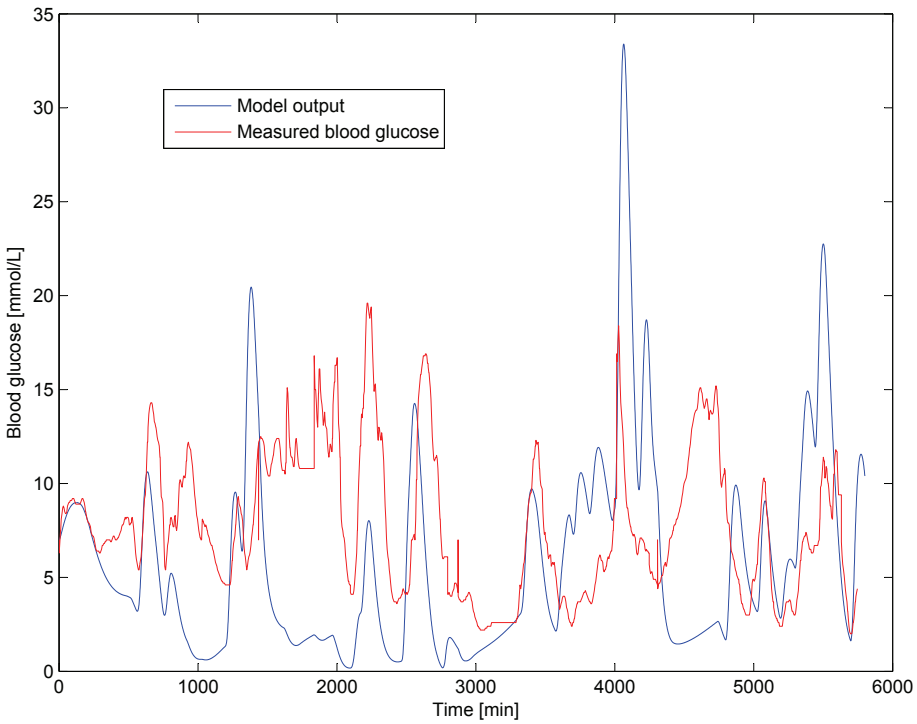



**Figure 14:** Comparison between the measured blood glucose and the model output with estimated insulin parameters during the total experiment period for patient 1.

Figure 14 compares measured data with the model output for the whole experiment period of patient 1. It illustrates how the time constants are now more accurate than they were when insulin submodel parameters were set to non-personalized values, see figure 9. However, the insulin sensitivity parameter is still not adequately identified, as can be observed from the mismatch in estimated and measured amplitude of blood glucose concentrations.

For the rest of the work done in this thesis, the insulin submodel parameters are set to the estimated values found in this section for each individual patient.

## 3.6 Glucose submodel - closed loop identification

The glucose submodel consists of the blood plasma and subcutaneous compartment. This is because the glucose monitor measures glucose concentrations in the subcutaneous compartment $Y(t)$, even though this value lags some time behind the actual blood glucose concentration $G(t)$. Meal glucose contribution $E_g(t)$ is set as an input to the system, even though it, for the purpose of this analysis, is to be considered as a measured disturbance.

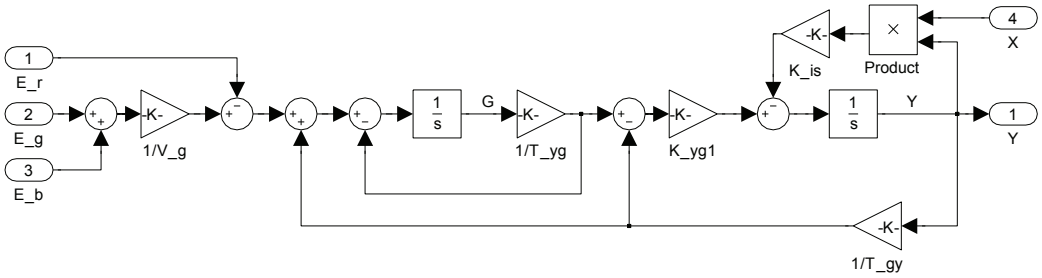



**Figure 15:** Glucose kinetics

**Table 4:** Preset parameter values

| Parameter | Value | Description |
|---|---|---|
| $T_i[min]$ | 9.12 | Time constant of insulin diffusion in the subcutaneous compartment |
| $V_G[L]$ | 9.91 | Distribution volume of the blood glucose compartment |
| $K_{YG}[-]$ | 0.95 | Rate between the distribution volumes of interstitial and blood compartment |
| $T_{YG}[min]$ | 11.64 | Time constant of glucose diffusion from blood to interstitial compartment |
| $T_{GY}[min]$ | 11.64 | Time constant of glucose diffusion from interstitial to blood compartment |

The values of $V_G$, $K_{YG}$, $T_{YG}$ and $T_{GY}$ are obtained from litterature, and set to the values obtained by Fabietti et al in[33]. The parameter values are given in table 4. The numerical coefficients of the renal clearance and hepatic balance equations are taken from [33], where they have been chosen as to reproduce the biological effects that have been shown in several other studies [35], [10], [36], [28], [40].

The value of $K_{is}$, which is related to insulin sensitivity of the individual subject, is chosen to be estimated online. $K_{is}$ is a coefficient that describes how much insulin that is needed to reduce the blood glucose concentration by a certain amount, see equation 5, section 2.3. This parameter varies a lot from individual to individual, and also changes within the individual through time, due to changes in exercise level, stress and other factors. For this reason, $K_{is}$ needs to be identified online during automatic blood glucose control.

**Table 5:** Estimated insulin sensivity parameter $K_{is} \cdot 10^{-4}$.

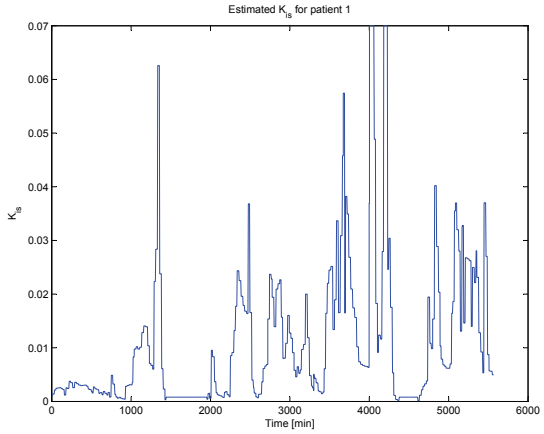
| Subject | Day 1 | Day 2 | Day 3 | Day 4 | Average | Whole period |
|---|---|---|---|---|---|---|
| Patient 1 | 14.0 | 5.3 | 41.0 | 25.0 | 21.0 | 22 |
| Patient 2 | 1.2 | 0.4 | 7.8 | 4.1 | 3.37 | 0.62 |
| Patient 3 | 1.7 | 0.6 | – | – | 1.15 | 7.8 |

### 3.6.1 Day by day estimates

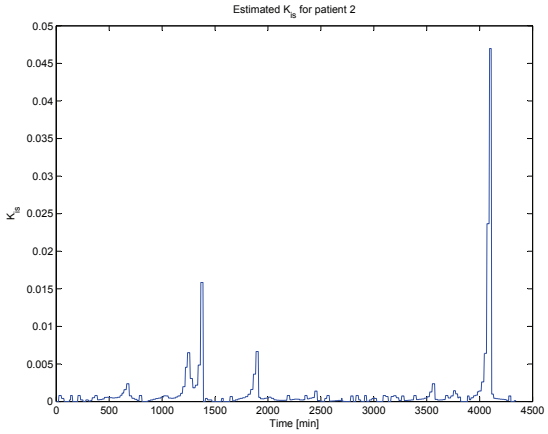
To illustrate why online estimates of $K_{is}$ is a necessity, parameter estimation of the insulin sensitivity coeffisient was done seperately for the four experiment days in all the patients. The parameter values of the insulin submodel were set to the ones that were found in the offline estimation in section 3.5 for each individual. Table 5 shows the result of the day by day parameter estimation for each patient. The identified values of $K_{is}$ demonstrates large variations in insulin sensitivity, both within and between subjects. Patient 1 has a insulin sensitivity value that is a lot higher than patient 2 and 3 in general. Also, the parameter of patient 1 varies a lot over time, while patient 2 and 3 both have a more narrow range of insulin sensitivity.

### 3.6.2 Online estimation results

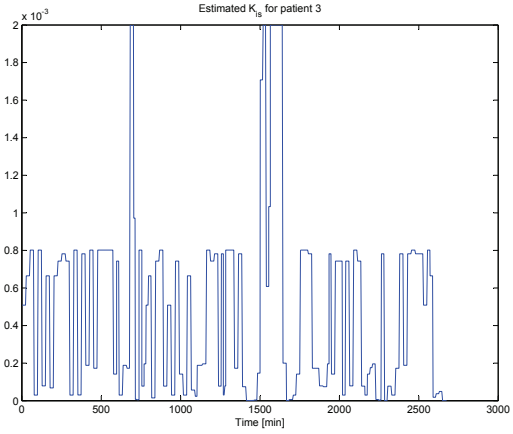
By looking at figure 9, where measured and model estimated blood glucose is compared, one gets an impression of how fast and to what extent insulin sensitivity is able to change. The information in figure 9 suggests that the insulin sensitivity parameter needs to be identified on the basis of data reaching no longer than 4 hours back in time, since measurements going further back than this contain little information about the present sensitivity towards insulin. However, it is also important that the estimation interval is above a certain length, due to the possibility of measurement errors and other uncertainties in the model. For this reason, the online parameter estimation was performed by considering data from the past 3.5 hours and updated every 25 minutes. MATLAB code for the identification is given in the attached file $identify\_online.m$. For an illustration of how $K_{is}$ is found to change through time in each subject, the time course of the identified parameter for all three patients is given in figure 16. One sees that the insulin sensitivity of patient 1 is identified to be higher than normal after approximately 3400 min, as was suggested to happen in section 3.3 as a reaction to the patient's exercise. The reader should be aware of the different resolutions on the y-axes, and thereby see that patient 1 has the highest insulin sensitivity, followed by patient 2. Patient 3 is found to have the lowest insulin sensitivity, and also the least varying one. The peak value right after $t = 4000$ min for patient 2 is due to what seems to be an erroneous entry in the meal diary, see appendix Appendix A.1. The collected data sets are used in their original form through all of this thesis, but it should be noted that some of the results, like this one identified high insulin sensitivity for patient 2, suggests that some of the obtained data is incorrect or inaccurate.




16a: Online estimated $K_{is}$ for patient 1.




16b: Online estimated $K_{is}$ for patient 2.




16c: Online estimated $K_{is}$ for patient 3.

**Figure 16:** The time course of the estimated $K_{is}$ with online parameter estimation using data from the past 3.5 hours.

**Table 6:** Some properties of the identified $K_{is}$. Values are given in $K_{is} \cdot 10^{-4}$.

| Subject | Average | Maximum | Minimum | Range |
|---|---|---|---|---|
| Patient 1 | 111 | 1105 | 1.4 | 1104 |
| Patient 2 | 40 | 470 | 1.0 | 469 |
| Patient 3 | 12 | 385 | 0.1 | 385 |

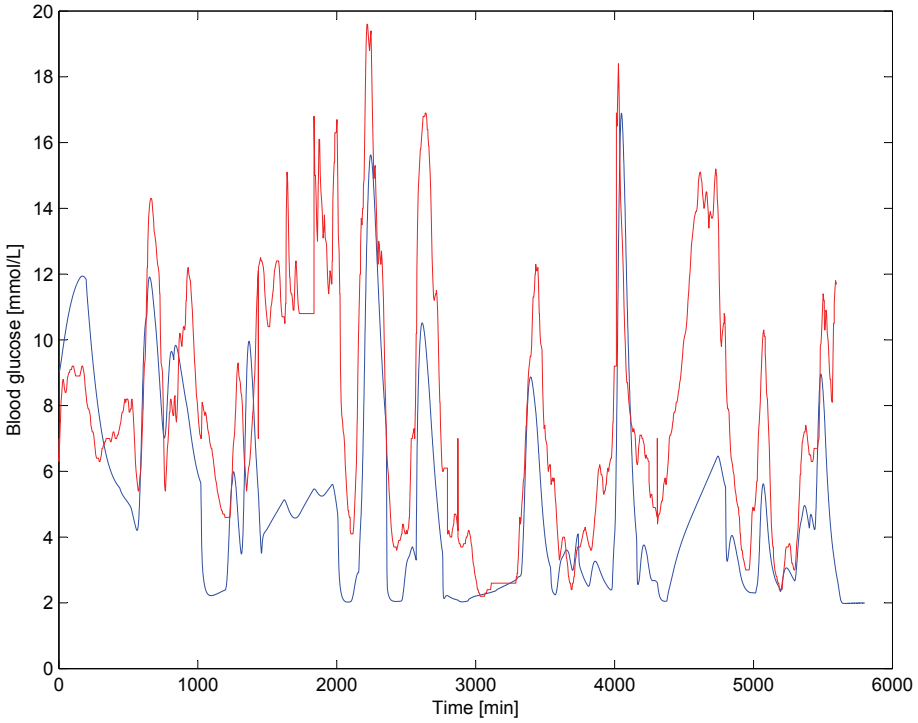



**Figure 17:** Measured value and model output blood glucose concentration for patient 1 with online estimated $K_{is}$. The red line represents measured blood glucose, and the blue line represents the model output.

Some properties of the identified parameter $K_{is}$ for the three patients are given in table 6.

When applying the online estimated $K_{is}$ for patient 1 to the model, the curve fit shown in figure 17 was achieved. This is the best model identification achieved in the work of this thesis, all though it is clear by looking at the figure that the blood glucose concentration is not well estimated at all times. An important observation, which is to be used in the model validation process in section 3.8, is the fact that the model at no time is found to overestimate the blood glucose concentration. Issues regarding performance of this identified model when it comes to its ability to be used in closed-loop glucose control are discussed in section 6.1.

## 3.7 Analysis of the Identified Parameters

The identified parameters that will be discussed in this section are listed in table 3 and table 7 in the previous sections 3.5.1 and 3.6.2.

### 3.7.1 Parameter variability between patients

In this study, it will be difficult to draw any conclusions on parameter variability between subjects, because only three subjects are analysed. What will be done, is to provide a brief overview and some comments on the parameter variation between patients and how this will affect closed-loop control.

For the insulin submodel parameter set, there is a quite significant difference between each subjects parameters. Patient 2 has a value of $T_{xi}$ that is 5.9% higher than patient 1, but $T_m$ is 8.9% lower for patient 2 than for patient 1. This means that the overall time delay from subcutaneous injection until insulin reaches the remote compartment is approxematly the same for the two subjects. But patient 1 will have a faster uptake from subcutaneous tissue in to the blood plasma, and an equivalently slower transportation of insulin to the cells and peripheral tissue, according to the identified parameters. The value of $K_i$ is 15.3% higher for patient 2 than for patient 1. Patient 1 and 3 have quite similar parameter values for $T_{xi}$ and $T_m$, but the plasma insulin distribution volume parameter $K_i$ is identified to be as much as 20 times larger for patient 3 than for the other two patients. $K_i$ is related to the plasma insulin distribution volume, and a high value here must be seen in relation to the low estimate of insulin sensitivity for patient 3, as these parameters will have a balancing effect on each other.

The difference in average insulin sensitivity between the subjects in this study is high, that is for example almost three times higher in patient 1 than in patient 2 and as much 9.25 times higher in patient 1 than in patient 3. The low estimated insulin sensitivity of patient 3 could to some extent be explained by the high estimate of the same patient's insulin distribution volume parameter. But even when this is adjusted for, insulin sensitivity of patient 3 is still found to be lower than for patient 1. The range of the parameter value is also a lot larger for patient 1 than for patient 2 and 3. This means that change in insulin sensitivity will have a larger impact in blood glucose control for patient 1 than the other two patients.

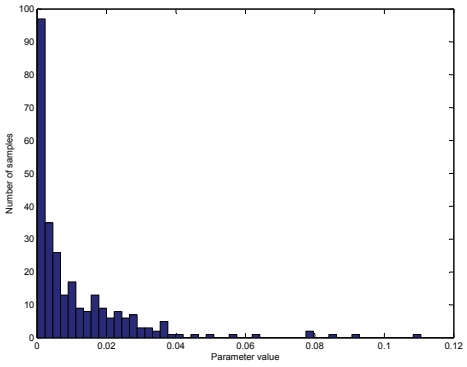
One conclusion can be made based on the otherwise insufficient analysis of this section: Parameter values need to be identified and personalized for each individual diabetic patient. With such large variation between each patient's parameters as is shown in the experiments of this thesis, it is obvious that a general model cannot produce satisfactory results for different individuals.

**Table 7:** Statistical properties of the identified $K_{is}$. Numbers are given as $K_{is} \cdot 10^{-3}$

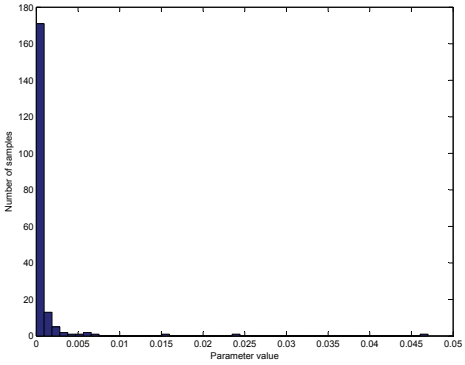
| Parameter | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| $K_{is}$ | $111 \pm 154$ | $40 \pm 71$ | $12 \pm 45$ |

### 3.7.2 Parameter variability within each patient

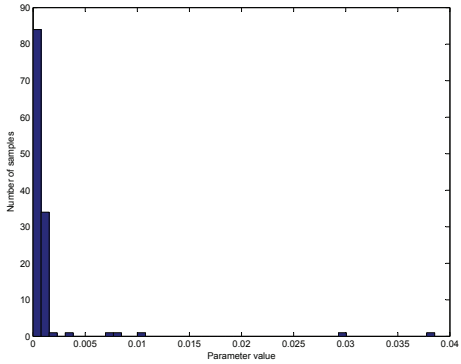
The parameters of the insulin submodel were estimated off-line, so any changes in these parameters in time are not reflected in the model identification process of this thesis. Thus, no analysis of the insulin submodel parameters is done in this section. The only time-varying identified parameter is the insulin sensitivity coefficient $K_{is}$. Table 7 lists some statistical properties of the identified $K_{is}$ for each patient. In all the three cases, the standard deviation of the identified parameter has a higher value than the estimate. This suggests that parameter variability is high.




18a: Histogram of estimated values of $K_{is}$ for patient 1.




18b: Histogram of estimated values of $K_{is}$ for patient 2.




18c: Histogram of estimated values of $K_{is}$ for patient 3.

**Figure 18:** Histogram showing the distribution of estimated $K_{is}$ for each patient.

By looking at figure 18, which illustrates the probability distribution of $K_{is}$, it is evident that the parameter variability is highest for patient 1, where $K_{is}$ is seen to obtain the largest variety of parameter values compared to the other two patients. The histograms are divided into bins of 50 from the lowest to the highest identified parameter of each patient. It should be noted that patient 3 only had data from 2 days available, and therefore have half as many identified insulin sensitivity parameters than patient 1 and 2. With this in mind, one can see that patient 2 and 3 have quite similar parameter distributions, with almost all the identified parameters at low values, and some single incidents of higher estimated $K_{is}$.

## 3.8 Model validation

In addition to the goal of minimizing the difference between measured data and estimated model output, two criteria are identified as crucial for the model to be able to be used as a basis for control decisions in automatic feedback control.

- Model validation criterion 1: The estimated model should never fail to predict hypoglycemia or close to hypoglycemic blood glucose concentrations.
- Model validation criterion 2: Time delays should be restricted to those already imposed by the natural dynamics of the system.

Section 6.1 contains a discussion on how the identified model performs with respect to the two model validation criteria listed here.

# 4 Control structure

## 4.1 Requirements for the controller

Once a patient specific model is identified, closed loop control can be introduced. In this thesis, the goal of automatic blood glucose control in diabetic patients is set to be a reduction in average blood glucose concentration compared to what is achieved with manual glucose control. Another, and more important, control criterion is to avoid hypoglycemia. Under no circumstances must the blood glucose concentration fall below $3.0\frac{mmol}{L}$. These are the two control criteria that are imposed on the system, and that the controller performance will be measured from:

- Control criterion 1: A hard lower constraint on the output. Under no circumstances should the system output be less than $3.0\frac{mmol}{L}$.
- Control criterion 2: Minimize the average output value, where an average blood glucose concentration of less than $7\frac{mmol}{L}$ is the ultimate goal. This is, however, not a strict condition, like criterion 1, but rather a measure of the performance of the controller.

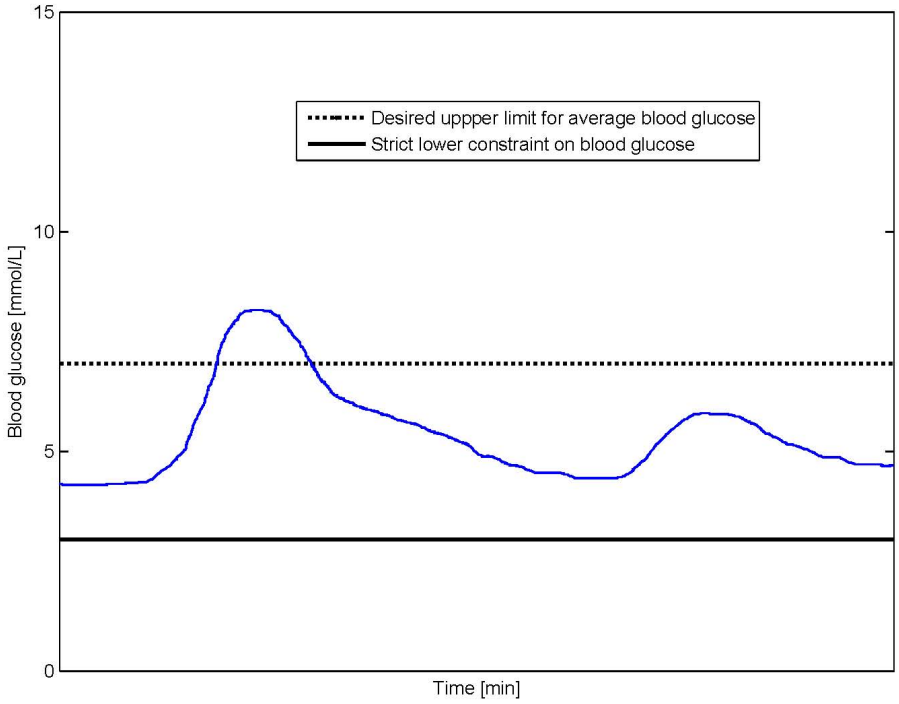



**Figure 19:** The goal of the control algorithm is to keep average blood glucose concentrations between the lines. The solid line shows the strict lower constraint, and the dotted line shows the desired upper limit for the average blood glucose value. The blue line is an example of a desired controlled output.

It should be emphasized that the control criteria here offers no constraint on the upper limit for single values of the blood glucose concentration. As long as the average output value is low enough, shorter time periods of hyperglycemia is tolerated.

## 4.2 The challenges of automatic blood glucose control

In this section, the main challenges of closed-loop blood glucose control will be identified, and some possible solutions to them will be discussed.

### 4.2.1 Time delays

One of the main challenges of blood glucose control in diabetes is illustrated in figure 20. The figure illustrates that subcutaneous glucose concentration lags behind blood glucose concentration by a factor of $6 - 10$ minutes. Because of this time delay, a good decision based on real time data will possibly be a poor one based on the actual present blood glucose concentration. Therefore, in order to make the optimal decision from measured data, the control algorithm should be able to predict the blood glucose value 10 minutes into the future based on the present information available.

### 4.2.2 Underestimation of blood glucose

Another effect that can be seen from figure 20 is that the subcutaneous glucose concentration is lower than the blood glucose one in general. This is because some glucose from the blood is transported out to cells and peripheral tissue. At low blood glucose concentrations, this works as an extra safety in glucose control, because decisions are made based on output values that are somewhat lower than the real glucose concentration, resulting in some extra time to act if hypoglycemia should occur.

### 4.2.3 Unpredictable insulin absorption in subcutaneous tissue

Because of the time delay from insulin is injected until it's effect can be seen in the measured blood glucose concentrations, infused insulin tends to accumulate in the subcutaneous layer when control action is set on reducing a too high blood glucose concentration. When the glucose concentration start sinking, and no more insulin is needed, this built up storage of insulin in the subcutaneous layer could cause glucose concentrations to fall too low, resulting in hypoglycemia and violation of control criterion 1. To avoid this, aggressive injection of insulin must be avoided, even when blood glucose is high and increasing. The controller should also keep track of how much of the earlier injected insulin that is active in the body at all times.

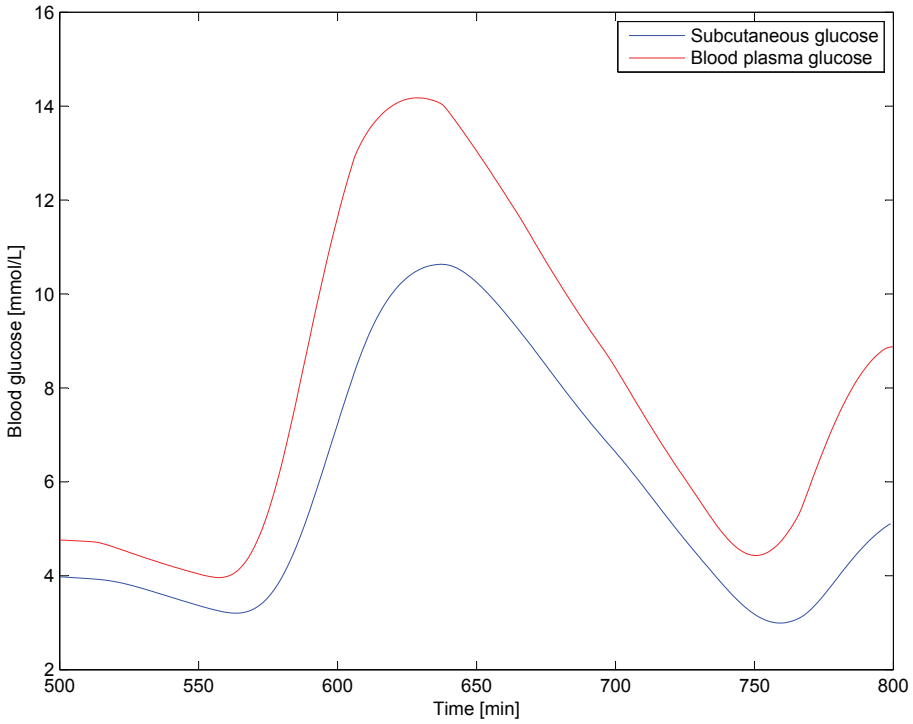



**Figure 20:** Subcutaneous glucose concentration $Y(t)$ and blood glucose concentration $G(t)$ are plotted after a simulated meal intake for patient 1, and shows that subcutaneous glucose concentration lags behind the blood glucose concentration.

For sinking blood glucose concentrations, the situation is quite different. The only available control input is insulin, which only has the ability to reduce blood glucose. If a situation that could lead to hypoglycemia is detected, aggressive control is required to set insulin input to zero immediately.

### 4.2.4 Meal blood glucose response

The rapid increase in blood glucose following a meal, makes it difficult to fulfill control criterion 2 with pure feedback control. Due to the time delay before post-meal increase in blood glucose concentration is seen on the output, closed-loop control reaction will be slow. Without implementation of a feed forward mechanism in the controller, hyperglycemic peaks after meal intake are likely to be unavoidable.

## 4.3 Tools for decision making

Figure 21 illustrates the decission making pattern of automatic blood glucose control used in this thesis. 6 different zones, indicated by the numbers in blue,

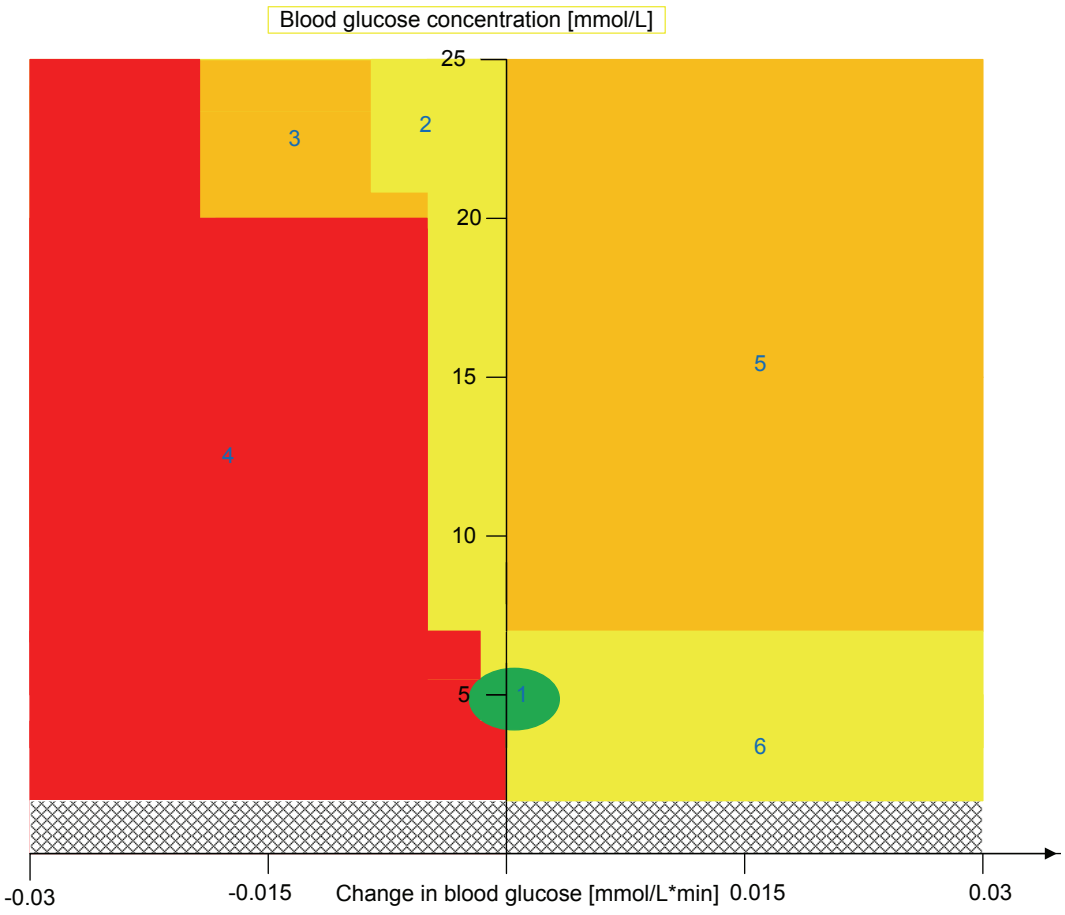



**Figure 21:** Diagram showing the decision making scheme for the controller. Blue numbers identify the six different zones.

are identified, based on information about measured blood glucose concentration $Y(t)$ and how it changes through time $\frac{dY(t)}{dt}$. Each zone requires its own set of control actions to ensure a healthy glucose level. An overview of each specific zone and its control requirements is given in the list below figure 21.

- 1: Green zone
  This is the preferable state. Blood glucose concentrations are in the desired range and changes little over time. Control structure 2 should be used.

- 2: Yellow zone downwards
  Glucose concentrations are decreasing towards the green zone at a desirably low rate. Control structure 2 should be used.

- 3: Orange zone downwards
  Glucose concentrations are higher than desired and decreasing at a relatively high rate. To avoid ending up in the red zone, control structure 1 should be used.

- 4: Red zone
  The most critical zone. Blood glucose concentrations are too low and falling, or in the normal range and falling at a disturbingly high rate. Control structure 3 should be used.

- 5: Yellow zone upwards
  Glucose concentration are increasing towards the green zone at a desirable rate. Control structure 2 should be used.

- 6: Orange zone upwards
  Blood glucose concentrations are higher than desired and increasing. The concentration must be reduced, but aggressive input action must be avoided. Control structure 1 should be used.

## 4.4 Control algorithm

The controllers that are implemented in this thesis are deliberately kept simple, using only pure proportional feedback control. Focus has been kept on designing the algorithm for choosing control structure, and assuring safe output values. It should be made clear that different, and maybe better, results could be achieved by introducing more sophisticated controllers.

### 4.4.1 Control implementation

Three different control structures were identified to assure optimal control in accordance to the control criteria and the challenges stated above:

- Control structure 1:
  Simple proportional feedback control. The control parameter is set to $K_p = 80$. The control response here is slow acting and it's goal is to force output values to fall within the desired range, without introducing large changes on the administered insulin input.

- Control structure 2:
  Simple proportional feedback control. The control parameter is set to give a more aggressive response than for control structure 1: $K_p = 160$. This structure is used when blood glucose concentrations show no indication of approaching hypoglycemic values, and thus a more aggressive insulin infusion scheme can be tolerated. The goal here is to keep values within the desired range.

- Control structure 3:
  All insulin infusion is stopped immediately. If hypoglycemia is likely to occur, an alarm notifies the patient about the situation.

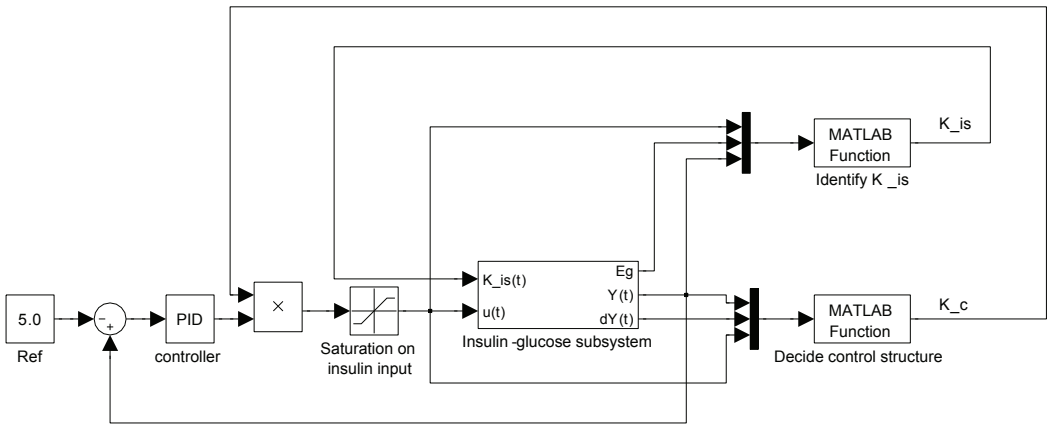



**Figure 22:** How gain scheduling is implemented in the simulink diagram.

Implementation of the three different control structures is done by introducing a control decission parameter $K_c$, as illustrated in figure 22. The control gain parameter $K_c$ has a value of either 0, 1 or 2, based on the value of the measured blood glucose $Y(t)$ and its derivative $\frac{dY(t)}{dt}$. The decission rules for deciding $K_c$ are set as illustrated in figure 21 in the matlab function *decisionrules.m*, which is called from the *Decidecontrolstructure* - block in the simulink diagram.

The described control structure guarantees that control is tight when blood glucose concentrations are in the yellow zone. For those values of $Y(t)$ and $\frac{dY(t)}{dt}$, $K_c$ is set to 2, and thus the proportional gain of the PID controller is twice as high as it is in the orange zone. This is reasonable because aggressive control is acceptable when blood glucose is too low and for smaller deviations upwards in blood glucose concentrations. However, if the measured concentration of blood glucose is significantly higher than the reference value, aggressive control is undesired, as it would lead to large amounts of infused insulin input, which again may lead to a state that of hypoglycemia, conflicting with control criterion 1.

### 4.4.2 Keeping track of active insulin

To ensure insulin from accumulating in the body, the parameter *Active_ins* is introduced to keep track of how much insulin that is injected in the past 10 minutes. If this number exceeds $10000\frac{\mu U}{min}$, insulin infusion is stopped. The same is done when blood glucose concentrations are in the red zone; $K_c$ is set to 0, and no insulin is infused whatsoever. MATLAB code for the update of *Active_ins* is found in the attached file *Update_active_ins.m*, which is called from the *Decidecontrolstructure* - block in the simulink diagram.

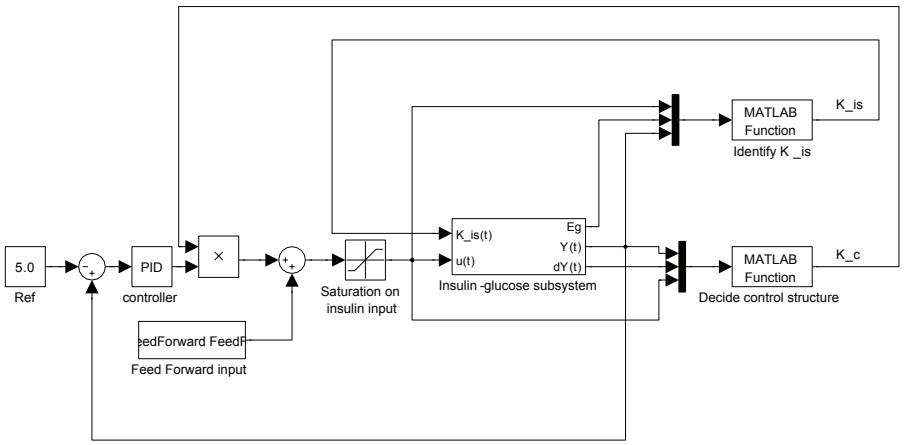



**Figure 23:** How feed forward is implemented in the simulink diagram.

### 4.4.3 Feed forward

Feed forward in the control algorithm is introduced through the input vector $Feed\_Forward$. This vector is obtained by injecting a insulin bolus 10 minutes before every meal. The amplitude of the bolus is proportional to the size of the meal. MATLAB code for construction of the $Feed\_Forward$-vector is given in the attached file $Control\_init.m$

Some results of the implemented control schemes are plotted in section 5.

# 5 Results

In this section, the results of the attempted closed-loop blood glucose control are shown. All plots in this section are from patient 1. The corresponding results for the other two patients are given in appendix Appendix A.2 and Appendix A.3, but only patient 1 and 2 will be discussed in this thesis. MATLAB code and simulink diagrams for the cases illustrated in this chapter is given in the attached files *Control_algorithm.m* and *Controlstructure.mdl*. For further details on how control was implemented, the reader is referred to section 4.

## 5.1 Closed-loop control

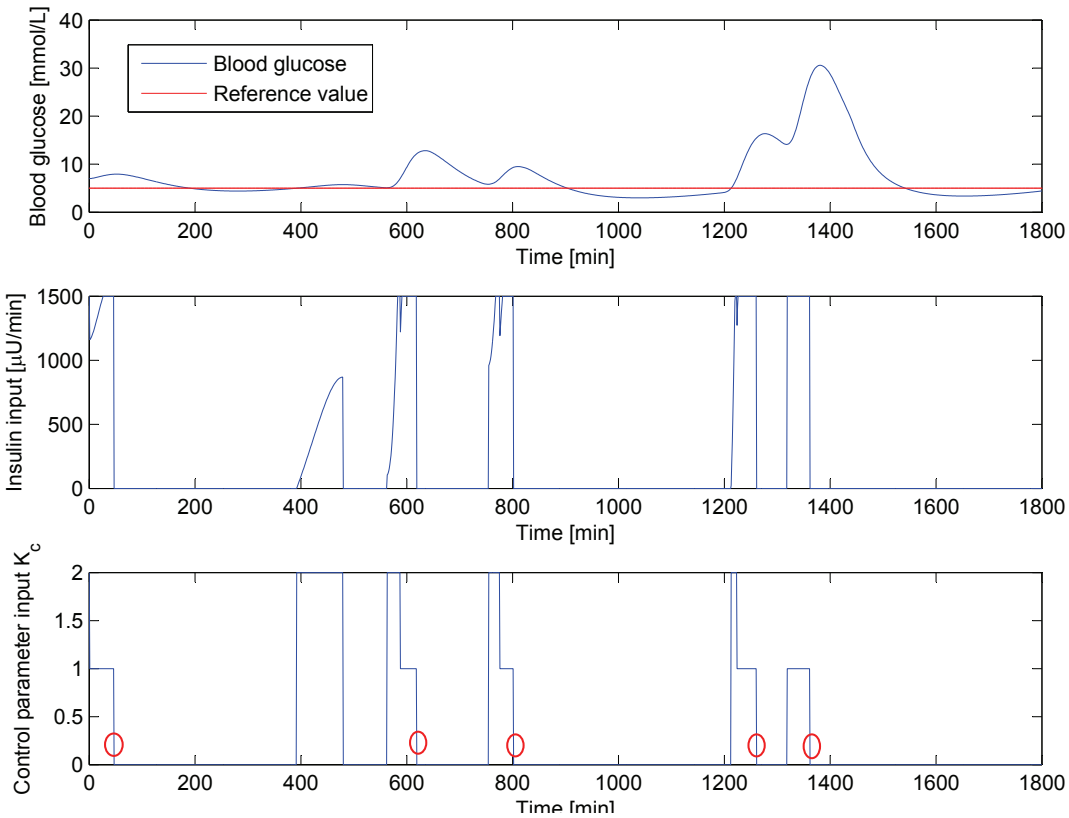
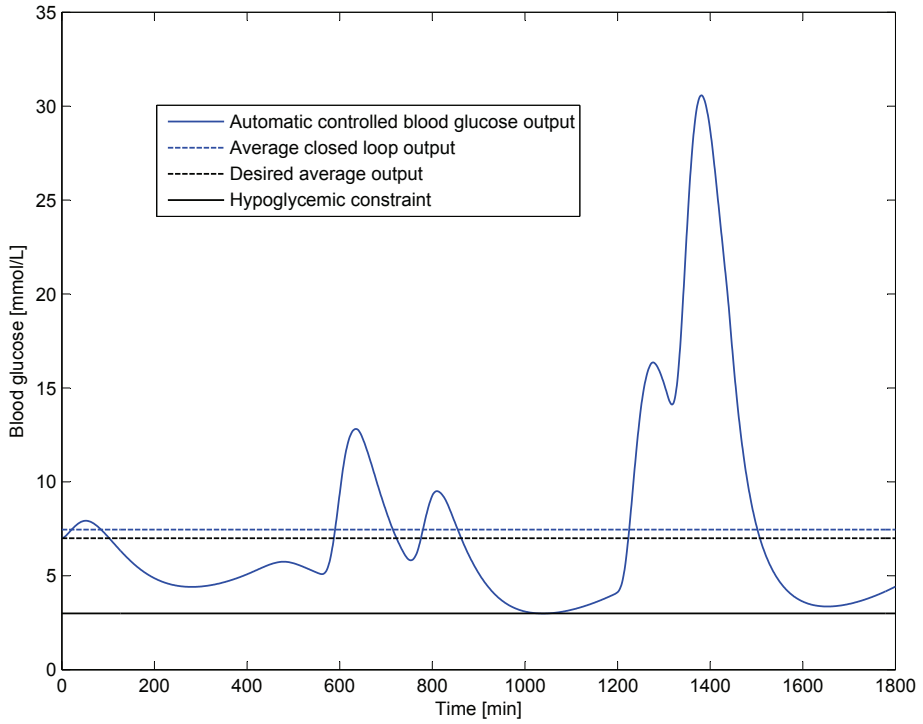



**Figure 24:** Blood glucose output and insulin input after the control algorithm has been implemented.

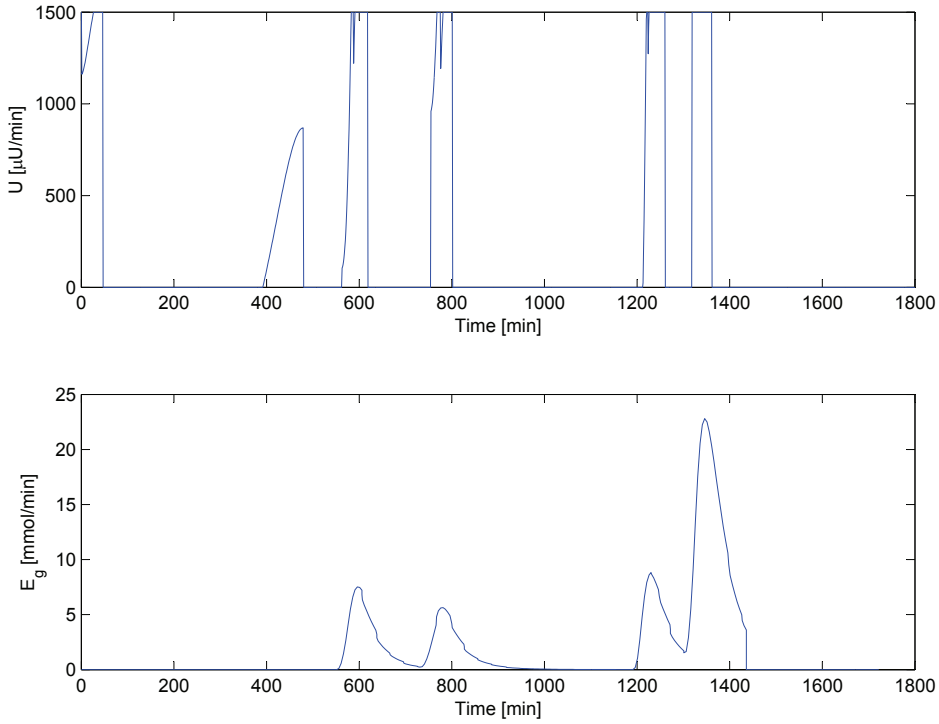
Figure 24 illustrates how the control algorithm alternates between the three different values for the control decision parameter $K_c$, and how insulin input and blood glucose output is affected by this. The upper plot shows blood glucose concentrations for patient 1 when feedback control is implemented. The reference value is set to $5.0\frac{mmol}{L}$, and the meal input is taken from the meal diary of patient 1. The plot in the middle shows the insulin input that was applied by the control algorithm, and the lower plot illustrates which control structure that was used throughout the control period. $K_c = 1$ and $K_c = 2$ means control structure 1 and 2 are active. $K_c = 0$ means control structure 3 is active. Control structure 3 represents control response to output values in the red zone, unless a red marker is shown on the x-axis, which illustrates that the setting of insulin infusion to zero is set by the *Active_ins*-parameter.

Figure 25a illustrates how the control algorithm performs regarding the control criteria defined in section 4.1. The solid black line represents control criterion 1, and the dotted black line represents control criterion 2. It is seen that criterion 1 is fulfilled at all times, all though the blood glucose concentration generally experiences a dip that brings it close to the hypoglycemic limit after meal intake. Control criterion 2 is violated, as the average blood glucose concentration in closed-loop control is found to be $7.5\frac{mmol}{L}$ in this experiment. Insulin and meal input during the control period is shown in figure 25b. Figure 31 shows the same plots for patient 2, and illustrates that the same general tendency of close to hypoglycemic blood glucose values after meal intake is seen in this patient too. Patient 2 is shown to have an average closed-loop blood glucose concentration of $7.6\frac{mmol}{L}$, which is very close to the one achieved in patient 1.

A comparison with the glucose concentrations achieved with traditional insulin administration is shown in figure 26. Even though the control algorithm is not able to fulfill criterion 2, it does result in a lower average glucose concentration than the $8.8\frac{mmol}{L}$ achieved during the manual control scheme. Looking at figure 32, one sees that the same analysis is valid for patient 2, who achieves an average blood glucose concentration of $8.9\frac{mmol}{L}$ in manual control.




25a: Controlled blood glucose output for patient 1




25b: Insulin and meal input during automatic control for patient 1

**Figure 25:** Figure showing output and inputs during automatic control without feed forward for patient 1.

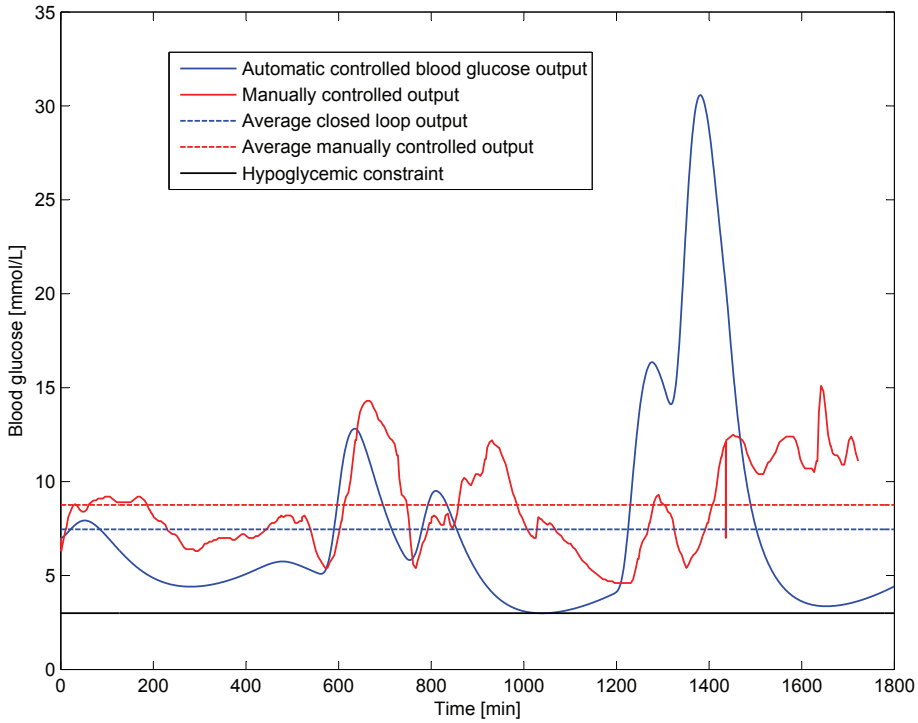


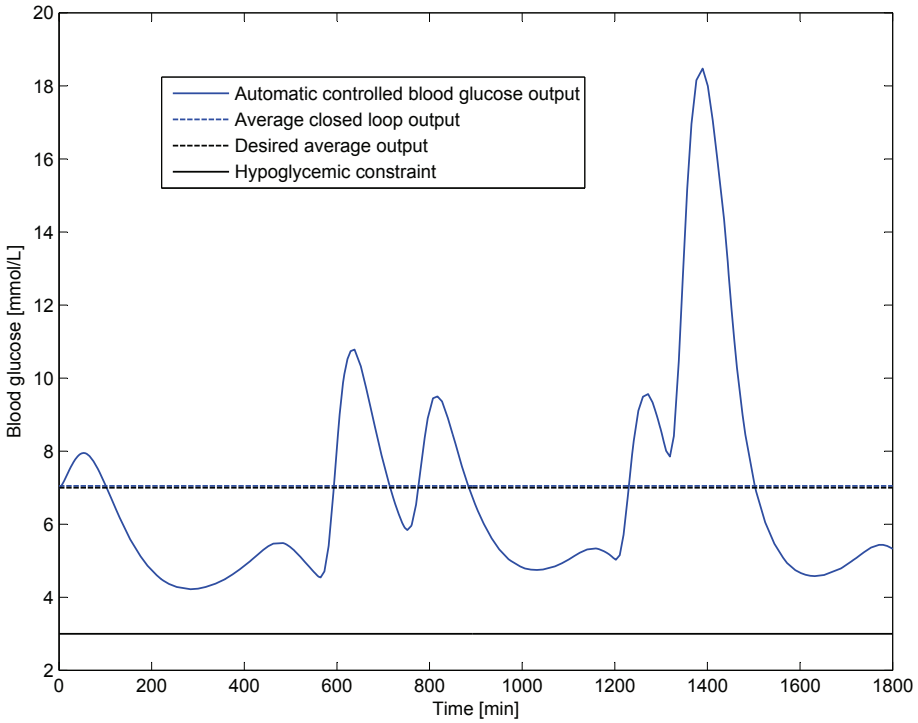

**Figure 26:** Comparison between manually administered and automatically controlled blood glucose.

## 5.2 Closed loop control with feed forward

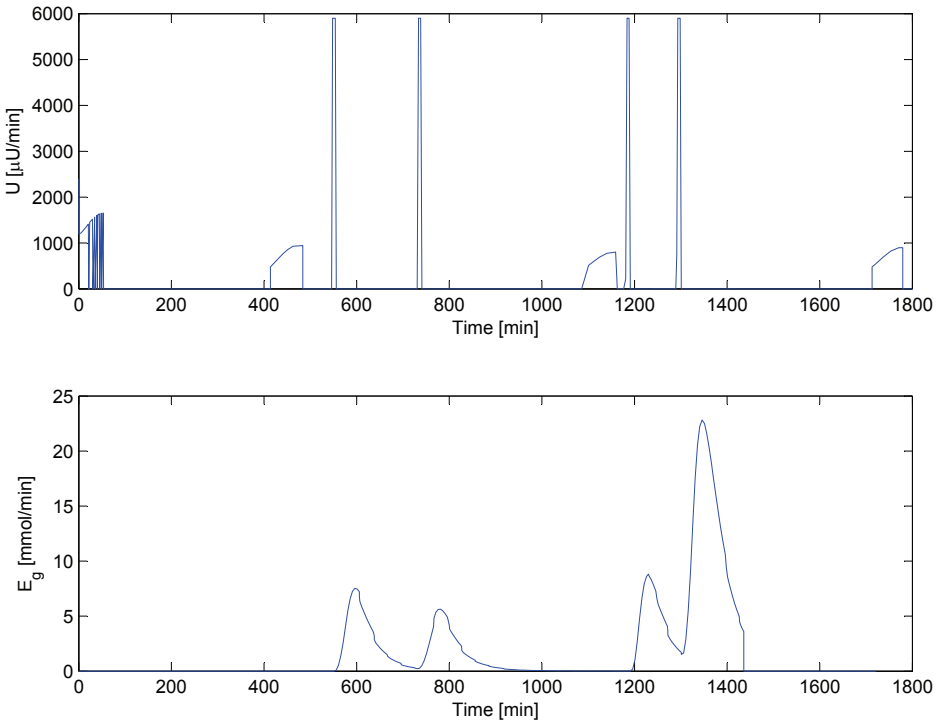
Performance of the control algorithm with feed forward implemented, is illustrated in figure 27. It is clear that the algorithm now performs better with respect to both control criteria. Blood glucose output is never close to the hypoglycemic limit, and the average glucose concentration is $7.0\frac{mmol}{L}$. The corresponding plot for patient 2 is shown in figure 33, which illustrates that the resulting average closed-loop blood glucose concentration for patient 2 is $6.9\frac{mmol}{L}$.

Figure 28 illustrates how glucose control with feed forward performs compared to manual control. Average blood glucose is significantly lowered, but the peak value in glucose concentrations after a meal is higher in closed-loop control than it is in the case of manually injected insulin. A comparison between closed-loop control with feed forward and manual control for patient 2 is shown in figure 34.

For a more thorough discussion of the results presented in this section is presented in section 6.




27a: Controlled blood glucose output with feed forward for patient 1




27b: Insulin and meal input during automatic control with feed forward for patient 1

**Figure 27:** Figure showing output and inputs during automatic control with feed forward for patient 1.

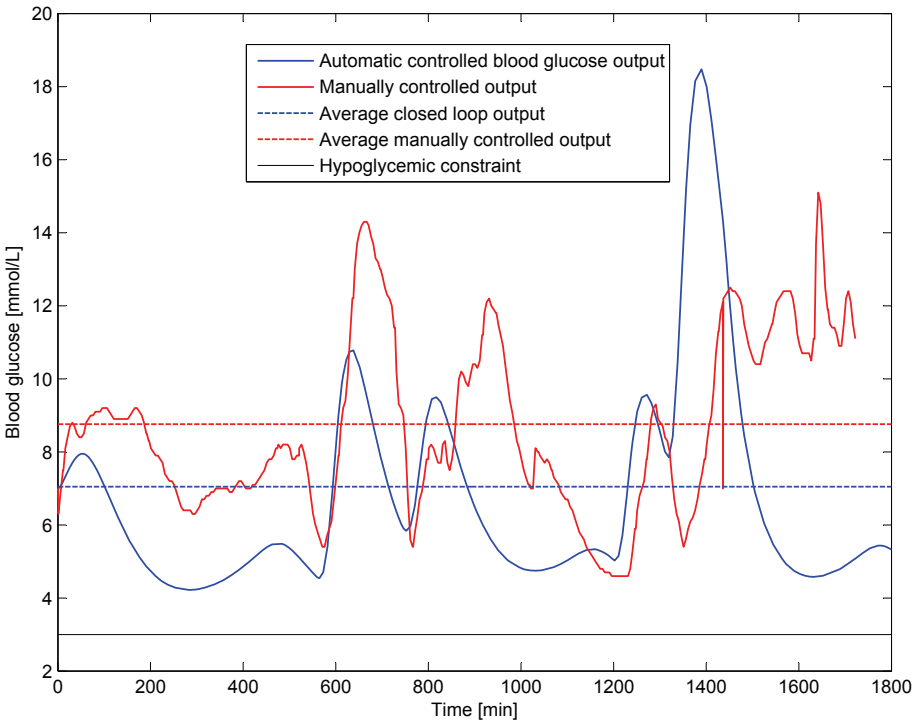



**Figure 28:** Comparison between manually administered and automatically controlled blood glucose with feed forward implemented.

# 6 Discussion

## 6.1 The identified model - how well does it perform with respect to closed loop control?

In section 3.8, two criteria for validating the identified model for control purposes were introduced. By looking at figure 17, which shows the model output after all the identified parameters have been applied, the performance of the model based on the validation criteria can be analyzed.

Criterion 1 is the most important element for models used in human glycemic control, and the plot shows that the lower constraint on the system output is never violated during the experiment period. In fact, the identified model tends to underestimate rather than overestimate blood glucose concentrations. This means that a control algorithm would react as if the blood glucose concentration was lower than its real value, stopping insulin infusion sooner than necessary, rather than later. This underestimating of glucose concentrations could lead to hyperglycemia, but it assures that insulin infusion at hypoglycemic levels is avoided. Criterion 1 is shown to be fulfilled for all three patients in this study. This does, however, not guarantee that overestimating could never occur. For that to be stated, several more patients would have to be studied, and more extreme conditions would have to be applied to the eating and insulin injection scheme, to see how robust the model identification would prove to be.

The identified model performs adequately when it comes to the second criterion. One sees that the rapid changes in measured blood glucose are being neatly followed by the estimated output. The ability to fulfill the second criterion is highly dependent on the data series chosen for identifying the insulin parameters, because this is where the patient specific time constants $T_{xi}$ and $T_i$ are identified. Patient 1, whos data is used in figure 17, has the best fit for these parameters, whereas the other two patients seem to have less consistent insulin compartment time constants. This could be explained by inaccurate meal information obtained from the patients, but could also be an indication of a need for online identification of these parameters, as they could turn out to be time-varying, like the insulin sensitivity parameter $K_{is}$.

An effect that is not properly described by the model, is observed in figure 17 after approximately 1300 minutes. What happens is that measured blood glucose is rising to a hyperglycemic state, and stays high for some 700 min, even though multiple insulin injections are administered by the patient. This effect of decreased insulin sensitivity at high blood glucose concentrations is seen in the data of patient 3 as well. The model identification algorithm estimates a negative insulin sensitivity factor in these situations, but the identification algorithm is set to overwrite it with a small positive value, because negative insulin sensitivity is not physiologically possible according to the model. A better model fit would have been achieved if $K_{is}$ was allowed to have negative values, but this was not done in this thesis, partly because of a desire to keep the physical foundation of the model intact, and partly as a security measure,

because a negative insulin sensitivity would encourage insulin input when blood glucose concentrations are too low. For control purposes, the effect of decreased insulin sensitivity at high blood glucose concentrations is not crucial, because the model tends to underestimate the blood glucose concentration instead of overestimating it. What is disturbing about it is that it illustrates that there are elements in the human blood glucose dynamics that the identified model is not able to describe.

Even if a perfect model of each patients glucose regulation system were to be found, there would still be challenges involved in the parameter identification process. One issue to be considered is the time used for parameter identification. It was suggested above that the time constants related to interstitial insulin absorption might need to be identified in real time. But if more parameters were to be estimated online, the estimation time would increase, and might conflict with a need for quick parameter updates.

Another issue to be considered is how detailed the meal feed forward algorithm should be. The more information about a meal one was to inform the control algorithm of, the faster and better control response would be safe and achievable. However, the patient might not know in advance what, and how much, food that is to be eaten. Also, to be able to fully exploit the advantages of automatic control, it is desirable to keep user interference to a minimum.

One should keep in mind that the output of the control simulations performed in this thesis, are results of a theoretical model, and not real life data. All the errors and uncertainties of the model that were identified in section 3.3 affects the results of the control simulations in section 5.

## 6.2 The control algorithm - what is achieved compared to manually regulated blood glucose?

Figure 25 shows how controlled blood glucose concentrations perform compared to the control criteria identified in section 4.1. The control algorithm was improved several times during the work of this thesis to make sure that control criterion 1, which demands avoidance of hypoglycemia, should always be fulfilled. Even so, it is seen from the result of control in patient 1(figure 25a) and also in patient 2 (figure 31a) that the hypoglycemic limit generally is close to being crossed after meal-response insulin injection. It is likely that intake of more carbohydrate-rich meals than what was eaten in the experiments of this thesis, would cause hypoglycemia as a consequence of the control algorithm's insulin injection response to the meals. Thus, the way the control algorithm handles insulin bolus injection after meals needs to be improved. When it comes to control criterion 2, the control algorithm fails to fulfill this requirement, as average blood glucose concentrations in automatic control of patient 1 is $7.5\frac{mmol}{L}$, which is $0.5\frac{mmol}{L}$ above the desired upper limit. However, looking at figure 26, it is clear that the control algorithm performs better with respect to criterion 2 than the manually controlled glucose regulation scheme, which results in an

average blood glucose concentration of $8.8\frac{mmol}{L}$ for patient 1. The equivalent numbers for patient 2 are $7.6\frac{mmol}{L}$ with closed-loop control and $8.9\frac{mmol}{L}$ with manual control, which illustrates that closed-loop control achieves better results than the manual insulin injection scheme in this case too.

It is now clear that average blood glucose concentrations can be improved when closed-loop control is introduced, at least in the two example cases shown here. However, it is also indicated that the cosed-loop response to meal intake is unsatisfactory, since meals will give a high peak value in glucose concentrations followed by a rapid dip that often falls close to the hypoglycemic limit. The post meal glucose regulation is actually done better manually, where insulin is injected in advance of meal intake, thus reducing the size of the following peak blood glucose value and avoiding a dangerously low dip afterwards. In automatic control, insulin is not injected until a rise in blood glucose concentration can be measured in the subcutaneous layer, thus lagging behind manual control with up to 15 minutes.

To be able to achieve a more clever administration of meal-bolus insulin infusion in closed-loop control, feed forward as illustrated in figure 23 is implemented. The resulting course of blood glucose concentration is shown in figure 27 for patient 1 and in figure 33 for patient 2. In this case, both control criteria 1 and 2 are fulfilled by the implemented control algorithm. Glucose concentrations are never close to hypoglycemic values, and thus far from violating criterion 1. The average closed-loop blood glucose output for patient 1 is $7.0\frac{mmol}{L}$, which falls just within the desired range imposed by criterion 2. Closed-loop output with feed froward compared to manually controlled output for patient 1 is shown in figure 28, and illustrates that closed-loop control performs much better with regards to average glucose concentration, but that the manual control scheme is better suited to administer insulin boluses to deal with the large meal at the end of the experiment period. The achieved average blood glucose concentration for patient 2 with feed forward is $6.9\frac{mmol}{L}$, which is in accordance with control criterion 2 and also a dramatic improvement compared to the manual insulin injection scheme, which is illustrated in figure 34. In addition to the lowered average blood glucose concentration achieved with feed forward, control criterion 1 is now also less likely to be violated than in the case of pure proportional feedback without implementation of feed forward. Thus, the control algorithm with feed forward implemented have been shown to successfully fulfill the defined control criteria of this thesis for the two analyzed experiment scenarios. However, for this result to be made general, more tests must be executed.

The control criteria defined in this thesis are based on the assumption that low average blood glucose concentrations should be the goal of automatic blood glucose control. This is in accordance with the findings of DCCTs report in 1993, but recent research suggests that blood glucose variability could be an equally dominant factor in late complications of diabetes. [27; 1; 11; 24]. This topic is not fully investigated yet, and was frequently debatted under the annual ATTD conference in Athens 2009. If variability turns out to be an important factor in the long-term health of diabetics, different control criteria than what

is used in this thesis must be applied.

## 6.3 Safety - Is closed loop blood glucose control a safe alternative?

When control theory is applied to biological processes that are crucial for the vital functions of a human being, safety and quality of life for the individual should always be the number one priority. This is of extreme importance in blood glucose regulation, as overestimating insulin input by even small amounts could be lethal for the diabetic patient. Severe measures must be made to avoid hypoglycemia, and no course of actions, no matter how unlikely, must lead to a state of hypoglycemic blood glucose concentrations.

One way of achieving this, which is implemented in many of the continuous blood glucose monitors on the market today, is alarm systems that alert the patient, -either by sound, vibration or both. Typically, the alarm will go off if blood glucose concentrations are low, falling at a high rate or if a meal insulin bolus is infused, but no rise in glucose concentration is measured afterwords. Usually, the users can program what is defined as disturbingly low glucose values and fast falling rates themselves. The study of [25] found that many users were annoyed by the frequent alarms from the monitor. If many of the alarms are based on incorrect measurements or set to react in a too conservative manner, users are tempted to turn the alarms off, or disregard them. Consequently, the use of alarms could be helpful, but is not enough to ensure a safe blood glucose regulation.

A desirable feature of the control algorithm with regards to safety would be for it to include a reliable prediction of future blood glucose levels. If the algorithm contained information about how the present and recent insulin injections would affect the future glucose concentration, it could turn insulin input off in time to avoid any hypoglycemic state. However, for this to be possible, a detailed and precise model of the individual user‘s insulin - glucose - homeostasis, with online adaptive parameters, is required. Such a detailed and precise model is not yet developed, and the mathematical model in thesis should certainly not be relied upon for control based on glucose predictions. However, if such a model were to be implemented, it would make the control part of the regulation safe.

But even if a reliable blood glucose prediction algorithm was available, there would still exist safety issues that could offer large problems. One problem that is likely to occur is that the user activates the feed forward insulin bolus input, and then forgets to eat, or get hindered to do so. To avoid hypoglycemia in this situation, the feed forward bolus could be set to a smaller dose, by the cost of a higher peak in post meal blood glucose. Another solution proposed to avoid hypoglycemia in closed-loop control is subcutaneous glucagon injection, which would counteract the effect of insulin.

No matter how good a monitor, measurement errors could always be a source of uncertainty in glucose control. There will most likely always be a need for

calibration from other measurements, that being finger prick measurement, another continuous glucose monitor or another blood glucose measurement device. These calibrations should be made often enough to correct erroneous measurements before they contribute to hypo-, or hyperglycemic incidents. The prediction algorithm should also notify the user by alarms if glucose measurements deviates to a large degree from what was predicted, when this could be an indication of measurement error or blocked insulin input.

A possible effect of introducing automatic blood glucose control could be that diabetics trusts the control algorithm and measurement device more than their own intuition. This is not desirable, as the human senses often can provide the diabetic with more reliable information about the conditions in his or her body, than any electronic device.

# 7 Conclusion

In this thesis, a closed-loop control algorithm for regulating blood glucose concentration in diabetic patients has been developed. Performance of the algorithm has been analyzed with respect to two control criteria, one imposing an absolute lower limit of the allowed blood glucose concentration, and the other representing a desire to keep average blood glucose concentrations below $7.0\frac{mmol}{L}$.

To be able to carry out a realistic analysis of closed-loop control performance in diabetes, data from three diabetic patients participating in a study of continuous glucose monitors were used to identify some of the model parameters of a proposed mathematical model of the human insulin-glucose regulatory system. The identification process revealed large variations between individual patient's parameter values, and the difference in insulin sensitivity was found to be specially high, both between and within patients.

Simulations of the designed control algorithm resulted in a reduction in average blood glucose concentrations compared to what was achieved with traditional manual blood glucose control in two patients. Patient 1 experienced an average blood glucose reduction of 20%, from $8.8\frac{mmol}{L}$ to $7.0\frac{mmol}{L}$, and patient 2 was able to reduce blood glucose by 22%, from $8.9\frac{mmol}{L}$ to $6.9\frac{mmol}{L}$. This means that the upper constraint on average blood glucose concentrations was fulfilled. Also, both test cases resulted in blood glucose outputs that never fell close to, or below, the hypoglycemic limit, which means that both control criteria were obeyed. The results here were obtained with a closed-loop control algorithm with a feed forward mechanism implemented to deal with infusion of bolus doses of insulin before meals.

All though the requirements for satisfactory control output were met in the experiments of this thesis, a general conclusion on the success of the algorithm cannot be drawn. For this to be done, several more test scenarios would have to be applied to the algorithm, and issues regarding safety of the user would have to be thoroughly investigated.

# 8 Suggestions for Future Work

**Improving the model** The model identification performed in this thesis, did not produce a satisfactory result for it to could be implemented in real life automatic blood glucose control.

**Further experiments** More data should be obtained to get a better impression of parameter variability between patients. Also, more extreme meal intake and insulin injection schemes should be recorded, to get an indication of how well the model performs under abnormal circumstances.

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# Appendix A Plots from MATLAB

## Appendix A.1 `Collected Data Patient 2 Day 4`

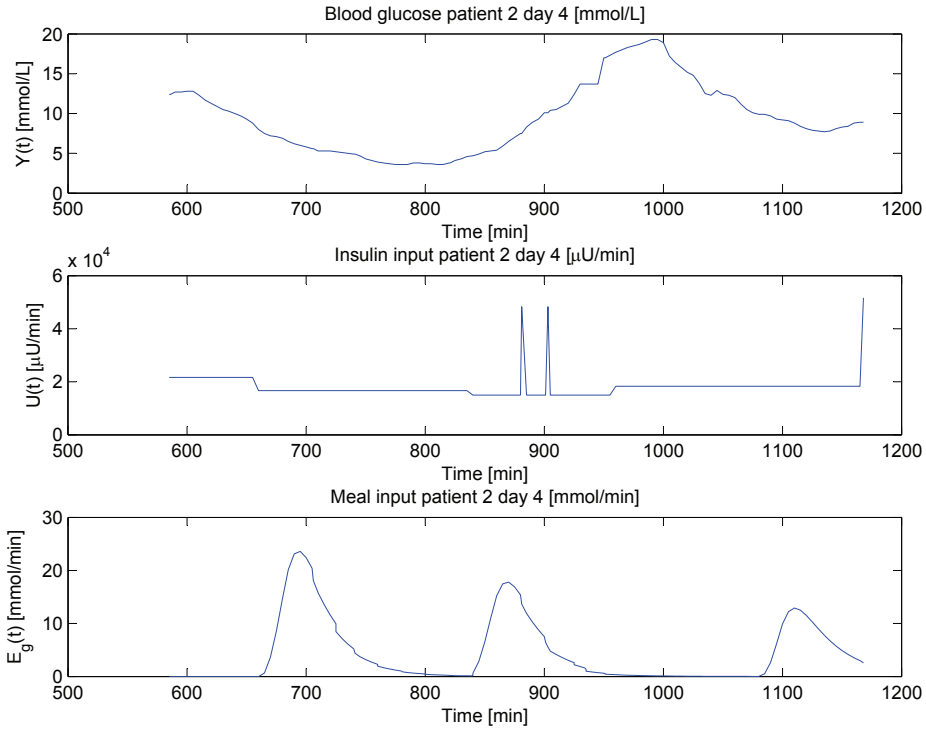



**Figure 29:** Illustration of what seems to be an erroneous entry in the meal diary for patient 2. The meal that is recorded at approximately $t = 700$ min is not followed by any bolus insulin dosage, and there is a decrease in blood glucose, instead of the expected post meal rise. It is therefore reason to believe that the meal never took place, and insulin sensitivity estimates based on these data will thus be wrong.

## Appendix A.2 `Results closed-loop control patient 2`

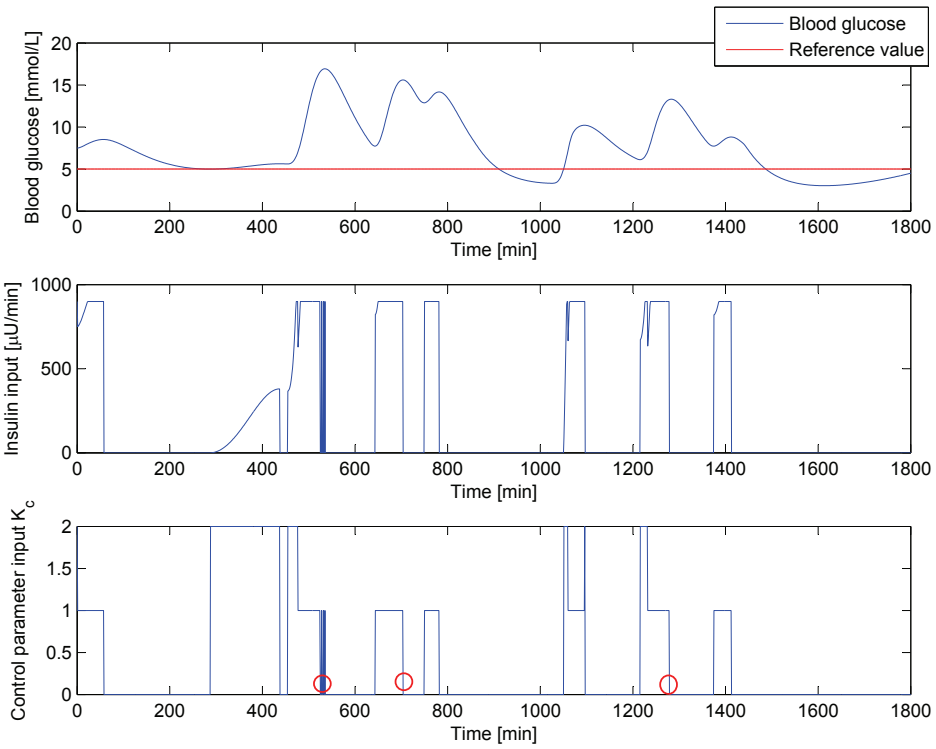
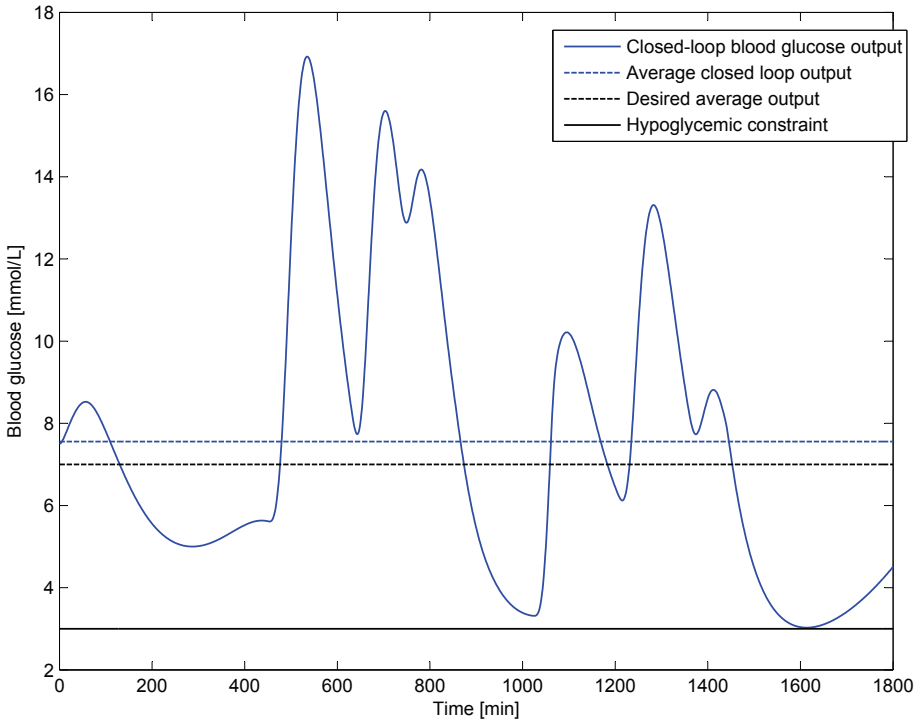
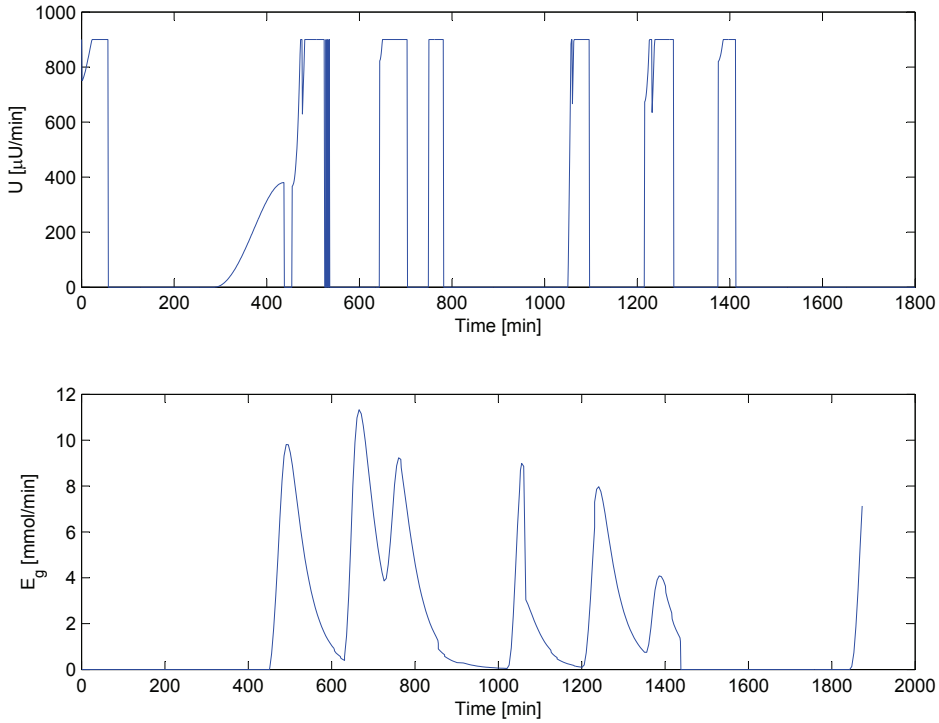



**Figure 30:** Blood glucose output and insulin input after the control algorithm has been implemented.




31a: Controlled blood glucose output for patient 2




31b: Insulin and meal input during automatic control for patient 2

**Figure 31:** Figure showing output and inputs during automatic control without feed forward for patient 2. Average closed-loop blood glucose is $7.6\frac{mmol}{L}$

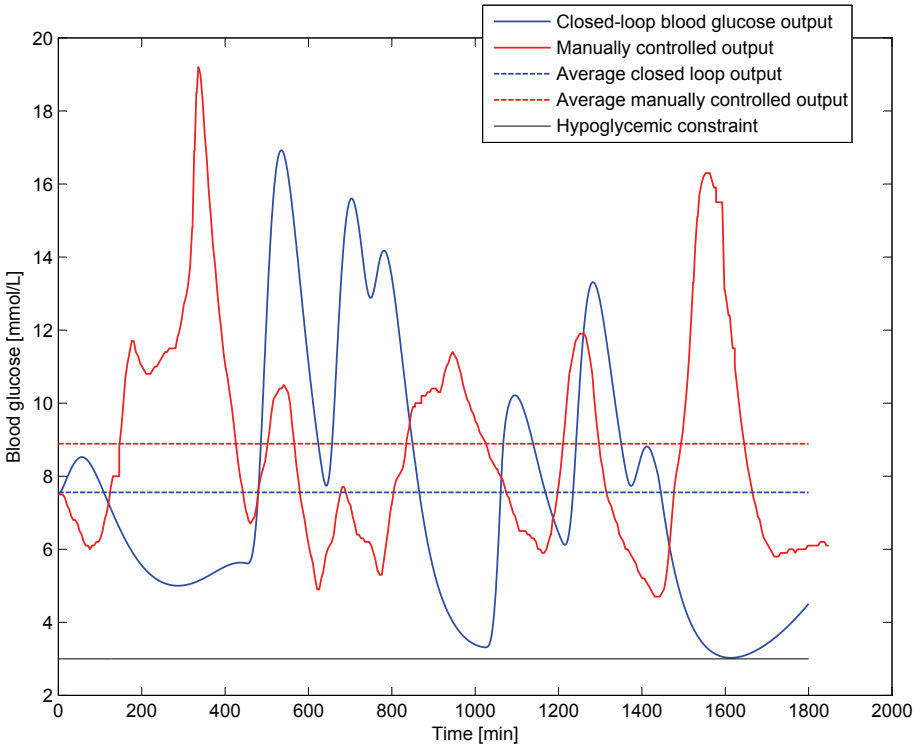
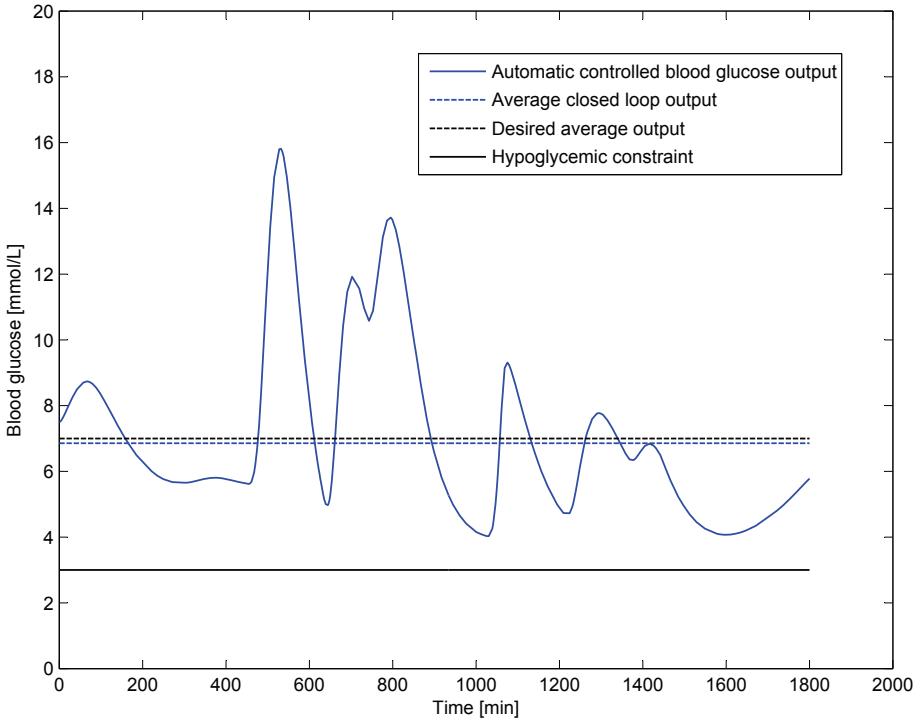
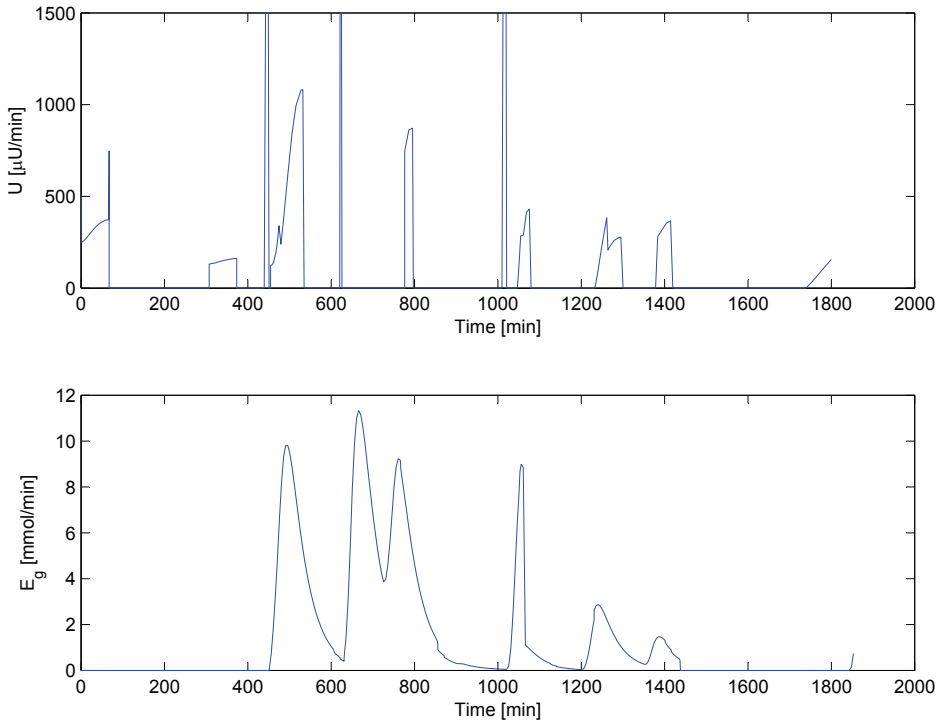



**Figure 32:** Comparison between manually administered and automatically controlled blood glucose. Average blood glucose concentrations with manual control is $8.9 \frac{mmol}{L}$




33a: Controlled blood glucose output with feed forward for patient 2




33b: Insulin and meal input during automatic control with feed forward for patient 2

**Figure 33:** Figure showing output and inputs during automatic control with feed forward for patient 2. Average closed-loop blood glucose concentration is $6.9 \frac{mmol}{L}$.

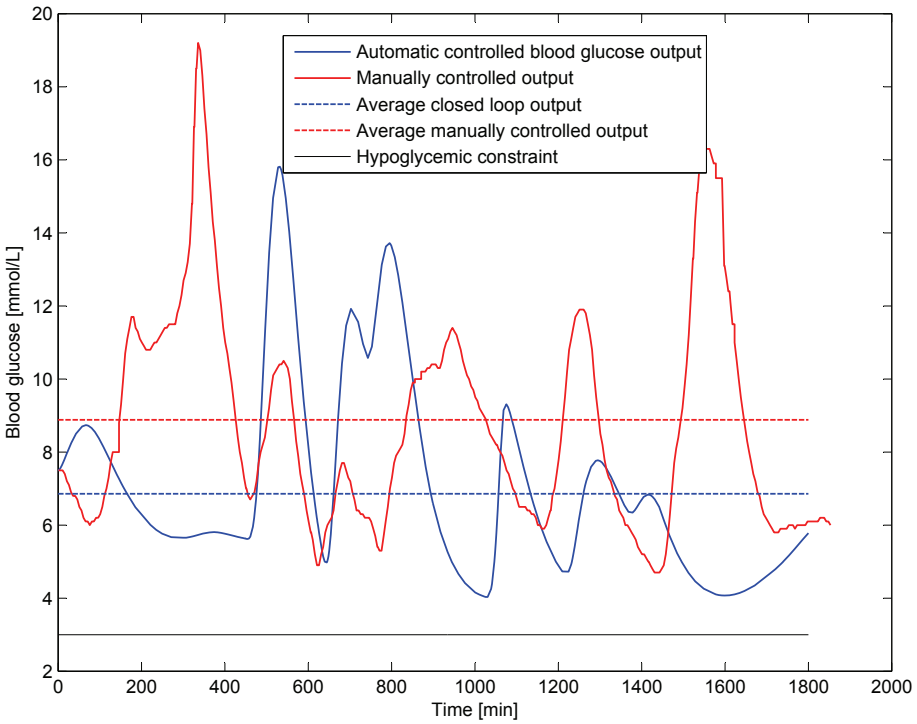



**Figure 34:** Comparison between manually administered and automatically controlled blood glucose with feed forward implemented.

## Appendix A.3 `Results closed-loop control patient 3`

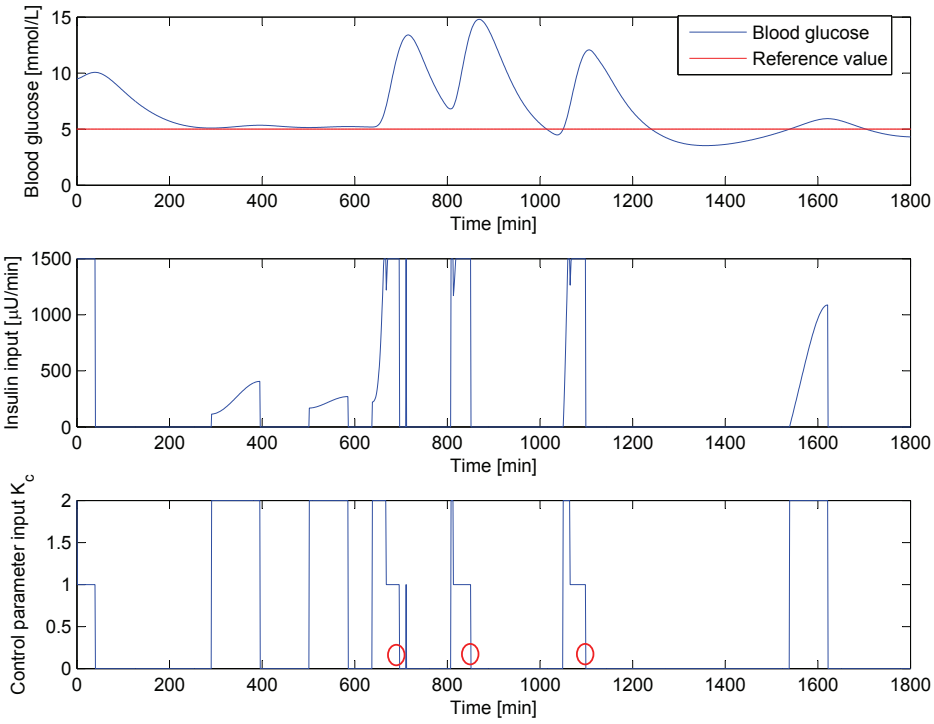
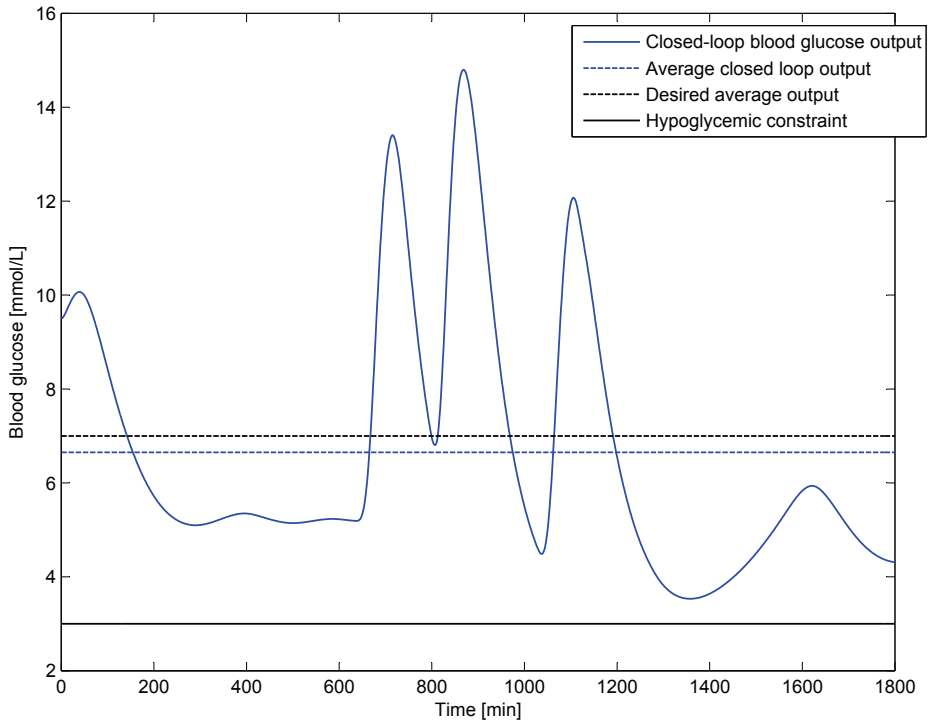
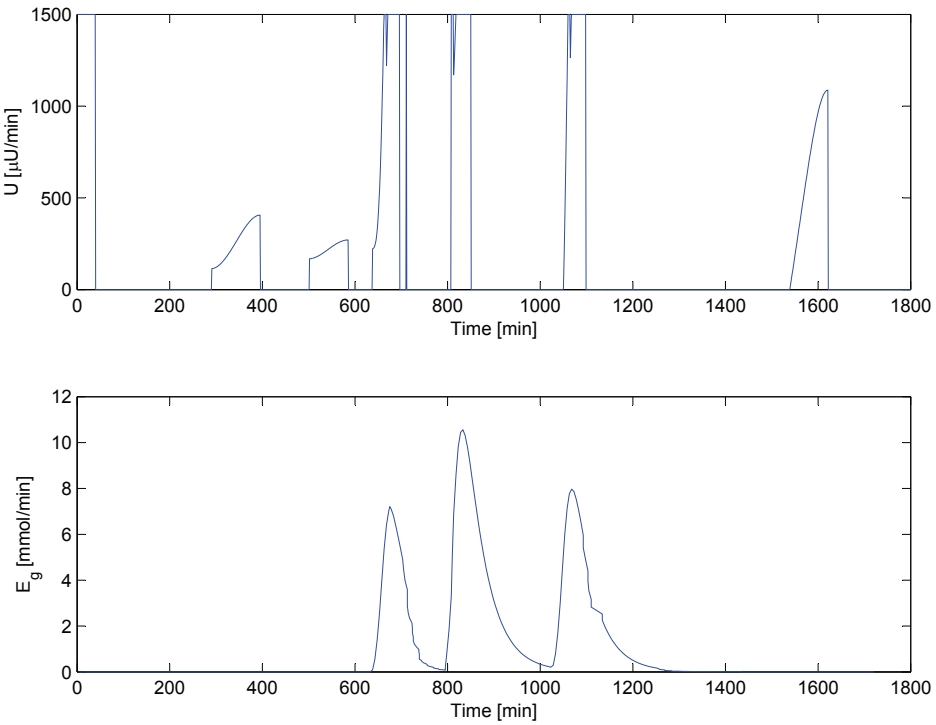



**Figure 35:** Blood glucose output and insulin input after the control algorithm has been implemented.




36a: Controlled blood glucose output for patient 3




36b: Insulin and meal input during automatic control for patient 3

**Figure 36:** Figure showing output and inputs during automatic control without feed forward for patient 3. Average blood glucose concentration is $6.7\frac{mmol}{L}$ when automatic control is implemented.

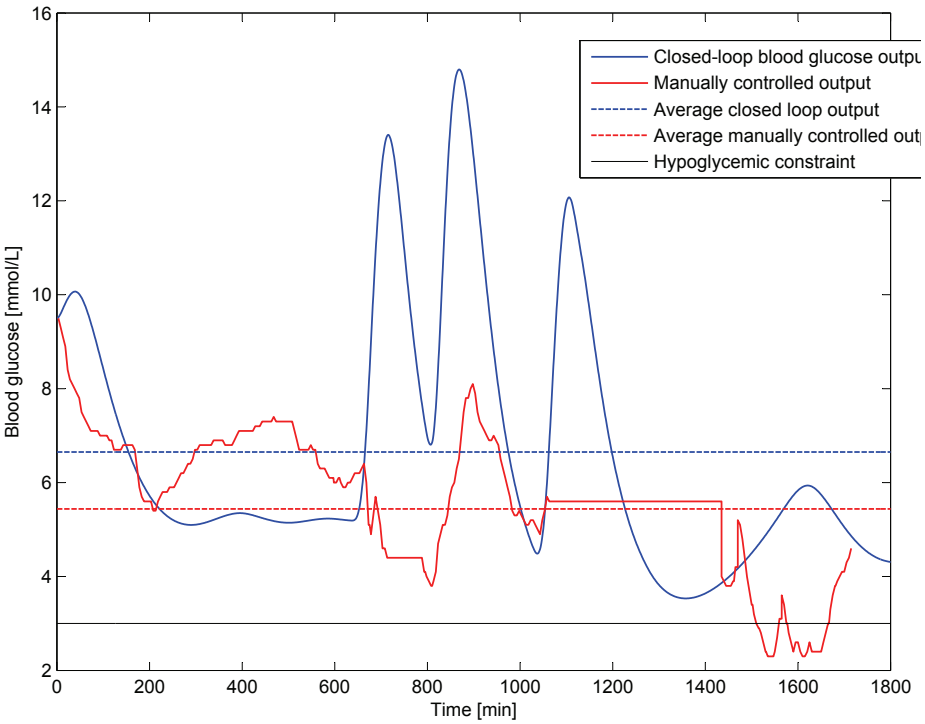
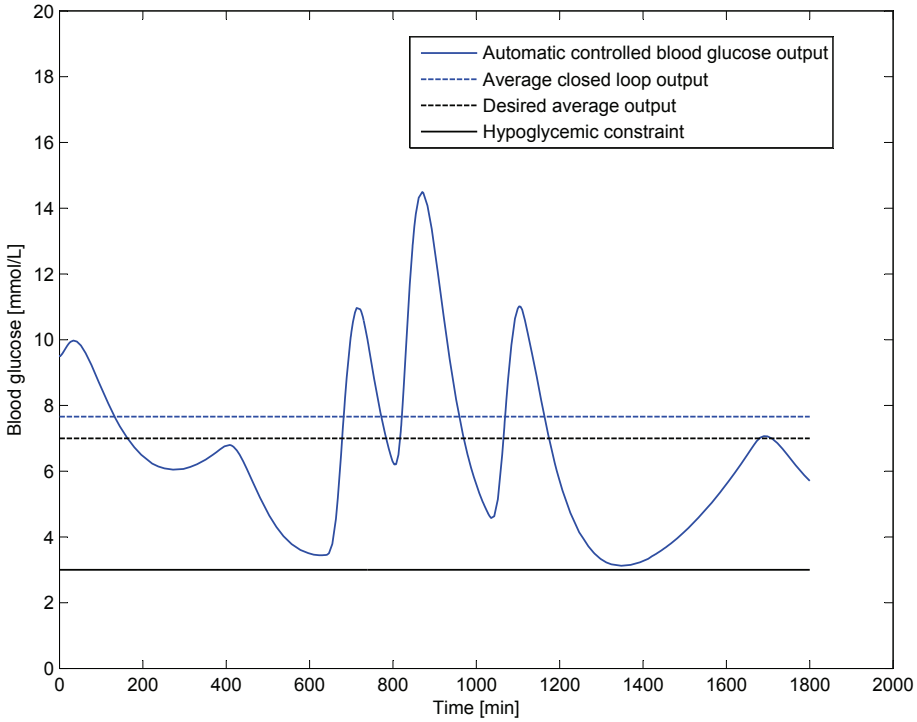
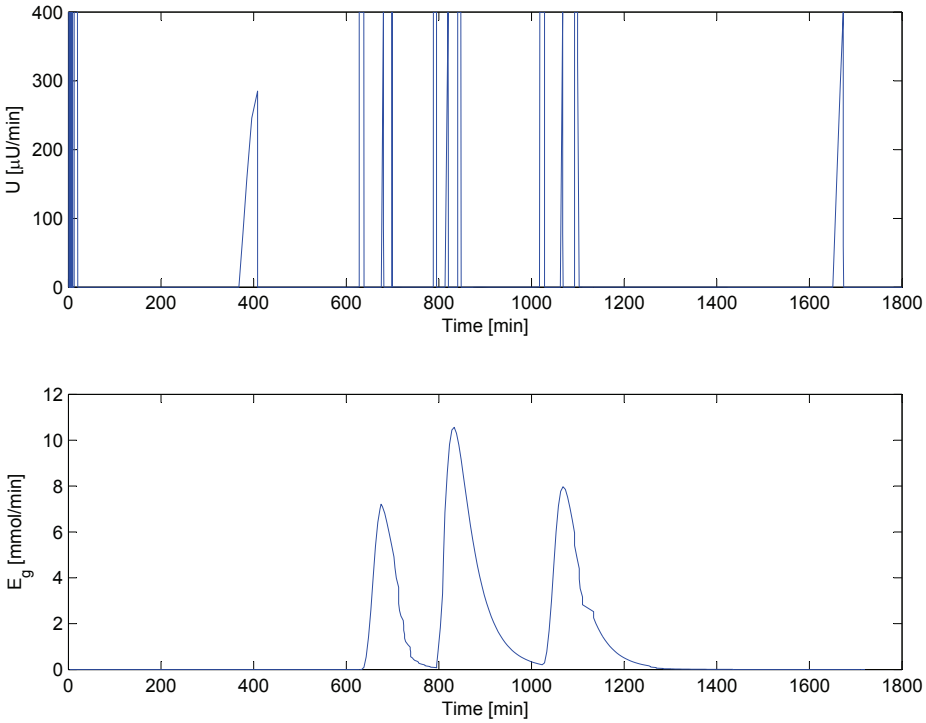



**Figure 37:** Comparison between manually administered and automatically controlled blood glucose. Averaged controlled output is $6.7\frac{mmol}{L}$, and manually administered average output is $5.4\frac{mmol}{L}$




38a: Controlled blood glucose output with feed forward for patient 3




38b: Insulin and meal input during automatic control with feed forward for patient 3

**Figure 38:** Figure showing output and inputs during automatic control with feed forward for patient 3

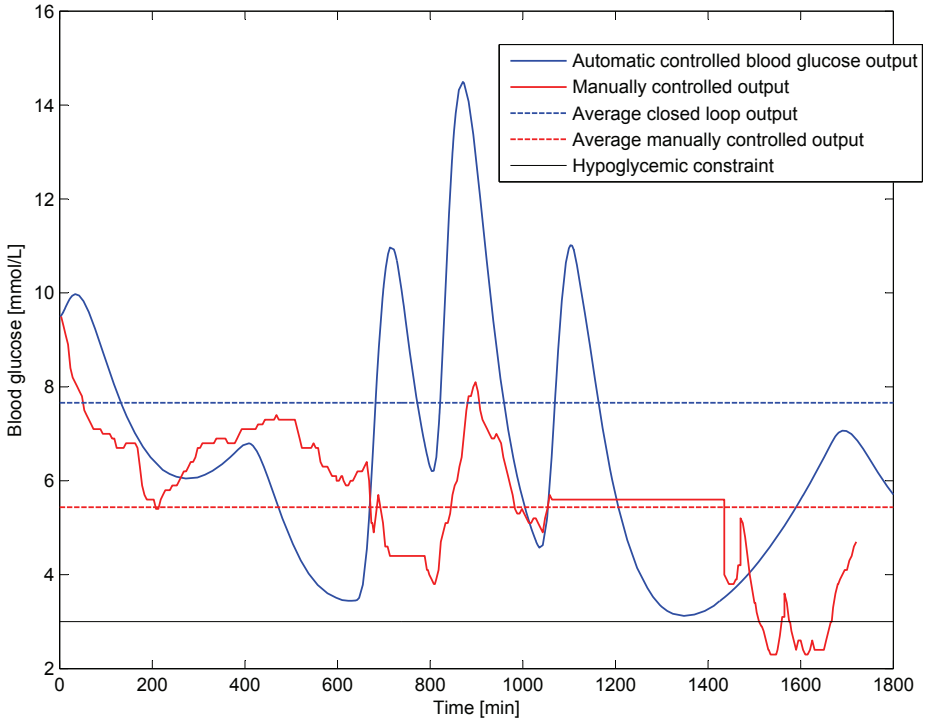



**Figure 39:** Comparison between manually administered and automatically controlled blood glucose with feed forward implemented.

# Appendix B Attached files

Here is a short explanation of the attached files.

**load_patient_data.m** Loads the data sets of each patient from excel sheets into the MATLAB workspace. This file has to be run initially.

**model_simulation.mdl** Simulink diagram of the model structure with inputs obtained from the measured data sets.

**iddata_anydataset.m** Creates an iddata object z from the information of anydataset. The iddata object is used in the model identification algorithm Identify_anydataset.m.

**glucose.m** Describes the model structure and defines the value of the fixed parameters. The idnlgrey-model created here is used in the model identification algorithm identify_anydataset.m

**identify_anyset.m** Identifies the optimal parameter set of anyset, by comparing the iddata information from iddata_anydataset.m and the idnlgrey model structure defined in glucose.m.

**online_estimation.m** File used for the adaptive estimation of insulin sensitivity parameter $K_{is}$.