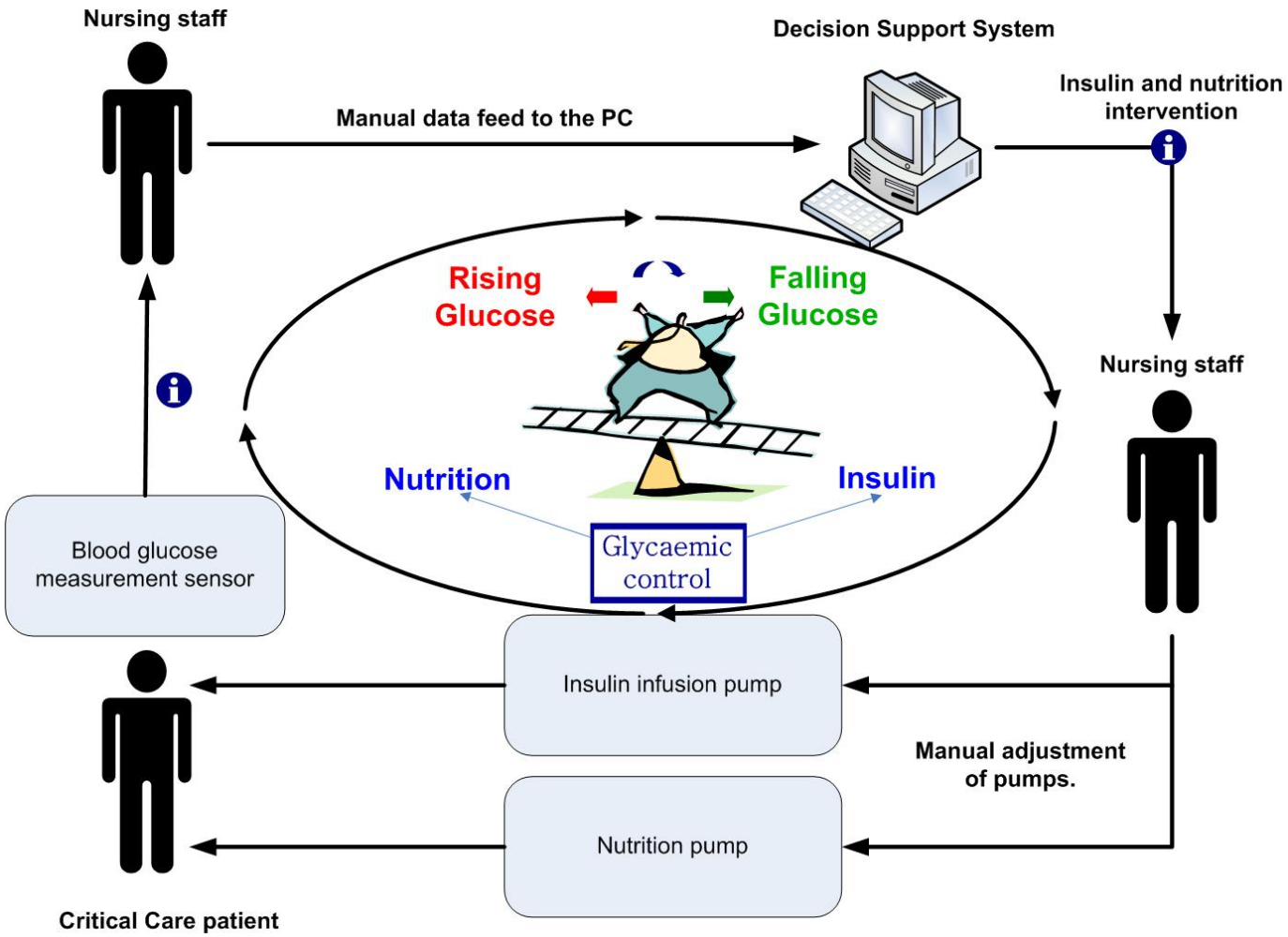
Decision Support for treatment of critically ill patients in intensive care.



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Institut for Sundhedsteknologi

10. semester 2008 – Gruppe 08gr1088e

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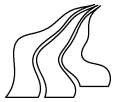

Title:
'Decision Support for treatment of critically ill patients in intensive care.

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Group member:
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Synopsis:

Background: Hyperglycaemia is prevalent in critically ill patients and can increase mortality. This report presents and validates a glycaemic control system using a physiologically based metabolic control model (Glucosafe) and an associated integral based parameter identification method. The intended application for this glycaemic control system, and the associated model and parameter identification method is glycaemic control of critically ill patients. Methods: The glycaemic control system uses the Glucosafe glucose-insulin metabolic model. Time varying insulin sensivity, S_I, is determined between measurements using an integral-based method. The glycaemic control system is validated by its ability to keep patients in a normoglycaemic range (4.4-7.75 mmol/L). Clinical control interventions are determined by optimization over a series of penalty functions. The system is validated against 20 virtual patients by using patient specific insulin sensivity profiles based on clinical data from 20 critical care patients at Christchurch Hospital (New Zealand). Results: The overall median blood glucose concentration for all 20 patients is 6.05 mmol/L, and the IQR is 5.54-6.62 mmol/L. The overall number of hypoglycaemic measurements per patient is 0 (blood glucose measurements below 2.2 mmol/L). The overall mean percent of measurements inside the normoglycaemic range (4.4-7.75 mmol/L) is 87.7 %. Conclusions: The results for the glycaemic control validation presented are comparable to other similar studies by Chase et al. (2008) and are acceptable for later use in clinical pilot trials.

Chapter 1

Preface

This report represents my collection of worksheets, and together with my two articles named *Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model* (Article 1) and *Development and Validation of a Decision Support System for Critically Ill Patients utilizing the Glucosafe Glycaemic Control Model* (Article 2), is this my (Group 08gr1088e) written result of the 9. and 10. semester of my study of Health Science and Technology at Aalborg University in the period from 1. September 2007 to 2. June 2008.
The study is written under the area of specialisation of Medical Signals and Systems (MSS, AAU) and Model-based Medical Decision Support (MMDS, AAU). The study is accomplished on the basis of the research of Steen Andreassen, Ulrike Pielmeier (MMDS, AAU) and Geoffrey J. Chase (University of Canterbury, Dept. of Mechanical Engineering - New Zealand.). The study is intended to solve a specific health technological problem thesis regarding medical decision support for glycaemic control.
The report contains introduction for the problem background, followed by concept description, implementation and test. To fully understand the extend of this study, this report has to be read together with the two articles.

Brian Juliussen

Contents

Chapter 2

Introduction

2.1 Hyperglycaemia is prevalent for critical care patients

Written in the period from 1. September - 1. November 2007. - updated in the period from 1. April - 1. may 2008

This introduction documents the problem background of the full concept of my study of designing a glycaemic control system. More dedicated introductions to each half of my study can be seen in Article 1 and 2.

Patients who are critically ill due to surgery, trauma or life-threatening illness often require vital organ function support and often prolonged intensive care [Van den Berghe, 2002]. Many of these patients present, even with no prior diabetes, with stress induced hyperglycaemia (above 7.75 mmol/L), suggesting overall insulin resistance, due to the treatment and/or their condition [Langouche et al., 2007] [Chase et al., 2006].
These conditions are characterized by reduced inhibition of hepatic gluconeogenesis and impaired glucose uptake in insulin-sensitive tissues such as skeletal muscles [Langouche et al., 2007].

Insulin resistance and the resulting hyperglycaemia, for patients in critical care, may with time, contribute to micro- and macro-angiopathy, neuropathy and organ failure [Langouche et al., 2007].

A number of clinical studies, beginning with a milestone study by Van Den Berghe in 2001, showed a significant relationship between the mortality of patients and high blood glucose concentrations [Van den Berghe et al., 2001].
Tight glucose control has been shown to reduce mortality by up to 43 % [Chase et al., 2006] [Van den Berghe et al., 2001] [Krinsley, 2004].
In addition to increased levels of insulin resistance, only limited reductions of the blood glucose concentration can be made using insulin alone [Lonergan et al., 2006a].
As a result, exogenous nutritional inputs must be reduced under certain conditions, due to excessive nutrition feeding can cause or exacerbating hyperglycaemia [Patino et al., 1999].

In critical care, with lower glucose nutrition alone has seen significant reductions in average blood glucose concentrations. [Van den Berghe et al., 2001], [Patino et al., 1999].
Hence, reduced glucose nutrition combined with insulin administration can act to control both sides (input and removal) of the glucose balance [Wong et al., 2006].

2.2 Modelling involving given nutrition and insulin

Only a few studies have been performed to control the blood glucose concentration in critical care using models, most use only exogenous insulin including: [Chee et al., 2003], [Plank et al., 2006], [Wong et al., 2006], [Vogelzang and Nijsten, 2005].
The regulation of blood glucose concentration, which is based on the mathematical models of glucose metabolism has given promising results, indicating that it is possible to achieve normoglycaemia under model-based control.

Glucosafe is a new composite model that makes use of previous work in metabolic modelling and insulin modelling [Pielmeier et al., 2008].
Mathematical models that are designed to achieve normoglycaemia have been put into the Glucosafe model, which uses information about the insulin sensitivity (S_I) and the production of the endogenous insulin (EP) [Cauter et al., 1992]. Moreover, the system also utilizes a glucose transporter model, which calculates the glucose balance for a given set of inputs and the gut absorption rate [Arleth et al., 2000].
The main use of Glucosafe is prediction of the blood glucose concentration [mmol/L].
Model-based methods, as the Glucosafe model, can be very accurate, but require the ability to identify patient specific parameters in clinical realtime to update the model dynamics. A fast, accurate patient specific parameter identification method is therefore also important in the process of refining and testing this type of model. More importantly, a fast, accurate method also enables real-time application of model-based control and medical decision support applications.
The identification method uses an integral based approach, which together with Glucosafe can model a patients blood glucose concentration accurately by utilizing the time varying patient parameter insulin sensivity (S_I).

2.3 Limitations and the aim of this study

The aim of this study is to use the Glucosafe model, and develop it to also incorporate an integral parameter identification method, and the use of penalty functions into an advice module. These penalty functions are used in glycaemic control process, where the advice module predicts the outcome of a insulin [U/h] and nutrition [ml/h] intervention. Thus, every blood glucose predictions that are made, has to be examined in terms of the quantities of exogenous insulin usage, nutrition given to the patient, and the current concentration of the patients blood glucose. The goal is then to find the prediction with the lowest sum of penalties, via optimization calculation. The final validation aims to be virtual trials, where the glycaemic control system is validated against virtual patients.

Even though this project, because of the limited time frame, stops at virtual trials, this area of research, using Glucosafe and the advice module is an ongoing process which will lead to also include a user friendly user interface to work as a decision support system for medical staff. The future decision support system is intended to work together with the medical staff, and help them controlling a patients blood glucose concentration, in terms of presentations what the near future feeding- and exogenous insulin rate should be.
Therefore the result documented in this report is to develop a proof of concept system, which in the future when added a user friendly interface, can give the medical staff a computerized

decision support system to improve patient management and provide tight glycaemic control.

Out of the prior introduction, the thesis statement can be formulated:

How is it possible to design and implement a glycaemic control system to work as decision support for treatment of virtual patients created upon critically ill patients in intensive care? How is it possible when the glycaemic control system has to be build upon the Glucosafe model, an integral based parameter estimation method and penalty functions?

Chapter 3

Method

3.1 Reading guidance

Written in the period from 1. Marts - 15. May 2008.

This report is my full collection of work sheets, and documents in a chronological manner the full work flow done during the project period. This chapter will therefore give the reader an overview of the extend of the study.

Figure 3.1 illustrates the flow of development, and does not show the full picture of the work process with the different obstacles the development of the system has been exposed for. On the other hand does this report include these development and implementations obstacles, which will be to find in section 4.2 on page 15, to document all aspects of the project together with my two articles:

- '*Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model*' (Article 1).
- '*Development and Validation of a Decision Support System for Critically Ill Patients utilizing the Glucosafe Glycaemic Control Model*' (Article 2)

These two articles are not included in this report.
However, an early (and UNEDITED) edition of the article '*Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model*' (Article 1 old) can be found in the Appendix of this report to illustrate the total work progress.

To see all patientdata used in this report and the figures in full size use the DVD located in Appendix A.3 on page 82.

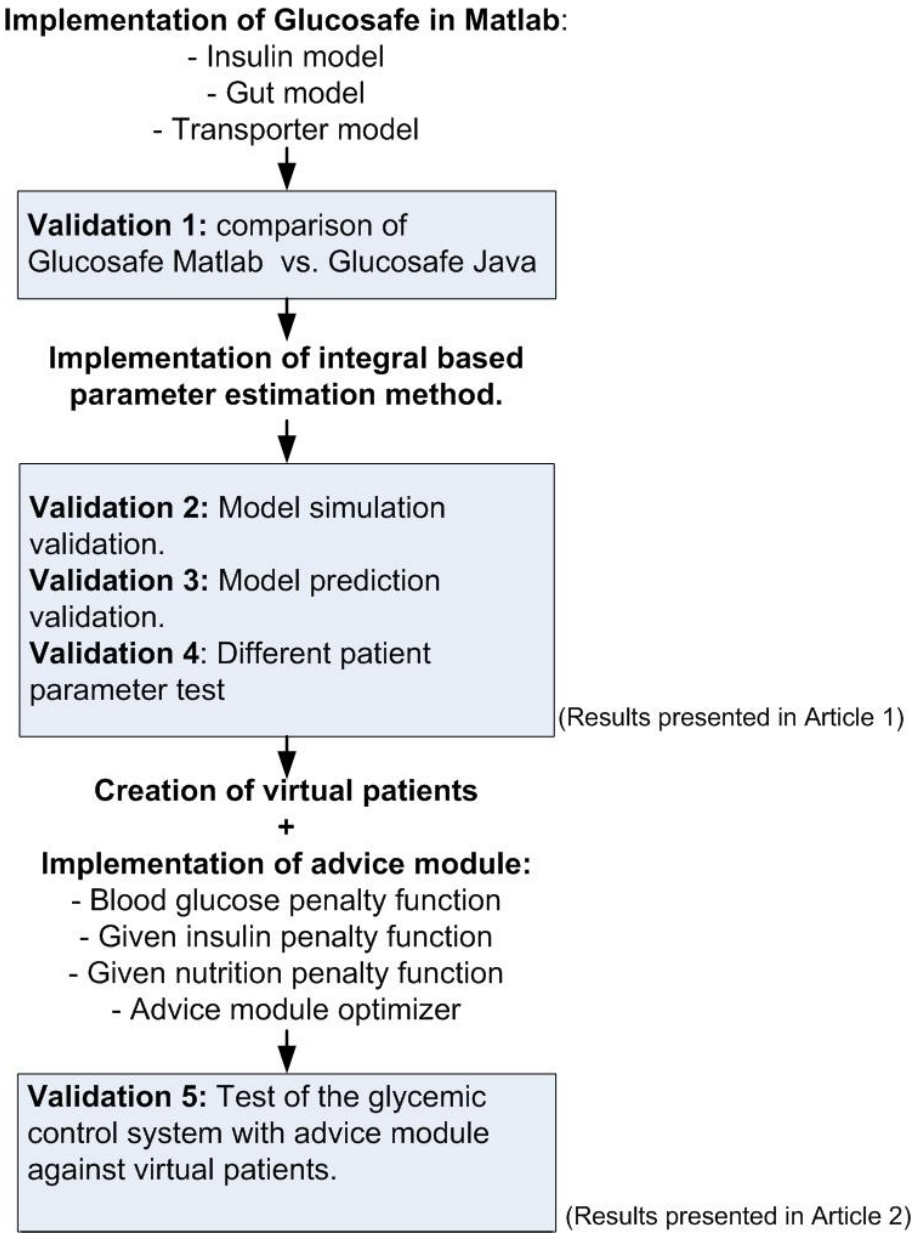

Figure 3.1: *This illustrates the different main steps and tests during the development of the system.*

3.2 Overview over the full concept

The purpose of the section is to give the reader an overall overview of the concept of the full system.

Figure 3.2 illustrates the dynamics of the full glycaemic control system concept which is validated in the final test in 'Validation 5' in Figure 3.1 on the previous page. To develop the system model (and the belonging penalty functions) patient data are needed.

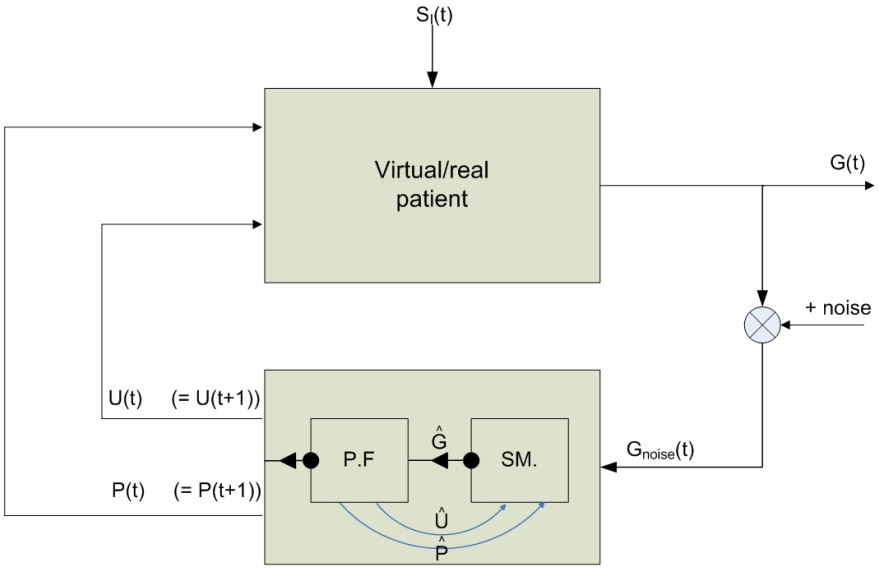

Figure 3.2: *This illustrates the general flow of the glycaemic control system. Also how known inputs from virtual patients are used to implement and fine tuning of the system model (SM.) and the penalty functions (P.F.)*

Figure 3.2 shows that the patient data can come from real patients, or virtual patients, in the shape of sampled data from real patients, also known as the virtual trial data, see Appendix A.2 on page 80 for documentation of the SPRINT dataset.
Data from the patients includes data about the blood glucose (G(t) [mmol/L]) and the control process, in terms of given nutrition (U(t) [ml/h]) and given insulin (P(t) [U/h]).
The sampled blood glucose measurement includes sampling noise from the blood glucose sampling device, therefore the blood glucose used as input is $G_{noise}(t)$.
After having found an advice solution in terms of a new P(t) and U(t) these are used in the physiological model to get a new blood glucose prediction, which keeps the patients blood glucose concentration normoglycaemic (4.4-7.75 mmol/L).
This complete process happens once every hour, so the first change in the blood glycose concentration is expected to show after one hour. Next hour the penalty functions produces a new result as U(t+1) and P(t +1), and so on. Furthermore, the system model also uses an estimate of the insulin sensitivity (S_I). This parameter is estimated and updated once every hour during the procedure, to give the a optimum glycaemic control for each specific patient with different S_I profile.

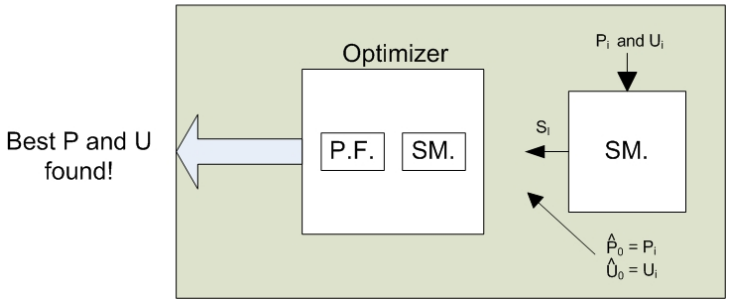

Figure 3.3: *This figure points out the essential steps in the advice process - also given as an overview in Figure 3.2 on the preceding page. P is given insulin [U/h] and U is given nutrition [ml/h]*

Figure 3.3 illustrates the advice module optimizer utilizing the system model, integral based parameter estimator and penalty functions.
The advice process illustrated in Figure 3.3 is created as the following:

1: Create system model to simulate a patients blood glucose.

2: Add a parameter estimator to the system model, which then will have the ability to estimate patient specific parameters in terms of the time varying insulin sensivity (S_I).

3: Create penalty function shapes templates.

4: Created advice module optimizer.

5: Fit the shapes of the penalty functions by using the advice module optimizer in tests.

6: Optimum and fitted penalty function shapes are found, hence the best possible glycaemic control for virtual patient cohort.

Chapter 4

Model Development and Implementation

4.1 General description of system

Written in the periode from Thursday the 27. Marts - 15. May 2008

In this section the intended later development of glycaemic control system into a decision support system is being defined and general described. Furthermore, the area of application and the system environment is described.
The purpose of this section is to identify the clinical context, of which the future system of this study has to be used in, and to make a basis for the further development of the glycaemic control system implemented and tested in this report.

Figure 4.1 illustrates the hardware which are needed to use the decision support System. This project only focus on the software on the PC of the glycaemic control system, and does therefore not involve all the necessary hardware to be seen in Figure 4.1. However, in a future clinical situation, the glycaemic control system needs a blood glucose measurement device, a insulin infusion pump, a nutrition pump, and medical staff for blood glucose measurements, adjustments of the pumps and control of the decision support system (the glycaemic control system and user interface).

Area of application

The glycaemic decision support system documented in this chapter aims to help critical ill patients, placed in the ICU in a longer period. The goal of the system is to reduce the episodes of which the critical ill patients suffer from hypoglycaemia and hyperglycaemia, and increase the normoglycaemic periods of which the blood glucose concentration ranges between 4.4-7.75 mmol/L, see Appendix A on page 78.
It is intended that the decision support system has to be implemented as an addition to the existing hardware in the ICU, in terms of insulin-, nutrition pumps and blood glucose measurement equipment. The decision support system has to be implemented on a stand alone independent PC.

As mentioned in the introduction the consequents for critical ill patients suffering from hypoglycaemia or hyperglycaemia can be severe. Therefore the goal of the system is to reduce

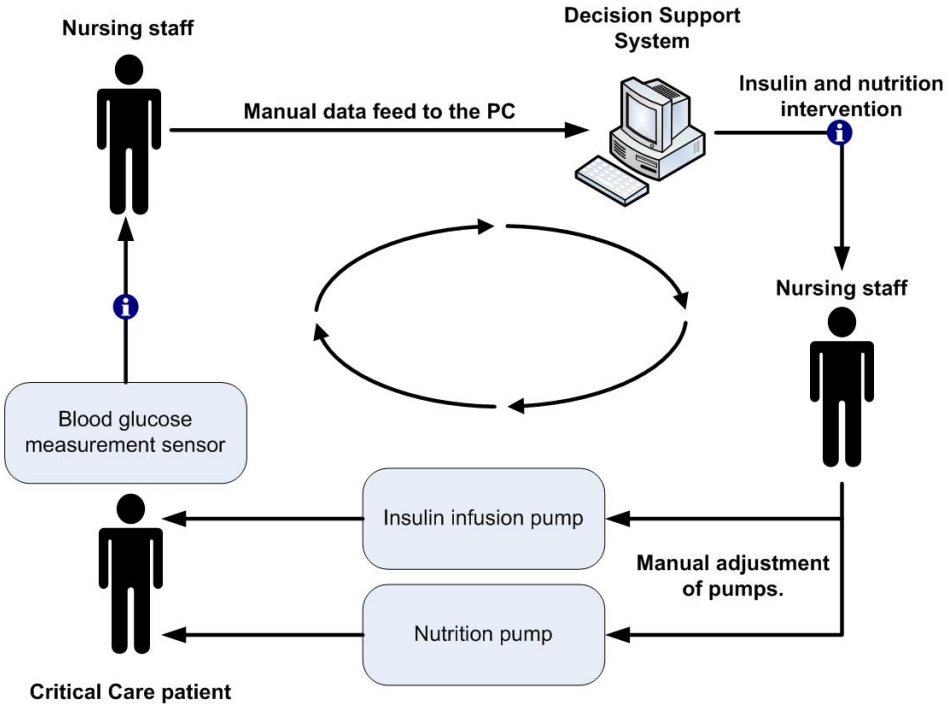

Figure 4.1: *This figure shows an overview of the involved hardware in the system and the actors that the glycaemic control system has to work with when it is developed to work as a decision support system. As the figure illustrates, the glycaemic control of a patient is a repeating process, repeated every time a new blood glucose measurement is available, which depends of the medical staff.*

these outcomes, but if the medical staff wants to ignore the intervention advices which the system produces, this is accepted, and the system will calculate the next intervention advice as normal. Therefore this system has to be seen as a supplement to the medical staffs own clinical knowledge and expertise.
The decision support system needs to be fed with data from the medical staff, in terms of given insulin [U/h], given nutrition [ml/h] and measured blood glucose [mmol/L]. Furthermore, before monitoring starts for a specific patient, the system needs to know this specific patients age, gender, weight, height, and if the patients suffer from diabetes type 1 or 2.

Moreover, will the decision support system which except a user interface is developed during this project and presented in this report, also be a valuable research tool, due to the ability to save all modelling data from a patient in terms of measured blood glucose, calculated blood glucose concentration, continues plasma insulin concentration, continues peripheral insulin level, interventions, gut content, gut absorption and the patients insulin sensivity (S_I).

System environment and involved hardware

The decision support systems environment involves 4 elements: The medical staff, the blood glucose measurement device, the insulin infusion pump and the nutrition pump.

Medical staff: In the future edition of the system, fully implemented in the ICU, the only user will be the medical staff for feeding the system with latest measured blood glucose, and the latest set of interventions, in terms of given insulin and given nutrition.

Blood glucose measurement device: This device measures the patients blood glucose, and displays the result on a screen, of which the medical staff has to type into the user interface in the glycaemic decision support system. How often the patients blood glucose is measured, depends of the medical staff.

Insulin infusion pump: The insulin infusion pump injects insulin into the critical ill patients vein. The dosis at which this happens depends of the medical staff. The insulin infusion pump can be configured to inject the insulin in a continues insulin infusion, or as a insulin bolus, depending of the medical staff.

Nutrition pump: The nutrition pump feeds the critical ill patient with various types of nutrition. The type of nutrition and the feed rate depends of the medical staff.

4.2 Glucosafe

Written in the periode from Monday the 29. October to 4. November 2007 - updated in the period from 1. May to 1. June 2008

This section describes the concept and my implementation of the insulin, gut and glucose modelling of the Glucosafe model.

The modelling part of the glycaemic control system, without the advice module is the physiological model-based glycaemic model, Glucosafe, from Aalborg University [Pielmeier et al., 2007]. The main function of this model is to predict the development in a patients bloodglucose concentration during the stay on the ICU. The model needs information about given insulin [U/h] and nutrition [ml/h].
As described in the Introduction Glucosafe is a new composite metabolic system model, which

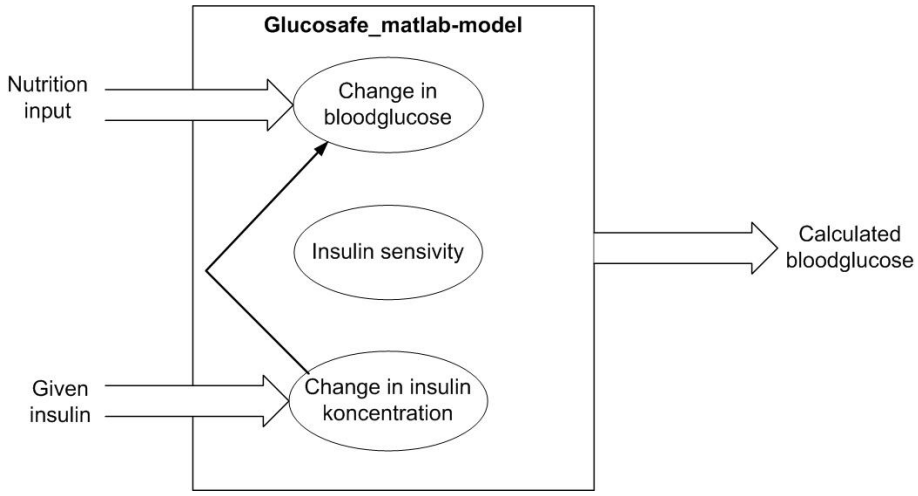

Figure 4.2: *This illustrates the Glucosafe model as a box with known inputs and the calculated output.*

makes use of previous research and models in insulin and metabolic modelling [Pielmeier et al., 2007] [Chase et al., 2008c] [Lotz, 2007] [Lotz et al., 2008] [Cauter et al., 1992] [Arleth et al., 2000].
The work progress has therefore been influenced by multiple a priori factors [Arleth et al., 2000] [Cauter et al., 1992] [Pielmeier et al., 2007]. Later, in section 4.3 the implementation of Glucosafe will be documented in a more thorough manner by using diagrams for illustrating the process.

4.3 Model overview

Except the modelling of the insulin kinetics [Cauter et al., 1992], Glucosafe represents the Transporter model [Arleth et al., 2000]. The kinetics of the underlying physiology in the Transporter model is illustrated in Figur 4.3 on the next page, where it illustrates the dynamics and behavior in the glucose transporter model.

After having identified the behavior in the Transporter model and the insulin kinetics model, all physiological sub-parts can be defined, which all are subparts of the overall model illustrated in

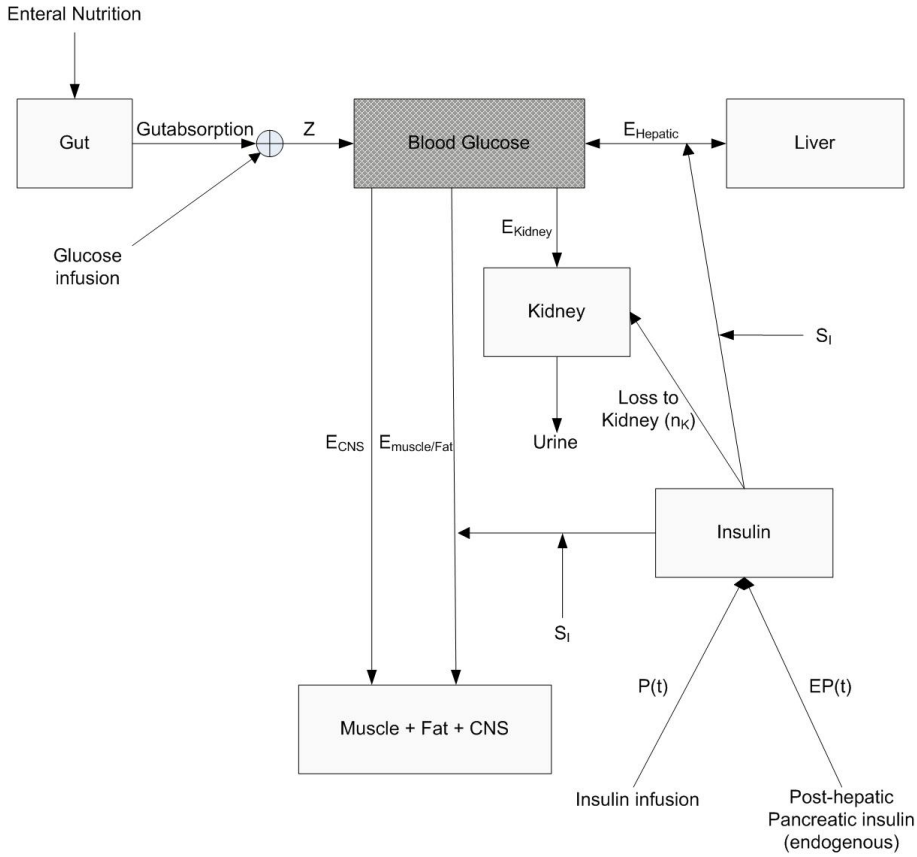

Figure 4.3: *Glucosafe physiological overview, where exogenous insulin is assumed to be intravenous. In this figure CNS = central nerve system, which together with the muscle cells, fat cells, liver and kidney results in a negative change in blood glucose (and a positive change in the blood glucose if the concentration is very low). The enteral nutrition and glucose infusions result in a positive change in blood glucose.*

Figure 4.3.
In the following paragraphs these are listed as functionalities in the Matlab implementation of the Glucosafe model:

Calculation of change in insulin concentration (Insulinchange): A part of the model has to calculate the change in plasma and peripheral insulin concentration [mU/L], by using knowledge about the given insulin ($P(t)$ [U/h]) and the endogenous insulin production ($EP(t)$ [mU/min]).

Calculation of the amount of available active insulin (Insulinsensivity): When knowing the insulin concentration [mU/L], it is also necessary to know how big a part of the available insulin is actually used in the muscle and fat cells (active insulin). To do this calculation the patient specific parameter insulin sensivity S_I is needed.

Calculation of change in blood glucose concentration (Bloodglucosechange): Calculation of the change of the current blood glucose concentration, is done by knowing the glucose input from the gut and glucose infusions, and by calculating the usage of blood glucose in kidney, muscle cells, fat cells, the central nerve system and liver.

Calculation of sum of absorption (Glucoseinput): The input in glucose (Z) [$mmol/(kg \times$

min)] is found by adding the nutrition input from intravenous nutrition and enteral nutrition. Enteral nutrition passes through the gut, and therefore the rate of absorption in the gut has to be calculated before the sum of absorption (Z) is known.

Model controller: The Glucosafe is a mathematical model simulation of the concentration of blood glucose for a patient during a certain time periode. Each of the previous subparts work as input-output functions. Therefore there need to be a model-controller that uses all subparts to calculate a patients blood glucose..

To complete the documentation of the code architecture of the Matlab implemented Glucosafe model, there also need to be sub parts to handle the data input in terms of given insulin and nutrition. These parts are identified to be the following:

Setup: Before the model can simulate the development of blood glucose concentration for a specific patient, there has to be a setup function to load all necessary data about this patient to be given to the model.

Getdata: During the simulation, the function Getdata handles the preloaded patient data from the Setup function to continually feed the model with data.

Next, each of the listed part of the model are explained, in terms of description and implementation.

Insulinchange

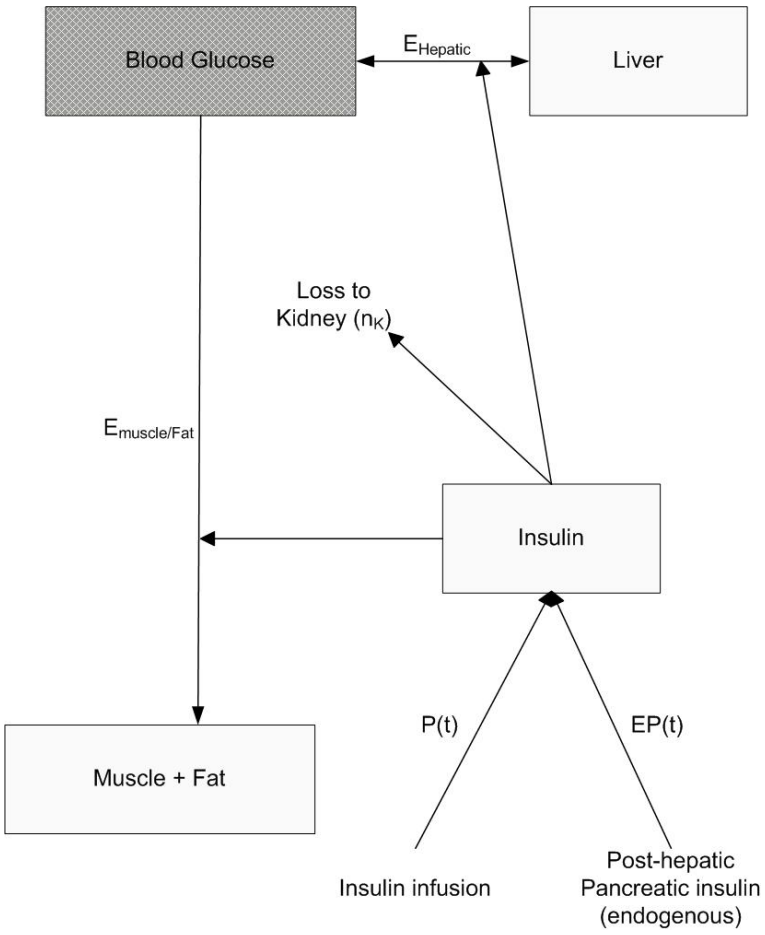

Figure 4.4: *This figure illustrates the scope of the insulin modelling in Glucosafe.*

The implementation of the insulin part of Glucosafe is performed by using previous work in insulin modelling [Arleth et al., 2000]. Furthermore, the endogenous insulin production, EP [mU/min], is set as a constant at 27.77 mU/min.
As seen on Figure 4.4 the insulin stimulates the glucose uptake for muscle and fat cells, and also stimulates the hepatic balance (between blood plasma and the liver).
The purpose of modelling the insulin part is to calculate both the insulin concentration in the plasma compartment (I [mU/L]) and the insulin concentration in the peripheral compartment (Q [mU/L]).
The two main equations in the insulin modelling is equation 4.1 and 4.2 [Arleth et al., 2000], which calculates the insulin concentration in the plasma and peripheral compartment, also shown in figure 4.5 on the facing page.

$$\frac{dI}{dt} = (-n_K - n_L) * I(t) - \frac{n_I}{V_P} * (I(t) - Q(t)) + \frac{P(t) + EP(t)}{V_P} \tag{4.1}$$

$$\frac{dQ}{dt} = -n_C * Q(t) + \frac{n_I}{V_Q} * (I(t) - Q(t)) \tag{4.2}$$

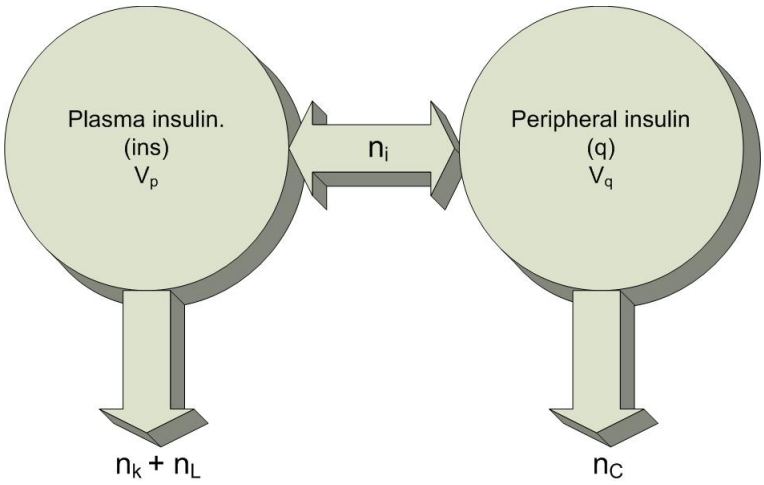

Figure 4.5: *This figure illustrates the kinetics of insulin in the model. Where muscle cells, fat cells and the hepatic balance are insulin dependent.*

The calculation of and the change in plasma insulin concentration $I(t)$ [mU/L] and the change in peripheral insulin concentration $Q(t)$ [mU/L] depends on the parameters n_L, n_C and V_Q defined in [Pielmeier et al., 2008], and n_K, n_I and V_P, which are functions of basic patient parameters, defined in [Cauter et al., 1992].
The parameter n_K is the kidney clearance $[min^{-1}]$, n_I is the transport rate between the plasma and peripheral compartments $[L/min]$, n_L is the liver clearance $[min^{-1}]$ and n_C is the irreversible loss of insulin in the periphery $[min^{-1}]$. Finally, V_P is the plasma volume [L] and V_Q is the peripheral interstitial volume [L]. The patient specific parameters are calculated in the Glucosafe model by using the patients gender, age, height, weight and diabetic state, and are set as static for the patient during the glycaemic control procedure [Pielmeier et al., 2008] [Cauter et al., 1992].

Implementation of 'Insulinchange'

As mentioned before, the calculation of I(t) and Q(t) happens in two fases, represented in two equations. When implemented in Matlab this is done using two m-files, respectively named *plasmainsulinchangefunction.m* and *periphinsulinchangefunction.m*, for calculation of change in concentration of plasma insulin $I(t)$ [mU/L] and the change in concentration of peripheral insulin $Q(t)$ [mU/L].
Furthermore, *periphinsulinchangefunction.m* uses the m-file *constants.m*, to the calculation of n_C, presented in Equation 4.3, which is needed to the calculation of change in the peripheral insulin concentration:

$$n_C = \frac{n_I \times (I/Q - 1)}{V_Q} \tag{4.3}$$

The following table illustrates the input-output relations in these functions:

function name	plasmainsulinchangefunction.m
Input	$I(t)$, $P(t)$, $Q(t)$, n_I, n_L, n_K, V_P, V_Q
Output	$I(t+1)$, $Q(t+1)$
function name	periphinsulinchangefunction.m
Input	$I(t)$, $Q(t)$, n_I, V_Q
Output	$Q(t+1)$
function name	constants.m
Input	(none)
Output	$GAMMA$

Figure 4.6 illustrates the code architecture of the calculation of insulin.

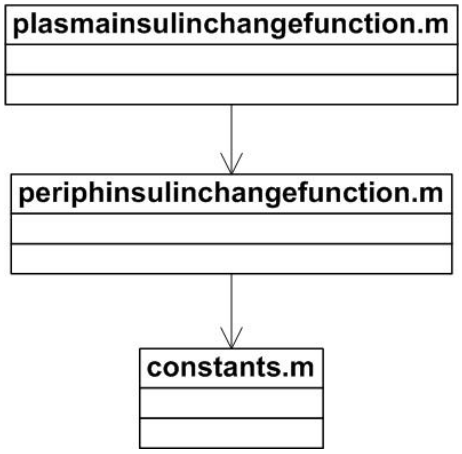

Figure 4.6: *This figure illustrates that plasmainsulinchangefunction.m uses periphinsulinchangefunction.m to calculate change in $I(t)$ and $Q(t)$. Furthermore, periphinsulinchangefunction.m uses constants.m to calculate n_C - the irreversible loss of insulin because of binding to cells*

Insulinsensivity

The implementation of the insulin sensivity has been done by using a modification [Pielmeier et al., 2008] of a previously published nonlinear transformation method [Arleth et al., 2000]. As seen on figure 4.7 the insulin sensivity, S_I, decides the fraction of the total amount of insulin that is active insulin, $A(t)$, that stimulates the uptake of glucose in muscle and fat cells, and the hepatic balance.
The method to calculate the fraction of existing insulin that is active insulin, $A(t)$, is shown in

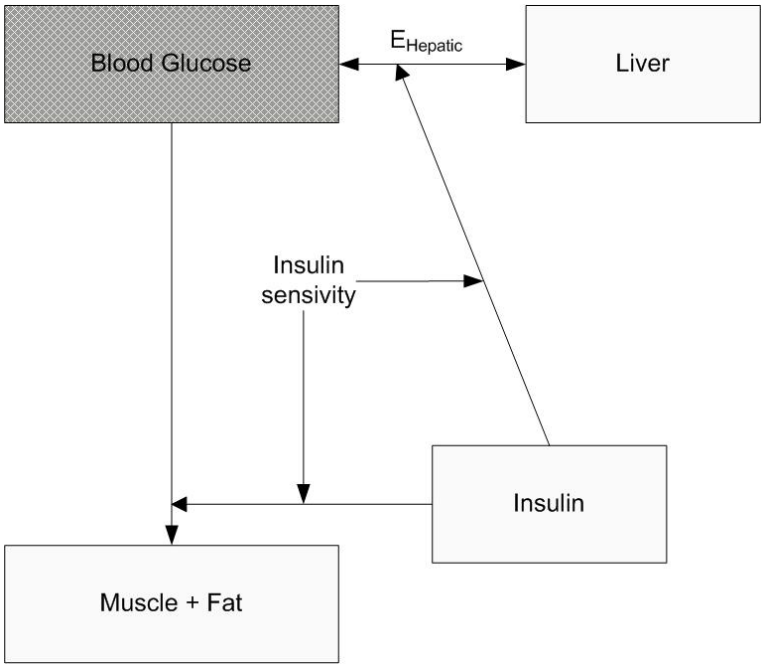

Figure 4.7: *Simplified model of which processes the insulin sensivity controls, which is the hepatic balance, and the glucose uptake from muscle and fat cells*

the following equations (modification from Arleth et al. [Pielmeier et al., 2008]):

$$Ins_{absorption} = \frac{Q(t) * GAMMA}{C} \tag{4.4}$$

where $Ins_{absorption}$ is the insulin absorption rate [mU/kg/min]. The constant $GAMMA$ (value = 5/3) is the steady state gradient between plasma and interstitium, that is used to calculate the maximum amount of active insulin in the interstitium. C (value = 98.1 $[kg \times min/L]$) is the default conversion factor to convert the $Ins_{absorption}$, from absorption to plasma value.

$$f(Q(t)) = \frac{Ins_{absorption} - I_0}{\sqrt[d]{(Ins_{absorption} - I_0)^d + k^d}} \tag{4.5}$$

$f(Q(t))$ is the nonlinear result from $Ins_{absorption}$, by meaning that $f(Q(t))$ is the nonlinear effect (fraction of maximum endogenous balance) from the insulin infusion [U/h] and insulin presence [mU/L] [Katz et al., 1993], [Rizza et al., 1981].
k (value = 0.539) and d (value = 1.773), both $[mU/(kg \times min)]$, are fitting constants for $f(Q(t))$ in equation 4.5, and I_0 is the fasting steady state specific insulin absorption $[mU/(kg \times min)]$ (value = 0.083).

It is convenient to have values of $f(Q(t))$ in the range 0-1, therefore $f(Q(t))$ is subjected to a linear transformation into the range:

$$f(Q(t))' = \frac{f(Q(t)) - f(0)}{1 - f(0)} \tag{4.6}$$

where $f(Q(t))'$ is the range-transformed nonlinear fractional insulin effect.
The final result is given in equation 4.7:

$$A(t) = f(Q(t))' \times S_I \tag{4.7}$$

After using Equation 4.7, $A(t)$ represents the actual fraction of the insulin in the peripheral compartment that is active. In other words $A(t)$ can be defined to be the physiological limit of the potential amount of insulin used in the peripheral compartment, meanwhile S_I is a multiplication factor for $A(t)$ and thus to decide how big a part of the available insulin in the peripheral compartment that is active. Hence, S_I have influence on the change of blood glucose concentration.

Model-based methods can be very accurate, but require the ability to identify patient specific parameters, such as the S_I in clinical realtime to update the model dynamics. A fast, accurate identification method is therefore important in the process of refining this type of model. An integral based parameter estimation method to calculate and update the S_I value used in the model is explained in section 4.5 on page 35.

Implementation of 'Insulinsensivity'

'Insulinsensivity' is implemented in Matlab this is done using two functions, respectively named *activeinsulinglucosafefunction.m* and *nonlineartransformation.m*, for calculation of active insulin, $A(t)$.
The following table illustrates the input-output relations in these functions:

function name	activeinsulinglucosafefunction.m
Input	$Q(t)$, S_I
Output	$A(t)$
function name	nonlineartransformation.m
Input	$Ins_{absorption}$
Output	$f(Q(t))'$

Figure 4.8 on the next page illustrates the code architecture of the calculation of A.

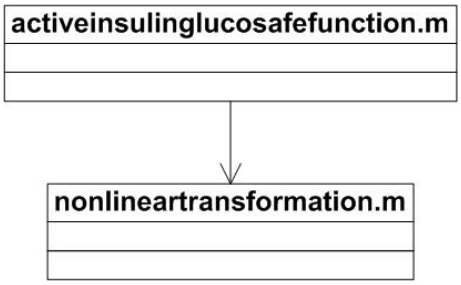

Figure 4.8: *This figure illustrates that activeinsulinglucosafefunction.m uses nonlineartransformation.m to calculate 'Active insulin'*

Bloodglucosechange

The implementation of calculation of the blood glucose is done by using previous research concepts [Arleth et al., 2000].
As seen on Figure 4.9 The calculation of change in blood glucose concentration [mmol/L] is a result of the sum of glucose input and the sum of glucose usage in liver, central nerve system, muscle cells, fat cells and the kidney [Arleth et al., 2000]. Pharmacodynamic changes in

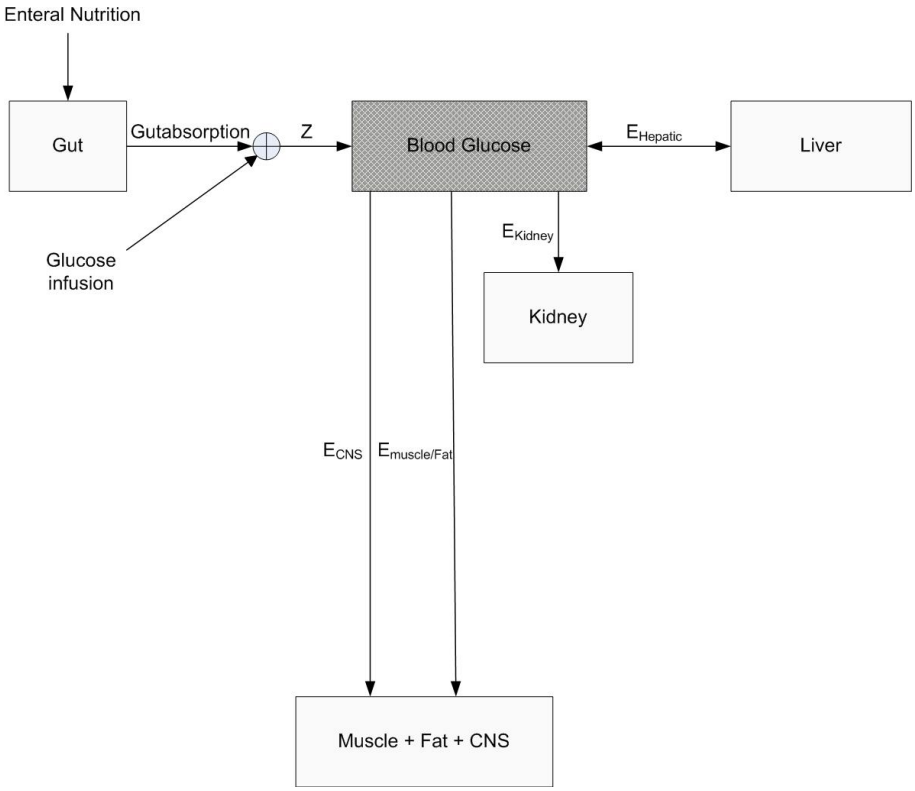

Figure 4.9: *Simplified model of the change in blood glucose due to the sum of glucose input from the gut and glucose infusion, and the total glucose usage in muscle cells, fat cells, CNS, kidneys and the liver.*

blood glucose concentration, due to endogenous and exogenous inputs of insulin and nutrition are illustrated in Figure 4.9 and are defined [Pielmeier et al., 2007] [Arleth et al., 2000]:

$$\frac{dG}{dt} = (Z(t) + E_{Hepatic}(G, A) - E_{Kidney}(G, BSA) - E_{CNS}(G) - E_{Muscle/Fat}(G, A)) \times (BM/GV) \tag{4.8}$$

where $Z(t)$ is the sum of absorption from the nutrition input $[mmol/(kg \times min)]$, $E_{Hepatic}(G, A)$, $E_{Kidney}(G, BSA)$, $E_{CNS}(G)$ and $E_{Muscle/Fat}(G, A)$ (all $[mmol/(kg \times min)]$) are the turnover of blood glucose to the liver, kidneys, fat cells and muscle cells, respectively ($E_{Hepatic}$ is bidirectional transport of glucose to and from the liver). BSA is the patients body surface area $[m^2]$ and is used to calculate the renal glucose clearance, described in Equation 4.10 on the facing page. The mass-volumen quotient BM/GV [kg/L], which is the bodymass (BM) [kg] divided by the glucose distribution volume (GV) [L], can be calculated by knowing the patients weight [Pielmeier et al., 2008]. The glucose distribution volume is defined to be 0.19 [(L/kg)·BM] [Pielmeier et al., 2008]. The constants in Equations 4.9 on the next page, 4.11 on the facing page and 4.12 on the next page are explained in Table 4.1, where $A(t)$ is the active insulin.

Name of constant	Value
$Hepatic_1$	0.46 L/(kg·min)
$Hepatic_2$	1.475 mmol/(kg·min)
$Hepatic_3$	1.34 mmol/(kg·min)
CNS_1	0.56 mmol/(kg·min)
CNS_2	1.5 mmol/l
$Muscle/Fat_1$	5.09 mmol/(kg·min)
$Muscle/Fat_2$	5 mmol/l

Table 4.1: List of constants used to calculate the sum of glucose usage in the kidneys, liver, CNS and fat/muscle cells

The parameters $E_{Muscle/Fat}(G, A)$ and $E_{Hepatic}(G, A)$ represent the peripheral uptake of GLUT4 transporters (S_I dependent), and the parameter $E_{CNS}(G)$ and $E_{Kidney}(G, BSA)$ represents the peripheral uptake of GLUT1 and GLUT3 transporters (S_I independent) [Arleth et al., 2000]. $E_{Hepatic}(G, A)$, $E_{Kidney}(G, BSA)$, $E_{CNS}(G)$ and $E_{Muscle/Fat}(G, A)$ are defined [Arleth et al., 2000]:

$$E_{Hepatic}(G, A) = -Hepatic_1 \times G(t) - Hepatic_2 \times A(t) + Hepatic_3 \tag{4.9}$$

$$E_{Kidney}(G, BSA) = SMOOTH(max(0, GFR(BSA) \times G(t) - T_{max})) \tag{4.10}$$

The renal reabsorption saturates when a blood glucose concentration exceeds 10-15 mmol/L. The maximal reabsorption rate T_{max} is 120 mmol/h [Rave et al., 2006]. The glomerular filtration rate GFR is 7.2 L/h per 1.73 m^2 body surface area. The function $SMOOTH()$ is a function that calculates a 7 mmol/L wide moving average.

$$E_{CNS}(G) = CNS_1 \times \frac{G(t)}{G(t) + CNS_2} \tag{4.11}$$

$$E_{Muscle/Fat}(G, A) = Muscle/Fat_1 \times A(t) \times \frac{G(t)}{G(t) + Muscle/Fat_2} \tag{4.12}$$

The functions $E_{CNS}(G)$ and $E_{Muscle/Fat}(G, A)$ are both Michaelis-Menten functions, thus they both have a saturating effect, depending on the blood glucose concentration [mmol/L].
The resulting new blood glucose concentration [mmol/L] is presented:

$$Newbloodglucose = \frac{dG}{dt} + oldbloodglucose \tag{4.13}$$

Implementation of 'Bloodglucosechange'

When implementing 'Bloodglucosechange' in Matlab this is done using 6 Matlab functions. The functions have the names *bloodglucosechangefunctionendobal.m*, *glucoseturnover.m*, *glucoseturnoverrenalclearence.m*, *glucoseturnoverperi4.m*, *glucoseturnoverextendhepbal.m* and *glucoseturnoverextend.m*.
As seen in Figure 4.10 on page 27 the function *bloodglucosechangefunctionendobal.m* is the main function in 'Bloodglucosechange', and therefore uses the other functions to calculate $Newbloodglucose$ from Equation 4.13.
The function *glucoseturnover.m* calculates $E_{turnover}(G, A)$ by using the four functions *glucoseturnoverrenalclearence.m*, *glucoseturnoverperi4.m*, *glucoseturnoverextendhepbal.m* and *glucoseturnoverextend.m*.

Equation 4.8 on page 24 describes that the change in blood glucose is a result from the turnover of blood glucose to the liver, kidneys, fat cells and muscle cells and Z, which is the sum of absorption.
The following table illustrates the input-output relations in the functions for 'Bloodglucosechange' (the turnover of blood glucose to the liver, kidneys, fat cells and muscle cells).
Z is described in section 4.3 on page 28, thus are the parameters only relevant to the calculation of Z in brackets ():

function name	bloodglucosechangefunctionendobal.m
Input	BM $G(t)$, BSA, $A(t)$ (gutcontent(t)), (Enteral nutrition) (glucoseinfusion), (patienttype)
Output	$G(t+1)$, *changeinbloodglucose*, (gutcontent(t+1))
function name	glucoseturnover.m
Input	$G(t)$, $A(t)$, BSA
Output	$E_{turnover}$
function name	glucoseturnoverrenalclearence.m
Input	$G(t)$, BSA
Output	E_{Kidney}
function name	glucoseturnoverperi4.m
Input	$G(t)$, $A(t)$
Output	$E_{Muscle/Fat}$
function name	glucoseturnoverextendhepbal.m
Input	$G(t)$
Output	$E_{Hepatic}$
function name	glucoseturnoverextend.m
Input	$G(t)$, $A(t)$
Output	E_{CNS}

$E_{turnover}$ in *glucoseturnover.m* is the sum of glucose turnover from $E_{Hepatic}(G, A)$, $E_{Kidney}(G, BSA)$, $E_{CNS}(G)$ and $E_{Muscle/Fat}(G, A)$, defined by [Arleth et al., 2000].
Figure 4.10 on the facing page illustrates the code architecture of the calculation of change in blood glucose.

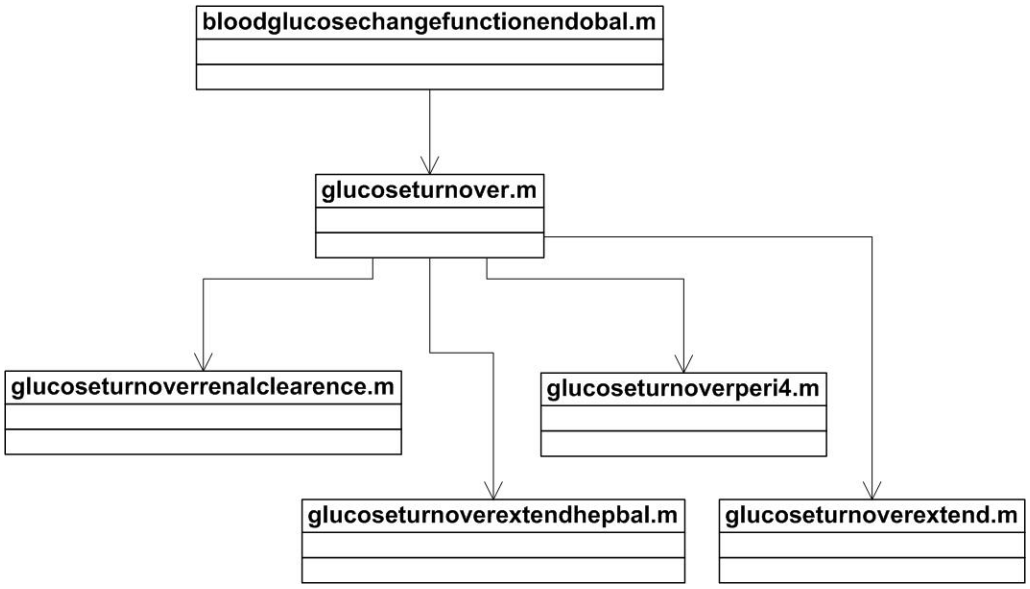

Figure 4.10: *This figure illustrates the code architecture in the calculation of change in blood glucose.*

Glucoseinput

The implementation of calculation of the glucose input, $Z(t)$ $[mmol/(kg \times min)]$, is done by using previous work [Arleth et al., 2000], .
As seen on figure 4.11 the total amount of glucose input (absorption rate, $Z(t)$) is the sum of

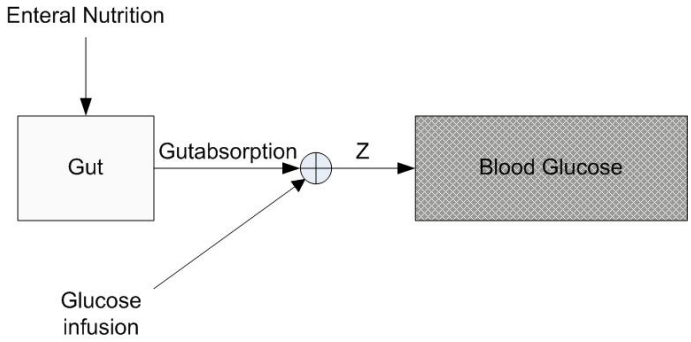

Figure 4.11: *Simplified model of the total amount of glucose input (absorption rate, Z(t)) depends on the sum of enteral nutrition and glucose infusions*

the gut absorption [mmol/kg/min] from enteral nutrition [mmol/min] and glucose infusion given intravenous [mmol/min]. The calculation of the total absorption rate, $Z(t)$, is done in the following equations:

$$\frac{dgutcontent}{dt} = \frac{enteralnutrition}{BM} - gutabsorption \tag{4.14}$$

$$gutabsorption = ((-0.026 * gutcontent^2 + 0.45 * gutcontent) * (1/60)) * K_{delay} \tag{4.15}$$

Equation 4.14 calculates the change in gut content [mmol/kg], by using the parameters *enteralnutrition* [mmol/min], *gutabsorption* [mmol/kg/min] and the patients bodymass BM. Equation 4.15 calculates the gut absorption rate [mmol/kg/min]. The constants used in 4.15 are fitting constants, defined by using previous work [Arleth et al., 2000].
Finally, the constant K_{delay} (value = 0.5), is a result of critical ill patients slow digestion (delayed gut absorption).

$$Z(t) = \frac{glucoseinfusion}{bodymass} + gutabsorption \tag{4.16}$$

Finally, Equation 4.16 calculates the total absorption rate, $Z(t)$, which can be seen in Figure 4.11. $Z(t)$ is calculated by the intravenous nutrition infusion rate [mmol/kg/min] divided by the patients bodymass, subtracted with the gut absorption rate [mmol/kg/min].

Implementation of 'Glucoseinput'

The implementation of the calculation of the glucose input in Matlab is done by using the two functions *gutcontentfunction.m* and *mealabsorbtiondiasfunction.m*.
The calculation of the gut absorption rate is done in *mealabsorbtiondiasfunction.m*, and the calculation of the change in gut content is done in *gutcontentfunction.m*. Finally, the total absorption rate, $Z(t)$, is calculated in *gutcontentfunction.m*.
The following table illustrates the input-output relations in the functions for 'Glucoseinput'.

function name	gutcontentfunction.m
Input	$gutcontent(t)$, $enteralnutrition$, BM, $glucoseinfusion$
Output	$gutcontent(t+1)$, $gutabsorption$, $Z(t)$
function name	mealabsorbtiondiasfunction.m
Input	$gutcontent(t)$
Output	$gutabsorption$

Figure 4.12 illustrates the code architecture of the calculation of total glucose input.

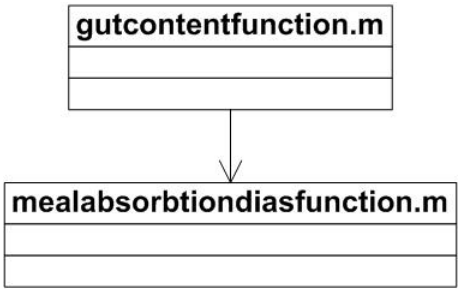

Figure 4.12: *This figure illustrates that the calculation of the glucose input is done by the functions* gutcontentfunction.m *and* mealabsorbtiondiasfunction.m

controlmodel

The physiological model-based Glucosafe is implemented using a Matlab solver function (ODE45), which is used to calculate the dynamics in the physiologic of the human body. The ODE45 solver function is a predefined Matlab tool, which calculates and continuous updates all the parameters in the included differential equations. The time line for these calculations has to be predefined, due to be an imitation of the physiological dynamics in a human body. Hence, the maximum time between the parameters are being calculated and updated, are 1 minute (fx. change in blood glucose concentration is calculated every minute).
The differential equations included in the sub parts, explained in the list in section 4.3 on page 16, have to be controlled inside and outside the ODE solver function.
The following describes the different functions in the part 'Controlmodel' in Glucosafe:

model.m: When implemented in Matlab the main m-file that runs the model is called *model.m*. The main function of *model.m* is to initiate the ODE45 solver function, which controls the model. Furthermore, *model.m* sets up the ODE45 controller, in terms of how long time the model should run, which patient data it should use and finally, saving the modelled data, after it has been through the ODE45 solver function. Finally, *model.m* include the part 'Setup' for setting up the system and organizing data, which defines the initial conditions also needed in the ODE45 solver function, such as starting points for blood glucose, insulin plasma and peripheral concentration, insulin sensivity and gut content.

glucosafehandler.m: The m-file *glucosafehandler.m* is a necessary sub-function file to have for the ODE45 solver function, due to its ability to control and calculate the involved m-files and differential equations parameters. Finally, *glucosafehandler.m* include the part 'Getdata', whose function is to use the data chosen in the part 'Setup', and feed this to the model at the correct current time point.

Setup

The 'Setup' part of Glucosafe has the purpose to organize and choose a set of patient data. Furthermore, it defines and calculates physiological constants for the specific patient, which is used in the rest of Glucosafe's functions. The part 'Setup' is located in the m-file *model.m*.
The following list describes the different functions in the part 'Setup' in Glucosafe:

Patientsetup.m Here the model defines the specific patients weight, height, age, gender, body surface area (BSA) and the state of diabetes. The output of this function is used by the rest of the model.

Sprintdatafunction.m The Glucosafe model simulates and models the patient data from the SPRINT cohort, achieved at Christchurch Hospital, see Appendix A.2 on page 80. By choosing a specific patient in the SPRINT cohort, the relevant data can be used in the model. The function of *Sprintdatafunction.m* is to find and organize the SPRINT data for a specific patient, regarding given insulin, given nutritional glucose, given glucose infusion and measured blood glucose. These data sets also include the necessary time stamp, used in the part 'Getdata'.

setpatientcharacteristics.m This function uses the output from *Patientsetup.m* to calculate the 5 static parameters n_I, n_L, n_K, V_P and V_Q for each specific patient, used in the part 'Insulinchange', see section 4.3 on page 18.

constants.m: The function *constants.m* is a m-file with several predefined fitting constants and physiological constants defined using previous research [Arleth et al., 2000]. The purpose of *constants.m* is to feed *setpatientcharacteristics.m* with these constant, due to the calculations of the 5 static patient parameters n_I, n_L, n_K, V_P and V_Q, which are all needed to calculate the change in plasma insulin concentration.
Furthermore, *constants.m* is used in the m-file *periphinsulinchangefunction.m*, due to the calculation of the patient specific constant n_C, which is needed to calculate the change in peripheral insulin concentration.

Getdata

The part 'Getdata' of Glucosafe is located inside the m-file *glucosafehandler.m*, and has the purpose to feed data to the model at the correct current time point.
'Getdata' includes the function *givepatientmonitordata.m*, that will be described in the following:

givepatientmonitordata.m: The function *givepatientmonitordata.m* uses the relevant SPRINT data from 'Setup' (*Sprintdatafunction.m*), and has the output parameters 'injected insulin', 'glucose infusion', 'nutritional glucose' and 'measured blood glucose' to give to the model each minute.

4.4 Model code architecture

The simulation part of Glucosafe is implemented in Matlab including 19 m-files. Figure 4.13 on the next page illustrates where and when the different functions are being called to calculate the next step in the model. As seen in figure 4.13 on the following page the parts 'Insulinchange', 'Insulinsensivity', 'Bloodglucosechange', 'Glucoseinput' are being called several times, depending on the ODE45 solver function, from the main part 'Controlmodel'.

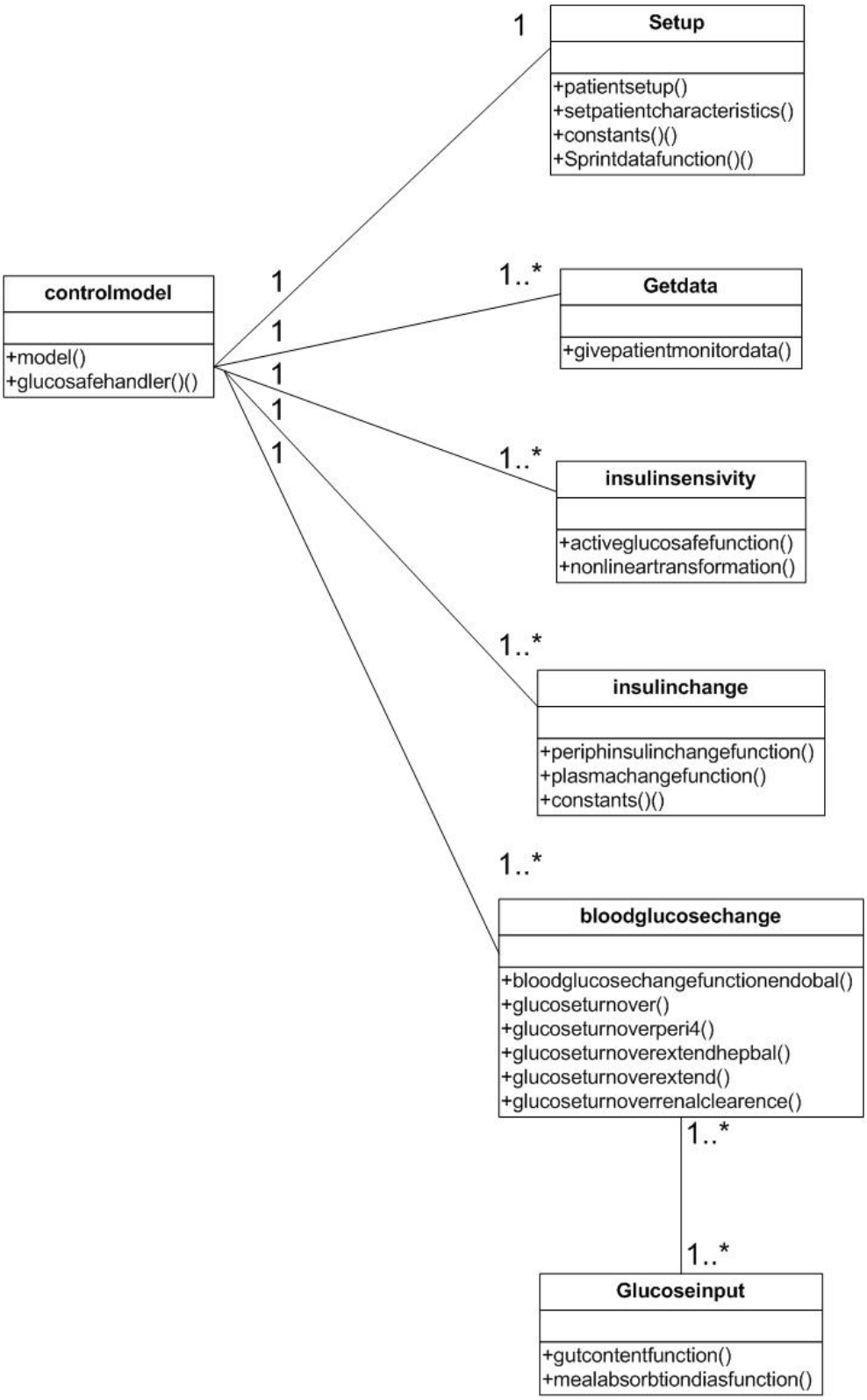

Figure 4.13: *This figure illustrates the architecture for all the functions inside Glucosafe implemented in Matlab*

Validation 1

Written in the periode from Thursday the 1. December - 15. December 2008

The purpose of this test is to validate if the Glucosafe model implemented in Matlab can produce the same graphical result as the original Glucosafe [Pielmeier et al., 2007], when using the same patientdata and interventions.
The patientdata used in this test is from a woman with a weight of 70 kg, 1.6 meter tall, 60 years old, who does not suffer from any type of diabetes. Furthermore, the test has been performed using a fixed insulin sensivity at 0.1625 throughout the entire test period.
Figure 4.14 shows the graphical result from the Glucosafe implemented in Matlab, while Figure 4.15 on the following page shows the graphical result, achieved from the Java implemented Glucosafe [Pielmeier et al., 2007] from the same patient.

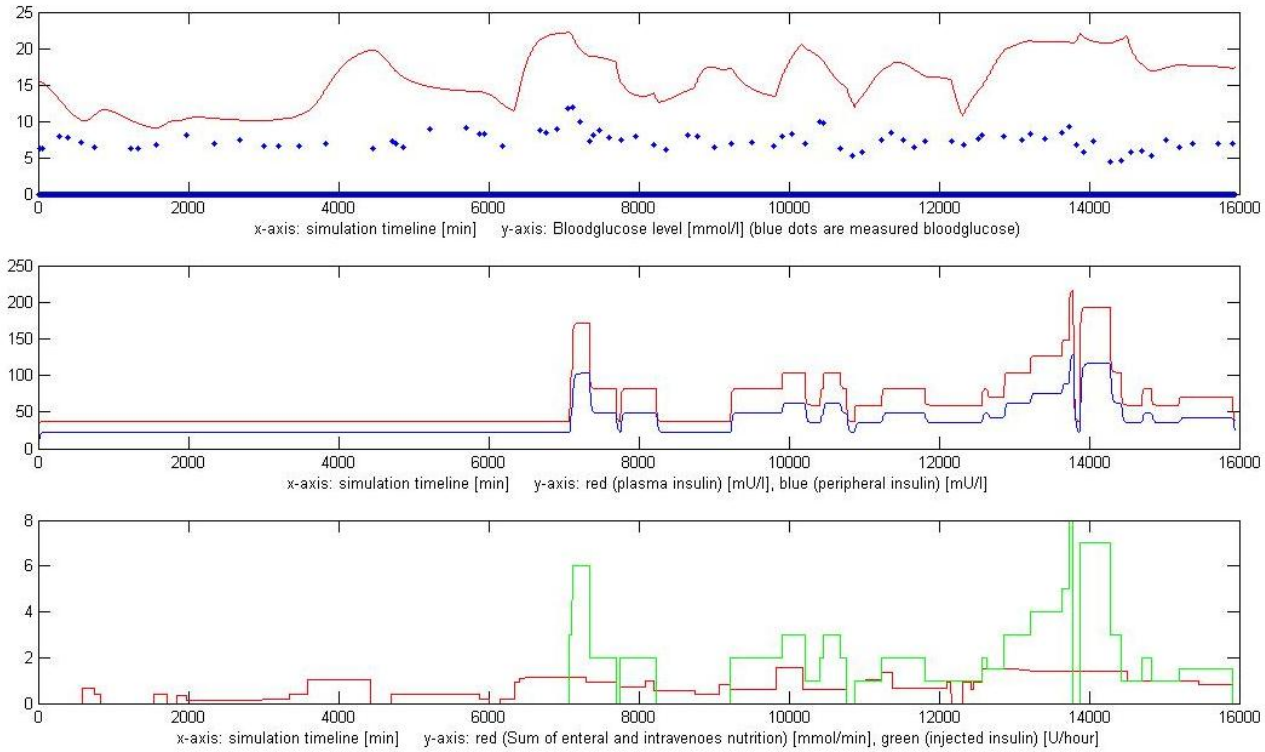

Figure 4.14: *The graphical result from Glucosafe in Matlab*

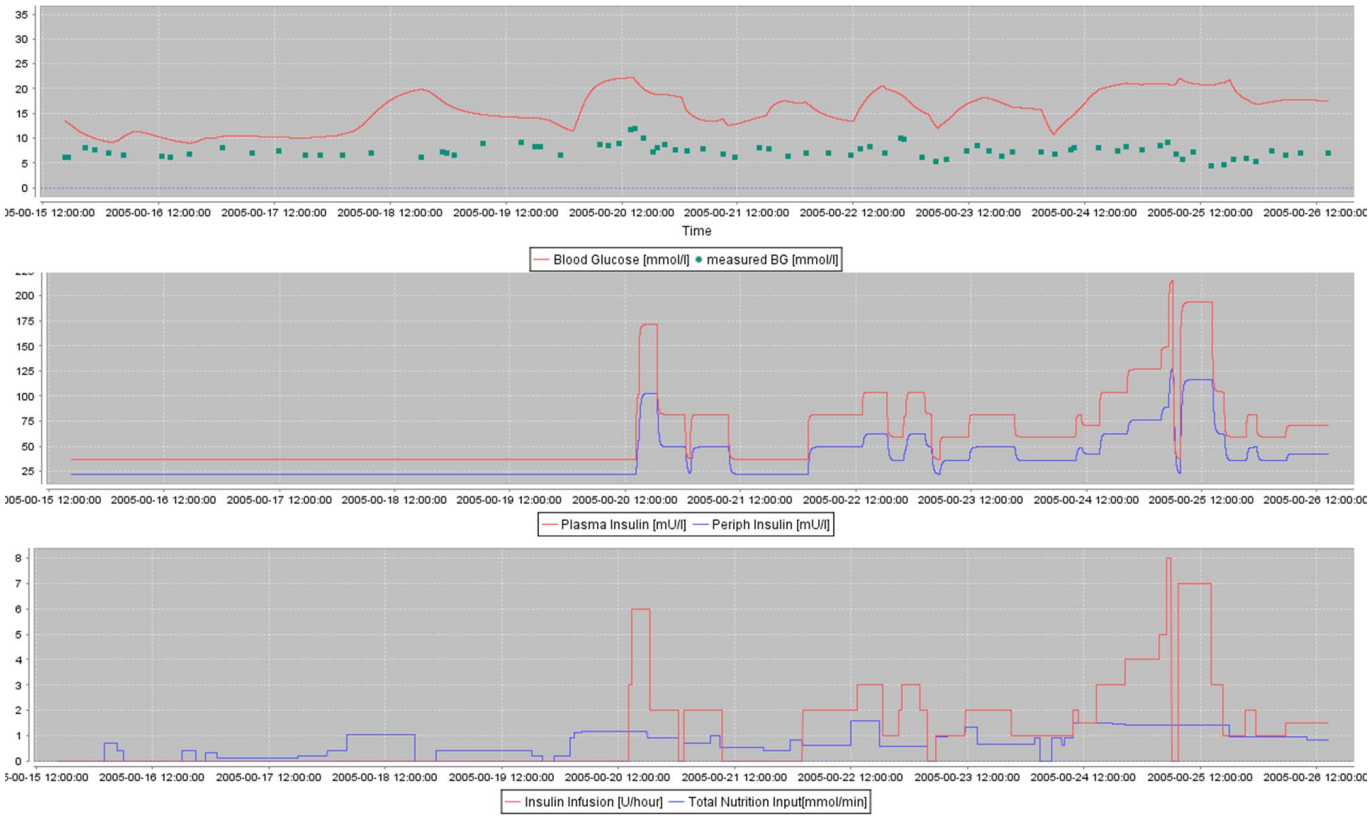

Figure 4.15: *The graphical result from Glucosafe in Java, ref. Ulrike Pielmeier AAU*

Conclusion of validation 1

Glucosafe implemented in Matlab works like the original Glucosafe [Pielmeier et al., 2007].

Next, the integral based parameter estimation method is being documented. By implementing this function into the system. This will give the system the ability to predict with real-time fitted patient parameter.

4.5 Integral based ID.

Written in the periode from the 1. February - 15. May 2008

This section describes the design of concept and isolated test of the integral based parameter estimation method.

The Glucosafe glucose-insulin metabolic model is used to calculate the time-varying response of blood glucose for given insulin and nutrition. The Glucosafe model itself uses fixed patient parameters for the patient in any given time period. However, with help from a parameter estimator it can update these values as required.

To be able to calculate a more accurate blood glucose prediction for the patient, it is necessary to implement a function that updates a patient specific parameter. The purpose is to adjust the model to be more accurate for the specific patient. This study uses the integral based parameter estimation method.

The patient specific parameter used in this study is the time varying insulin sensivity, S_I.
To estimate S_I at any given period, an integral based parameter estimation method is used. The integral based parameter estimation implemented, is the same method as Hann et al. [2005]. In this case, it is used to identify S_I and all other values are held as constants (Arleth et al. [2000] Lotz [2007]).

By substituting Equations 4.17- 4.25 on the following page and separating the S_I dependent parts, it is possible to isolate and calculate S_I every hour. The value of S_I is assumed piecewise constant over the identification interval. In this case, the time interval is set to one hour, to fit the available blood glucose measurements once every hour in the SPRINT cohort.

The change in plasma insulin concentration, $I(t)$, is defined in Equation 4.17:

$$\frac{dI}{dt} = (-n_K - n_L) * I(t) - \frac{n_I}{V_P} * (I(t) - Q(t)) + \frac{P(t) + EP(t)}{V_P} \tag{4.17}$$

The change in peripheral insulin concentration, $Q(t)$, is defined in Equation 4.18:

$$\frac{dQ}{dt} = -n_C * Q(t) + \frac{n_I}{V_Q} * (I(t) - Q(t)) \tag{4.18}$$

The sum of glucose turnover ($E(G, A, BSA)$) to the central nerve system, muscle cells, fat cells, kidneys and the liver, where G is the current blood glucose concentration, A is the active insulin, is defined in Equation 4.19 and BSA is the patients body surface area [m^2]. The constants in Equations 4.20, 4.21 and 4.23 on the following page are explained in Table 4.2.

$$E(G, A, BSA) = E_{Hepatic}(G, A) - E_{Kidney}(G, BSA) - E_{CNS}(G) - E_{Muscle/Fat}(G, A) \tag{4.19}$$

Where $E_{Hepatic}(G, A)$, $E_{Kidney}(G, BSA)$, $E_{CNS}(G)$ and $E_{Muscle/Fat}(G, A)$ are defined in Arleth et al. [2000] as:

$$E_{Hepatic}(G, A) = -Hepatic_1 \times G(t) - Hepatic_2 \times A(t) + Hepatic_3 \tag{4.20}$$

$$E_{Kidney}(G, BSA) = SMOOTH(max(0, GFR(BSA) \times G(t) - T_{max})) \tag{4.21}$$

Name of constant	Value
$Hepatic_1$	0.46 L/(kg·min)
$Hepatic_2$	1.475 mmol/(kg·min)
$Hepatic_3$	1.34 mmol/(kg·min)
CNS_1	0.56 mmol/(kg·min)
CNS_2	1.5 mmol/l
$Muscle/Fat_1$	5.09 mmol/(kg·min)
$Muscle/Fat_2$	5 mmol/l

Table 4.2: List of constants used to calculate the sum of glucose turnover in the liver, CNS and fat/muscle cells

$$E_{CNS}(G) = CNS_1 \times \frac{G(t)}{G(t) + CNS_2} \tag{4.22}$$

$$E_{Muscle/Fat}(G, A) = Muscle/Fat_1 \times A(t) \times \frac{G(t)}{G(t) + Muscle/Fat_2} \tag{4.23}$$

The relationship between the active insulin $A(t)$ and S_I is defined in Equation 4.24:

$$A(t) = S_I * f(Q(t))' \tag{4.24}$$

where $f(Q(t))'$ is the range-transformed (in the range 0-1) nonlinear fractional insulin effect.
Finally, the total result for the change in blood glucose concentration is defined in Equation 4.25:

$$\frac{dG}{dt} = (Z(t) + E(G, A, BSA)) \times constant \tag{4.25}$$

where *constant* is equal to BM/GV, which is the patients bodymass [kg] divided by the glucose distribution volume (GV) [L], also described in section 4.3 on page 24. Combining Equations 4.17-4.25, the S_I non-dependent parameters are presented in Equation 4.26 and the S_I dependent parameters are presented in Equation 4.27.

$$'a' = Z(t) + (1/60) \times (-Hepatic_1 \times \overline{G} + Hepatic_3) - (1/60) \times (E_{CNS} + E_{Kidney}) \tag{4.26}$$

Where $\overline{G}$ comes from the calculation of $E_{Hepatic}(G, A)$ in Equation 4.20, where a blood glucose roof concentration is set at 11.98 mmol/L if the current calculated blood glucose is larger.
By noticing Equation 4.26, it can be seen that E_{CNS} and E_{Kidney} are not separated in subparts like $E_{Hepatic}$ and $E_{Muscle/Fat}$. The reason for this is that none of the parameters inside the functions E_{CNS} and E_{Kidney} are depending to $A(t)$. $Z(t)$, the sum of absorption explained in section 4.3 on page 28 is calculated each minute by using the nutrition interventions (enteral and parenteral).

$$'b' = \frac{-Hepatic_2}{60} \times A - \frac{Muscle/Fat_1}{60} \times A \times \frac{G}{G + Muscle/Fat_2} \Rightarrow \tag{4.27}$$

Where $A(t)$ is the active insulin (fractional effect on glucose turnover).

$$'b' = \frac{-Hepatic_2}{60} \times S_I \times f(Q(t))' - \frac{Muscle/Fat_1}{60} \times S_I \times f(Q(t))' \times \frac{G}{G + Muscle/Fat_2} \tag{4.28}$$

The number 1/60 often occurs in both part $'a'$ and part $'b'$. This is due to the length of the estimation interval of S_I is 1 hour (60 minutes).

Equation 4.29 uses Equations 4.26 on the facing page and 4.28 on the preceding page to integrate over the prior hour. Using the blood glucose measurements $G(60)$ and $G(0)$ and the nutrition information from the previous hour, S_I can be calculated for the previous hour. This identified S_I value is then used for the next hour to Model Prediction, by using Equation 4.30.

$$\frac{G(60) - G(0)}{constant} = \int_0^{60} ('a')dt + S_I \times \int_0^{60} ('b')dt \iff \tag{4.29}$$

$$S_I = \frac{1}{\int_0^{60} ('b')dt} \times \frac{G(60) - G(0)}{constant} - \int_0^{60} ('a')dt \tag{4.30}$$

Every hour a new blood glucose measurement is available from the SPRINT data set, and a new S_I value can therefore be identified for that time interval, which Equation 4.30 illustrates. Figure 4.16 shows an example of an identified S_I profile. Using that hour to hour S_I and the known interventions, the new blood glucose measurement can be predicted and compared to the clinical data to test the models prediction capability. Alternatively, new interventions can be tested to predict and determine the best set of given nutrition and injected insulin.

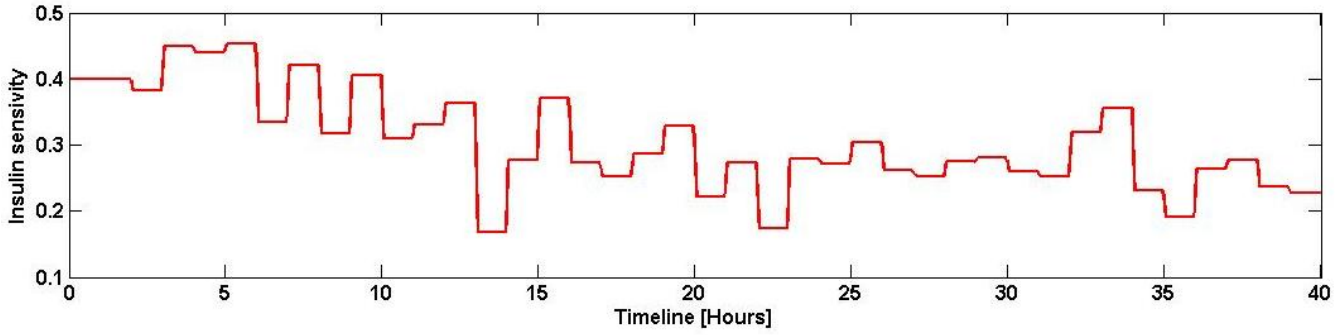

Figure 4.16: *This figure illustrates how the patient specific parameter S_I changes every hour. Integral based parameter estimation methods are used to determine these values.*

Isolated validation and conclusion of the integral parameter estimation method

Having estimated the S_I values for the entire length of the patient data, it is possible to validate if these calculated S_I values are correct. Figure 4.17 on the following page shows the isolated validation of the integral parameter estimation method for Patient 2 used in the study (see Table 4.3 and 4.4). Here the S_I profile for Patient 2 is calculated, and then used in a model re-simulation to see how good the calculated blood glucose fits the measured blood glucose values. As seen on Figure 4.17 the calculated blood glucose fits the measured blood glucose values and the validation of the integral based ID method is therefore accepted.
These results also show that the model of Equation 4.17 - 4.25 has all the necessary dynamics to capture the behavior seen in the clinical SPRINT data. This validation and examination have used retrospective data from SPRINT patients.

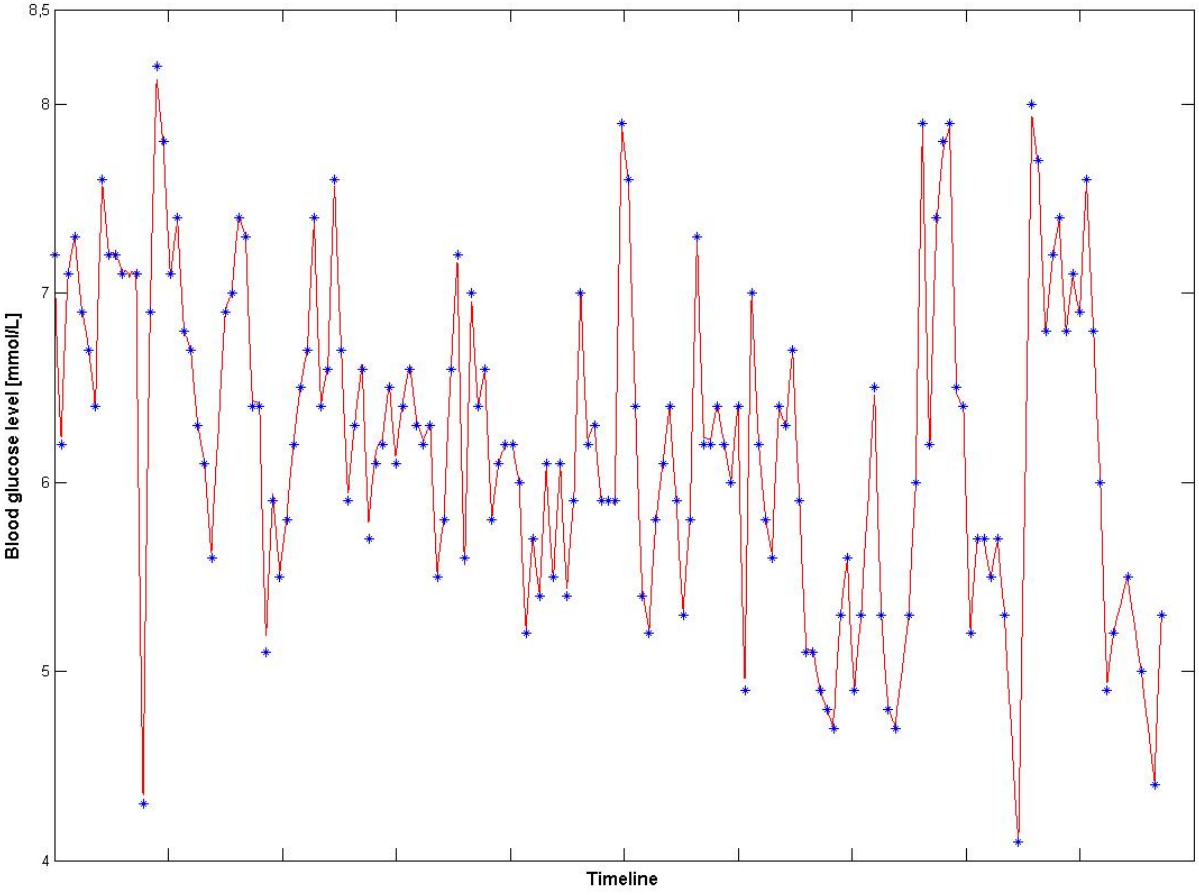

Figure 4.17: *The Figure illustrates the validation of the integral based parameter estimation method. The line is the calculated blood glucose and the blue dots are the measured blood glucose values, available every hour.*

The result is considered acceptable for later use in Model Simulation Validation and Model Prediction Validation, which are presented in section 4.6 on the next page.

4.6 Validation 2-4

Written in the periode from the 1. February - 15. May 2008

This section describes the tests performed on the Glucosafe model and integral based parameter estimation method without the advice module. These results are also to find in Article 1: 'Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model'

The tests performed on the model and integral parameter estimation method are listed in the following:

Validation 2: This test deals with the Model Simulation validation.

Validation 3a: This test validates the Model Prediction first version.

Validation 3b: This test validates the Model Prediction second/final version.

Validation 4: This test validates the chosen Model Prediction method's ability to predict from 1-10 hour, and validation using different EP [mU/min].

The results are presented in term of the absolute percent error, APE, of blood glucose calculated as:

$$APE_i = \frac{|BG_i^{GS} - BG_i|}{BG_i} \tag{4.31}$$

Where BG_i^{GS} is the calculated blood glucose concentration at time i, and BG_i is the measured blood glucose concentration at time i.

Patient cohort used for validation 2 - 4

The patientdata used in validation 2 - 4 comes from 10 patients in the SPRINT study [Chase et al., 2007] [Lonergan et al., 2006b]. The basic cohorts details can be seen in Tables 4.3 and 4.4. All of the SPRINT patient data in 1-2 hour intervals are thus relatively dense. Ethics approval to use this data was obtained from the South Island Regional Ethics Committee, New Zealand.

Patient	Age	APACHE II score:	Diagnosis
1	77	22	Sepsis
2	67	33	Acute renal failure, infarction
3	42	11	Suicide attempt (non drug), respiratoty failure, smoke inhalation
4	44	21	Ventricular drain
5	79	31	infarction, cardiac catheter, hypoxic/ischaemic
6	44	23	Meningitis, ventricular drain
7	53	13	Aspiration, motor vehicle crash
8	53	18	Heavy obesity, Obstructive sleep apnoea
9	59	22	Donor
10	51	29	Acute renal failure, systemic

Table 4.3: Patient data for the 10 SPRINT patients used in validation 2 - 4

Patient	Length of stay in hospital (hours)	Length of stay on SPRINT (hours)	Gender	Diabetes
1	580.8	312	M	No
2	458.4	162	M	No
3	408	253	M	No
4	223.2	207	F	No
5	55.2	39	F	No
6	280.8	161	F	No
7	861.6	17	M	No
8	477.6	182	M	No
9	99.6	93	F	No
10	520.8	360	M	No

Table 4.4: Length of stay and further patient data for the 10 SPRINT patients used in Validation 2 - 4.

Validation 2

This test documents the Model Simulation validation, which also is presented in the article 'Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model'.
The Model Simulation process finds a patient specific S_I (= S_{I1},...,S_{Ii},...,S_{IN}) profile over time

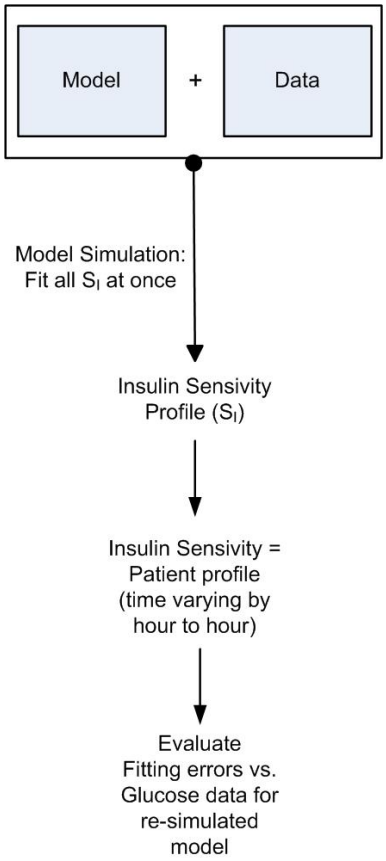

Figure 4.18: *Flowchart over the work process for the Model Simulation Validation. First the model simulates and finds the entire S_I profile for a patient at once. Thereafter the model repeats the same simulation using the founded S_I profile from the first simulation.*

for a given set of patient data (glucose measurements BG_i and insulin and nutrition interventions, IV).
When a new blood glucose measurement BG_i becomes available at time t_i a new value S_{Ii} can be identified from the measurements BG_{i-1} and BG_i.
In the Model Simulation mode, Glucosafe can use S_{Ii} to simulate BG_i, using BG_{i-1} as the initial value for the simulation:

$$BG_i^{GS} = GS(BG_{i-1}, S_{Ii}; IV)$$

where BG_i^{GS} is the simulated blood glucose at time t_i using S_{Ii} and the interventions IV starting from time t_{i-1} with the measured blood glucose value BG_{i-1}.
A close match between BG_i^{GS} and BG_i will confirm that the identified patient profile S_I actually describes the dynamics of the patients metabolic state (APE_i).
Figure 4.19 illustrates the results for Patient 4 in the Model Simulation validation. In Appendix A.4 on page 83, Article 1 first edition, more of these Model Simulation validation can

be seen. Dots with error bars show measured clinical data and the line is the identified model. The overall fits are qualitatively very good. The second panel shows the S_I profile. The fitted data error results for the Model Simulation validation for all 10 SPRINT patients are presented in Table 4.5. Table 4.5 shows mean and median APE's per patient over the cohort are 0.45 and 0.24 % and 100 % of measurements per patient being less than 10 % APE.

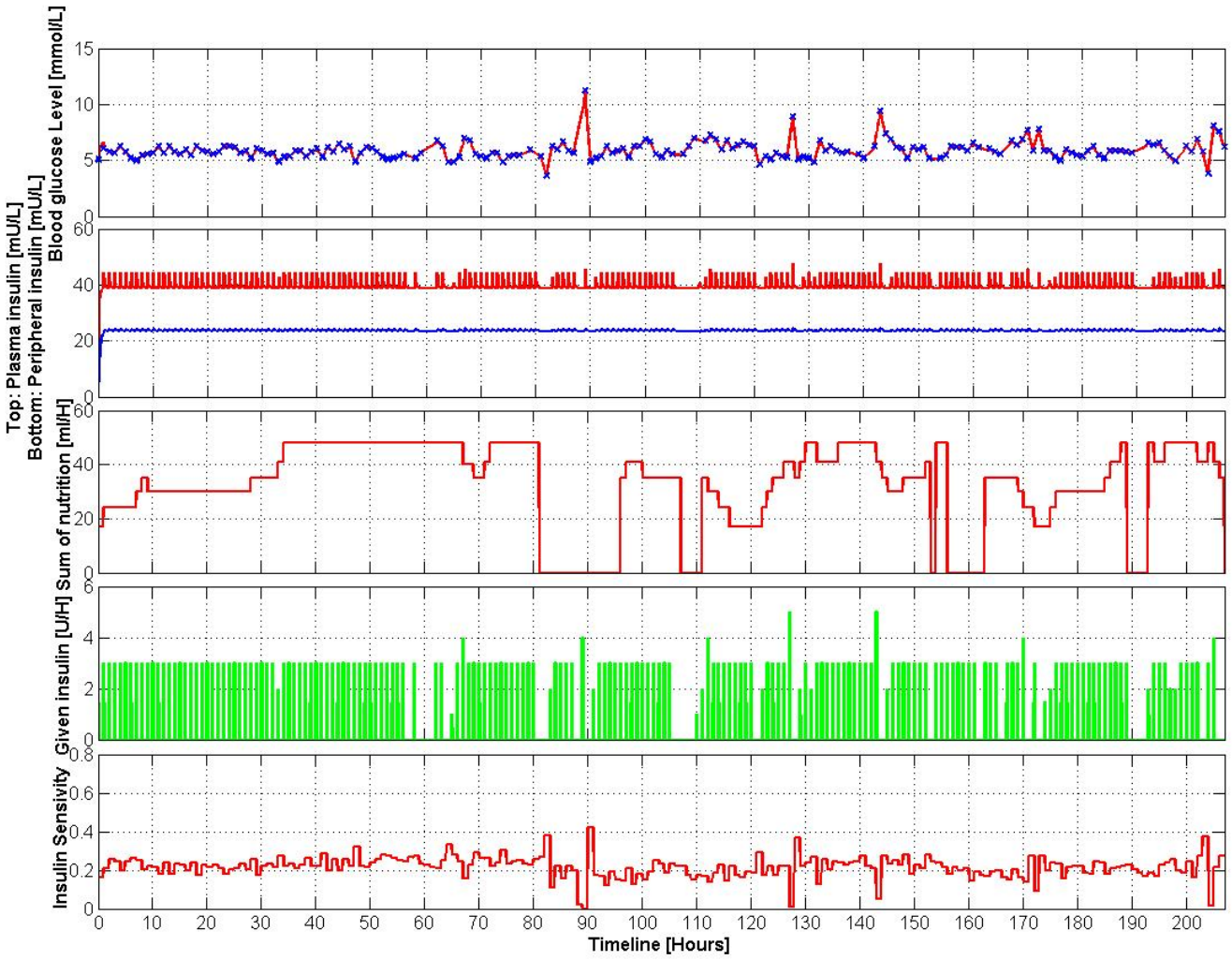

Figure 4.19: *Model Simulation validation of Patient 4. Panel 1 shows the simulated blood glucose, meanwhile the dots are the measured blood glucose. Panel 2 is the calculated plasma and peripheral plasma concentration. Panel 3 is the given nutrition, and Panel 4 is the given insulin. Finally, panel 5 is the S_I identified in simulation mode (identified in Model Simulation, see Figure 4.18 on the preceding page). The entire data set is fit as a whole.*

SPRINT patient	Number of simulations	Mean	Median	IQR	5-95% Range	Percent APE_i $< 10\%$
1	234	0.50	0.18	[0.07 0.45]	[0.01 1.32]	100
2	154	0.34	0.23	[0.08 0.46]	[0.01 1.07]	100
3	170	0.56	0.38	[0.18 0.69]	[0.02 1.62]	100
4	192	0.49	0.29	[0.14 0.57]	[0.02 1.59]	100
5	32	0.72	0.51	[0.18 0.98]	[0.05 2.72]	100
6	112	0.53	0.30	[0.12 0.64]	[0.03 2.17]	100
7	12	0.84	0.29	[0.12 0.63]	[0.02 2.61]	100
8	114	0.60	0.23	[0.12 0.55]	[0.03 1.65]	100
9	83	0.51	0.35	[0.16 0.55]	[0.05 1.71]	100
10	252	0.34	0.20	[0.07 0.42]	[0.02 1.05]	100
Overall	1355	0.45	0.24	[0.10 0.51]	[0.01 1.33]	100

Table 4.5: Results for the Model Simulation validation of Glucosafe of all SPRINT patients in validation 2. The Overall result is weighted by the amount of data for each patient. IQR = interquartile range.

Conclusion of Validation 2

The results of the validation presents a mean APE at 0.45 %. This result proves that the model dynamic of Glucosafe during Model Simulation fits the measured blood glucose data within an acceptable error range, and ready for being used in Model Prediction..

Validation 3

The development of the Glucosafe model and the integral based parameter estimation method has been through several states of improvements.
Due to fully document my work process, it is necessary to illustrate the two ways of Model Predictions I have used during the development of the project.
Figure 4.20 illustrates the two different Model Prediction methods, and therefore also two states

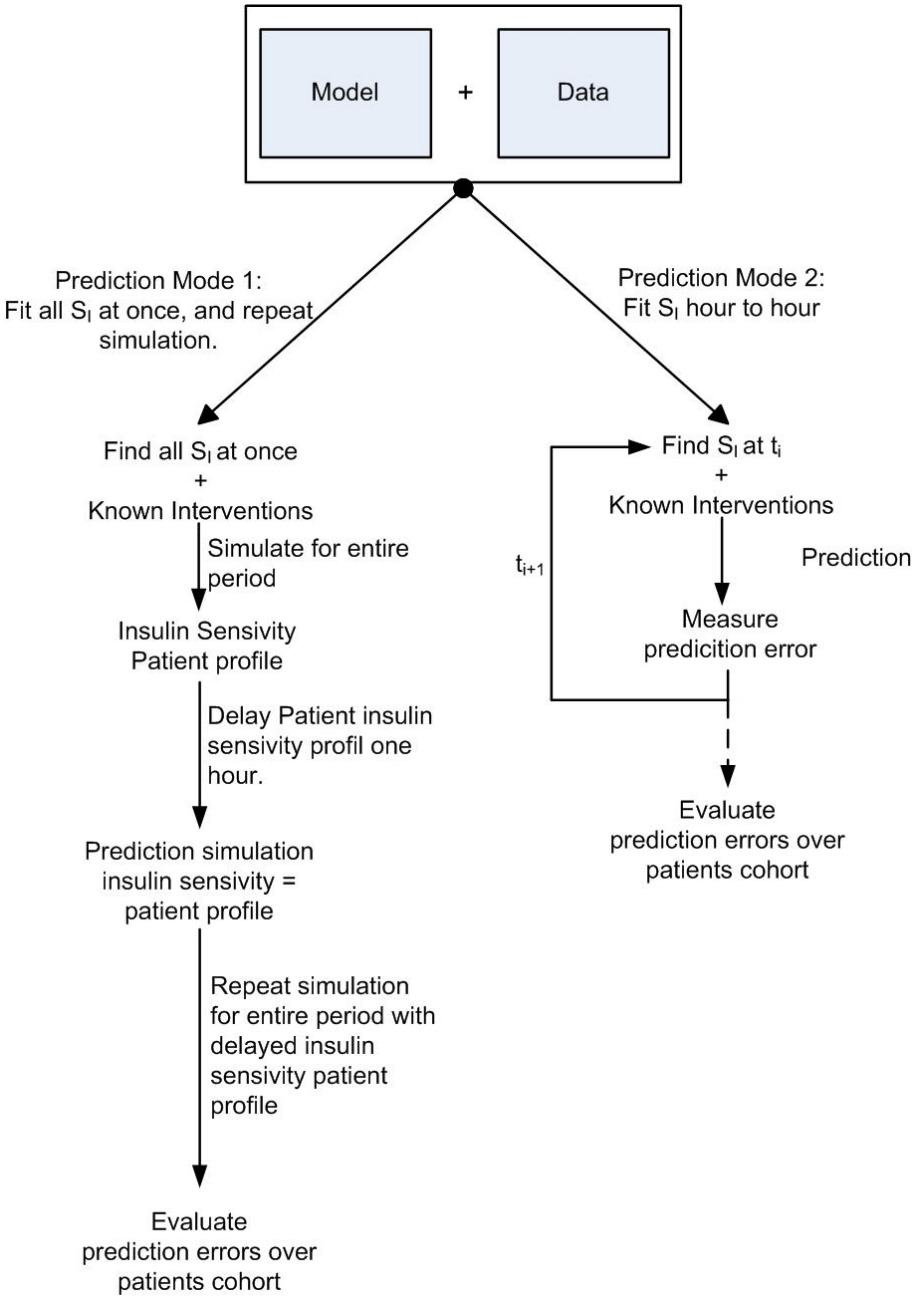

Figure 4.20: *This figure illustrates the two Model Prediction methods, which have been used. The first prediction method is shown in the left column, meanwhile the second, and final Model Prediction method is presented in the right column*

of development, to initiate Model Prediction.
Both Model Prediction methods have the ability to identify the patient parameter S_I to minimize the APE_i between BG_i^{GS} which is the calculated blood glucose concentration at time i, and BG_i which is the measured blood glucose concentration at time i.
The first Model Prediction method shown in the left column in Figure 4.20, presents the first edition of the Model Prediction.
The prove of need of always using a combined system utilizing both a model and a parameter estimator, can be seen by observing Figure 4.14 on page 33, where the result is presented of using the Glucosafe model alone, without the ability to estimate S_I, but instead a fixed S_I during the total simulation period. Figure 4.19 presents the combined system utilizing both the model and the parameter estimator.
Simply by observing these two figures, it is possible to see that the need of parameter estimator is important.

The first Model Prediction method had a big disadvantage, due to the missing ability to predict S_I in realtime.
Model Prediction method working in realtime became necessary, when the system had to be used against a patient, whose data also becomes accessible en realtime depending on a real blood glucose measurement device, or virtual patients with unknown interventions - In other word it became necessary if the current system should work as a part of a glycaemic control system.

After developing the second, and final edition of the Model Prediction method, presented in the right column in Figure 4.20, the ability to predict in realtime was achieved.
To fully document both Model Prediction methods, these are both validated:

Validation 3a: Validation of the first Model Prediction method. The full result of this method is presented in Appendix A.4 on page 83, which includes the first edition of the article *Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model.*

Validation 3b: Validation of the second, and final Model Prediction method. This method is later used in the development of the Decision Support System, using the Advice Module.

The results of this validation is presented in Article 2.

Validation 3a

This test validates the first Model Prediction method, which is shown in the left column in Figure 4.20 on page 44.
Visuel results for Validation 3a can be seen in Appendix A.4 on page 83, where Article1old presents this. The results for the first Model Prediction method is done as illustrated in the left column in Figure 4.20 on page 44.
The results for the Model Prediction validation for all 10 SPRINT patients included in this test is presented in Table 4.6.

SPRINT patient	Number of Predictions	Mean (APE)	Median (APE)	IQR	5-95% APE Range	Percent of measurements $< 10\%$ APE
1	234	11.58	9.51	[4.83 15.08]	[0.58 29.50]	53.02
2	154	11.32	8.12	[3.46 17.69]	[0.50 29.50]	54.61
3	170	18.12	14.31	[6.89 27.36]	[0.56 41.93]	36.90
4	192	10.73	7.46	[3.37 13.93]	[0.58 34.60]	60.00
5	32	15.35	13.02	[7.19 22.57]	[0.71 38.73]	36.67
6	112	9.26	5.89	[2.56 11.97]	[0.34 29.07]	71.81
7	12	14.65	13.73	[11.90 17.72]	[6.76 18.20]	18.18
8	114	16.28	11.50	[5.83 19.78]	[1.35 47.49]	40.18
9	83	15.81	12.50	[5.95 18.65]	[1.25 44.41]	41.98
10	252	12.58	9.93	[4.43 17.58]	[0.79 31.95]	50.4
Overall	1355	13.02	9.91	[4.74 17.78]	[0.75 34.75]	50.78

Table 4.6: Results for Model Prediction validation (3a) with integral parameter estimation of all SPRINT patients in this test. The Overall result is weighted by the amount of data for each patient. IQR = interquartile range

Validation 3b

The results for the Model Prediction validation for all 10 SPRINT patients included in this test is presented in Table 4.7.
Figure 4.6 illustrates the results for Patient 8 in the Model Prediction validation 3b. Dots with error bars show measured clinical data and the line is the identified model. The overall fits are qualitatively very good.

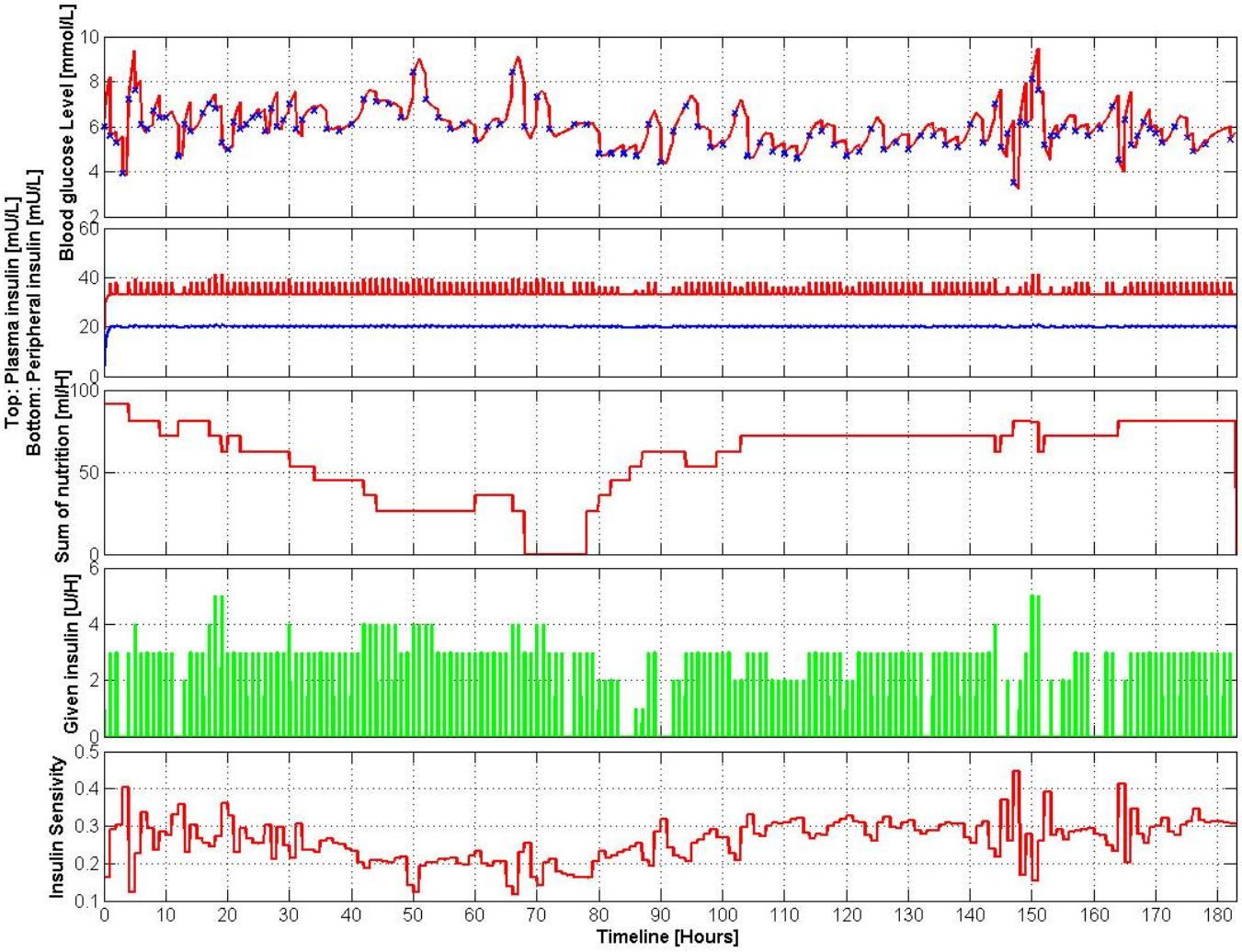

Figure 4.21: *Model Prediction validation of Patient 8. Panel 1 shows the predicted blood glucose, meanwhile the dots are the measured blood glucose. Panel 2 is the calculated plasma and peripheral plasma concentration. Panel 3 is the given nutrition, and Panel 4 is the given insulin. Finally, panel 5 is the S_I identified during prediction. The data seen are fitted hour to hour as seen in the right column in Figure 4.20*

SPRINT patient	Number of Predictions	Mean (APE)	Median (APE)	IQR	5-95% APE Range	Percent of prediction measurements < 10% APE
1	234	9.7	7.1	[3.6 13.0]	[1.6 25.7]	66.5
2	154	9.9	7.5	[3.9 13.4]	[1.5 25.3]	61.8
3	170	12.3	10.6	[3.9 18.6]	[1.5 30.6]	48.1
4	192	11.2	7.9	[3.7 12.1]	[1.7 32.2]	62.8
5	32	14.8	14.3	[6.5 20.4]	[2.3 35.8]	33.3
6	112	9.1	6.1	[3.2 12.5]	[0.8 32.6]	69.7
7	12	13.4	8.5	[3.8 15.1]	[2.4 30.9]	54.5
8	114	11.2	7.1	[4.5 12.6]	[0.6 37.3]	63.6
9	83	16.4	12.3	[7.0 19.6]	[1.6 36.8]	41.0
10	252	9.3	6.3	[3.4 11.8]	[0.8 24.5]	67.3
Overall	1355	10.8	8.0	[4.0 13.9]	[1.2 29.5]	60.9

Table 4.7: Results for Model Prediction validation (3b) with integral parameter estimation of all SPRINT patients in this study. All results are shown in percent. The Overall result is weighted by the amount of data for each patient. IQR = interquartile range

Conclusion of Validation 3a + 3b

The test results for validation 3a presents a mean APE at 13.02 and a median APE at 9.91. The test results for validation 3a presents a mean APE at 10.8 and a median APE at 8.0.
Only Validation 3b present a acceptable low Model Prediction error, as compared to the Glucometers used at Christchurch Hospitals with 7-12 % measurement error [Hann et al., 2005]. The results for validation 3a have a bigger APE than the results presented in validation 3b, the preferred method is therefore the Model Prediction tested in validation 3b.
The reason for the difference in predictions errors (APE) between Validations 3b and 3a, is that the Model Prediction method validated in 3b handles sudden big changes in a patients blood glucose [mmol/L] better than 3a.
Besides the better prediction error, the Model Prediction tested in validation 3b is the only method estimating S_I in realtime, see the right column in Figure 4.20 on page 44, and therefore the only method that can be used in a glycaemic control system with unknown future interventions.
Hence, in the chosen Model Prediction mode (3b), S_{Ii} is used to simulate the next measurement, BG_{i+1}, using BG_i as the initial value for the simulation:

$$BG_{i+1}^{BG} = GS(BG_i, S_{Ii}; IV)$$

A close match between BG_{i+1}^{BG} and BG_{i+1} shows that the identification of S_I can provide an accurate prediction of the response to clinical intervention.

A more comprehensive documentation of the results achieved in validation 3b can be seen in Article 1.

Validation 4

This test validates the chosen Model Prediction methods ability (3b) to predict from 1-10 hour, see Figure 4.22, and testing the prediction errors (1 hour predictions only) using different EP values, see Figure 4.23 on the facing page.

The Model Prediction validated in validation 3 has used a fixed EP at 27.77 mU/min. Due

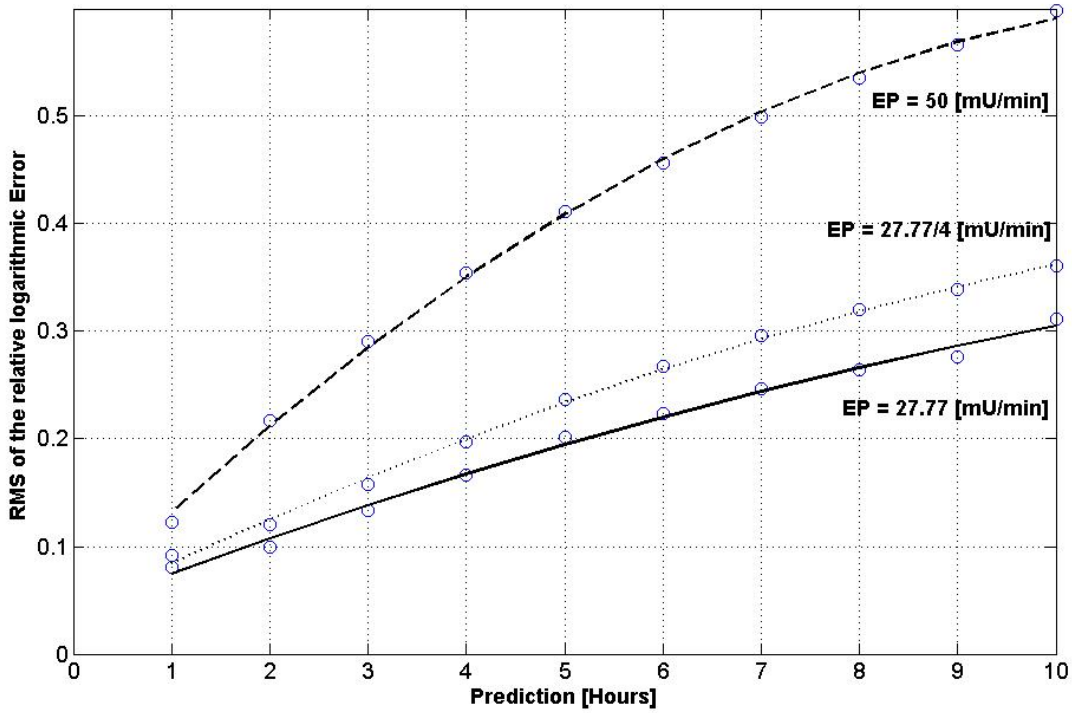

Figure 4.22: *This figure illustrates the systems ability to predict over a period up to ten hours for the close-to-average Patient 6 in the study, using different EP values. The result for this capability is presented using the unit Root Mean Square of the Relative Logarithmic Error.*

to minimize the model Prediction error APE, different values of EP has been tested.
Figure 4.23 on the next page illustrates that the parameters EP and S_I are interdependent in the model as it is defined. A change in EP therefore changes the patients S_I profile over the patient.
It also shows how EP and S_I are dependent and trade off for Patient 6. As EP increases S_I falls and vice versa, with similar dynamics in the S_I profiles.

Figure 4.24 on the following page illustrates the relationship between choice of EP and resulting overall median APE for all 10 patients. The overall median APE for model Prediction has been testet for choices of EP at 20, 27.77, 30, 35, 40 and 45 mU/min. The dots in Figure 4.24 the Model Prediction result (overall median) for all 10 patients, and the best overall choice for EP to have, is a EP value at 27.77 mU/min. However, using a EP value at 27.77 mU/min may not be the optimum solution in other situations, with another/lesser critically ill patient cohort (higher S_I).

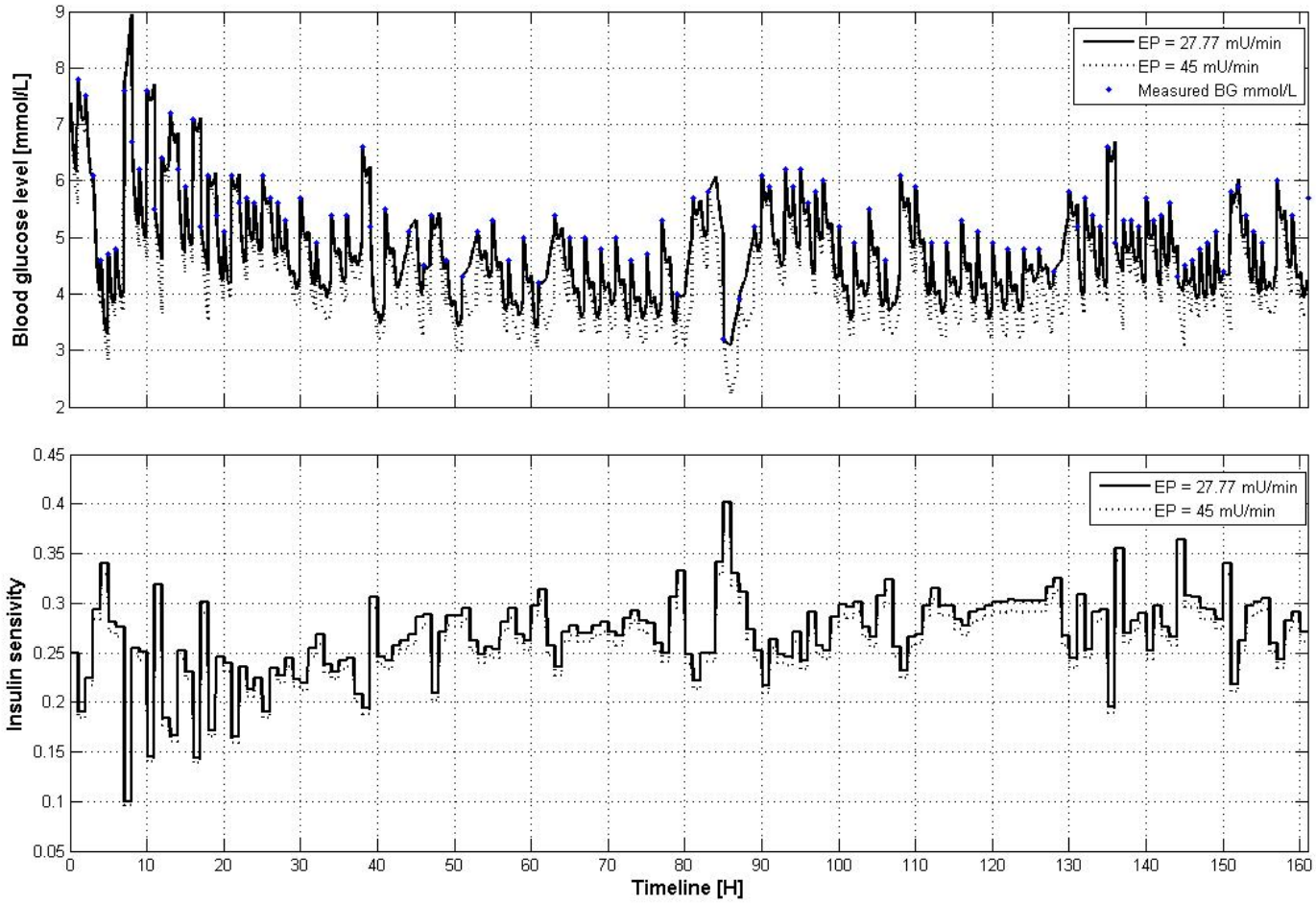

Figure 4.23: *This figure illustrates how the predicted blood glucose for Patient 6 is effectively the same by using different dependent set of EP and S_I profiles. The top picture shows 3 predictions produced by using 3 different EP and S_I profiles. The lower picture shows 3 different S_I profiles. The upper S_I profile is produced by using a EP = 27.77 mU/min and the lower S_I profile is produced by using a EP = 45 mU/min. The prediction lines in the top panel are close to be the same. This figure is produced by 1 hour prediction only.*

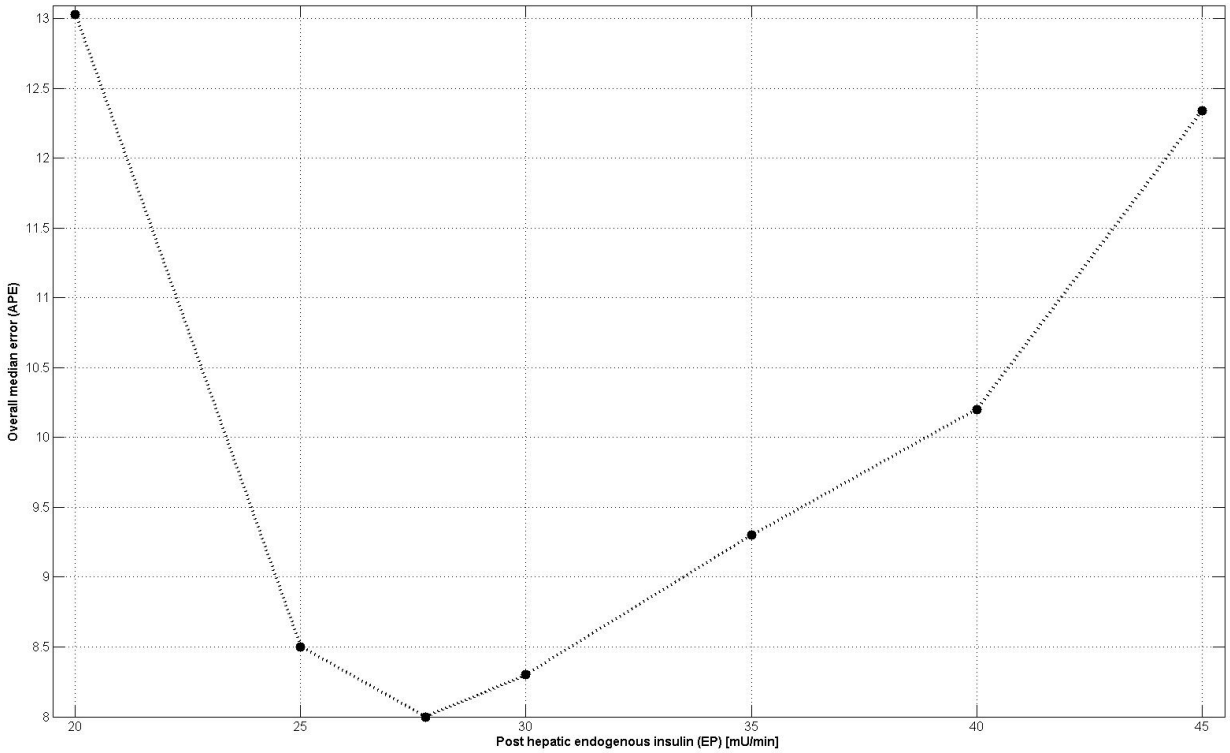

Figure 4.24: *This figure illustrates the overall median error (APE) for all 10 patients used in this study, using a different value of EP.*

Conclusion of Validation 4

The tested Model Prediction method has shown to be acceptable for later use in a control scenario with unknown interventions. Furthermore, the Model Prediction are considered acceptable for later use in control applications in a clinical setting out to approximately 3 hour predictions levels, as see in Figure 4.22. These results validate using these models in proof of concept pilot clinical trials and the later development of a advice module to complete the study. The fixed EP value at 27.77 mU/min are found to be the optimum value for the tested cohort, and are used in the later development of the system.

Chapter 5

Advice Module Development and Implementation

5.1 Advice module

Written in the periode from Thursday the 7. May - 2. June 2008

In this section the advice module of the glycaemic control system is being defined and described. This part of my work is also presented in Article 2: 'Development and Validation of a Decision Support System for Critically Ill Patients utilizing the Glucosafe Glycaemic Control Model'.

The development of the advice module, in the glycaemic control system, depends on the presence of the earlier implemented Glucosafe model, see section 4.2 on page 15, and integral based parameter estimation method, described in section 4.5 on page 35. The development and implementation of the Glucosafe model and the integral based parameter estimation method, mainly represents my work done in the first half of this study.

Figure 5.1 on the next page illustrates the build up of the full glycaemic control system, which includes the model, integral based parameter estimation method, advice module (all in the right column in the figure) and a patient - which in this study is a virtual patient (left column in the figure). This chapter will focus on the development of the advice module, and the virtual patient needed for validation of the glycaemic control system.

The included parts of the advice module are presented in the following:

Blood glucose penalty function: The purpose of the glycaemic control system is to keep the patient normoglycaemic, and therefore is the blood glucose penalty function designed to give a high penalty when a set of intervention can cause that the patients blood glucose gets outside the normoglycaemic range.

Nutrition penalty function: Even though the main purpose of the glycaemic control system is to maintain a state of normoglycaemia, the patient also has to have a certain amount of calories during the glycaemic control. The glycaemic control is because of the nutrition penalty function, a compromise between always being normoglycaemic and getting optimal feeding.

Insulin penalty function: The purpose of this penalty function is to give a high penalty when

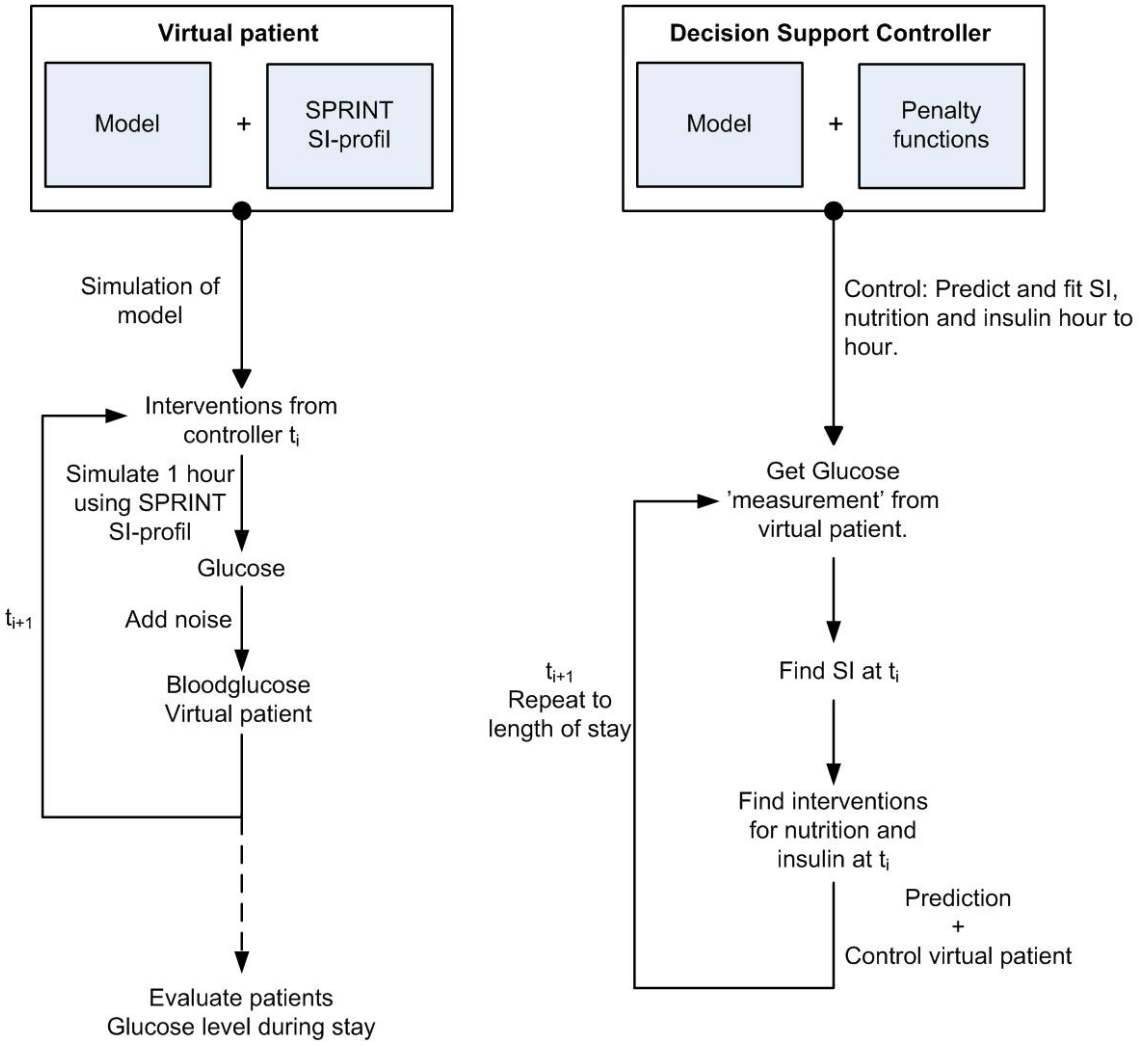

Figure 5.1: *This figure illustrates the full glycaemic control system, which includes the model, integral based parameter estimation method, advice module and a virtual patient. Further explanation of the nutrition and insulin advices can be seen in the sections of penalty functions and the advice module optimizer*

a high amount of insulin is given, due to stay in control of the patients blood glucose concentration.

Advice module optimizer: The given sets of interventions are a result of the advice module optimizer, which uses the three mentioned penalty functions to find the lowest possible sum of penalty to chose the optimum sets of nutrition and insulin to give to the patient.

Next, each of the listed parts of the advice module, followed by the virtual patients are explained in terms of concept and implementation.

Blood glucose penalty function

In addition to the Glucosafe glucose-insulin system model and integral based parameter estimation method, the glycaemic control system utilizes three penalty functions and an optimizer, due to the control of the blood glucose concentration of patients.

All three shapes have influence on glycaemic control, and the size or values of each penalty function are weighted against the desired criteria of 1: keeping the patients blood glucose concentration inside the normoglycaemia range between 4.4-7.75 mmol/L [Van den Berghe et al., 2001] [Krinsley, 2004]. 2: giving the patient an adequate amount of calories, and 3: keeping the control of the patients blood glucose concentration while minimizing the amounts of insulin given to the patient.

The approach of design of the penalty functions, has in this study been the blood glucose penalty shape, see Figure 5.2, with basis in previous work [Andreassen et al., 1994]:

$$BG_{penalty} = (ln(\frac{BG}{BG_0}))^2 \times K_{BG-Penalty} \tag{5.1}$$

where BG is the current blood glucose values, and BG_0 (= 5.5 mmol/L) is the point at which the penalty function value is 0. $K_{BG-Penalty}$ is a fitting constant (value = 4). The blood glucose penalty function results in a penalty range between: [0 0.47] in the targeted blood glucose range of 4.4-7.75 mmol/L.

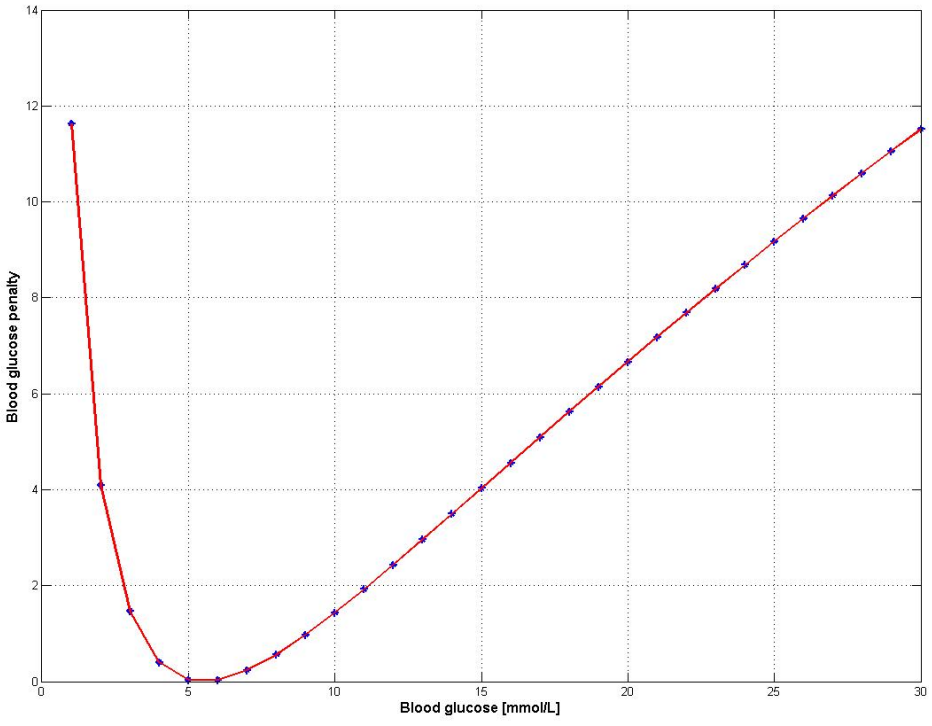

Figure 5.2: *This figure illustrates the shape of the blood glucose penalty function*

Nutrition penalty function

The nutrition penalty function, illustrated in Figure 5.3 on the next page, is designed on the basis of keeping the patient normoglycaemic while continually giving the patient as close to 100 % of daily intake (DI) as possible. The penalty range for the nutrition penalty function is [0.00 0.05] in the feeding range between 40-140 % of DI. Equation 5.2 represents the nutrition penalty function:

$$Penalty(NUT) = (NUT - 100\%)^2 \times K_{NUT-Penalty} \tag{5.2}$$

where NUT is given nutrition in the range 40-140 % of DI and $K_{NUT-Penalty}$ is a fitting constant (value = 0.15) to weight the nutrition penalty range against the two other penalty functions.

The nutrition advice range illustrated in Figure 5.3 is presented in % of DI, and has to be converted into caloric intake for the specific patient. The Harris Benedict metabolism equation [Harris and Benedict, 1918] is used to calculate 100 % of daily calorie intake DI from the patients gender, weight, age and height, from which calories per day (CD) can be calculated as: $CD = NUT \times DI$ [kcal/day]. The Harris Benedict metabolism equation is presented in the following, where CD in Equation 5.3 is full daily calorie need for men [kcal/day], and CD in Equation 5.4 is full daily calorie need for women [kcal/day]:

$$CD = 66.5 + 13.8 \times weigth + 5 \times height - 6.8 \times age \tag{5.3}$$

$$CD = 655.1 + 9.6 \times weigth + 1.8 \times height - 4.7 \times age \tag{5.4}$$

where *weight* is in [kg], *height* in [cm] and *age* in [years] [Harris and Benedict, 1918].
Finally, the advised feeding rate (FR) [ml/h] can be calculated as FR = CD/CV from the calorie value CV [kcal/ml] of the enteral or parenteral solution. Additionally, see Appendix A.2 on page 80 for documentation of CV and nutrition type given to the SPRINT cohort.
The nutrition used in this study is an enteral formula named Diabetic Resource (Novartis Medical Nutrition, Minneapolis, MN, USA), which was also used in earlier studies from which the underlying SPRINT patient data for the virtual patients in this study originates [Chase et al., 2008b] [Chase et al., 2007] [Lonergan et al., 2006a] [Chase et al., 2008a] [Lonergan et al., 2006b]. Importantly it is also a low carbohydrate formula, where 34 % of the calories come from carbohydrates.

The design criteria for limiting the nutrition to 40-140 % of DI, is that there is no need for excessive nutrition feeding, due to the cause of or exacerbating hyperglycaemia [Patino et al., 1999]. The lower limit of 40 % of DI is set as the minimum possible calorie intake for patients without increasing mortality [Krishnan et al., 2003].

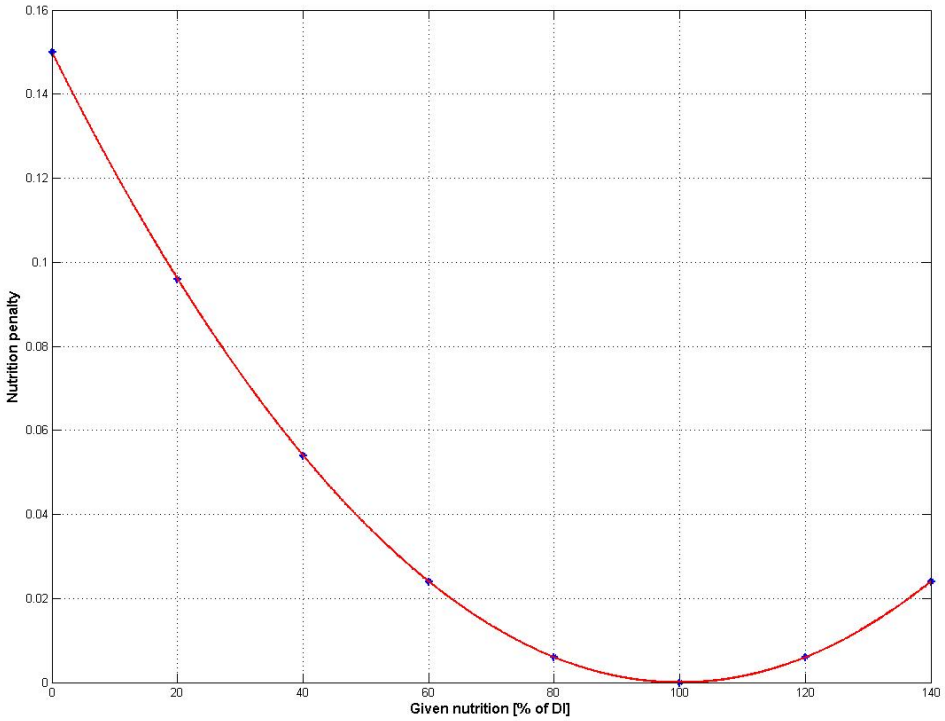

Figure 5.3: *This figure illustrates the shape of the nutrition penalty function*

Insulin penalty function

The insulin penalty shape is based on the saturation effect of insulin action on glucose uptake [Rizza et al., 1981] [Katz et al., 1993]. The shape for the insulin penalty function is illustrated in Figure 5.4 on the next page.
Saturation has effect when calculating the nonlinear fraction of maximal endogenous balance as a function of the insulin infusion/absorption rate.
The calculation of the insulin penalty functions is presented in Equation 5.5 and 5.6:

$$Penalty(INS) = (\frac{(I + K_m)^2}{(K_m)^2} - 1) \times K_{INS-Penalty} \tag{5.5}$$

where K_m is the insulin saturation constant (value = 28 mU/L) [Andreassen et al., 2008] and $K_{INS-Penalty}$ is a insulin penalty function fitting constant (value = 1/280).
Finally, I [mU/L] depends on the insulin bolus given [U/h] defined in Equation 5.6:

$$I = INS \times C \times BM_{70} \tag{5.6}$$

where INS is the insulin bolus from 0-6 U/h (presented as $P(t)$ in Figure 4.3 on page 16), and C is the default conversion factor (value = 98.1 [kg × min/L]) [Pielmeier et al., 2008] to convert absorbed insulin to plasma insulin, and BM_{70} is a bodymass constant (value = 1/70 kg^{-1}).
The system limits the insulin bolus range to 0-6 U/h, and to minimize saturation effects the insulin penalty range is [0 0.13]. The constant $K_{INS-Penalty}$ in Equation 5.5 is thus a fitting

constant, whose purpose is to weight the insulin penalty range against the two other penalty functions.

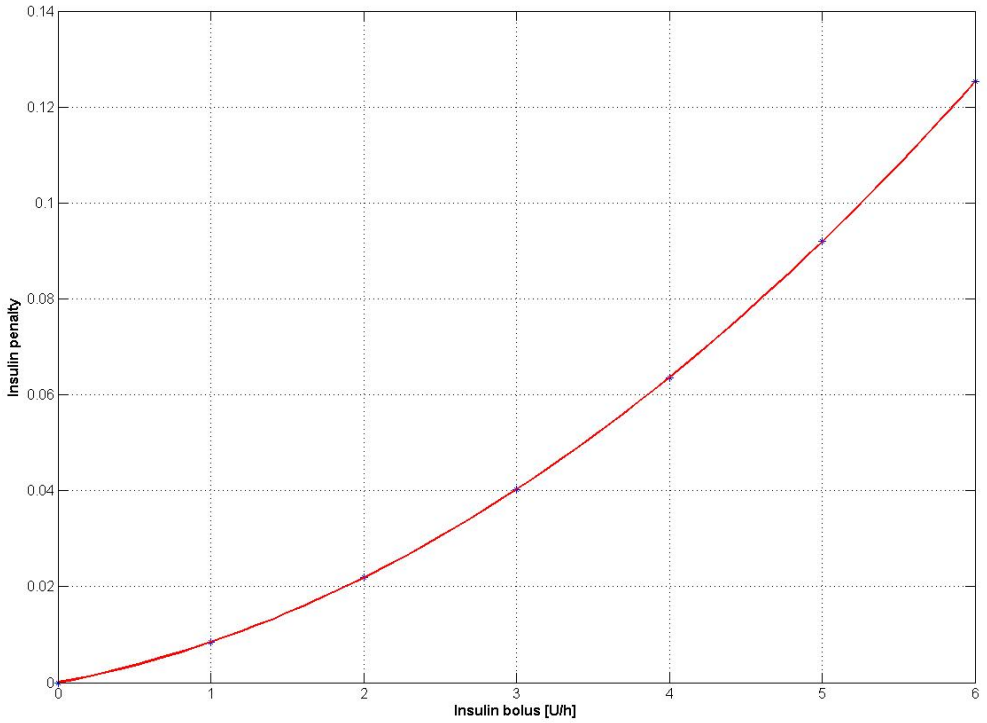

Figure 5.4: *This figure illustrates the shape of the insulin penalty function*

Advice module optimizer

As seen on Figure 5.5 on page 60 the advice module optimizer uses all three penalty functions ($Penalty(INS)$, $Penalty(NUT)$ and $Penalty(BG)$), and forward simulates the model ($simulation(INS, NUT)$) every intervention interval to choose the advice choice with the lowest sum of penalty error (Advice = min(Total Penalty(INS,NUT))).

In the top of the figure an array of different combinations of given insulin (INS) and given nutrition (NUT) can be seen. The optimizer searches this grid of choices before every new intervention advice is given to the virtual patient. The optimizer calculates the penalty for each of 7 possible insulin combinations (0-6 U/h). Meanwhile, the nutrition to be given is calculated for each possible combination over the range: 40, 60, 80, 100, 120, 140 % of DI. This search thus results in $7 \times 6 = 42$ sets of possible interventions, and therefore 42 times where the optimizer forward simulates how the blood glucose concentration will respond to each different set of interventions.

As seen on Figure 5.5 each field of the grid involves a simulation for 3 hours, using the same set of interventions and S_I for the three hour period. The result from this simulation is the set of blood glucose concentrations: bg_{60}, bg_{120} and bg_{180}, which are the blood glucose concentrations after 1,2 and 3 hours, respectively. As seen in Figure 5.5 each set of possible interventions include the blood glucose penalty sum over 3 hours (Equation 5.7), achieved from the simulation:

$$BG_{sum} = Penalty(bg_{60}) + Penalty(bg_{120}) + Penalty(bg_{180}) \tag{5.7}$$

At each field in the grid, having a set of insulin and nutrition, and the resulting development in the calculated blood glucose concentration (bg_{60}, bg_{120} and bg_{180}), these values are used as inputs to the penalty functions to find a penalty sum. The resulting advice is given after repeating this method for each field in the grid (42 times), and yields the combination with the lowest sum of penalties.

The functionality and success of the advice module controller depends on that there always only is given one advice (Advice = min(Total Penalty(INS,NUT))), by meaning that the advice module controller chooses only one minimum of sum of penalty.
The chance of the advice module optimizer chooses more than one advice is very little, especially because of the amount of digits involved in each penalty functions calculations. Also, is the final glycaemic validation involving all 20 virtual patients, described in Article 2, done successfully with the risk of having two advices.
Conclusively, the risk of a advice module controller breakdown due to the calculation of an advice results in more than one advice, is theoretical.
Even though, to ensure the glycaemic control systems stability on larger cohorts, a solution is necessary, which is implemented into the advice module controller in form of two catches and described in the following:

- Catch 1: In case of two or more global minimums in the calculation: (Advice = min(Total Penalty(INS,NUT))), then choose the result which will give the smallest blood glucose penalty BG_{sum} for the blood glucose concentrations (bg_{60}, bg_{120} and bg_{180}).
- Catch 2: In case Catch 1 results in more than one solution, then choose the advice, which will result in the lowest nutrition penalty.

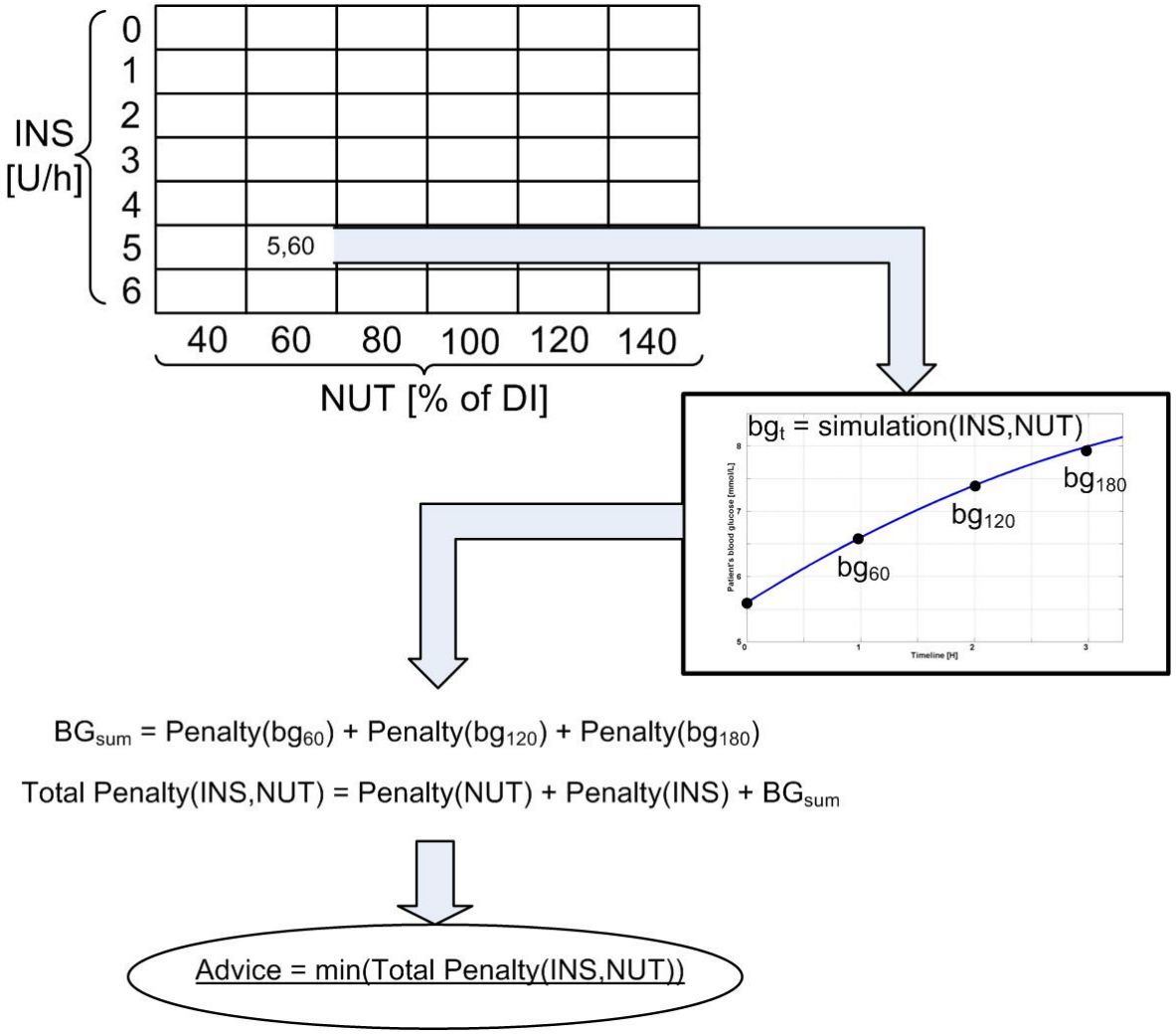

Figure 5.5: *This figure illustrates how the advice module optimizer calculates all relevant combinations of nutrition and insulin in a grid to choose the advice choice with the lowest sum of penalty. During each 3 hours penalty simulation, the same S_I estimated for that hour is used.*

Design of virtual patient

All retrospective data and measurements are available in 1-2 hour intervals, and are thus relatively dense. Ethics approval to use this data was obtained from the South Island Regional Ethics Committee, New Zealand.

As seen in the left column in Figure 5.1 on page 54 this study's concept of a virtual patient, is the blood glucose response using the Glucosafe model for a model simulation. This virtual patient simulation utilizes a previously generated S_I profile, which original comes from 20 critical care patients also used in an earlier study with a specific SPRINT cohort [Chase et al., 2007] [Lonergan et al., 2006a] [Lonergan et al., 2006b], also see Appendix A.2 on page 80. The general criteria for the Benchmark dataset is that the entry blood glucose concentration is higher than 8 mmol/L, and all 20 patients have been on SPRINT for at least 5 days [Chase et al., 2008a]. To imitate a blood glucose measurement on a real patient, noise is added to the virtual patients

Patient number	Age	APACHE II score:	Diagnosis	Hospital stay (hours)	Duration of stay on SPRINT (hours)	Gender
1	75	17	Hypoxemic	1416	828	M
2	68	18	On pump	439	178	M
3	73	22	Perforation	391	310	M
4	68	19	Laparotomy	185	145	M
5	60	13	Chronic obstructive airways disease	254	205	F
6	70	31	Community acquired pneumonia	648	512	M
7	70	42	Obstruction	770	159	F
8	65	25	Septic shock	298	287	F
9	76	20	Acute abdominal aortic aneurysm	511	458	F
10	58	15	Hip replacement	142	139	F
11	49	30	Hypoglycaemia	302	297	M
12	73	16	Pancreatitis	156	150	M
13	20	15	Trauma	1178	971	M
14	74	23	Infarction/ischaemia	230	192	M
15	63	29	Ventilatory	770	323	F
16	49	14	Pancreatitis	929	923	M
17	45	16	Pancreatitis	653	524	M
18	72	16	Post op.	295	265	M
19	73	22	Orthopaedic	257	253	M
20	65	7	Community acquired pneumonia	149	140	F

Table 5.1: Patient data for the 20 SPRINT patients used to validate the advice module. None of the involved patients have any type of diabetes

blood glucose response. The noise added is done as in Equation 5.8:

$$BG_{virtual} = BG_{simulation} + BG_{simulation} \times Normal_{\mu,STD} \tag{5.8}$$

Where the $BG_{simulation}$ is the virtual patients blood glucose response, in terms of a model simulation with a duration of 1 hour. $BG_{simulation}$ is added normal distributed noise with a mean value (μ) at 0 and a standard deviation (STD) at $0.10 \times BG_{simulation}$.

The patient cohorts details used to the advice validation can be seen in Table 5.1.

5.2 Validation 5

Written in the periode from Thursday the 10. May - 2. June 2008

In this section the advice module of the glycaemic control system is being validated. This section only contains the preliminary validation of the system, meanwhile the final tests and statistics are presented in Article 2: 'Development and Validation of a Decision Support System for Critically Ill Patients utilizing the Glucosafe Glycaemic Control Model'.
This validations main focus is to test the advice module, hence, is this also a test of the entire glycaemic glucose system, due to the results from this validation also reflects the Glucosafe model (see dedicated test for this part starting in section 4.6 on page 39) and integral based parameter estimation method (see section 4.5 on page 35 for dedicated test of this part).

The advice module preliminary validations included in Validation 5 covers the following:

- Validation of the glycaemic control systems ability to lower a patients blood glucose concentration [mmol/L], when the patients blood glucose concentration is hyperglycaemic (in this test a starting blood glucose concentration at 26 mmol/L). Furthermore, this is also a test of how long time it takes to achieve normoglycaemia (4.4-7.75 mmol/L).
- Validation of the glycaemic control systems ability to rise a patients blood glucose concentration [mmol/L], when the patients blood glucose concentration is hypoglycaemic (below 2.2 mmol/L). Furthermore, this is also a test of how long time it takes to achieve normoglycaemia (4.4-7.75 mmol/L).
- Validation of the glycaemic control systems ability to keep at patients blood glucose concentration normoglycaemic (4.4-7.75 mmol/L) when the patients state of health is normal with a insulin sensivity, S_I equal to 1.

In Figure 5.6 the implementation of virtual patients can be seen. During a glycaemic control of a given virtual patient, a predefined S_I value is given to the virtual patient each hour, and noise is added (like Equation 5.8 on the previous page) to the virtual patients blood glucose response, to the current intervention, to imitate a clinical situation with measurement noise. In this study, a normal distributed noise with a standard deviation of 10 % of the measured blood glucose is used matching the glucometers used in the SPRINT study Chase et al. [2008b]. All listed validation of the glycaemic control system are done using the same starting criteria: plasma insulin concentration at 20 mU/L and a peripheral insulin concentration at 12 mU/L. In the first two validations the virtual patient utilizes the underlying S_I profile from Patient 1, listed in Table 5.1.
For the two first preliminary validations included in this section Patient 1's S_I profile are loaded into the virtual patient every hour to give the virtual patient a hour to hour changeable insulin sensivity profile ($S_{I,i}$). After having calculated $SI_{estimated(i+1)}$, the advice module, comes up with the new set of intervention to the virtual patient in the following hour ($Nutrition_{i+1}$ and $Insulin_{i+1}$), see Figure 5.6.

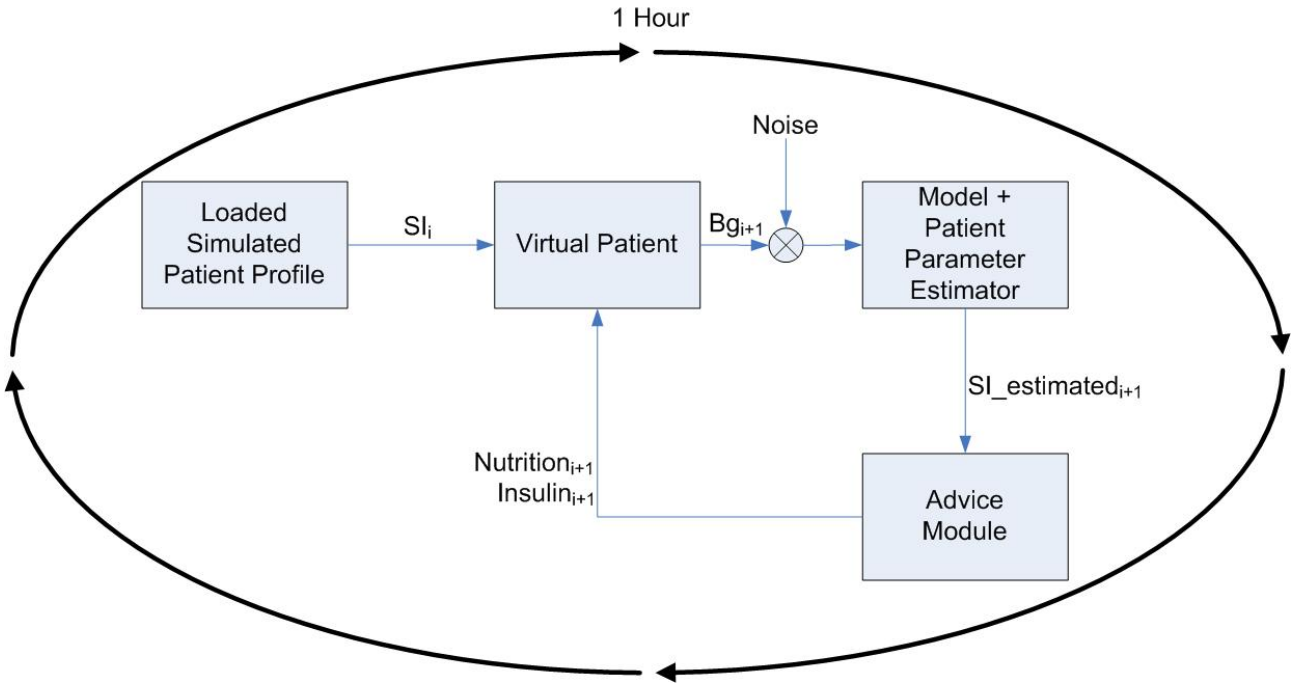

Figure 5.6: *This figure illustrates the dynamics of the glycaemic control system working on a virtual patient imitating a clinical scenario with blood glucose measurement noise*

Advice Module Validation for patient coming from hyperglycaemia

Figure 5.7 illustrates the result for a hyperglycaemic patient (in this case a starting blood glucose concentration on 26 mmol/L) coming under glycaemic control. At hour 1 the first advice is calculated to be used for the time interval between hour 1 and hour 2: 4 U/h insulin and 60 % of DI nutrition is given to lower the blood glucose concentration [mmol/L]. At hour 4 the glycaemic control system has achieved normoglycaemia for the patient (4.4-7.75 mmol/L).

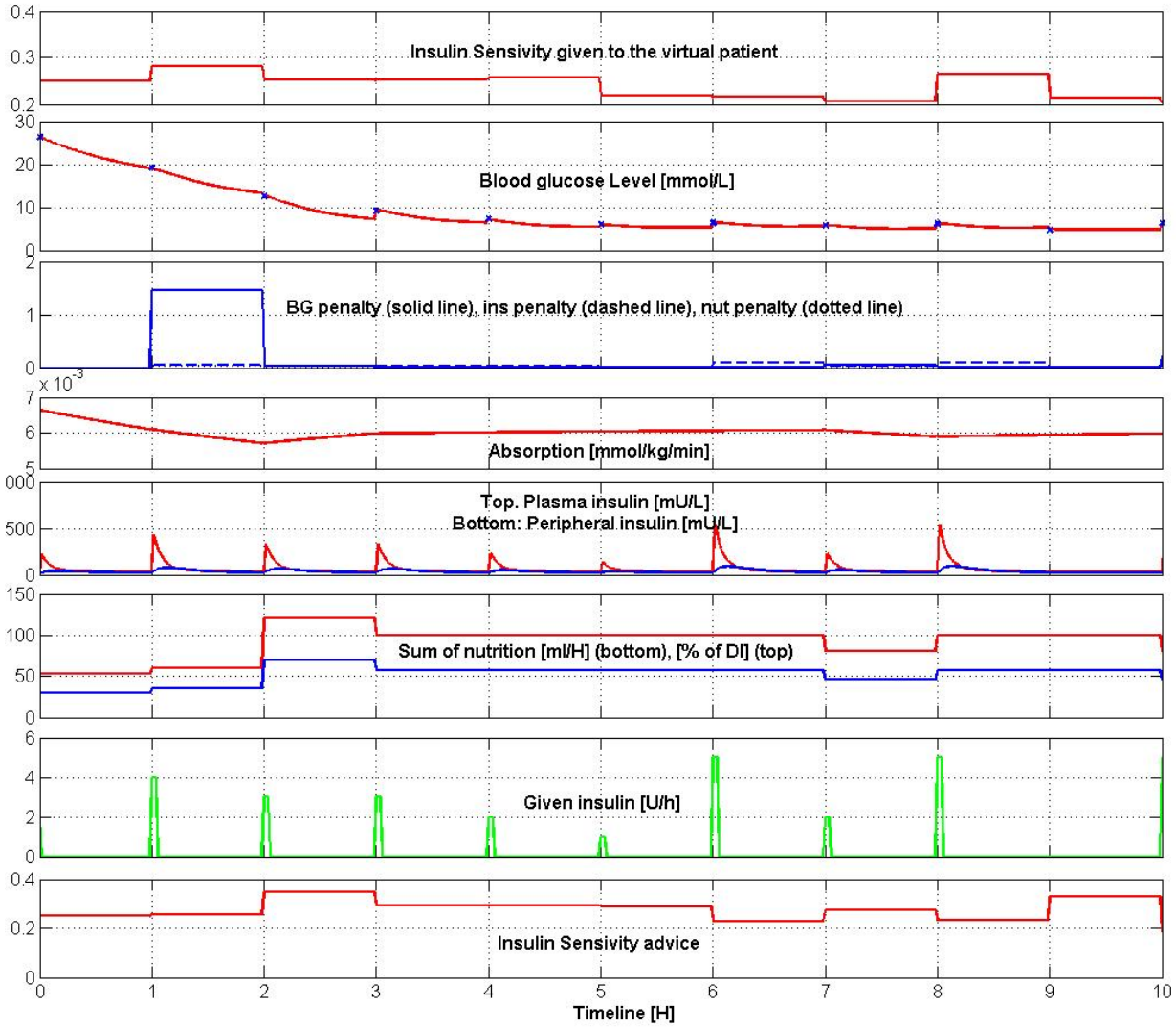

Figure 5.7: *This figure illustrates a hyperglycaemic patient coming on glycaemic control. The starting gut content 2 mmol/kg, which result in a decreasing absorption rate [mmol/kg/min] in the start because of the low nutrition feeding rate. The given S_I profile originates from Patient 1 described in Table 5.1*

Advice Module Validation for patient coming from hypoglycaemia

Figure 5.8 illustrates the result for a hypoglycaemic patient (the starting point for the blood glucose concentration is 2.2 mmol/L) coming under glycaemic control. At hour 1 the first advice is calculated to be used for the time interval between hour 1 and hour 2: 0 U/h insulin and 120 % of DI nutrition is given to rise the blood glucose concentration mmol/L. After two hours of control, at hour 3, the glycaemic control system has achieved normoglycaemia for the patient (4.4-7.75 mmol/L).

At hour 1 the glycaemic control system chooses to give the patient 120 % of DI instead of 140 % of DI, even though the patients is hypoglycaemic. The reason for this is that the absorption rate [mmol/kg/min] responds slowly, representing in that the difference in nutrition penalty between 120 and 140 % of DI is bigger than the penalty difference of the two resulting blood glucose concentrations (BG_{sum}).

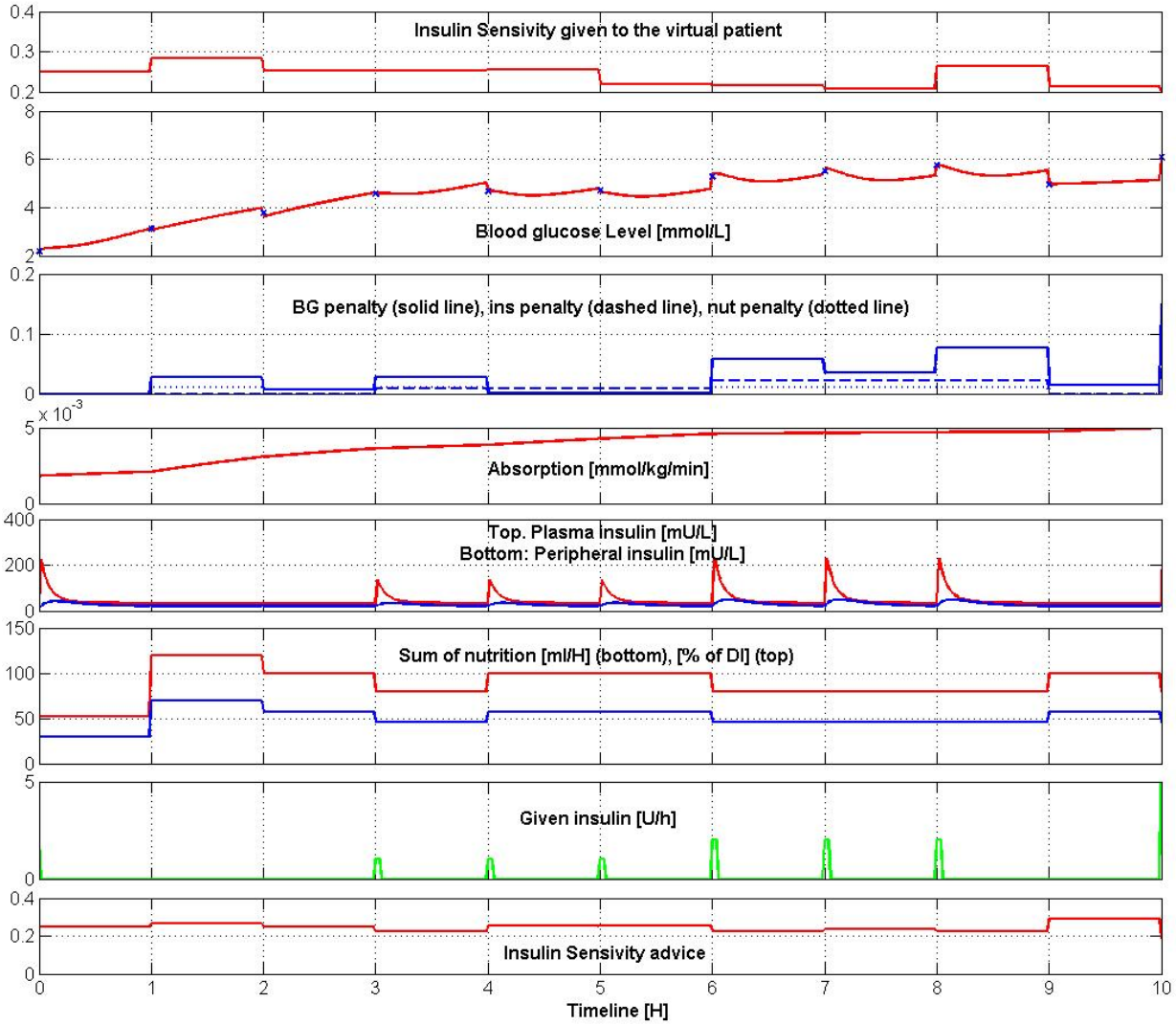

Figure 5.8: *This figure illustrates a hypoglycaemic patient coming on glycaemic control. The starting gut content 0.5 [mmol/kg], which result in a increasing absorption rate [mmol/kg/min] because of the high nutrition feeding rate. The given S_I profile originates from Patient 1 described in Table 5.1*

Advice Module Validation for healthy patient

Figure 5.9 illustrates the result for a healthy patient coming on glycaemic control. The aim of this validation is to shown that the glycaemic control system can keep a patients blood glucose concentration normoglycaemic (4.4-7.75 mmol/L) even though the patients insulin sensivity is 1, and therefore differs a lot from the cohort used in this study, see Table 5.1.
Like in the two previous validation the advice calculation begins at hour 1. The starting blood glucose value in this validation is hyperglycaemic at 26 mmol/L, the goal is to keep and get the patient inside the 4.4-7.75 mmol/L range.
Overall during this validation, the nutrition feeding rate was close to 100 % of DI.

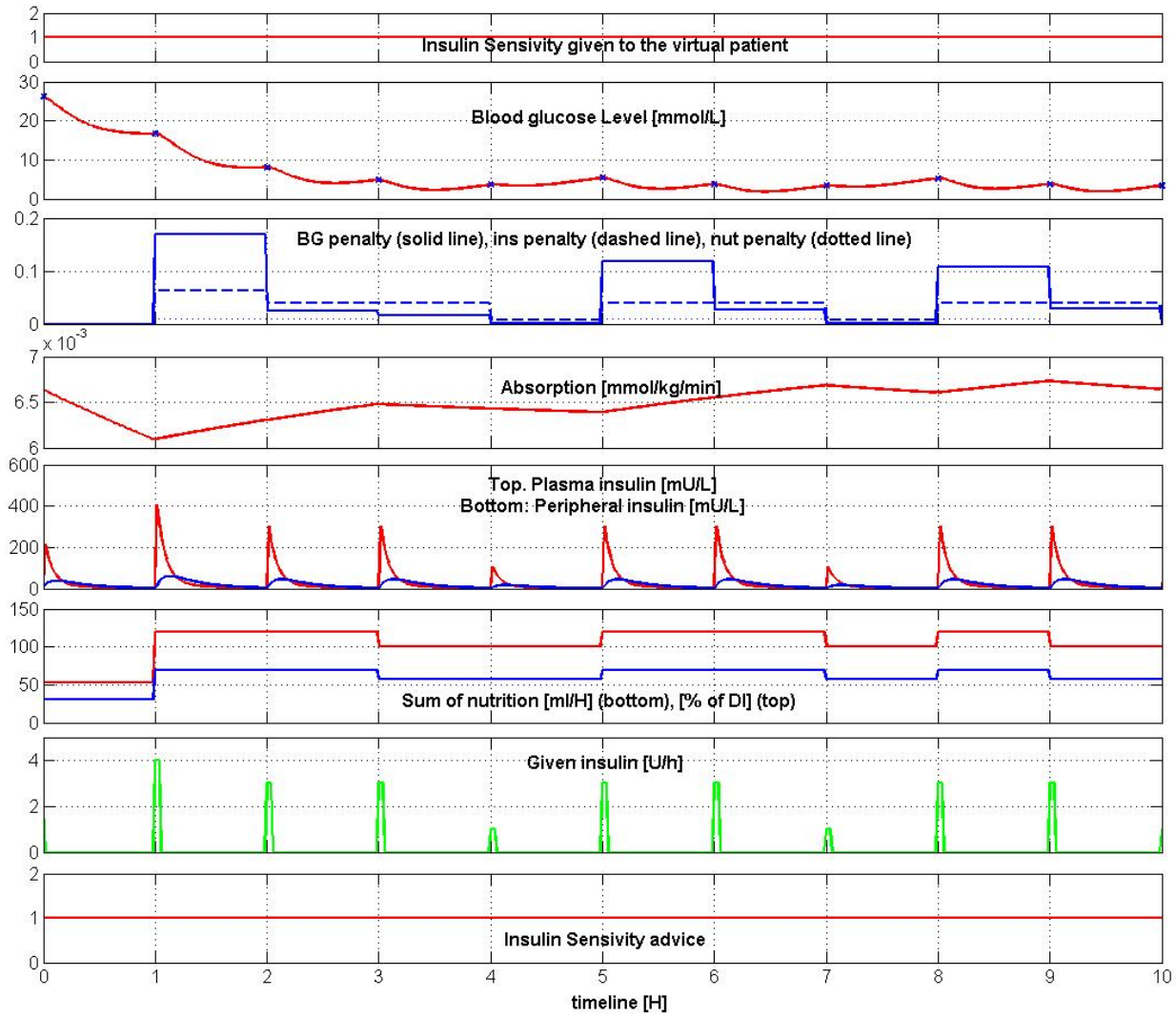

Figure 5.9: *This figure illustrates a healthy patient coming on glycaemic control. The starting gut content is 2 [mmol/kg]. The given S_I profile is made up and set as a constant to imitate a healthy patient.*

Conclusion to advice module preliminary validations

Through all 3 validations the Glycaemic control system succeeded in getting the patient into the normoglycaemic range (4.4-7.75 mmol/L), and keeping the patient there.
For the hyperglycaemic patient it took 4 hours, or 3 advice calculated interventions to achieve normoglycaemia. For the hypoglycaemic patient it took 3 hours, or 2 advice calculated interventions to achieve normoglycaemia. The validation with the healthy patient also proved that the glycaemic control system can keep the patient normoglycaemic.

From these preliminary validations of the advice module, the glycaemic control system is ready to be tested on a bigger scaled patient cohort, described in Table 5.1. The Validation of these 20 critical care patients are presented in Article 2: 'Development and Validation of a Decision Support System for Critically Ill Patients utilizing the Glucosafe Glycaemic Control Model'.

Chapter 6

Evaluation

6.1 Discussion

Written in the periode from Thursday the 25. May - 2. June 2008

In this section the full discussion of the project is presented by meaning that this discussion includes both the topics of the Model Prediction design and result and the final design and results of the glycaemic control system. This discussion is consistent to both discussions in Article 1 and 2.

The Glucosafe model presented is physiologically defined and utilizes the concept of a remote compartment for insulin transport to account for the delay between insulin secretion, or infusion, and utilization.
The integral based fitting method proves effective in reducing a typically non-linear optimization problem to a linear, rapidly solved convex optimization problem. Overall, the fitted model matches all observed clinical dynamics, as seen in Table 4.7 in validation 3b and does so have minimal error. These fitting results indicate that the model possesses all necessary mathematical dynamics.
The low Model Prediction error of Table 4.7 (and presented in Article 1), as compared to the Glucometers used at Christchurch Hospitals with 7-12 % measurement error [Hann et al., 2005], helps to further justify this choice of approach.

The system prediction model estimates only one parameter S_I. As a result, the endogenous insulin production (EP) is kept constant. However, this assumption only shifts the identified S_I value if examined in a parametric study. Fitting both parameters in this model is problematic, as they are not uniquely identifiable without measured insulin data, which is rarely available in critical care. An added argument for only using S_I as a variable parameter is that little is known about the kinetics of EP secretion, both in magnitude or variation over time, in the critically ill.

The parameters EP and S_I are thus dependent and a change in EP therefore mostly scales the S_I profile by a given value over the patient. Figure 4.23 on page 51 shows how 2 different values for EP and the same S_I profile scales the predicted blood glucose values for Patient 6 (in Model Prediction validation). The shifted dynamics for the three different cases are otherwise close to the same. It also shows how EP and S_I are dependent and trade off for Patient 6. As EP increases, S_I falls and vice versa, with similar dynamics in the S_I profiles.
The Glucosafe model validated in this study has used a fixed EP at 27.77 mU/min. Due to minimize the model Prediction error APE, different values of EP has been tested.

Figure 4.24 on page 52 illustrates the relationship between choice of EP and resulting overall median APE for all 10 patients.
The overall median APE for model Prediction has been tested for choices of EP at 20, 27.77, 30, 35, 40 and 45 mU/min. The dots in Figure 4.24 on page 52 represents the Model Prediction result for all 10 patients, and the best overall choice for EP to have, is a EP value at 27.77 mU/min. However, using a EP value at 27.77 mU/min may not be the optimum solution in other situations, with a less critically ill patient cohort (higher S_I).
In general, the 1-hour prediction validation errors are relatively low and consistent. The cumulative distribution figure presented in Article 1 shows that 90 percent of the Model Prediction results are below 25 % APE, and 60 percent are below 10 % APE. The same figure also shows an error distribution that is clearly not normal. Hence, this study reports median and IQR values to better represent the data than normal statistics.

The Glucosafe model used in this glycaemic control system presented, is physiologically defined and utilizes the concept of a remote compartment for insulin transport to account for the delay between insulin secretion, or infusion, and its utilization. A prior validation shows that the fitted model matches all observed clinical dynamics [Lotz, 2007] [Pielmeier et al., 2008]. This verifies the use of blood glucose response of virtual patients, who are constructed using the same model added noise, to be the single scale of which the validation of the glycaemic control system is tested against.

In terms of the design of the advice module in the glycaemic control system where the results showed in section 5.2 on page 62 that there is a need to adjust the nutrition and insulin given, to keep the patient inside the normoglycaemia range (4.4-7.75 mmol/L).
The results of glycaemic control validation (presented in Article 2), regarding the average nutrition rate, and the ability to keep the patients inside the range of normoglycaemia, are good examined in isolation. However, more importantly, in combination the compromise between nutrition given (87.17 % of DI), and the ability to keep patients normoglycaemic (87.73 % of measurements), can be hard to achieve with this general ICU cohort.
The overall normal average calorie intake per day was 1250 kcal/day, and the overall average given insulin was 2.2 U/h, which makes the results from this study comparable to other similar studies - for example the SPRINT clinical implementation and evaluation study by Chase et al. [Chase et al., 2008b], where the overall lognormal average calorie intake per day were 1283 kcal/day and overall average given insulin per hour were 2.8 U/hour.

In a later clinical scenarios, there are potential limitations in the advices of the glycaemic control. Some hospitals use fixed nutrition feeding rates (fx. 100 % of DI), so that insulin [U/h] is the only adjustable parameter ensure patients are kept normoglycaemic. Observing Table II in Article 2 it can be seen that most of the average feeding rates for all 20 patients are in the 80-100 range [% of DI], depending on the patients average S_I. Hence, without modulating nutritional inputs many similar general ICU patients will have periods of hyperglycaemia where insulin alone may not be fully effective.

6.2 Conclusion

Written in the periode from Thursday the 25. May - 2. June 2008

In this section the conclusion of the full project is presented regarding the topics of the Model Prediction design, results and the final design and results of the glycaemic control system. This conclusion is consistent to both conclusions in Article 1 and 2.

This study examines and validates the Glucosafe glycaemic control model for critical care patients in simulation using retrospective clinical data. The model is also validated for its predictive ability (also presented in Article 1). The Model Prediction utilizes an integral based parameter estimation method for fitting the patient specific insulin sensivity S_I. The goal is to ensure prediction with minimal absolute percent error, and to assess the models potential clinical utility. The Model Prediction validation and examination (Validation 3b) used retrospective clinical data from glycaemically controlled critical care patients. The basic patient data for this cohort are presented in Tables 4.3 and 4.4.

The overall mean and median absolute percent error for both Model Simulation and Model Prediction are within measurement error.
Both results for Model Simulation validation (Validation 2) and Model Prediction validation (Validation 3b) are considered acceptable for later use in control applications in a clinical setting out to approximately 3 hour predictions levels, as seen in Validation 4. These results validate using these models in proof of concept pilot clinical trials.
Furthermore, this study presents and validates a glycaemic control system, utilizing the Glucosafe model Pielmeier et al. [2008] and an integral based parameter estimation method for fitting the patient specific insulin sensivity S_I [Hann et al., 2005] (also presented in Article 2). The goal of the glycaemic control validation is to prove the glycaemic control systems ability to keep 20 virtual patients (produced by patientdata using retrospective clinical data (SPRINT)) inside the range of normoglycaemia (4.4 - 7.75 mmol/L).

The overall median blood glucose concentration for all 20 patients in the glycaemic control validation is 6.05 mmol/L, and the IQR is 5.54-6.62 mmol/L. The basic patient data for this cohort are presented in Table 5.1. The overall number of hypoglycaemic measurements per patient is 0 (blood glucose measurements below 2.2 mmol/L). The overall mean percent of measurements inside the normoglycaemic range (4.4-7.75 mmol/L) is 87.7 %.

Because of the low variation of average feeding given to the virtual patients, and that the overall average feeding is very close to reach full calorie need, the glycaemic control system is considered comparable to other similar studies [Chase et al., 2008b], and acceptable for later use in control applications in a clinical setting using real patients.
The results presented in this study validates using the current version of the glycaemic control system in proof of concept pilot clinical trials.

6.3 Future work

Written in the periode from Thursday the 25. May - 2. June 2008

This section contains the aspects for future work of the results achieved during the period of developing the glycaemic control system. This section can be read together with the full overview of the decision support system described in section 4.1 on page 12.

The current state of the glycaemic control system is its ability to keep virtual patients blood glucose concentration normoglycaemic (4.4-7.75 mmol/L). These virtual patients are build upon real patient data (SPRINT) [Chase et al., 2008b] [Chase et al., 2008a]. The next step of developing of the glycaemic control system is to add a user friendly interface to medical staff at the ICU, and by that make it a stand alone decision support system to help medical staff and real critical ill patients, in terms of the nutrition feeding rate [ml/h] and given insulin [U/h] to these patients.
The primary task of the decision support systems user interface should be to give insulin [U/h] and nutrition [ml/h] advices to the medical staff, and to be the systems input user interface, from where the decision support system can receive the latest measured blood glucose measurement [mmol/L], of the patient under control, to update the model for continuing the glycaemic control. It is intended for the decision support system to work together with the local medical staff, and it should be possible for the staff to bypass the advice given from the system, and instead give independent nutrition and insulin advices. when that happens, the medical staff should inform the decision support system with the new intervention, so that the glycaemic control system can be updated to continue as normal.
Furthermore, different intensive care units can have different treatment politics, in terms of the interventions given to the critical ill patients under glycaemic control. Therefore, the advice module optimizer shall have a build in functionality to work after the local rules of intervention: fx. always feed at a 100 % of DI, different insulin and nutrition limitations ([% of DI] and [U/h]).
Finally, the decision support system's imbedded physiological model, has to be upgraded to have an adaptive patient specific post-hepatic endogenous insulin production (EP) functionality, due to improve the advice given for each patient under glycaemic control.

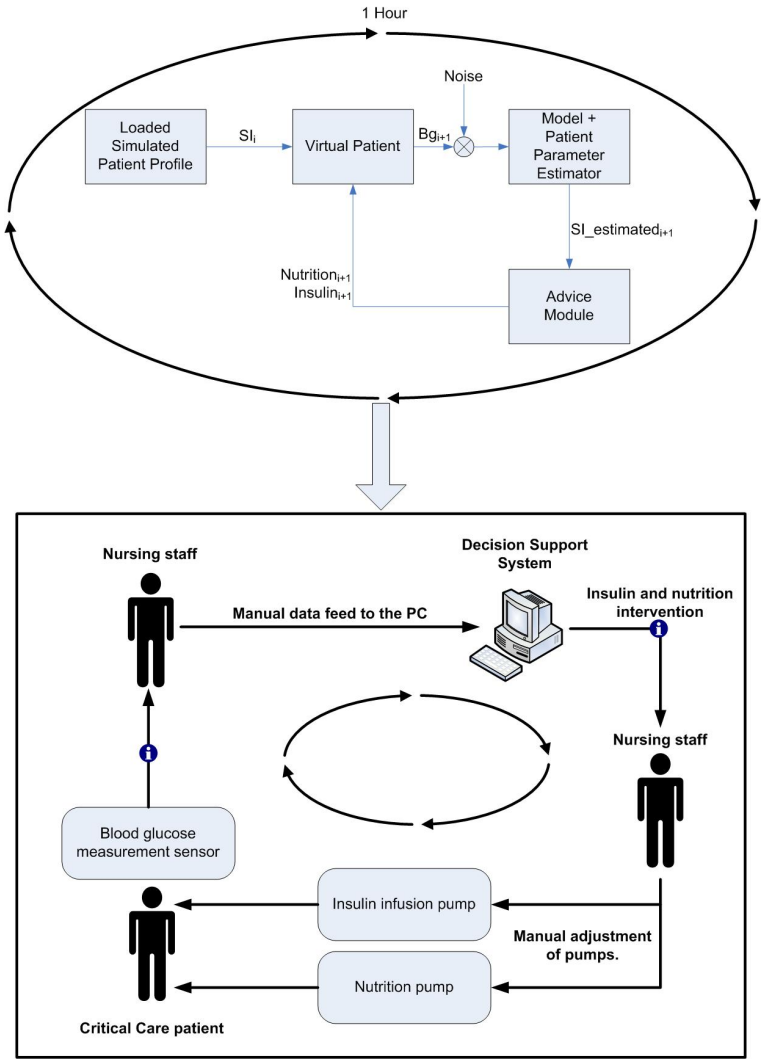

Figure 6.1: *This figure shows the step from going from a glycaemic control system working on virtual patients, to be a decision support system working together with medical staff to optimize the treatment of real critical ill patients. The top part illustrates the dynamics of the glycaemic control system working on a virtual patient imitating a clinical scenario with blood glucose measurement noise, meanwhile the lower part gives an overview of the involved hardware in the system and the actors that the system has to work with when the glycaemic control system is developed to work as a decision support system.*

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Appendix A

Blood glucose

Blood glucose concentration [mmol/L], is tightly regulated in the healthy non-diabetic human body.
Normally, the blood glucose concentration is maintained between about 4.4 and 7.75 mmol/L (70 to 150 mg/dL). The total amount of glucose in the circulating blood is therefore about 3.3 to 7 g, assuming an ordinary adult blood volume of 5 litres (glucose = 180 mol/g).
Glucose concentrations rise after meals and are usually lowest in the morning, before the first meal of the day.
Failure to maintain blood glucose in the normal range leads to conditions of persistently high (hyperglycaemia) or low (hypoglycaemia) blood glucose concentration [Despopoulos and Silbernagl, 1991], [Martini, 2004].

Carbohydrate metabolism and Pancreatic hormones

To understand the kinetics of the regulation of the blood glucose concentration, it is necessary to understand the origin of the different types of cells used for glucose regulation.
This is done by describing the pancreas. More specifically the pancreatic islets, where the production of these hormones they excrete occurs.
The Pancreatic Islets produce four types of cells that excrete hormones [Martini, 2004]:

Alpha cells Produce the hormone glucagon, which raises the blood glucose concentration when released, by increasing the rates of glucose released by the liver.

Beta cells Produce the hormone Insulin, which lowers the blood glucose concentration, by activation the insulin dependent GLUT4 glucose transporter to rise the glucose absorption in the peripheral uptake of glucose into sceletal and cardiac muscle, and adipose tissues. The hepatic balance also is insulin dependent (GLUT2 - glucose bidirectional transport) and more insulin therefore results in a increasing rate of glucose uptake in liver.
The production of C-peptide also takes place in the Beta cells. C-peptide is produced when the present proinsulin is split into insulin and C-peptide. The split is done when proinsulin is released from the pancreas into the blood in response to a rise in glucose - one C-peptide for each insulin.

Delta cells Produces a peptide hormone, GHIH. When released, this hormone suppresses the production of glycagon.

F cells Pancreatic polypeptide. It suppresses the pancreatic secretion and stimulates gastric secretion

The regulation of concentration of blood glucose primarily depends on insulin and glucagon. Insulin is released in the pancreas when glucose concentrations exceed normal and is thus stimulated during digestion, as carbohydrate reaches the bloodstream as glucose.
The glucose can also be removed by the kidney and liver, which also play a role in removing insulin.

A.1 Hyperglycaemia in the ICU patient

Hyperglycaemia is typically defined as a blood glucose concentration above 7.75 mmol/L.
The early study from Van Den Berghe et al. suggest that hyperglycaemia is an overall factor for mortality risk [Van den Berghe et al., 2001].

In contrast later studies from other researchers and Van Den Berghe et al. show a more varied outcome as a consequence of having hyperglycaemia in the ICU. These studies point out that the result also is cohort depended.

Age-adjusted mortality is twice that of patients without diabetes [Turina et al., 2006].

Patients who are not diabetic, but who present during acute illness with high blood glucose concentration have a poorer prognosis than patients who are normoglycaemic. This outcome has been observed in patients with myocardial infarction [Capes et al., 2000], heart failure [Barsheshet et al., 2006], trauma [Capes et al., 2001], and patients with severe traumatic head injury [Jeremitsky et al., 2005]. Krinsley et al. (2003) retrospectively reviewed 1826 patients in the intensive care unit, finding that mortality increases progressively as glucose increases, even when matched for APACHE 2 severity of illness scoring [Knaus et al., 1985].

A.2 Documentation of SPRINT dataset

Written in the periode from Thursday the 23. May - 2. June 2008

This appendix shortly describes the patient data used in the study. The patient data used to the Model Prediction validation (3a and 3b) is different than the patient cohort used to validate the full glycaemic control system (validation 5).

The patientdata used in this study originates from Christchurch Hospital, New Zealand, from where the SPRINT studies have been performed Chase et al. [2007] Lonergan et al. [2006a] Lonergan et al. [2006b]. All data and measurements are available in 1-2 hour intervals, and are thus relatively dense. Ethics approval to use this data was obtained from the South Island Regional Ethics Committee, New Zealand.
The full SPRINT patient dataset contains of 394 patients with various length of stay, but with the same informations for each patient.
The information each SPRINT patient contains are presented in the following:

Age: The age of the patient in full years.

Gender: Man or woman.

Length of stay: presented in days. This is the length of stay at the hospital included the time on SPRINT.

Outcome ICU: The state of health for the patient when leaving the ICU.

Outcome hospital: The state of health when leaving the hospital.

Apache II: The patients risk of mortality proportional to the Apache II score: the higher Apache II score the lower risk to survive.

Principal diagnosis: The most important diagnosis given to the patient.

Associated diagnosis: Parallel diagnosis' less important than the principal diagnosis, and/or other diagnosis caused by the principal diagnosis.

Underlying diagnosis: The cause of the current state of health or diagnosis for the patient. It could be an old diagnosis resulting in an other later developed diagnosis.

T.real: The time stamps for the real patients measured blood glucose.

G.real: The value of blood glucose measurements [mmol/L] at the time stamps of T.real.

T.insulin: The time stamps for the given insulin [U/h] to real patient during SPRINT.

Insulin: The bolus size of the given insulin [U/h] at time T.insulin to the real patient during SPRINT.

T.Feed.rate: The time stamps for the given nutrition to the real patients during SPRINT.

Feed.rate: The feeding rate to the time stamps of which the nutrition [ml/h] is given to the real SPRINT patients.

Feed.type: The nutrition type given to the real SPRINT patients at time TFeed.rate. The different types of nutrition are presented in Table A.1.

Nutrition type	[kcal/ml] (CV)	glucose [g/ml]	input method
Diabetic Resource	1.06	0.0872	Enteral
Glucerna	1	0.0812	Enteral
Jevity	1.5	0.202	Enteral
Osmolyte	1.2	0.158	Enteral
Peptinex	1	0.16	Enteral
Isosource	1.2	0.17	Enteral
Renal	2	0.2	Enteral
Novasource	2	0.2	Intravenous
Vivonex	1	0.21	Intravenous

Table A.1: This table presents the types of nutrition given to the real patients during SPRINT. For approximately 90 % of all time stamps for all SPRINT patients the nutrition type given is the enteral nutrition 'Diabetic Resource', which also is the nutrition type used to give the virtual patients in the virtual trials of the glycaemic control system presented in this report.

In the article *Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model*' (Article 1), and in validation 1-4, the patient cohort used count the SPRINT patient 1-10. The basic patient details for these patients are presented in Table 4.3 and Table 4.4.
In the article'*Development and Validation of a Decision Support System for Critical Ill Patients utilizing the Glucosafe Glycaemic Control Model*' (Article 2), and in validation 5, the patient cohort used counts the 20 SPRINT patient: 17,21,22,23,28,30,43,44,55,56,58,67,69,83,92,99,105,133,137 and 153. The basic patient details for these patients are presented in Table 5.1 as patient 1-20. The same patient cohort are used in similar studies by Chase et al. [Chase et al., 2008a].

The SPRINT dataset does not include information about the patients height and weight. Because of the need of these to patient constants in the study the following rule has been made:

If gender is male: Weight is set to 75 kg, and height is 175 cm.

If gender is female: Weight is set to 65 kg, and height is 165 cm.

The result for the Model Simulation validation presents with an overall mean APE at 0.45 %, which justifies this choice of approach.

A.3 DVD guide

Written in the 29. May 2008

This appendix shortly describers the material on the attached DVD in the bottom of this page. When opening the DVD five folders can be seen with the names 1, 2, 3, 4 and 5.

1: This folder contains: rapport.pdf, pictures included as '.jpg' versions (I have given the files the same name as in the report).

2: This folder contains: Article 1 old in pdf, pictures included as '.jpg' versions (I have given the files the same name as in the Article 1 old).

3: Article 1 in pdf, pictures included as '.jpg' versions (I have given the files the same name as in the Article 1)

4: Article 2 in pdf, pictures included as '.jpg' versions (I have given the files the same name as in the Article 2)

5: The patient data of the two patient cohorts in two folders: Article 1 (10 patients from SPRINT) and Article 2 (20 patients from SPRINT, Benchmark cohort). Patient data are explained in Appendix A.2 on page 80

Parameter Estimation and Prediction Validation for the Glucosafe Glycemic Control Model

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Written in the period 27. November - 6. January 2007.

Abstract

Background: Hyperglycaemia in critically ill patients increases the risk of complications and mortality. This paper presents and validates a model for clinical glycemic control. The main application for this model and integral based identification method presented is the real-time automated control of glucose levels in ICU patients and similar medical decision support systems.

Methods: The Glucosafe glucose-insulin metabolic model is used to calculate the time-varying response of blood glucose to interventions in terms of insulin and nutrition given to the patient. The model dynamics are validated in their ability to fit retrospective data, as well as by prediction accuracy for a given intervention. Data from 10 patients at Christchurch hospital on 1786 hours of data are utilized.

Results: The overall mean absolute procent error for the simulation validation fitting data is 4.35 %.
In 1 hour prediction mode, the mean absolute procent error is 10.31 %.

Conclusions: Both results for model dynamic validation and prediction validation are acceptable for later use in control applications in a clinical setting.

Index Terms

Glucosafe, SPRINT, Glycemic control, Physiologic modelling, Blood glucose, Insulin Sensivity, Integral Parameter Estimation, Intensive Care, Virtual Trials

I. INTRODUCTION

Patients who are critically ill due to surgery, trauma or life-threatening illness can require vital organ function support and prolonged intensive care [1]. Many of these patients present, even with no prior diabetes, with stress induced hyperglycemia, suggesting overall insulin resistance due to the treatment and/or their condition [1] [2] [3]. Insulin resistance and the resulting hyperglycemia may contribute to micro- and macro-angiopathy, neuropathy and organ failure [3] [4]. A number of clinical studies have shown a significant relationship between the mortality of patients and high blood sugar levels [5].
Tight glucose control has been shown to reduce mortality by 15-43 % [3] [6] [7] [8] [].

In critical care, lower glucose nutrition alone has seen significant reductions in average blood glucose levels. [3], [9]. In some cases insulin alone may not be enough to reduce blood glucose to normal level. As a result, exogenous nutritional inputs must be reduced under certain conditions, due to excessive nutrition exacerbating hyperglycemia [9] [10]. More specifically, reduced glucose nutrition combined with insulin administration can act to control both sides (input and removal) of the glucose balance [11] [3]. Only a few studies have been made to control blood glucose in critical care using models. Most of these efforts use only exogenous insulin for control [12] [13] [11] [14]. Later studies have combined the insulin and nutrition paths to control [3] [11] [15] [16]. Overall tight regulation of blood glucose based on the mentioned mathematical models of glucose metabolism has given promising results, indicating that it is possible to achieve normoglycaemia.

Glucosafe is a new composite model that makes use of previous work in insulin and metabolic modelling [17] [18] [19]. The system also utilizes a glucose transporter model, which calculates the glucose balance for a given set of inputs and the gut absorption rate [20]. Hence it contains clinically validated insulin kinetics and glucose insulin dynamics.

Model-based methods can be very accurate, but require the ability to identify patient specific parameters in clinical realtime to update the model dynamics. A fast, accurate identification method is therefore also important in the process of refining and testing a model. More importantly, a fast, accurate method also enables application in real-time model-based control and medical decision support applications.
This paper presents a blood glucose prediction and control system using Glucosafe and an integral based

parameter estimation method. The integral based approach turns a computotionally intense, non-linear and non-convex optimization, into a fast, convex parameter identification.

The result enables faster, and potentially more accurate, predictions of patient specific parameters and thus of a patient's glycaemic response to intervention.

II. Methods

A. Glucosafe glucose-insulin system model

The Glucosafe glucose-insulin metabolic model is used to calculate the time-varying response of blood glucose for given insulin and nutrition inputs. The Glucosafe model itself uses fixed patient parameters for the patient in any given time period, or interval. However, its parameters can be updated between sets of measurements.

The blood glucose and insulin kinetics of the Glucosafe model are illustrated in Figure 1, and are defined [19]:

$$\frac{dI}{dt} = (-n_K - n_L) * I(t) - \frac{n_I}{V_P} * (I(t) - Q(t)) + \frac{P(t) + U(t)}{V_P} \tag{1}$$

$$\frac{dQ}{dt} = -n_C * Q(t) + \frac{n_I}{V_Q} * (I(t) - Q(t)) \tag{2}$$

Equations 1 and 2 describe the change in plasma and peripheral insulin concentration, where n_K is the kidney clearance [1/min], n_L the liver clearence [1/min], n_C the irreversible loss of insulin in the periphery [1/min] and n_I is the transport rate between the plasma and peripheral compartments [L/min].

In this case, U_t is the endogenous insulin secretion rate, the insulin infusion rate, P_t, and the plasma blood volume is V_P. Finally, V_Q, is the peripheral interstitial volume.

Changes in blood glucose level for any set of inputs are defined:

$$\frac{dG}{dt} = Z(t) - E(G, A) \tag{3}$$

where Z(t) is the sum of absorption from the nutrition input, and E(G,A) is the positive or negative turnover of blood glucose to the liver, kidneys, fat cells and muscle cells, which are described in Equation

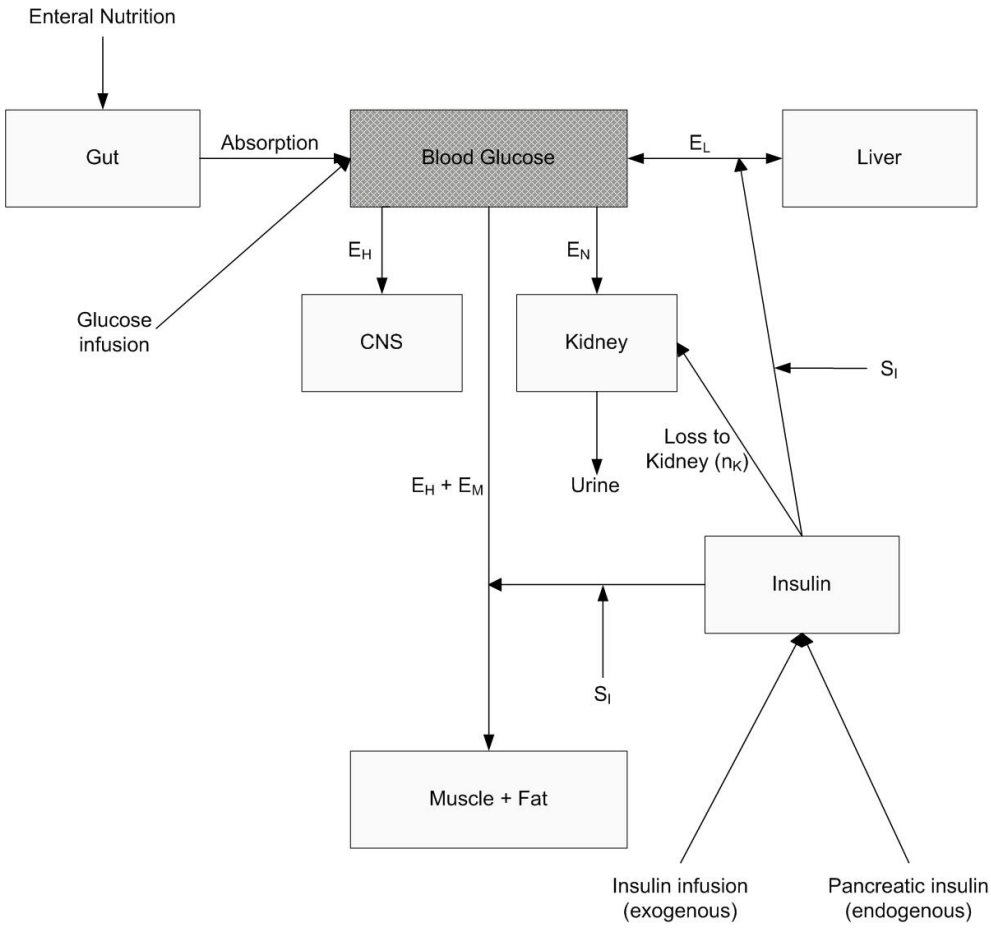

Fig. 1. *Glucosafe physiological overview, where exogenous insulin is assumed to be intravenous. In this figure CNS = central nerve system, which together with the muscle cells, fat cells, liver and kidney results in a negative change in blood glucose (and a positive change in the blood glucose if the level is very low). The enteral nutrition and glucose infusions result in a positive change in blood glucose.*

4 respectively, as $E_L(G, A)$, $E_N(G)$, $E_H(G)$ and $E_M(G, A)$.

$$E(G, A) = E_L(G, A) - E_N(G) - E_H(G) - E_M(G, A) \tag{4}$$

$E_L(G, A)$, $E_N(G)$, $E_H(G)$ and $E_M(G, A)$ are then defined [20]:

$$E_L(G, A) = -0.46 \times G(t) - 1.475 \times A(t) + 1.34 \tag{5}$$

$$E_N(G) = 0.00367485714 \times G(t)^2 - 0.06392476190 \times G(t) + 0.27765942857 \tag{6}$$

$$E_H(G) = 0.56 \times \frac{G(t)}{G(t) + 1.5} \tag{7}$$

$$E_M(G, A) = 5.0868 \times A(t) \times \frac{G(t)}{G(t) + 5} \tag{8}$$

The size of $E_L(G, A)$ and $E_M(G, A)$ depends on the current level of blood glucose and active or available insulin, A.

The active insulin, A, is calculated:

$$A(t) = S_I * f(Q(t)) \tag{9}$$

where $f(Q(t))$ is the fractional effect of peripheral insulin, which together with the insulin sensivity S_I determines the active insulin level [20]. The brief system model definition in Equations 1-9 are all clinically validated individually [20] [19].

The integral parameter estimation is implemented used the same method as Hann et al. [21]. In this case, it is used to identify S_I and all other values are held at population constants [20] [19]. By substituting Equations 1-9 and separating the S_I dependent parts from the rest, it is possible to isolate and calculate S_I every hour. The value of S_I is assumed piecewise constant over the identification interval.

Figure 2 shows the flowchart for the identification process to find a patient specific S_I profile over time for a given set of patient data. The prediction mode uses this patient specific S_I profile to test the models predeiction ability. In prediction mode, the identified S_I profile is used to simulate the patient, as a 'virtual patient' [15] [11] [22]. Every hour a new blood glucose measurement is available, a new S_I value can be identified for that preciding (hour) time interval. Using that hour to hour S_I value and the known interventions, the next blood glucose measurement can be predicted. Comparison of the clinical response in the data to the model prediction can be used to validate the model's predictive capability in a realistic control scenario.

Hence, Figure 2 shows how the model of Equation 1-9 and the integral based parameter identification can be used to provide two forms of model validation. First, is a fitting validation showing the model can match the clinically observed dynamics (simulation mode). Second, and more difficult, is predictive validation, showing it captures those dynamics in its patient-specific parameters well enough to enable consistent, accurate prediction of the response to clinical intervention.

Finally, all other parameters except S_I are held constant at population values based on the validation and sensivity analyses presented previosly [19] [20] [21] [17] [18]. Hence, the value of S_I found is relative to these assumed values, many of which could not be identified in a clinical control situation without many

extra glucose measurements per hour, as well as unavailable measurements of plasma and/or interstitial insulin. The identification and validation presented is therefore directly relevant to the clinical control scenario that Glucosafe will face [3].

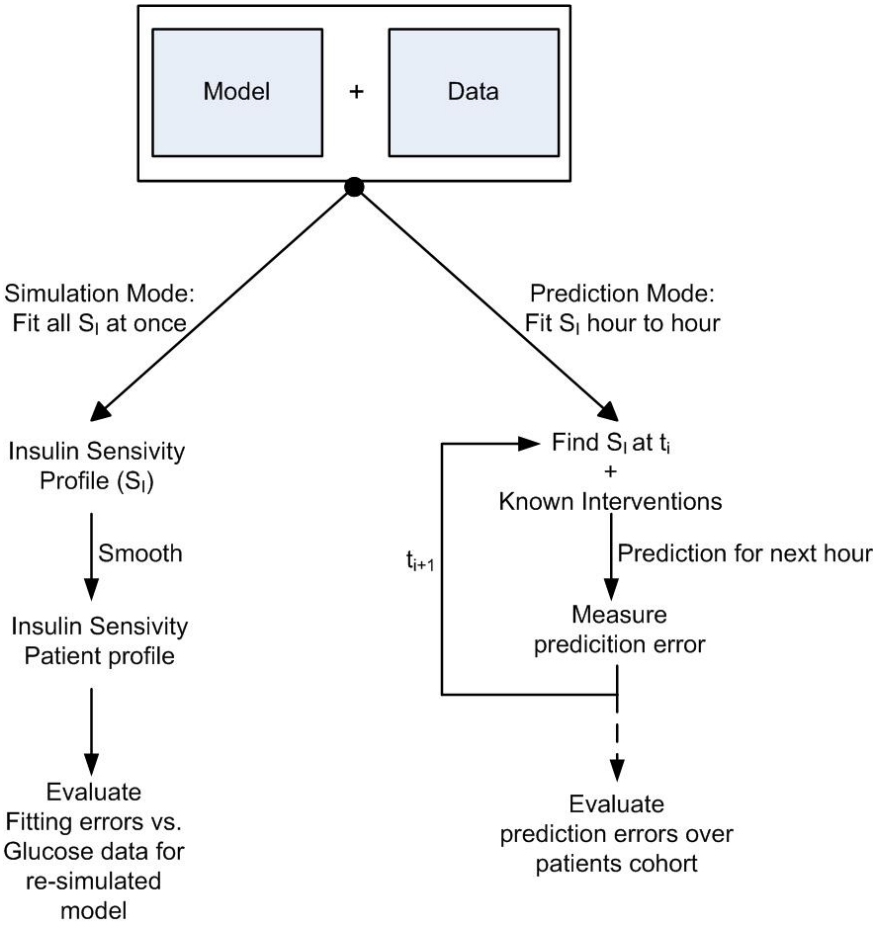

Fig. 2. *Flowchart over the workprocess for the different stages of validation of the system*

B. SPRINT patient cohort

The patientdata used in this study comes from 10 patients in the SPRINT study [15] [22]. The basic cohorts details can be seen in Tables I and II. All of the SPRINT patient data in 1-2 hour intervals are thus relativly dense. Ethics approval to use this data was obtained from the South Island Regional Ethics Committee, New Zealand.

Patient	Age	APACHE II score:	Diagnosis
1	77	22	Sepsis
2	67	33	Acute renal failure, infarction
3	42	11	Suicide attempt (non drug), respiratoty failure, smoke inhalation
4	44	21	Ventricular drain
5	79	31	infarction, cardiac catheter, hypoxic/ischaemic
6	44	23	Meningitis, ventricular drain
7	53	13	Aspiration, motor vehicle crash
8	53	18	Heavy obesity, Obstructive sleep apnoea
9	59	22	Donor
10	51	29	Acute renal failure, systemic

TABLE I
PATIENT DATA FOR THE 10 SPRINT PATIENTS USED IN THIS STUDY

Patient	Length of stay in hospital (hours)	Length of stay on SPRINT (hours)	Gender	Diabetes
1	580.8	312	Male	No
2	458.4	162	Male	No
3	408	253	Male	No
4	223.2	207	Female	No
5	55.2	39	Female	No
6	280.8	161	Female	No
7	861.6	17	Male	No
8	477.6	182	Male	No
9	99.6	93	Female	No
10	520.8	360	Male	No

TABLE II
LENGTH OF STAY AND FURTHER PATIENT DATA FOR THE 10 SPRINT PATIENTS USED IN THIS STUDY.

III. RESULTS

A. Model dynamic validation

Figures 3 and 4 illustrate the results for 2 close-to-average patient results from the study. Figure 5 illustrates the result for the poorest patient results in this part of the study. In all three figures, the integral parameter estimation is used to identify and re-simulate a patient's glucose data. Dots with error bars show measured clinical data and the line is the identified model. The overall fits are qualitatively very good. The second panel shows the S_I profile. The fitted data error results for the model dynamic validation for all 10 SPRINT patients are presented in Table III. Table III shows mean and median absolute percent errors (APE's) per patient over the cohort are 3.7-4.3 % and at least 90 % of measurements per patient being less than 10 % APE.

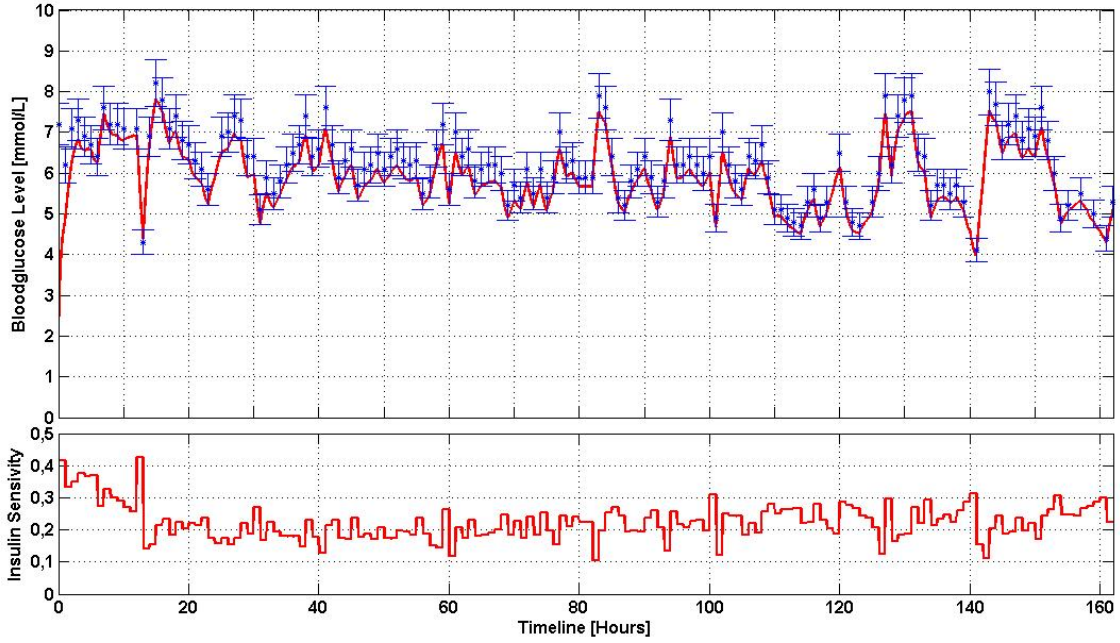

Fig. 3. *Model dynamic validation of Patient 2. Error bars are the measured blood glucose. Panel two is the "true" S_I identified in simulation mode. The entire data set is fit as a whole.*

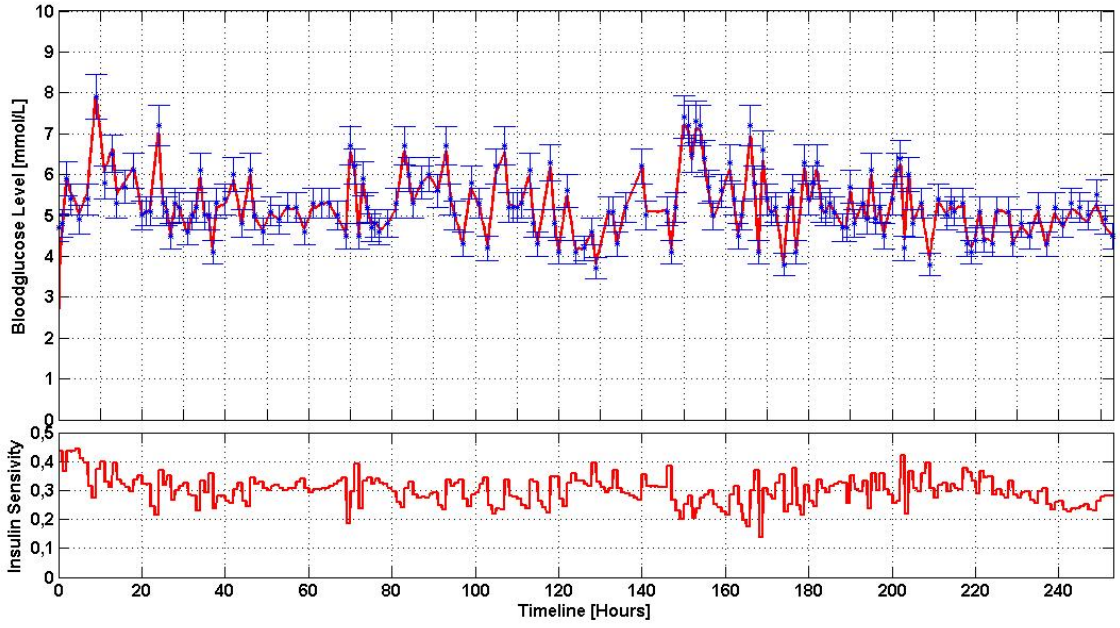

Fig. 4. *Model dynamic validation of Patient 3. Error bars are the measured blood glucose. Panel two is the "true" S_I identified in simulation mode. The entire data set is fit as a whole.*

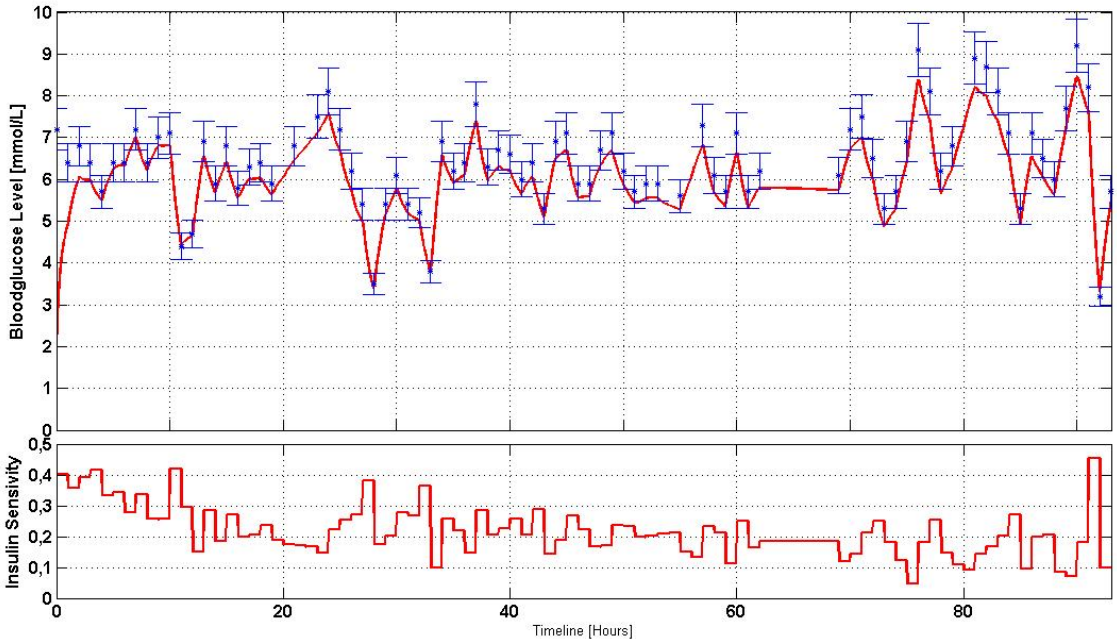

Fig. 5. *Model dynamic validation of Patient 9. Error bars are the measured blood glucose. Panel two is the "true" S_I identified in simulation mode. The entire data set is fit as a whole. The result for Patient 9 is the worst achieved result in the study.*

SPRINT patient	Number of Predictions	Mean (APE)	Median (APE)	IQR	5-95% APE Range	Percent of measurements < 10% APE
1	234	11.58	9.51	[4.83 15.08]	[0.58 29.50]	53.02
2	154	11.32	8.12	[3.46 17.69]	[0.50 29.50]	54.61
3	170	18.12	14.31	[6.89 27.36]	[0.56 41.93]	36.90
4	192	10.73	7.46	[3.37 13.93]	[0.58 34.60]	60.00
5	32	15.35	13.02	[7.19 22.57]	[0.71 38.73]	36.67
6	112	9.26	5.89	[2.56 11.97]	[0.34 29.07]	71.81
7	12	14.65	13.73	[11.90 17.72]	[6.76 18.20]	18.18
8	114	16.28	11.50	[5.83 19.78]	[1.35 47.49]	40.18
9	83	15.81	12.50	[5.95 18.65]	[1.25 44.41]	41.98
10	252	12.58	9.93	[4.43 17.58]	[0.79 31.95]	50.4
Overall	1355	13.02	0.91	[4.74 17.78]	[0.75 34.75]	50.78

TABLE III
RESULTS FOR THE MODEL DYNAMIC VALIDATION OF GLUCOSAFE OF ALL SPRINT PATIENTS IN THIS STUDY. ALL RESULT ARE SHOWN IN PERCENT. THE OVERALL RESULT IS WEIGHTED BY THE AMOUNT OF DATA FOR EACH PATIENT. ABSOLUTE PERCENT ERROR (APE). IQR = INTERQUARTILE RANGE.

B. Model prediction validation

Figures 6 and 7 illustrates the same 2 patients from Figures 3 and 4. In this case, S_I is identified every hour. Figure 8 illustrates the same patient in Figure 5. Figures 6, 7 and 8 therefore illustrate the realtime prediction validation result where the identified S_I value of every hour "j" is used to predict the blood

glucose level at hour "j+1" for the known insulin and nutrition intervention at hour "j" that were given under SPRINT.

The results for the model with prediction validation for all 10 SPRINT patients included in the study is presented in Table IV. Figure 9 illustrates the distribution of the prediction results shown in Table

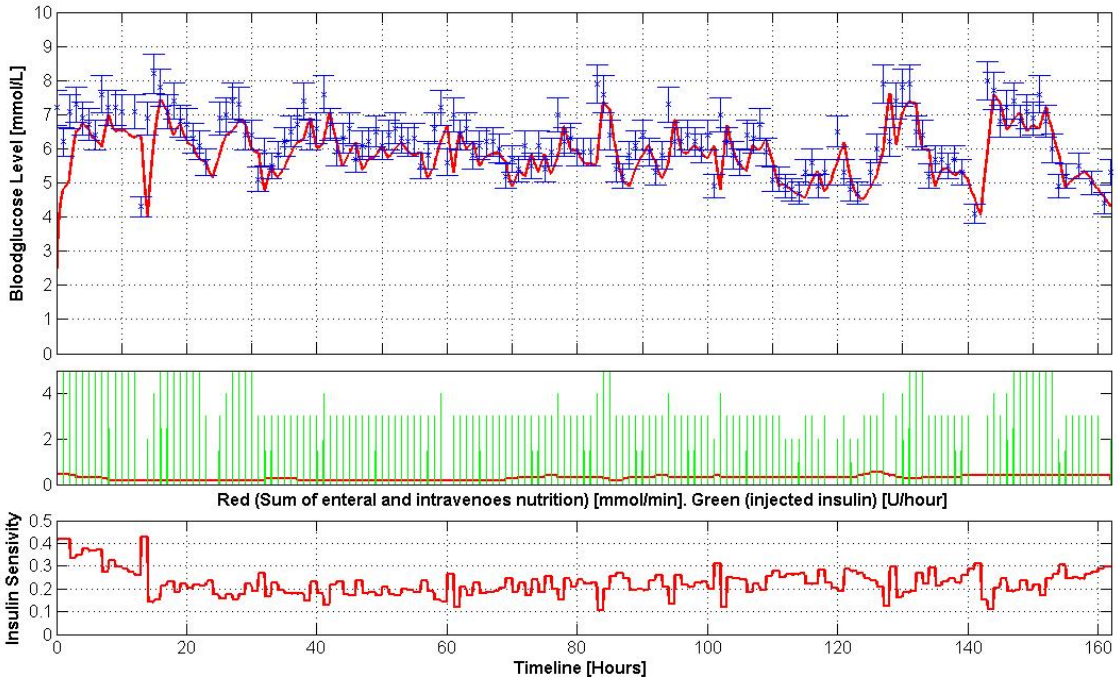

Fig. 6. *Model with prediction validation for Patient 2. The Error range is set to 7 % of measured data, which is the lower end of measurement error [15]*

IV that clearly shows low median and higher mean resulting from a smaller numbers of relatively large errors. Figure 10 illustrates the cumulative distribution of the absolute percent errors for each individual SPRINT patient in this study. Figure 11 illustrates the total cumulative distribution of all prediction errors over all for all SPRINT patients in this study.

IV. Discussion

The Glucosafe model presented is physiologically defined and utilises the concept of a remote compartment for insulin transport to account for the delay between insulin secretion, or infusion, and utilization. The integral based fitting method proves effective in reducing a typically non-linear optimization problem to a linear, rapidly solved convex optimization problem. Overall, the fitted model matches all observed clinical dynamics, as seen in Figure 3-5 and Table III and does so have minimal error. These fitting results

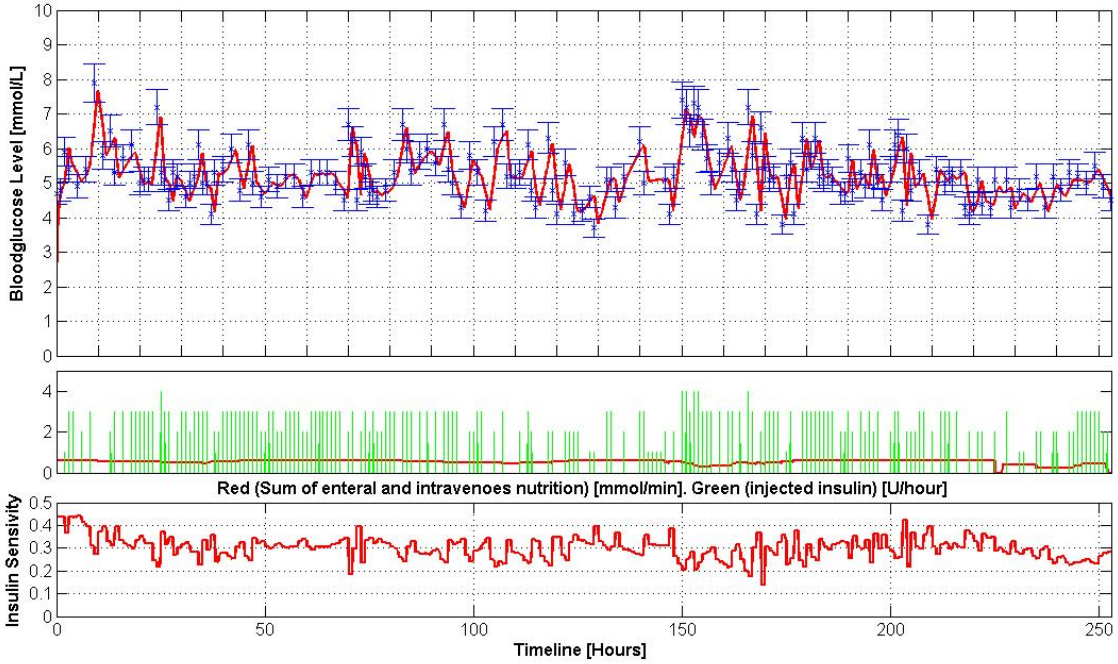

Fig. 7. *Model with prediction validation for Patient 3. The Error range is set to 7 % of measured data.*

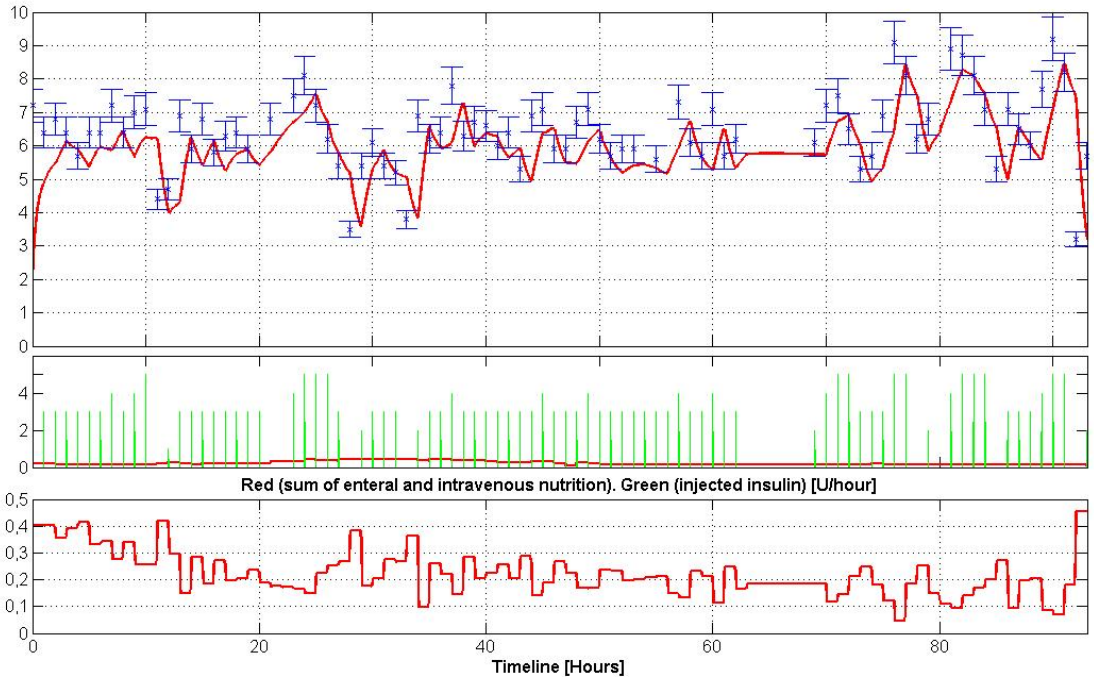

Fig. 8. *Model with prediction validation for Patient 9. The Error range is set to 7 % of measured data. The result for Patient 9 is the worst achieved result in the study.*

SPRINT patient	Number of Predictions	Mean (APE)	Median (APE)	IQR	5-95% APE Range	Percent of measurements < 10% APE
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8	114	16.28	11.50	[5.83 19.78]	[1.35 47.49]	40.18
9	83	15.81	12.50	[5.95 18.65]	[1.25 44.41]	41.98
10	252	12.58	9.93	[4.43 17.58]	[0.79 31.95]	50.4
Overall	1355	13.02	9.91	[4.74 17.78]	[0.75 34.75]	50.78

TABLE IV
RESULTS FOR PREDICTION VALIDATION WITH INTEGRAL PARAMETER ESTIMATION OF ALL SPRINT PATIENTS IN THIS STUDY. ALL RESULT ARE SHOWN IN PERCENT. THE OVERALL RESULT IS WEIGHTED BY THE AMOUNT OF DATA FOR EACH PATIENT. ABSOLUTE PERCENT ERROR (APE). IQR = INTERQUARTILE RANGE

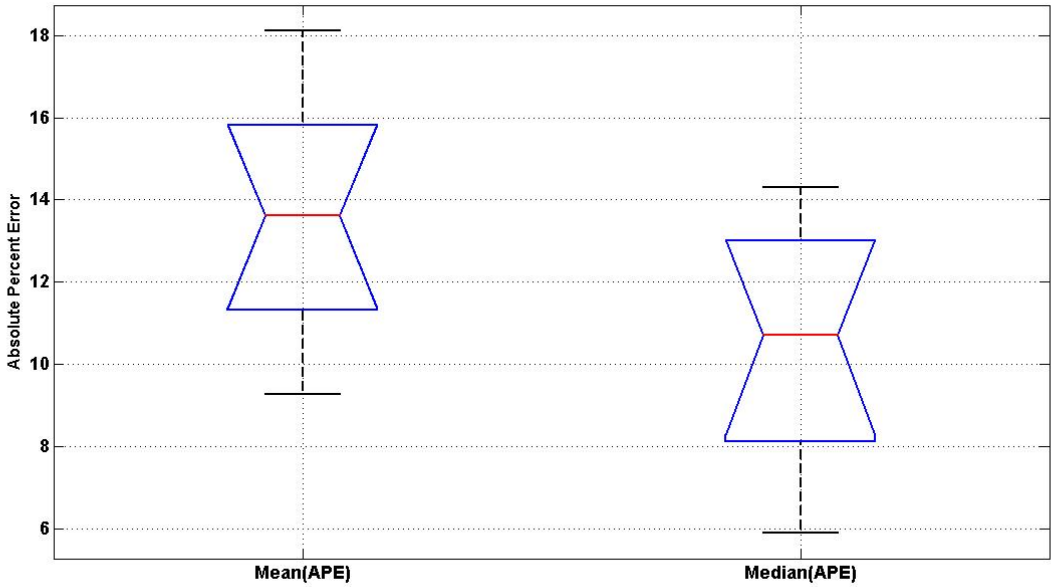

Fig. 9. *Box and whiskers plot of the mean and median APE prediction error achieved over all patients*

indicate that the model possesses all necessary mathematical dynamics.

More specifically, all fitted values for S_I are within physiologically valid ranges reported in the literature [21]. The system prediction model estimates only one parameter S_I. As a result, the endogenous insulin production ('EP') is kept constant. However, this assumption only shifts the identified S_I value if examined in a parametric study. Fitting both parameters in this model is problematic, as they are not uniquely

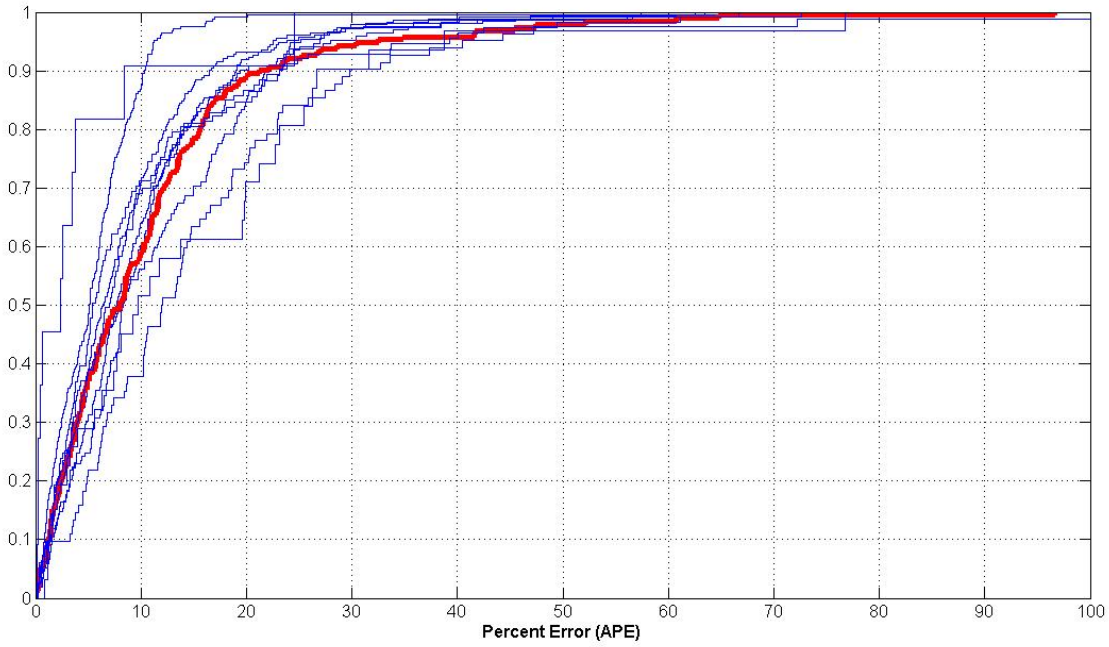

Fig. 10. *This figure illustrates the empirical Cumulative Distribution prediction error for each individual SPRINT patient in the study. The heavy/thick (red) line is the median Cumulative Distribution for all ten patients*

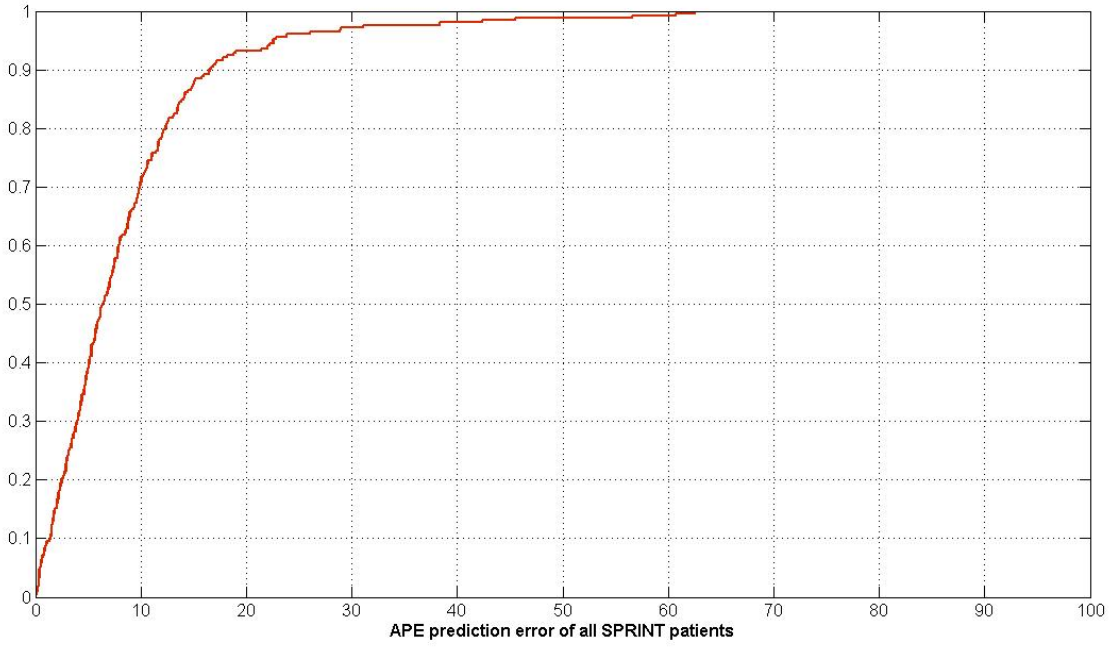

Fig. 11. *This figure illustrates the total empirical Cumulative Distribution prediction errors for all SPRINT patients included in the study*

identifiable without measured insulin data, which is rarely available in critical care. An added argument for only using S_I as a variable parameter is that little is known about the kinetics of EP secretion, both in magnitude or variation over time, in the critically ill.

The parameters EP and S_I are thus dependent and a change in EP therefore only scales the S_I profile by a given value over the patient. Figure 12 shows how 3 different values for EP and the same S_I profile scales the predicted blood glucose values for Patient 2. The shifted dynamics for the three different cases are otherwise the same. Figure 13 shows more clearly how EP and S_I are dependent and trade off. As

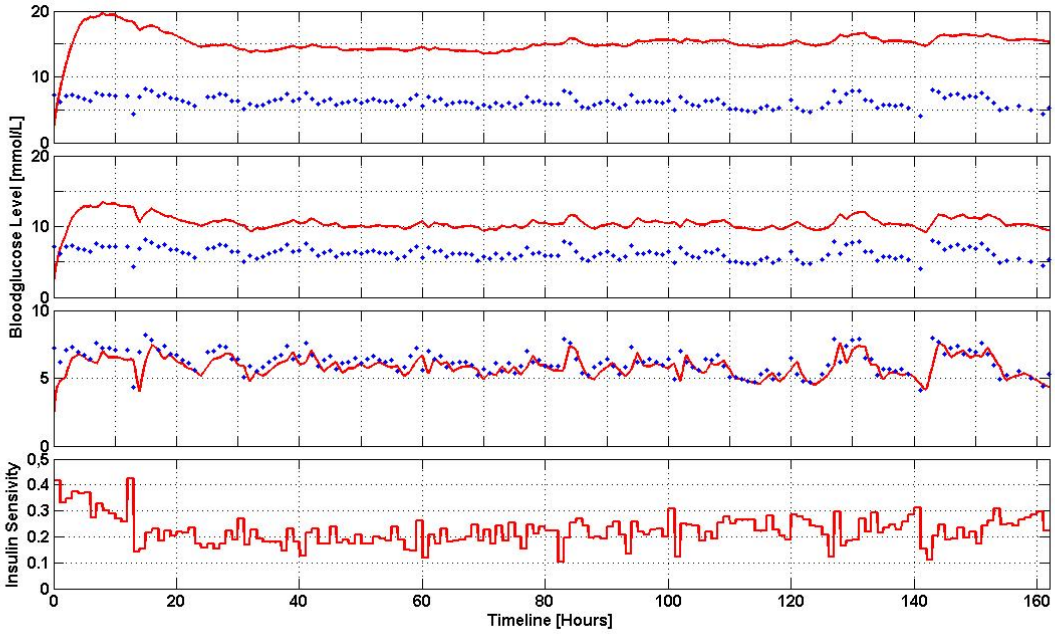

Fig. 12. *This figure illustrates how 3 different EP values scales the blood glucose prediction result for Patient 2 by using the same S_I profile. The dots are blood glucose measurements. The top picture is when using an EP = 27.77/4 [mU/min], number two picture when using an EP = 27.77/2 [mU/min] and number three picture when using an EP = 27.77 [mU/min]. The last picture shows the used S_I profile for producing the top three pictures*

EP increases S_I falls and vice versa, with very similar profiles. Note that the lower profiles in the button picture in Figure 13 are slightly different than the top one (less variable) as they are nearer the lower physiological limit of S_I in the parameter identification. Therefore, holding EP constant at a physiological value, as was done in this study, while identifying the potentially more dynamic and less known S_I variable has little effect on the outcome given their inter-dependence. The relatively low error prediction results of Table IV, as compared to 8-10 % measurement errors, further validates this choice of approach.

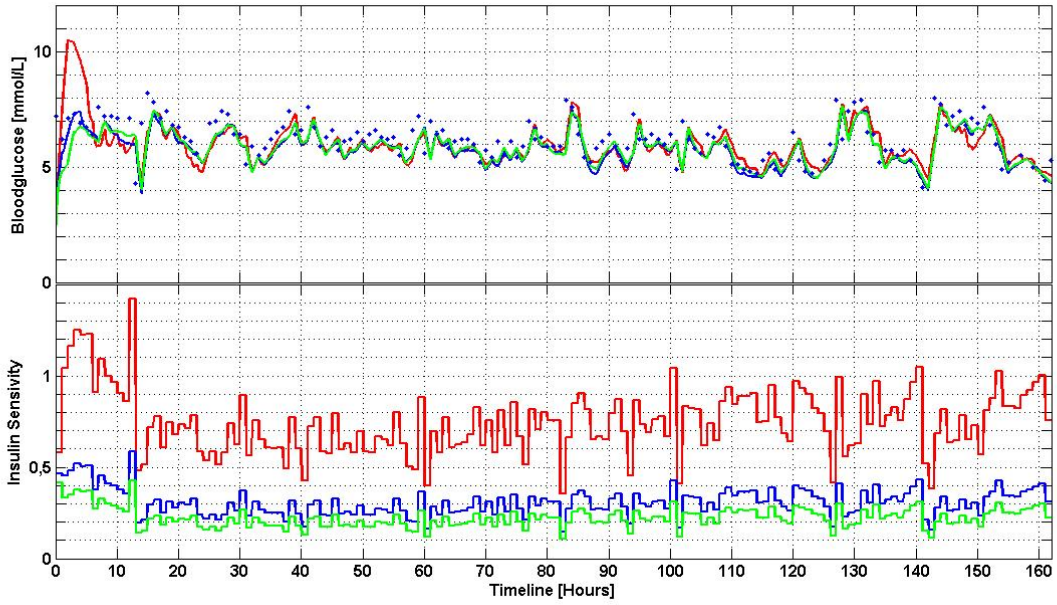

Fig. 13. *This figure illustrates how the predicted blood glucose for Patient 2 is the same by using different dependent set of EP and S_I profiles. The top picture shows 3 predictions produced by using 3 different EP and S_I profiles. The lower picture shows 3 different S_I profiles. The upper S_I profile is produced by using a EP = 27.77/4 [mU/min], the middle S_I profile is produced by using a EP = 27.77/2 [mU/min] and finally the lower S_I profile is produced by using a EP = 27.77 [mU/min].*

In general, the prediction errors are relatively low and consistent. Figure 10 shows that 90 percent are below 25 percent APE, and 70 percent are below 10 percent APE. these values should be considered relative to blood glucose measurement errors of 5-10 %. Figures 10 and 11 both show a clearly lognormal error distribution result skewed to a lower mode. Hence, this study reports median and IQR values to better represent the data than normal statistics. Large errors (more than 20 percent APE) all occur where sudden patient changes occur. These sudden changes are typically unpredictable, and therefore these errors are typically unavoidable.

If the system should be implemented in a hospital, it is also necessary to know if it could work in less acute settings with less staff than a typical critical care unit. To this end, Figure 14 shows the RMS of the relative logarithmic error for the entire cohort for predictions out to 10 hours forward. By 2 hours predictions the APE exceeds 15 % and >25 % for 5 hours. These larger errors indicate the difficulty of long term prediciton in a dynamic cohort.

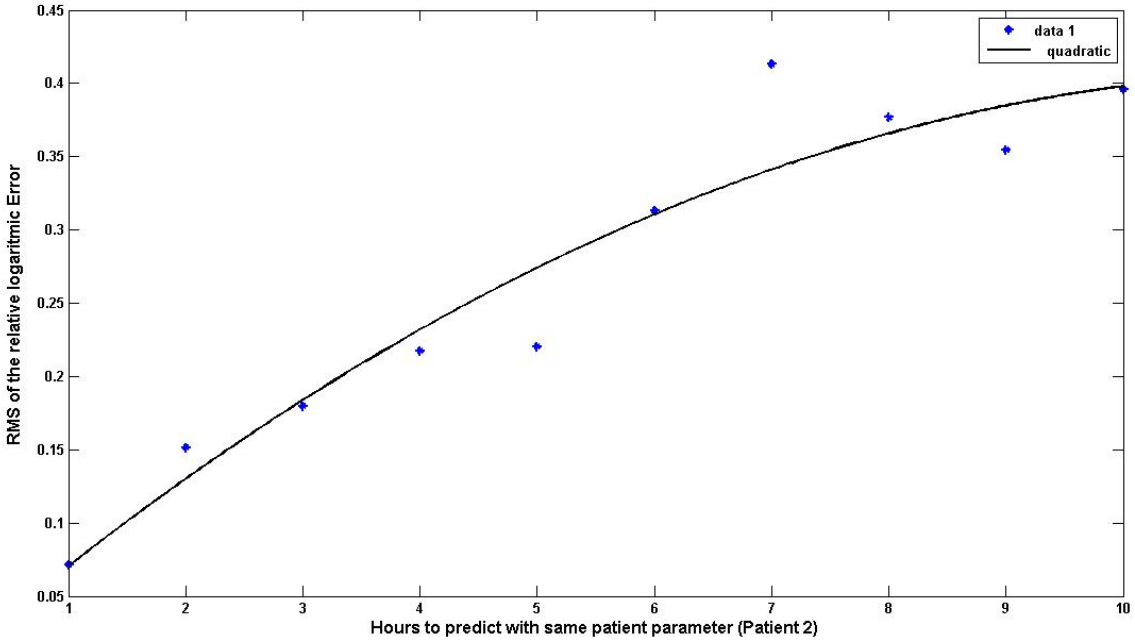

Fig. 14. *This figure illustrates the systems ability to predict over a period up to ten hours for the close-to-average Patient 2 in the study. The result for this ability is validated using the unit Root Mean Square of the Relative Logarithmic Error.*

V. Conclusion

This study examines and validates the dynamics of the Glucosafe glycemic control model in simulation using retrospective clinical data. The model is also validated for its predictive ability. The prediction mode utilizes an integral based parameter estimation method for fitting the patient specific insulin sensivity S_I. The goal is to ensure prediction with minimal absolute percent error, and to assess the models potential clinical utility.

This validation and examination has used retrospective data from SPRINT patients.

The overall mean and median absolute percent error for both fitting and prediction are at or within measurement error. The log-normal distributions ensure most predictions are relatively low. Both results for model dynamic validation and prediction validation are considered acceptable for later use in control applications in a clinical setting.

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Parameter Estimation and Prediction Validation for the Glucosafe Glycaemic Control Model

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Abstract

Background: Hyperglycaemia is prevalent in critically ill patients, and increases the mortality. This paper validates a physiologically based model for clinical glycaemic control (Glycosafe), and an associated integral based parameter identification, using a dataset of a critical care patient cohort. The intended application for this model and the associated parameter identification method is the real-time automated control of glucose levels in critically ill patients.

Methods: The Glucosafe glucose-insulin metabolic model is used to calculate a patient's time-varying response of blood glucose to insulin and nutrition interventions. Time varying insulin sensivity, S_I, is determined between measurements using an integral-based method. The model dynamics are validated by their ability to fit retrospective clinical data and their ability to predict blood glucose one hour ahead for the given intervention. Clinical data from 10 critical care patients at Christchurch Hospital (New Zealand), covering 1786 hours of data are utilized (SPRINT).

Results: The overall mean absolute percent error, APE, of simulated versus measured blood glucose when fitting the model is 0.5 % (IQR: [0.10 0.51] and the percent of measurements < 10% APE: 100 %). For 1 hour prediction validation, the mean APE is 11 % (IQR: [4.0 13.9] and the percent of measurements < 10% APE: 60.9 %).

Conclusions: The results for both model dynamic validation and the clinically important prediction validation are acceptable for later use in clinical pilot trials.

Index Terms

Glucosafe, SPRINT, Glycemic control, Physiologic modelling, Blood glucose, Insulin Sensivity, Integral Parameter Estimation, Intensive Care, Virtual Trials

I. Introduction

Patients who are critically ill due to surgery, trauma or life-threatening illness may require vital organ function support and prolonged intensive care [1]. Many of these patients present with stress induced hyperglycaemia, suggesting overall insulin resistance due to the treatment and/or their condition [2] [3] [4] [5] [6]. Insulin resistance and the resulting hyperglycaemia may contribute to micro- and macro-angiopathy, neuropathy and organ failure [3] [7]. A number of clinical studies have shown a significant relationship between the mortality of patients and high blood sugar levels [8], and tight glucose control has been shown to reduce mortality by 34 % [3] and by 29 % [9], as reviewed in [7] [10] [11].

In critical care, reduced glucose nutrition alone can significantly reduce average blood glucose [12]. Additionally, in some cases, insulin alone may not be enough to reduce blood glucose to normal levels [7].

As a result, exogenous nutritional inputs may need to be reduced under certain conditions, due to excessive nutrition exacerbating hyperglycaemia [12] [13] [14]. More specifically, reduced glucose nutrition combined with insulin administration can act to control both sides (input and removal) of the glucose balance [7] [15]. To achieve tight model-based control, on critically ill patients, some studies have used insulin alone [16] [17]. Later studies combined the insulin and nutrition paths to control [15] [18] [19]. Overall, tight regulation of blood glucose based on mathematical models of glucose metabolism has given promising results, indicating that it is possible to safely achieve a level of normoglycaemia in many, if not all, critical care patients.

Glucosafe is a composite model, consisting of the metabolic and insulin models presented by Pielmeier et al. [20]. It makes use of previous research and models in insulin and metabolic modelling [21] [22] [23] [24]. The system utilizes a glucose transporter model, which calculates the glucose balance for a given set of inputs and the gut absorption rate [24]. Hence, it combines clinically validated insulin kinetics and glucose-insulin dynamics into a new composite model [25].

Model-based methods can be very accurate, but require the ability to identify patient specific parameters

in clinical realtime to update the model dynamics. A fast, accurate identification method is therefore also important in the process of refining and testing this type of model. More importantly, using a fast, accurate method, enables real-time application of model-based control and medical decision support applications. A nonlinear least squares parameter identification method was used previously for model validation [25]. That method has the disadvantage of being computationally demanding.

This paper presents a blood glucose prediction and control system using a combination of the Glucosafe model [20], and an integral based parameter estimation method [26]. The integral based approach turns a computationally demanding, non-linear and non-convex optimization problem, into a fast, convex parameter identification. The result enables faster, and potentially more accurate, predictions of patient specific parameters and thus of a patient's glycaemic response to intervention.

II. METHODS

A. Glucosafe glucose-insulin system model

The Glucosafe glucose-insulin metabolic model is used to calculate the time-varying response of blood glucose for given insulin and nutrition inputs [25]. The insulin kinetics of the Glucosafe model are illustrated in Figure 1, and are defined [22] [23] [25]:

$$\frac{dI}{dt} = (-n_K - n_L) * I(t) - \frac{n_I}{V_P} * (I(t) - Q(t)) + \frac{P(t) + EP(t)}{V_P} \tag{1}$$

$$\frac{dQ}{dt} = -n_C * Q(t) + \frac{n_I}{V_Q} * (I(t) - Q(t)) \tag{2}$$

Equations 1 and 2 describe the change in plasma and peripheral insulin concentration. The parameter n_K is the kidney clearance $[min^{-1}]$, n_I is the transport rate between the plasma and peripheral compartments $[L/min]$, V_P is the plasma volume [L] and V_Q is the peripheral interstitial volume [L], which all are functions of basic patient parameters used to determine population values for distribution volumes. n_L the liver clearance $[min^{-1}]$ and n_C is the irreversible loss of insulin in the periphery $[min^{-1}]$ [20]. The Glucosafe model itself uses the patient's gender, age, height, weight and diabetic state to determine patient specific parameters n_K, n_L, n_C, n_I, V_P and V_Q [20] [27], which are set as static for the patient in any specific given time period, or interval. $EP(t)$ is the post-hepatic endogenous insulin secretion rate (which in Glucosafe is set as a constant at 27.77 mU/min) and $P(t)$ is the insulin infusion rate [mU/min].

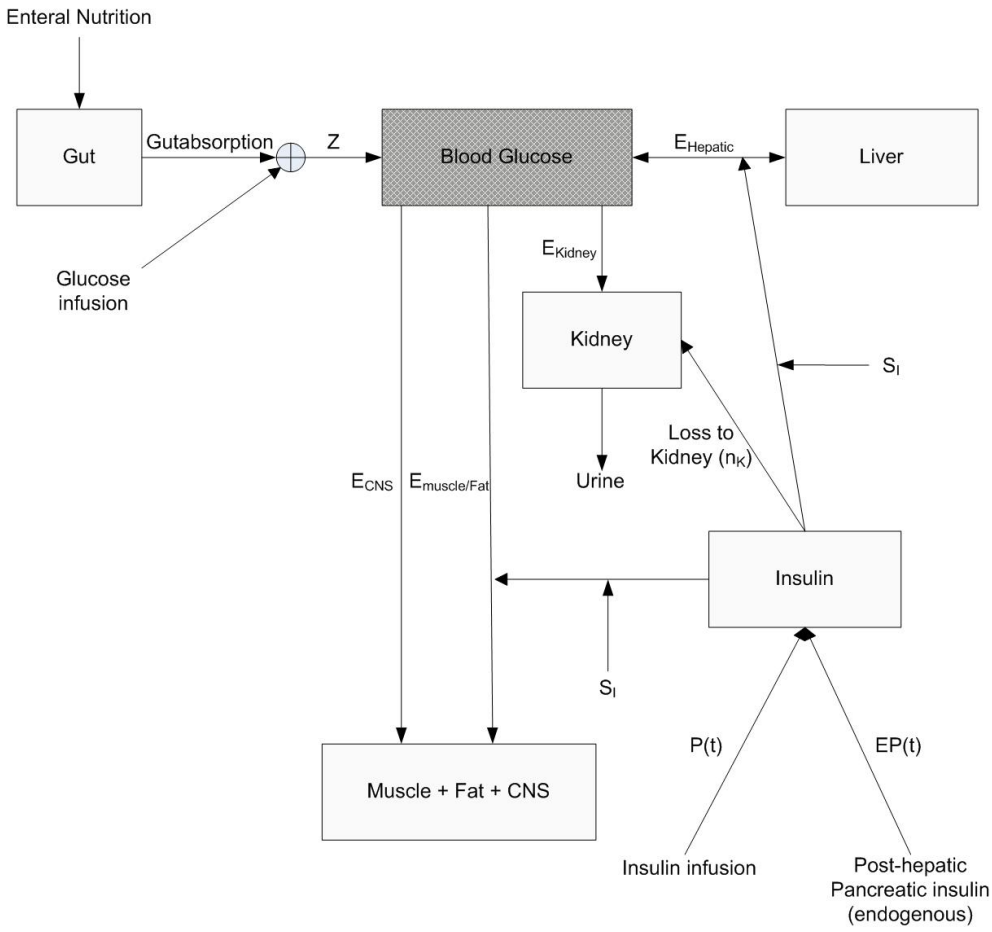

Fig. 1. *Glucosafe physiological overview, where exogenous insulin is assumed to be intravenous. The change in blood glucose, BG is a result of the sum of absorption, Z (positive change in BG). $E_{Hepatic}$ causes er positive change in BG if the current BG concentration is under 12 mmol/L. E_{Kidney}, $E_{Muscle/Fat}$ and E_{CNS} all causes a negative change in the BG concentration. In this figure CNS = central nervous system. The change in BG is calculated in Equations 3*

Pharmacodynamic changes in blood glucose concentration, due to endogenous and exogenous inputs of insulin and nutrition are illustrated in Figure 1 and are defined [24] [25]:

$$\frac{dG}{dt} = (Z(t) + E_{Hepatic}(G, A) - E_{Kidney}(G, BSA) - E_{CNS}(G) - E_{Muscle/Fat}(G, A)) \times (BM/GV) \quad (3)$$

where $Z(t)$ is the sum of absorption from the nutrition input $[mmol/(kg \times min)]$, $E_{Hepatic}(G, A)$, $E_{Kidney}(G, BSA)$, $E_{CNS}(G)$ and $E_{Muscle/Fat}(G, A)$ (all $[mmol/(kg \times min)]$) are the turnover of blood glucose to the liver, kidneys, fat cells and muscle cells, respectively. BSA is the patient's body surface area $[m^2]$ and is used to calculate the renal glucose clearance, described in Equation 5. The mass-volumen quotient BM/GV [kg/L], which is the bodymass (BM) divided by the glucose distribution volume (GV), can be calculated by knowing the patient's weight [20]. The glucose distribution volume is defined to be 0.19 [(L/kg)·BM] [20]. The constants in Equations 4, 6 and 7 are explained in Table I, where A is the

Name of constant	Value
$Hepatic_1$	0.46 L/(kg·min)
$Hepatic_2$	1.475 mmol/(kg·min)
$Hepatic_3$	1.34 mmol/(kg·min)
CNS_1	0.56 mmol/(kg·min)
CNS_2	1.5 mmol/l
$Muscle/Fat_1$	5.09 mmol/(kg·min)
$Muscle/Fat_2$	5 mmol/l

TABLE I
LIST OF THE FITTING CONSTANTS USED IN EQUATIONS 4, 6 AND 7.

active insulin.

$E_{Hepatic}(G, A)$, $E_{Kidney}(G, BSA)$, $E_{CNS}(G)$ and $E_{Muscle/Fat}(G, A)$ are defined [24]:

$$E_{Hepatic}(G, A) = -Hepatic_1 \times G(t) - Hepatic_2 \times A(t) + Hepatic_3 \tag{4}$$

$$E_{Kidney}(G, BSA) = SMOOTH(max(0, GFR(BSA) \times G(t) - T_{max})) \tag{5}$$

The renal reabsorption saturates at a blood glucose concentration exceeds 10-15 mmol/L. The maximal reabsorption rate T_{max} is 120 mmol/h [28]. The glomerular filtration rate GFR is 7.2 L/h per 1.73 m^2 body surface area. The function $SMOOTH()$ is a function that calculates a 7 mmol/L wide moving average.

$$E_{CNS}(G) = CNS_1 \times \frac{G(t)}{G(t) + CNS_2} \tag{6}$$

$$E_{Muscle/Fat}(G, A) = Muscle/Fat_1 \times A(t) \times \frac{G(t)}{G(t) + Muscle/Fat_2} \tag{7}$$

The magnitude of $E_{Hepatic}(G, A)$ and $E_{Muscle/Fat}(G, A)$ depends on the current concentration of blood glucose and active or available insulin, A. The active insulin, A, is calculated [25]:

$$A(t) = S_I * f(Q(t)) \tag{8}$$

where $f(Q(t))$ is the fractional pharmacodynamic effect of peripheral insulin (Q(t) [mU/L]). In this model, insulin sensitivity scales the pharmacodynamic insulin effect and determines the active insulin level [25] (modification from Arleth et. al. [24]). The model definitions in Equations 1-8 are all clinically validated individually [22] [23] [24].

Integral based parameter estimation is implemented using the same method as Hann et al. [26]. In this case, it is used to identify S_I and all other values are held at population constants [22] [23] [24] [25]. While details are presented elsewhere, in short, integrating and substituting Equations 1-8, and separating S_I dependent parts makes it possible to determine a time-varying S_I profile in one solution. The value of S_I is assumed piecewise constant over the identification interval [26]. The length of the identification interval in this study is 1 hour.

Figure 2 shows the flowchart for the identification process to find a patient specific S_I (= S_{I1},...,S_{Ii},...,S_{IN}) profile over time for a given set of patient data (glucose measurements BG_i and insulin and nutrition interventions, IV).

When a new blood glucose measurement BG_i becomes available at time t_i a new value S_{Ii} can be identified from the measurements BG_{i-1} and BG_i.

In the Model Simulation mode, Glucosafe can use S_{Ii} to simulate BG_i, using BG_{i-1} as the initial value for the simulation:

$$BG_i^{GS} = GS(BG_{i-1}, S_{Ii}; IV)$$

A close match between BG_i^{GS} and BG_i will confirm that the identified patient profile S_I actually describes the dynamics of the patient's metabolic state.

In the Model Prediction mode, S_{Ii} is used to simulate the next measurement, BG_{i+1}, using BG_i as the initial value for the simulation:

$$BG_{i+1}^{BG} = GS(BG_i, S_{Ii}; IV)$$

A close match between BG_{i+1}^{BG} and BG_{i+1} shows that the identification of S_I can provide an accurate prediction of the response to clinical intervention.

All other parameters except S_I are held constant at population values. Hence, the value of S_I found at any point in time is dependent to these assumed values, many of which could not be identified in a realistic clinical control situation without excessively frequent glucose measurements, as well as unavailable real-time measurements of plasma and/or interstitial insulin. The identification and validation approaches and

methods presented are therefore directly relevant to the clinical control scenario that Glucosafe eventually will face [7].

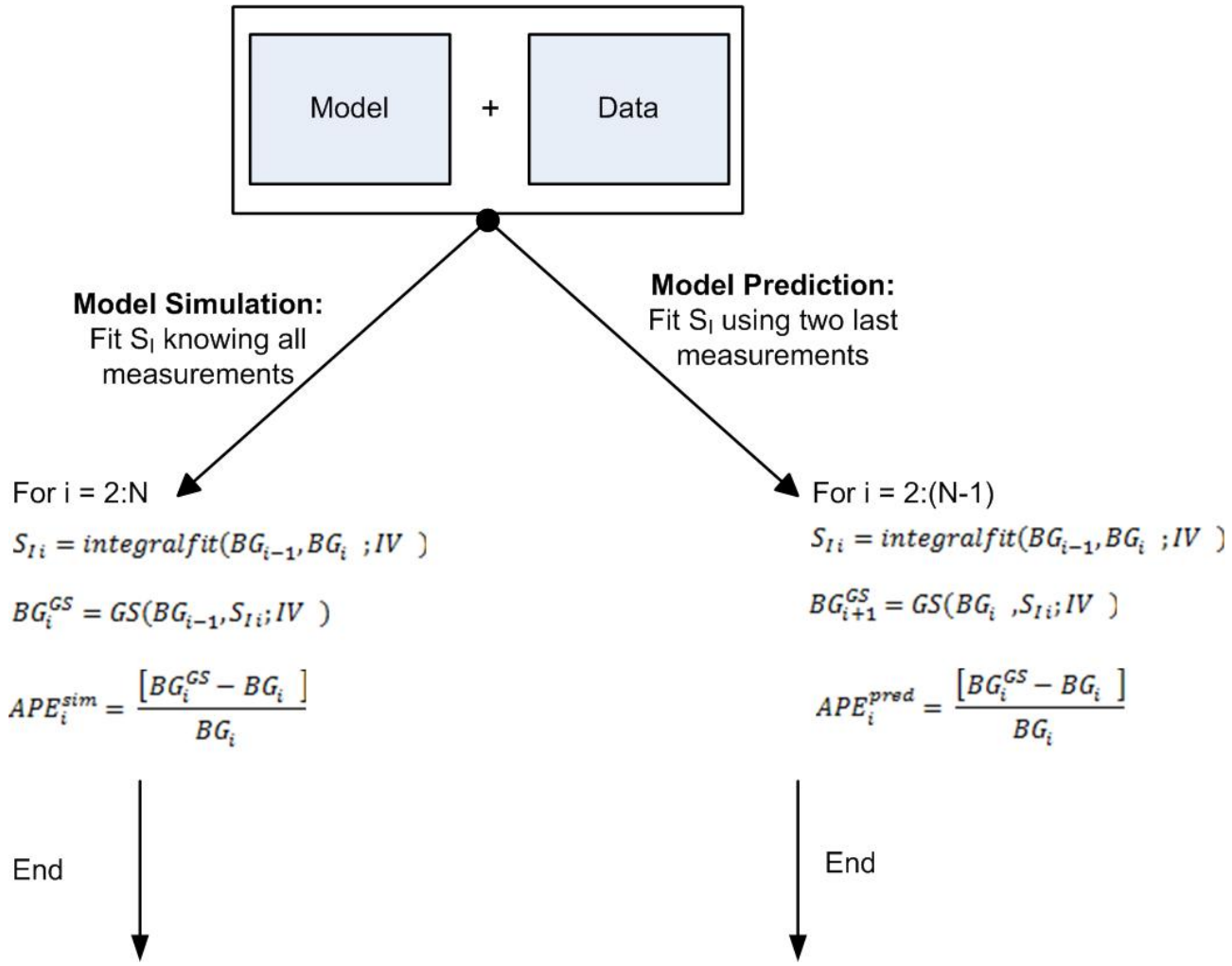

Fig. 2. *Flowchart over the work process for the different stages of validation of the system. Model simulation validation (left path) and model prediction validation (right path). GS is short for Glycosafe, and IV is short for intervention (given nutrition and insulin). Glycosafe calculates the blood glucose BG_i^{GS} starting from the measured BG_{i-1}^m. IV_{i-2} is the intervention given from $i-2$ to $i-1$. There is 1 hour between $i-2$ and $i-1$.*

The results are presented in term of the absolute percent error, APE, of blood glucose calculated as:

$$APE_i = \frac{|BG_i^{GS} - BG_i|}{BG_i} \tag{9}$$

Patient	Age	APACHE II score:	Diagnosis
1	77	22	Sepsis
2	67	33	Acute renal failure, infarction
3	42	11	Respiratory failure, smoke inhalation
4	44	21	Ventricular drain
5	79	31	infarction, cardiac catheter, hypoxic/ischaemic
6	44	23	Meningitis, ventricular drain
7	53	13	Aspiration, motor vehicle crash
8	53	18	Heavy obesity, Obstructive sleep apnoea
9	59	22	Donor
10	51	29	Acute renal failure, systemic
Patient	Length of stay in hospital (hours)	Length of stay on SPRINT (hours)	Gender
1	580.8	312	M
2	458.4	162	M
3	408	253	M
4	223.2	207	F
5	55.2	39	F
6	280.8	161	F
7	861.6	17	M
8	477.6	182	M
9	99.6	93	F
10	520.8	360	M

TABLE II
PATIENT DATA FOR THE 10 SPRINT PATIENTS USED IN THIS STUDY. NONE OF THE INVOLVED PATIENTS HAVE TYPE I OR TYPE II DIABETES

Where BG_i^{GS} is the calculated blood glucose concentration at time i, and BG_i is the measured blood glucose concentration at time i.

B. SPRINT patient cohort

The patient data used in this study comes from 10 critical care patients in the SPRINT study [18] [19] [29]. The SPRINT patient cohorts details can be seen in Table II. All data and measurements are available in 1-2 hour intervals, and are thus relatively dense. Ethics approval to use this data was obtained from the South Island Regional Ethics Committee, New Zealand.

III. RESULTS

A. Model Simulation validation

Figure 3 illustrate the result for Model Simulation validation of the close-to-average Patient 6. The known nutrition and injected insulin interventions are shown over 10 hours to illustrate the dynamics

SPRINT patient	Number of simulations	Mean	Median	IQR	5-95% Range	Percent APE_i < 10%
1	234	0.50	0.18	[0.07 0.45]	[0.01 1.32]	100
2	154	0.34	0.23	[0.08 0.46]	[0.01 1.07]	100
3	170	0.56	0.38	[0.18 0.69]	[0.02 1.62]	100
4	192	0.49	0.29	[0.14 0.57]	[0.02 1.59]	100
5	32	0.72	0.51	[0.18 0.98]	[0.05 2.72]	100
6	112	0.53	0.30	[0.12 0.64]	[0.03 2.17]	100
7	12	0.84	0.29	[0.12 0.63]	[0.02 2.61]	100
8	114	0.60	0.23	[0.12 0.55]	[0.03 1.65]	100
9	83	0.51	0.35	[0.16 0.55]	[0.05 1.71]	100
10	252	0.34	0.20	[0.07 0.42]	[0.02 1.05]	100
Overall	1355	0.45	0.24	[0.10 0.51]	[0.01 1.33]	100

TABLE III
ABSOLUTE PERCENT ERROR (APE) FOR THE MODEL SIMULATION VALIDATION OF GLUCOSAFE OF ALL SPRINT PATIENTS IN THIS STUDY. ALL RESULT ARE SHOWN IN PERCENT. THE OVERALL RESULT IS WEIGHTED BY THE AMOUNT OF DATA FOR EACH PATIENT. IQR = INTERQUARTILE RANGE.

between interventions and changes in the patients glucose level and plasma/peripheral insulin concentration. In the figure, the integral parameter estimation method is used to identify S_I from two consecutively blood glucose measurements as described in Figure 2. For example, the value of S_I = 0.17 plotted in the interval from hour 21 to hour 22 is determined from the measurements taken at 21 and 22 hours. The blood glucose measured at 21 hours is used as the starting value, and then the simulation is performed using the value of S_I = 0.17 for the interval between 21 and 22 hours. The APE, for that interval is calculated from comparing the simulated and the measured blood glucose at hour 22 (see Figure 3).

The APE result for the Model Simulation validation for all 10 SPRINT patients are presented in Table III. Table III shows mean and median APE's per patient over the cohort are 0.45 and 0.24 % and 100 % of measurements per patient have less than 10 % APE.

B. Model Prediction validation

Figure 4 shows (panel 1) the Model Prediction validation of the total data set for Patient 6. Figure 4 therefore illustrates the realtime Model Prediction validation result, where the $S_{I,i}$ identified from BG_{i-1} and BG_i is used to predict the blood glucose level at time $i+1$ (BG^{GS}_{i+1}), using the known insulin and nutrition interventions IV.

Quantitatively, the results for the Model Prediction validation for all 10 SPRINT patients included in

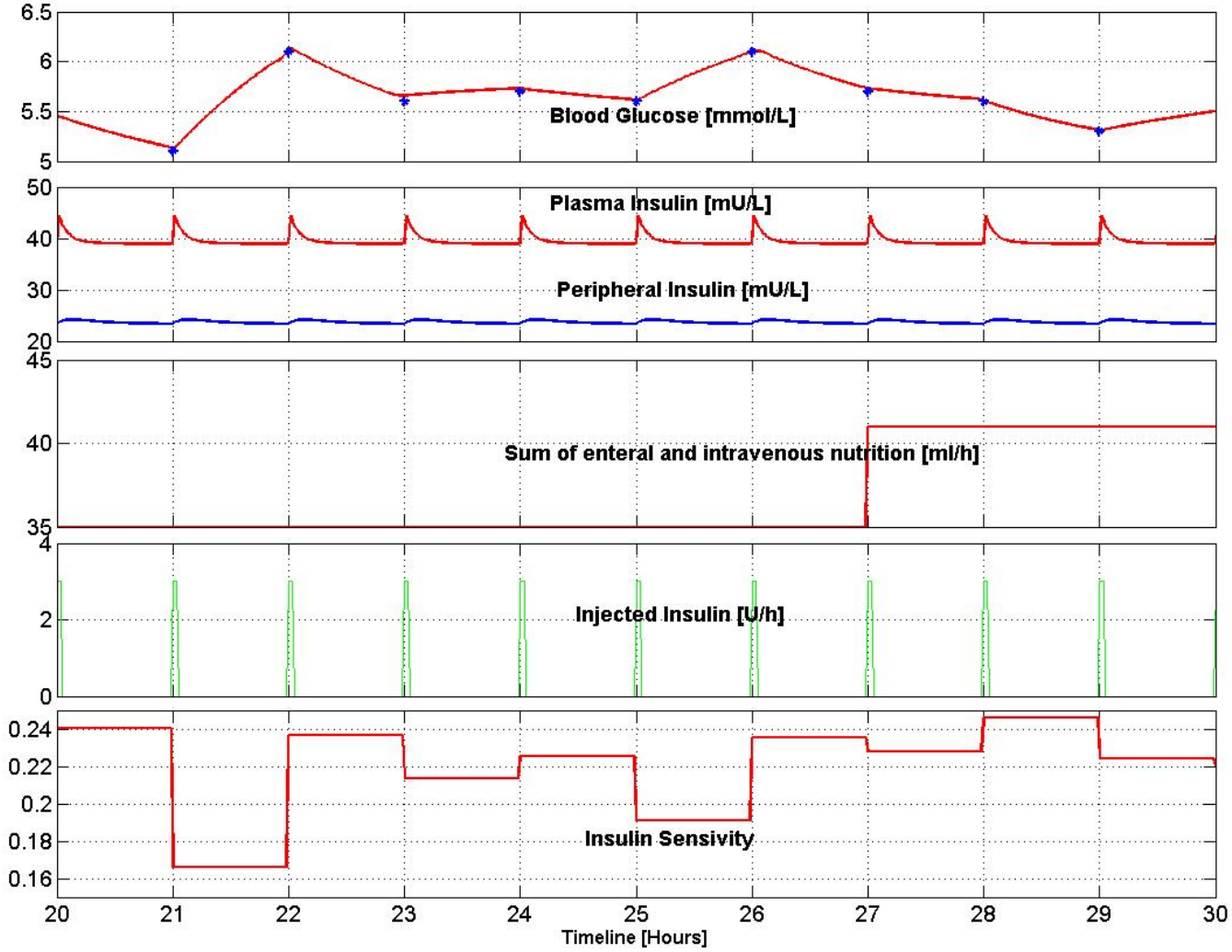

Fig. 3. *Model Simulation validation for Patient 6. The figure illustrates 10 hours, in the period 20-30 hours, from the total simulation period of 161 hours.*

the study is presented in Table IV. Figure 5 illustrates the distribution of the Model Prediction validation results shown in Table IV. Median errors (8.0 %) are lower than mean errors (10.8 %) due to a small number of relatively large errors. Figure 6 illustrates the cumulative distribution of the APE results for each individual SPRINT patient in this study, covering all 1355 1-hour predictions made.

C. The endogenous insulin production

The Glucosafe model validated in this study has used a fixed EP at 27.77 mU/min. Due to minimize the model Prediction error APE, different values of EP has been tested.

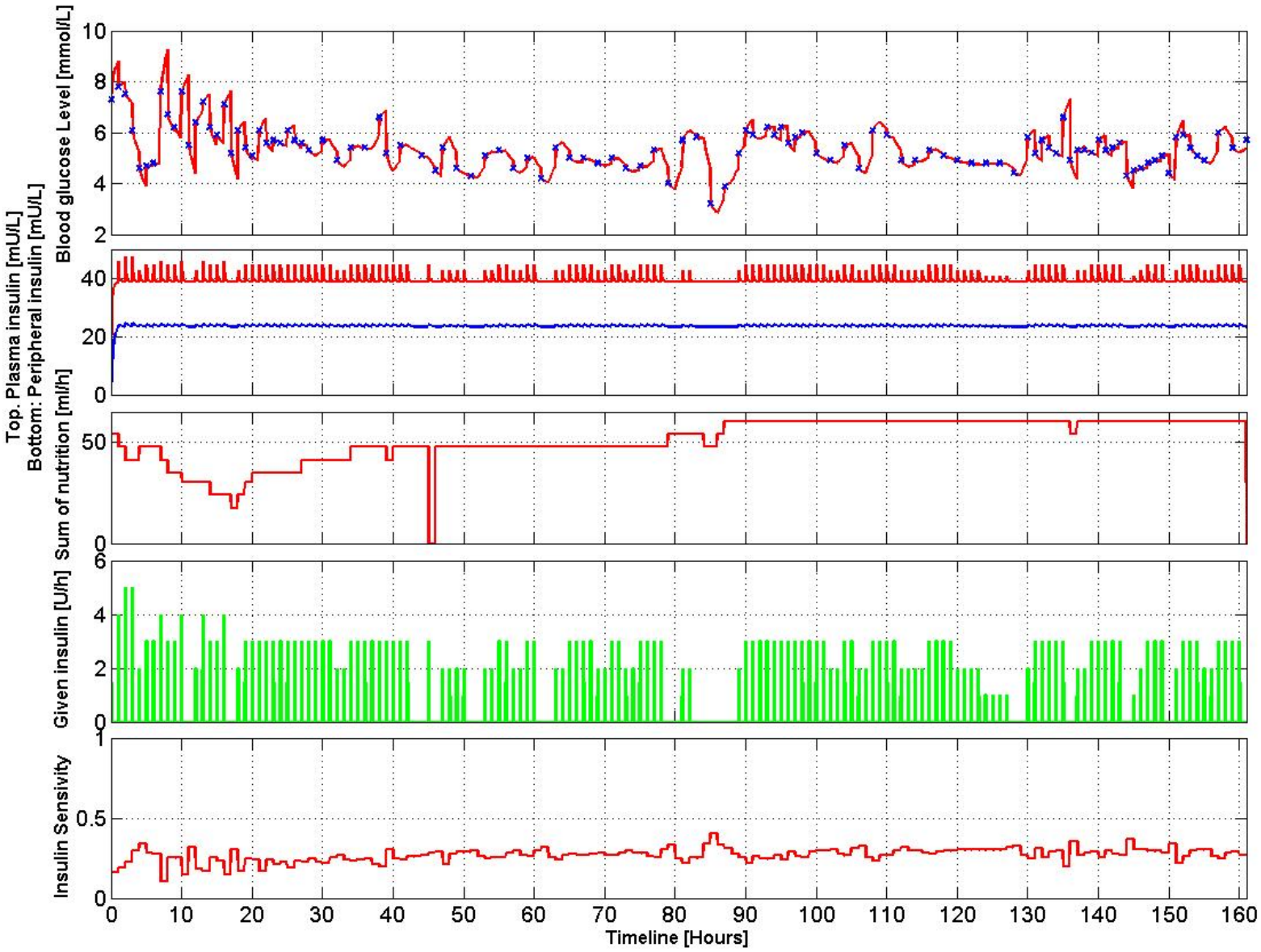

Fig. 4. *Model Prediction validation for Patient 6. Panel 1 shows Patient 6 blood glucose, where the dots are the measured blood glucose and the line is the blood glucose predicted by the model. Panel 2 shows the plasma and peripheral insulin concentration, panel 3 and 4 the nutrition and insulin and panel 5 shows Patient's 6 insulin sensivity profile S_I.*

Figure 7 illustrates that the parameters EP and S_I are interdependent in the model as it is defined. A change in EP therefore changes the patient's S_I profile over the patient.

It also shows how EP and S_I are dependent and trade off for Patient 6. As EP increases S_I falls and vice versa, with similar dynamics in the S_I profiles.

Figure 8 illustrates the relationship between choice of EP and resulting overall median APE for all 10

SPRINT patient	Number of Predictions	Mean (APE)	Median (APE)	IQR	5-95% APE Range	Percent of predictions with < 10% APE
1	234	9.7	7.1	[3.6 13.0]	[1.6 25.7]	66.5
2	154	9.9	7.5	[3.9 13.4]	[1.5 25.3]	61.8
3	170	12.3	10.6	[3.9 18.6]	[1.5 30.6]	48.1
4	192	11.2	7.9	[3.7 12.1]	[1.7 32.2]	62.8
5	32	14.8	14.3	[6.5 20.4]	[2.3 35.8]	33.3
6	112	9.1	6.1	[3.2 12.5]	[0.8 32.6]	69.7
7	12	13.4	8.5	[3.8 15.1]	[2.4 30.9]	54.5
8	114	11.2	7.1	[4.5 12.6]	[0.6 37.3]	63.6
9	83	16.4	12.3	[7.0 19.6]	[1.6 36.8]	41.0
10	252	9.3	6.3	[3.4 11.8]	[0.8 24.5]	67.3
Overall	1355	10.8	8.0	[4.0 13.9]	[1.2 29.5]	60.9

TABLE IV
RESULTS FOR MODEL PREDICTION VALIDATION WITH INTEGRAL PARAMETER ESTIMATION OF ALL SPRINT PATIENTS IN THIS STUDY. ALL RESULT ARE SHOWN IN PERCENT. THE OVERALL RESULT IS WEIGHTED BY THE AMOUNT OF DATA FOR EACH PATIENT. ABSOLUTE PERCENT ERROR (APE). IQR = INTERQUARTILE RANGE

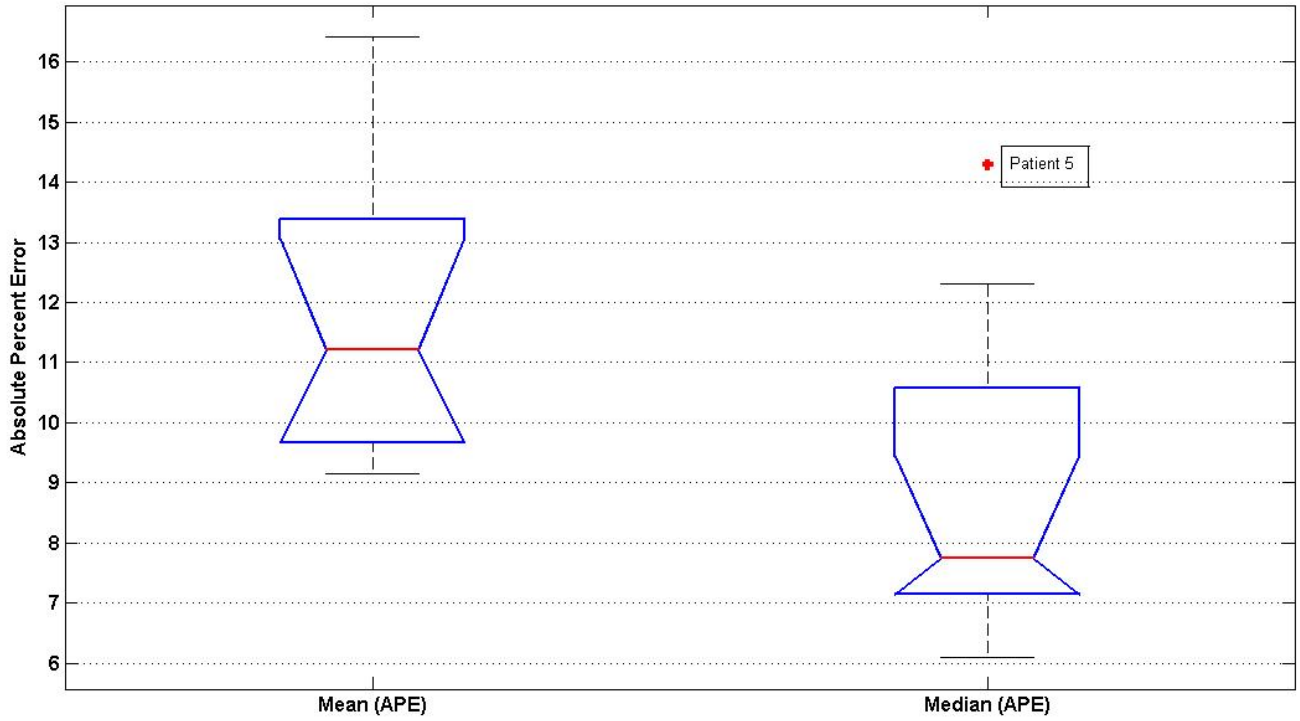

Fig. 5. *Box and whiskers plot (the smallest observation, lower quartile,, median, upper quartile, and largest observation). The figure is produced from the Model Prediction validation of the two observations: mean and median APE prediction errors for each 10 patients. The difference is due to a few large errors.*

patients. The overall median APE for model Prediction has been testet for choices of EP at 20, 27.77, 30,

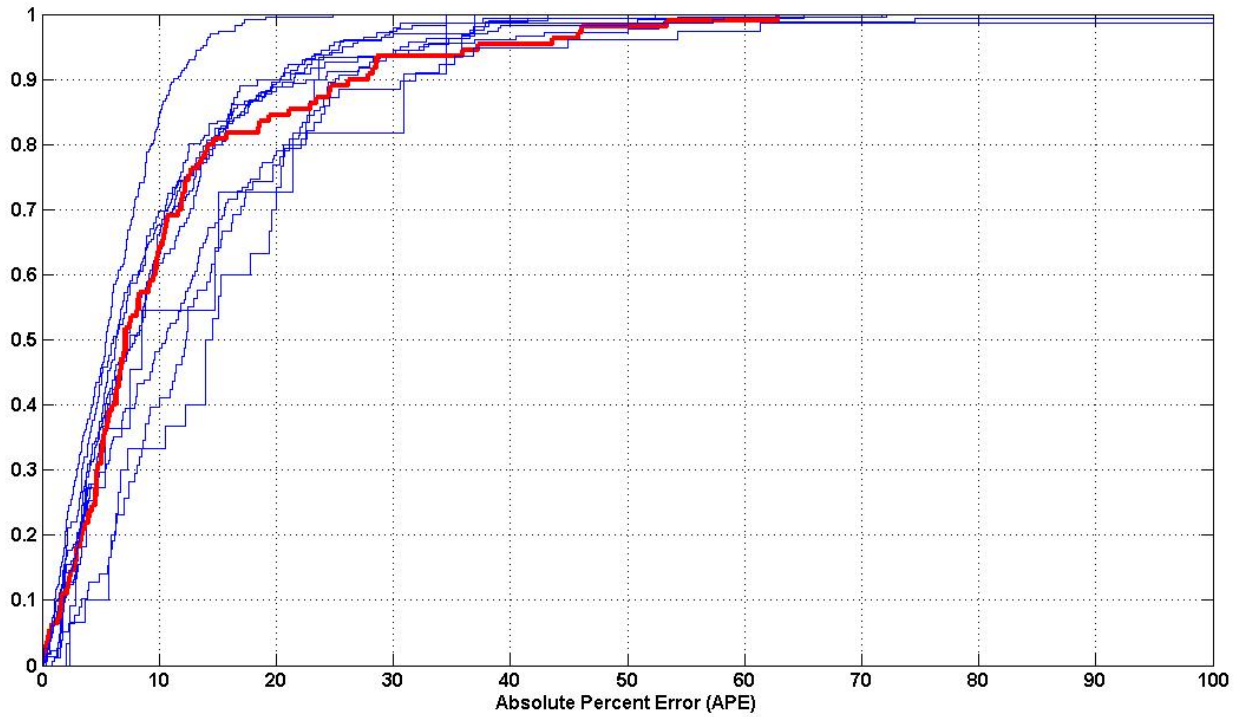

Fig. 6. *This figure illustrates the cumulative distribution prediction APE of the Model Prediction Validation for each individual SPRINT patient in the study. The thick line is the cumulative distribution APE for all ten patients*

35, 40 and 45 mU/min. The dots in Figure 8 represents the Model Prediction result for all 10 patients, and the best overall choice for EP to have, is a EP value at 27.77 mU/min. However, using a EP value at 27.77 mU/min may not be the optimum solution in other situations, with a lesser critically ill patient cohort (higher S_I).

IV. Discussion

The Glucosafe model presented is physiologically defined and utilizes the concept of a remote compartment for insulin transport to account for the delay between insulin secretion, or infusion, and its utilization.

Overall, the fitted model matches all observed clinical dynamics, as seen in Figure 4 and Table IV. These fitting results indicate that the model possesses all necessary mathematical dynamics seen in clinical data.

More specifically, all fitted values for S_I are within physiologically valid ranges reported in the literature [26]. Only one parameter, S_I, is estimated, meanwhile the endogenous insulin production (EP), which is

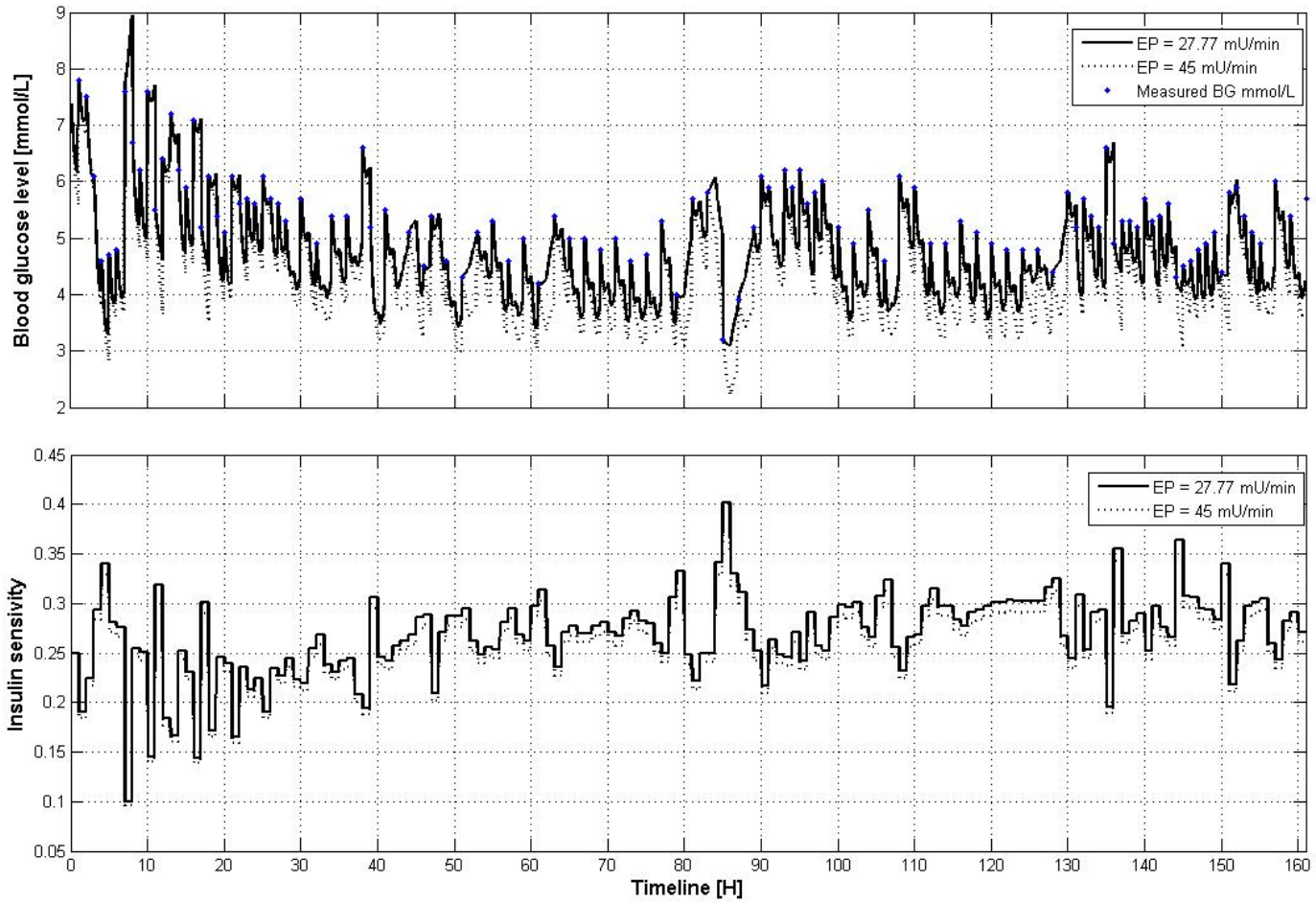

Fig. 7. *This figure illustrates how the predicted blood glucose for Patient 6 is effectively the same by using different dependent set of EP and S_I profiles. The top picture shows 2 predictions produced by using 2 different EP and S_I profiles. The lower picture shows 2 different S_I profiles. The upper S_I profile is produced by using a EP = 27.77 mU/min and the lower S_I profile is produced by using a EP = 45 mU/min. The prediction lines in the top panel are close to be the same that they are not labelled. This figure is produced by 1 hour prediction only.*

likely patient specific and potentially variable, is kept constant. Fitting both parameters in this model is problematic, as they are not uniquely identifiable from two blood glucose measurements without measured insulin data, which is rarely available in critical care.

The low Model Prediction error of Table IV, as compared to the Glucometers used at Christchurch Hospitals with 7-12 % measurement error [26], helps to further justify this choice of approach.

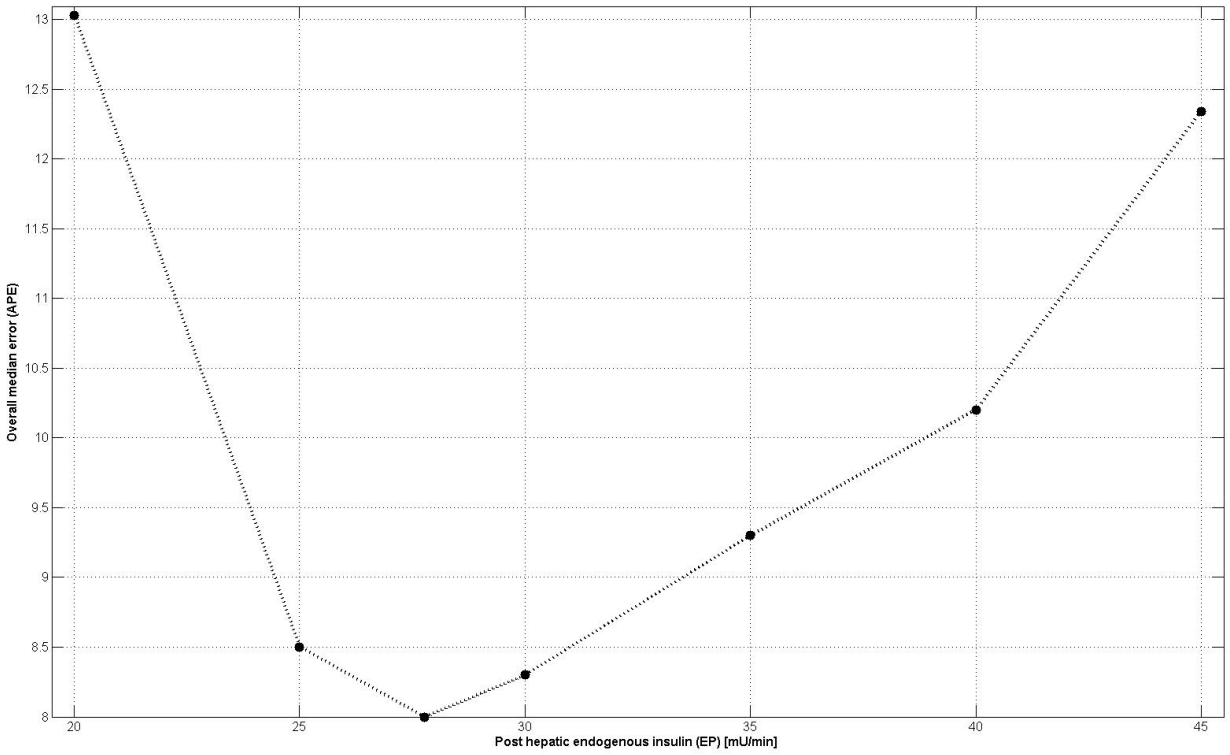

Fig. 8. *This figure illustrates the overall median error (APE) for all 10 patients used in this study using a different value of EP.*

In general, the 1-hour prediction validation errors are relatively low and consistent. Figure 6 shows that 90 percent are below 25 % APE, and 60 percent are below 10 % APE. Figure 6 also shows an error distribution that is clearly not normal. Hence, this study reports median and IQR values to better represent the data than normal statistics.

V. CONCLUSION

This study examines and validates the Glucosafe glycaemic control model for critical care patients in simulation using retrospective clinical data. The model is also validated for its predictive ability. The prediction mode utilizes an integral based parameter estimation method for fitting the patient specific insulin sensivity S_I. The goal is to ensure prediction with minimal absolute percent error, and to assess

the models potential clinical utility. This validation and examination used retrospective clinical data from glycaemically controlled critical care patients.

The overall mean and median absolute percent error for both fitting and prediction are at or within measurement error. The log-normal distributions ensure most predictions are relatively low. Both results for model dynamic validation and prediction validation are considered acceptable for later use in control applications in a clinical setting out to approximately 3 hour predictions levels. These results validate using these models in proof of concept pilot clinical trials.

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Development and Validation of a Decision Support System for Critically Ill Patients utilizing the Glucosafe Glycaemic Control Model

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Abstract

Background: Hyperglycaemia is prevalent in critically ill patients and can increase mortality. This paper presents and validates a glycaemic control system using a physiologically based metabolic control model (Glucosafe) and an associated integral based parameter identification method. The intended application for this glycaemic control system, and the associated model and parameter identification method is glycaemic control of critically ill patients.

Methods: The glycaemic control system uses the Glucosafe glucose-insulin metabolic model. Time varying insulin sensivity, S_I, is determined between measurements using an integral-based method. The glycaemic control system is validated by its ability to keep patients in a normoglycaemic range (4.4-7.75 mmol/L). Clinical control interventions are determined by optimization over a series of penalty functions. The system is validated against 20 virtual patients by using patient specific insulin sensivity profiles based on clinical data from 20 critical care patients at Christchurch Hospital (New Zealand).

Results: The overall median blood glucose concentration for all 20 patients is 6.05 mmol/L, and the IQR is 5.54-6.62 mmol/L. The overall number of hypoglycaemic measurements per patient is 0 (blood glucose measurements below 2.2 mmol/L). The overall mean percent of measurements inside the normoglycaemic range (4.4-7.75 mmol/L) is 87.7 %.

Conclusions: The results for the glycaemic control validation presented are comparable to other similar studies by Chase et al. (2008) and are acceptable for later use in clinical pilot trials.

Index Terms

Glucosafe, SPRINT, Glycemic control, Physiologic modelling, Blood glucose, Insulin Sensivity, Integral Parameter Estimation, Intensive Care, Virtual Trials, Virtual patients, Decision Support system

I. Introduction

Critically ill patients can, over long-term intensive care, often require significant help to maintain and support vital body functions [1].

Many critically ill patients have hyperglycaemia, due to stress of their condition, which results from significant stress induced insulin resistance [2] [3] [4] [5] [6]. Insulin resistance and the resulting hyperglycaemia may contribute to a higher mortality rate because of multiple-organ failure with sepsis [3] [7]. Several clinical studies have investigated and demonstrated that there is a significant correlation between the mortality of critically ill patients and high blood glucose concentrations [8]. Tight control of blood glucose values between 6.1-7.75 mmol/L, has been shown to reduce mortality by 15-43 % [3] [9] [10], as reviewed in [7] [11].

Most studies have only used insulin to reduce blood glucose [3] [9] [11]. Another, recent study modulated both insulin and nutrition to maintain a tight control of blood glucose, and thus reduced mortality [10]. In fact, lower nutrition alone has shown to result in significant reductions in average blood glucose concentrations [12], [13]. Thus, avoiding excessive nutrition, can help to avoid or reduce hyperglycaemia [13].

Two important results can therefore be drawn from these studies. First, tighter control with lower glycaemic limits appears to offer increased benefit in terms of reduced mortality and reductions in other measurable negative clinical outcomes. Second, the degree of critical illness is generally correlated to observed hyperglycaemia and lowered insulin sensivity [8] [14], which will result in a decreased ability to reduce blood glucose with insulin alone for more critically ill cohorts. Hence, reduced glucose nutrition combined with insulin administration can act to control both sides (input and removal) of the glucose balance [10] [15] [16] [17].

Only a few studies have controlled blood glucose in critical care patients using models [18], [19], [20], [21]. This area was reviewed in [7].

Glucosafe is a composite metabolic and insulin system model presented by Pielmeier et al. [22]. It makes use of previous models of insulin and metabolism [23] [24] [25] [26]. The glycaemic model presented utilizes a glucose transporter model, which calculates the glucose balance for a given set of inputs and the gut absorption rate [26]. Hence, it combines clinically validated insulin kinetics and glucose-insulin dynamics into a new overall system model.

This paper presents and validates a glycaemic control system using a combination of Glucosafe [27] and an integral based parameter estimation method [28]. Finally, the glycaemic control system uses an optimizer utilizing penalty functions for nutrition and insulin, presented in this study, and a penalty function for blood glucose, whose shape was defined in earlier studies [29]. The validation of the glycaemic control system is performed using virtual patients, created from identified patient specific parameters during model simulation using Glucosafe [27], and the integral based parameter estimation method [28]. This method is described in detail in [16].

II. METHODS

A. Glucosafe glucose-insulin system model and integral based parameter estimation method

The Glucosafe model is used to calculate the time-varying response of blood glucose for given insulin and nutrition inputs [22] [27]. The insulin kinetics of the Glucosafe model are illustrated in Figure 1, and are defined in detail elsewhere [24] [25] [27].

The calculation of and the change in plasma insulin concentration $I(t)$ [mU/L] and the change in peripheral insulin concentration $Q(t)$ [mU/L] depends on the parameters n_L, n_C and V_Q defined in [27], and n_K, n_I and V_P, which are functions of basic patient parameters [30].

The parameter n_K is the kidney clearance $[min^{-1}]$, n_I is the transport rate between the plasma and peripheral compartments $[L/min]$, n_L is the liver clearance $[min^{-1}]$ and n_C is the irreversible loss of insulin in the periphery $[min^{-1}]$. Finally, V_P is the plasma volume [L] and V_Q is the peripheral interstitial volume [L]. The patient specific parameters are calculated in the Glucosafe model by using the patients gender, age, height, weight and diabetic state, and are set as static for the patient during the glycaemic control procedure [27] [30]. Finally, $EP(t)$ is the post-hepatic endogenous insulin secretion rate, which in Glucosafe is set as a constant at 27.77 mU/min [27], and $P(t)$ is the given insulin infusion rate [U/h].

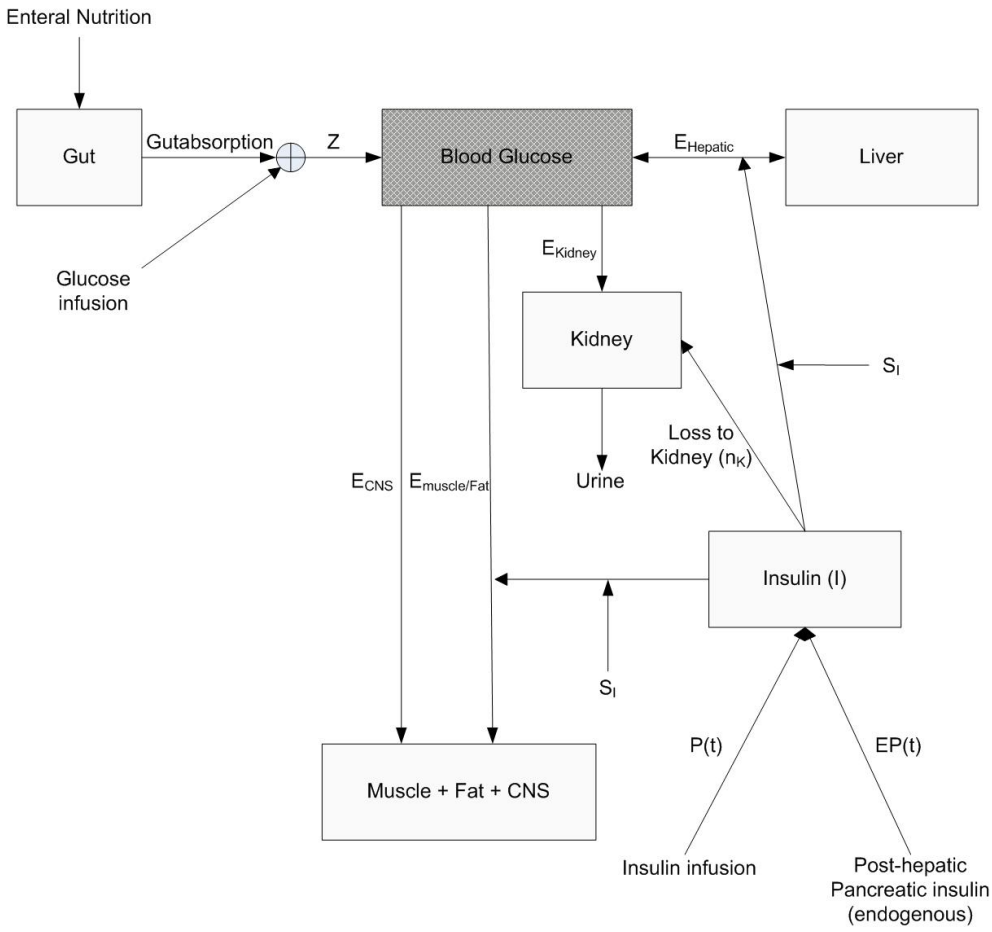

Fig. 1. *Glucosafe physiological overview, where exogenous insulin is assumed to be intravenous. The change in blood glucose, BG is a result of the sum of absorption, Z (positive change in BG).* $E_{Hepatic}$ *is the hepatic balance between the liver and the plasma compartment.* E_{Kidney}, $E_{Muscle/Fat}$ *and* E_{CNS} *all causes a negative change in the BG concentration. In this figure CNS = central nervous system.*

The pharmacodynamic changes in blood glucose concentration [mmol/L], due to endogenous and exogenous inputs of insulin and nutrition are illustrated in Figure 1, and are defined in detail in [22] [26]. Z is the sum of glucose absorption from the nutrition inputs $[mmol/(kg \times min)]$, $E_{Hepatic}$ is the bidirectional glucose transport to and from the liver $[mmol/(kg \times min)]$, and E_{Kidney}, E_{CNS} and $E_{Muscle/Fat}$, all $[mmol/(kg \times min)]$, are the turnover of blood glucose to the kidneys, central nervous system, fat cells and muscle cells, respectively. [27]. The blood glucose turnover to liver, fat and muscle cells $[mmol/(kg \times min)]$ is stimulated by the active insulin, which is proportional to the patients insulin sensitivity, S_I [22] (modification from Arleth et. al. [26]).

Integral based parameter estimation is implemented using the same method as Hann et al. [28]. In this

case, it is used to identify S_I and all other values are held at population constants [22] [24] [25] [26]. The value of S_I is assumed piecewise constant over any given identification interval [28]. The length of the identification interval is 1 hour for the SPRINT [10] patient cohort used in this study.

B. The decision support systems advice module

In addition to the Glucosafe glucose-insulin model and the integral based parameter estimation method, the glycaemic control system utilizes three penalty functions and an optimizer, to control the blood glucose concentration of patients. Figure 2 illustrates the penalty shapes for all of the penalty functions used in this study. These functions are related to patient state and intervention limitations in: insulin bolus [U/h], nutrition feeding rate [% of DI] and blood glucose concentration [mmol/L].

All three shapes have influence on glycaemic control, and the size or values of each penalty function are weighted against the desired criteria of 1: keeping the patients blood glucose concentration inside the normoglycaemia range between 4.4-7.75 mmol/L [3] [9]. 2: giving the patient an adequate amount of calories, and 3: keeping the control of the patients blood glucose concentration while minimizing the amounts of insulin given to the patient.

The design approach for the penalty functions are based on the blood glucose penalty shape, which was defined in [29]:

$$Penalty(BG) = (ln(\frac{BG}{BG_0}))^2 \times K_{BG-Penalty} \tag{1}$$

Where BG is the current blood glucose values, and BG_0 (= 5.5 mmol/L) is the point at which the penalty function value is 0. $K_{BG-Penalty}$ is a fitting constant (value = 4). The blood glucose penalty function results in a penalty range of: [0 0.47] in the targeted blood glucose range of 4.4-7.75 mmol/L.

The insulin penalty shape is based on the saturation effect of insulin action on glucose uptake [31] [32]. Saturation has effect when calculating the nonlinear fraction of maximal endogenous balance as a function of the insulin infusion/absorption rate. The calculation of the insulin penalty functions is presented in Equation 2 and 3:

$$Penalty(INS) = (\frac{(I + K_m)^2}{(K_m)^2} - 1) \times K_{INS-Penalty} \tag{2}$$

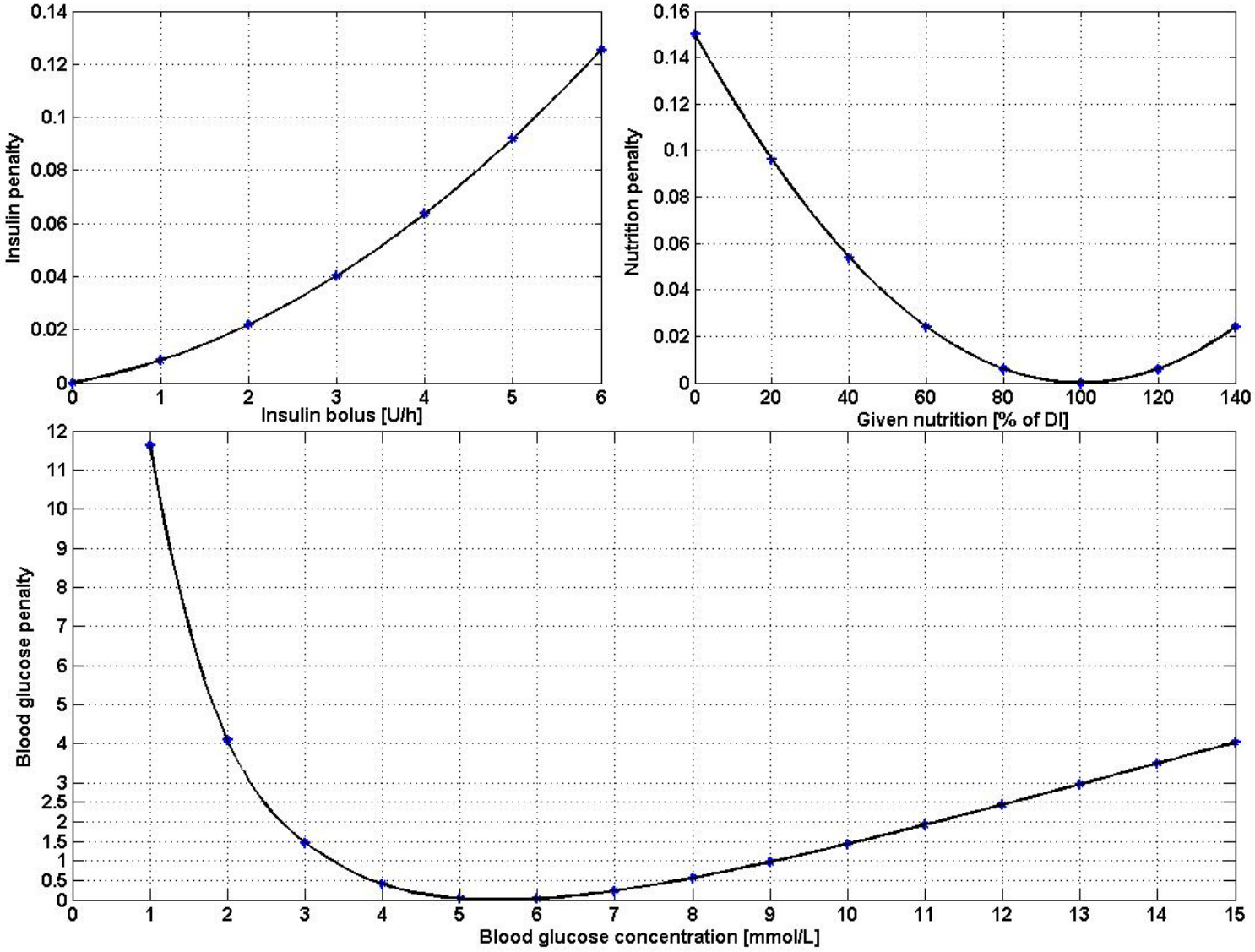

Fig. 2. *This figure illustrates the three penalty functions for insulin bolus [U/h], nutrition feeding rate [% of DI] and blood glucose concentration [mmol/L] used in the advice module*

where K_m is the insulin saturation constant (value = 28 mU/L) [33] and $K_{INS-Penalty}$ is a insulin penalty function fitting constant (value = 1/280).

Finally, I [mU/L] depends on the insulin bolus given [U/h] defined in Equation 3:

$$I = INS \times C \times BM_{70} \tag{3}$$

where INS is the insulin bolus from 0-6 U/h (presented as $P(t)$ in Figure 1), and C is the default conversion factor (value = 98.1 kg $\times$ min/L) [27] to convert absorbed insulin to plasma insulin, and BM_{70} is a bodymass constant (value = 1/70 kg^{-1}). The system limits the insulin bolus range to 0-6 U/h, and to minimize saturation effects the insulin penalty range is [0 0.13]. The constant $K_{INS-Penalty}$ in Equation 2 is thus a fitting constant, whose purpose is to weight the insulin penalty range against the two other penalty functions.

Finally, the nutrition penalty function is designed on the basis of keeping the patient inside normoglycaemia while continually giving the patient as close to 100 % of daily intake (DI) of calories as possible. The penalty range for the nutrition penalty function is [0.00 0.05] in the feeding range of 40-140 % of DI. Equation 4 represents the nutrition penalty function:

$$Penalty(NUT) = (NUT - 100\%)^2 \times K_{NUT-Penalty} \tag{4}$$

where NUT is given nutrition in the range 40-140 % of DI and $K_{NUT-Penalty}$ is a fitting constant (value = 0.15) to weight the nutrition penalty range against the two other penalty functions.

The nutrition advice range illustrated in Figure 2 is presented in % of DI, and has to be converted into caloric intake for the specific patient. The Harris Benedict metabolism equation [34] is used to calculate 100 % of daily calorie intake DI from the patients gender, weight, age and height, from which calories per day (CD) can be calculated as: CD = NUT $\times$ DI [kcal/day]. Finally, the advised feeding rate (FR) [ml/h] can be calculated as FR = CD/CV from the calorie value CV [kcal/ml] of the enteral or parenteral solution.

The nutrition used in this study is an enteral formula named Diabetic Resource (Novartis Medical Nutrition, Minneapolis, MN, USA), which was also used in earlier studies from which the underlying SPRINT patient data for the virtual patients in this study originates [10] [16] [17] [35] [36]. Importantly it is also a low carbohydrate formula, where 34 % of the calories come from carbohydrates.

As seen on Figure 3 the advice module optimizer uses all three penalty functions ($Penalty(INS)$, $Penalty(NUT)$ and $Penalty(BG)$), and forward simulates the model ($simulation(INS, NUT)$) every intervention interval to choose the advice with the lowest sum of penalty error (Advice = min(Total

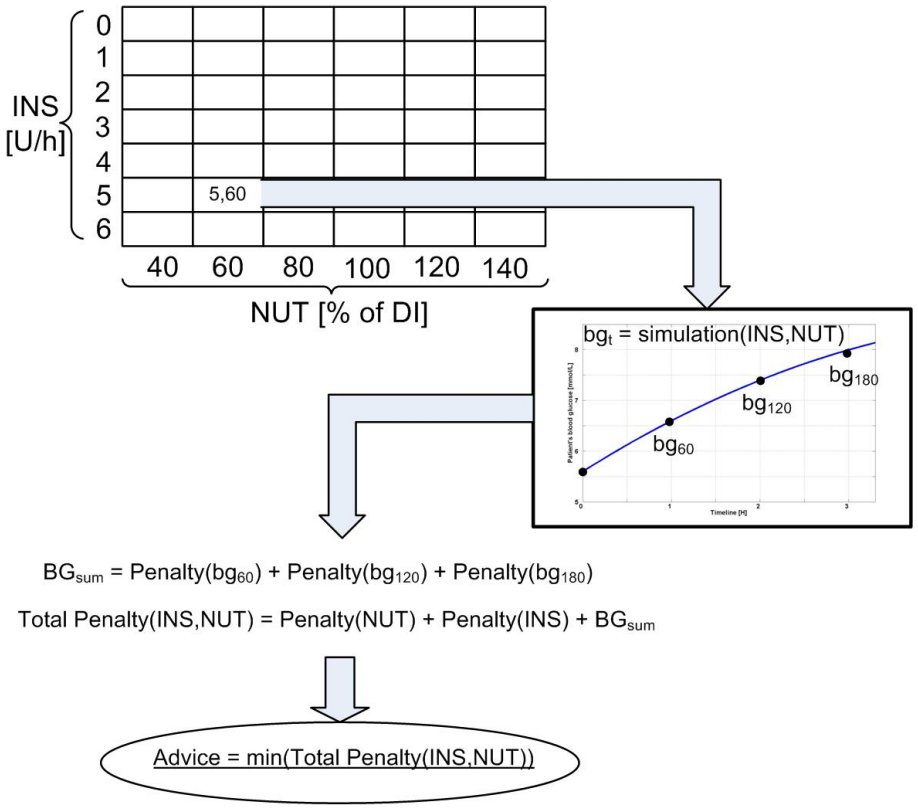

Fig. 3. *This figure illustrates how the advice module optimizer calculates all relevant combinations of nutrition and insulin in a grid to choose the advice choice with the lowest sum of penalty. During each 3 hours penalty simulation, the same S_I estimated for that hour is used.*

Penalty(INS,NUT))).

In the top of the figure an array of different combinations of given insulin (INS) and given nutrition (NUT) can be seen. The optimizer searches this grid of choices before every new intervention advice is given. The optimizer calculates the penalty for each of 7 possible insulin combinations (0-6 U/h). Meanwhile, the nutrition to be given is calculated for each possible combination over the range: 40, 60, 80, 100, 120, 140 % of DI. This search thus results in 7 $\times$ 6 = 42 sets of possible interventions, and therefore 42 times where the optimizer forward simulates how the blood glucose concentration will respond to each different set of interventions.

As seen on Figure 3 each field of the grid involves a simulation for 3 hours, using the same set of interventions and S_I for the three hour period. The result from this simulation is the set of blood glucose concentrations: bg_{60}, bg_{120} and bg_{180}, which are the blood glucose concentrations after 1,2 and 3 hours, respectively. As seen in Figure 3 each set of possible interventions include the blood glucose penalty sum

over 3 hours (Equation 5), achieved from the simulation:

$$BG_{sum} = Penalty(bg_{60}) + Penalty(bg_{120}) + Penalty(bg_{180}) \tag{5}$$

At each field in the grid, having a set of insulin and nutrition, and the resulting development in the calculated blood glucose concentration (bg_{60}, bg_{120} and bg_{180}), these values are used as inputs to the penalty functions to find a penalty sum. The resulting advice is given after repeating this method for each field in the grid (42 times), and yields the combination with the lowest sum of penalties.

An example of the glycaemic control system in action can be seen in Figure 4, which illustrates the first 20 hours of glycaemic control for Patient 2 in this study. Here, the chosen advice is presented in panels 6 and 7 for a given nutrition [% of DI] and given insulin [U/h], respectively. On panel 3 the advice resulting penalty of each penalty functions are shown.

C. SPRINT Benchmark patient cohort

The patient data used in this study comes from 20 critical care patients in the SPRINT study [10] (Benchmark patient cohort, [35]) some of which also have been used in other previous studies [16] [17] [36]. The patient cohorts details can be seen in Table I. All retrospective data and measurements are available in 1-2 hour intervals, and are thus relatively dense. Ethics approval to use this data was obtained from the South Island Regional Ethics Committee, New Zealand.

In Figure 5 the implementation of virtual patients can be seen. During a glycaemic control of a given virtual patient, a predefined S_I value is given to the virtual patient each hour, and noise is added to the virtual patients blood glucose response, to the current intervention, to imitate a clinical situation with measurement noise. In this study, a normal distributed noise with a standard deviation of 10 % of the measured blood glucose is used matching the glucometers used in the SPRINT study [10].

III. RESULTS

Table I shows that the length of stay for the 20 SPRINT patients included in this study varies in the range of [139 971] hours. In this study the glycaemic control system is validated over a 1 week long period (168 hours), where it was possible, for each of the virtual patients.

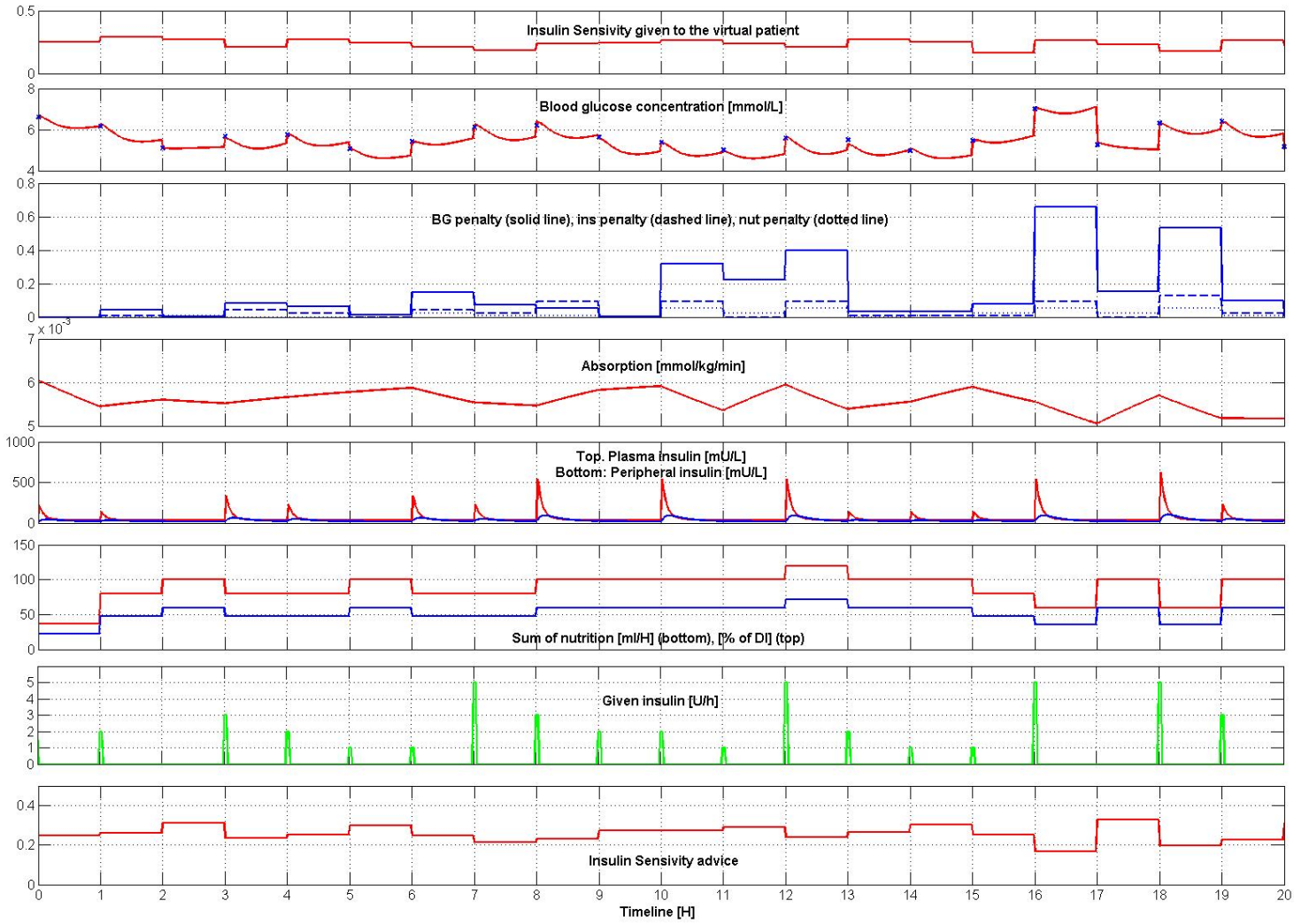

Fig. 4. *This figure illustrates the glycaemic control for the first 20 hours for Patient 2 included in this study. The second panel illustrates the results of the glycaemic control, where the first blood glucose measurements (at hour 0) are real measurement from the underlying SPRINT patient, meanwhile the subsequent measurements are the virtual patients response to the advice interventions supplied by the glycaemic control system.*

All virtual patients included in this study start at a blood glucose concentration that originates from the clinical SPRINT patient data. Furthermore, the gut content is set as a starting guess at 1.8 mmol/kg, plasma insulin concentration at 20 mU/L, and a peripheral insulin concentration at 12 mU/L. The normoglycaemia range is in this study defined to be 4.4-7.75 mmol/L. Hypoglycaemia is defined as a measurement less than or equal 2.2 mmol/L.

A. Glycemic control validation

The results for the advice validation for all 20 patients included in this study are presented in Table II, where it can be seen that the overall median blood glucose concentration is 6.05 mmol/L with IQR = [5.54

Patient number	Age	APACHE II score:	Diagnosis	Hospital stay (hours)	Duration of stay on SPRINT (hours)	Gender
1	75	17	Hypoxemic	1416	828	M
2	68	18	On pump	439	178	M
3	73	22	Perforation	391	310	M
4	68	19	Laparotomy	185	145	M
5	60	13	Chronic obstructive airways disease	254	205	F
6	70	31	Community acquired pneumonia	648	512	M
7	70	42	Obstruction	770	159	F
8	65	25	Septic shock	298	287	F
9	76	20	Acute abdominal aortic aneurysm	511	458	F
10	58	15	Hip replacement	142	139	F
11	49	30	Hypoglycaemia	302	297	M
12	73	16	Pancreatitis	156	150	M
13	20	15	Trauma	1178	971	M
14	74	23	Infarction/ischaemia	230	192	M
15	63	29	Ventilatory	770	323	F
16	49	14	Pancreatitis	929	923	M
17	45	16	Pancreatitis	653	524	M
18	72	16	Post op.	295	265	M
19	73	22	Orthopaedic	257	253	M
20	65	7	Community acquired pneumonia	149	140	F

TABLE I
PATIENT DATA FOR THE 20 SPRINT PATIENTS USED IN THIS STUDY. NONE OF THE INVOLVED PATIENTS HAVE ANY TYPE OF DIABETES

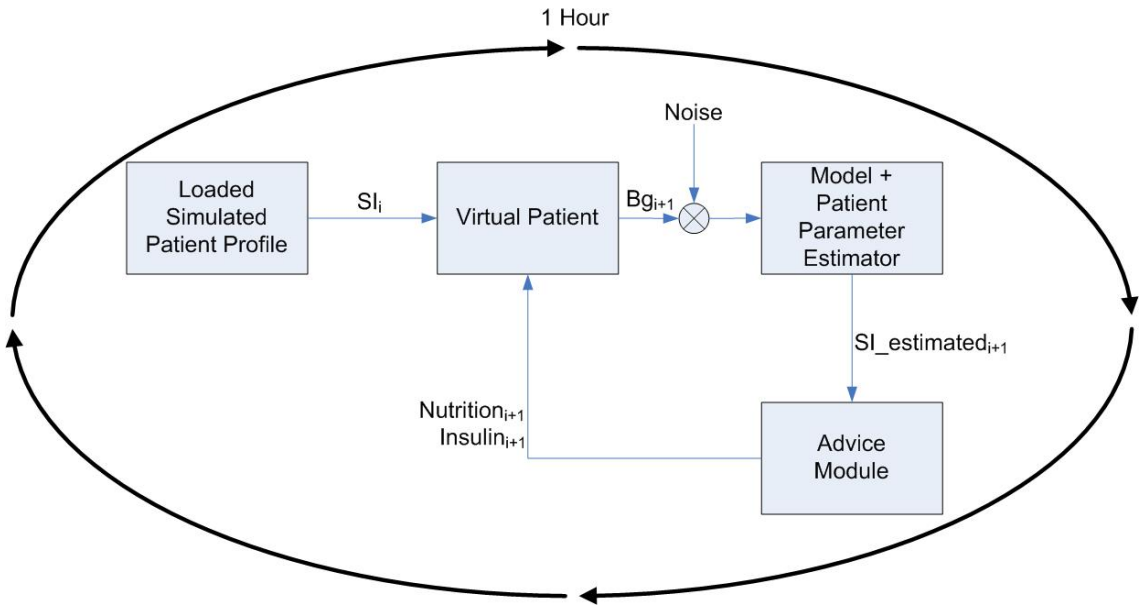

Fig. 5. *This figure illustrates the glycaemic control process as a whole.* $SIestimated_{i+1}$ *is used in the period i+1, but are estimated using data from the period i. The same applies to* $Nutrition_{i+1}$ *and* $Insulin_{i+1}$*. Due to the virtual patients used in this study originates from of SPRINT data, the length of this repeating process is 1 hour*

6.62] mmol/L. Table II also shows that the 20 patients are inside the normoglycaemic range (4.4-7.75 mmol/L) in 87.7 % of measurements. The length of the glycaemic control varies from 144 to 167 advices for each patient (145-168 hours of glycaemic control), which results in a total of 3233 advices and 3253 hours of measured blood glucose concentrations done in this study.

During glycaemic control the overall average feed was 87.2 % of DI, meanwhile the overall average calorie intake per day was 1250 kcal/day, of which 425 kcal/day were carbohydrates for all 20 patients. The overall average given insulin was 2.2 U/h for all 20 patients. The average number of blood glucose measurements below 4.4 mmol/L were 6 for each patient (approximately 3 % of measurements), the average number of blood glucose measurements below 3.4 mmol/L were 1 for each patient (below 1 % of measurements) and the number of hypoglycaemic measurements below 2.2 mmol/L were 0 for all 20 patients.
Finally, Table II shows that the estimated overall average S_I for all 20 patients was 0.23, and varied from 0.18 to 0.27.

Figure 6 illustrates the cumulative distribution of the blood glucose measurements recorded for each individual virtual patient in this study, covering all 20 blood glucose measurements for all 20 patients. The thick line in Figure 6 shows the overall cumulative distribution of the blood glucose values for all 20 virtual patients (3253 hours of blood glucose concentration measurements [mmol/L]). Finally, Figure 7 illustrates the box-and-whisker plot of hourly measured blood glucose concentrations [mmol/L] for all 20 virtual patients, covering the first 24 hours of glycaemic control adaptation period.

IV. Discussion

The Glucosafe model used in this glycaemic control system presented, is physiologically defined and utilizes the concept of a remote compartment for insulin transport to account for the delay between insulin secretion, or infusion, and its utilization. A prior validation shows that the fitted model matches all the observed and predicted clinical dynamics [22] [24] [27]. These studies validates the use of blood glucose response from virtual patients, who are constructed using the same model with added noise.

Figure 4 confirms that there is a need to adjust the nutrition and insulin given, to keep the patient inside the normoglycaemic range (4.4-7.75 mmol/L). The results of glycaemic control validation, regarding the

Patient number	Median BG	5-95th range	IQR	No. < 3.4 mmol/ L	No. < 4.4 mmol/ L	No. of advices	Average feed %	Mean Kcal/ day	Mean insulin [U/h]	Mean S_I	% in band
1	5.96	[4.60 7.14]	[5.44 6.48]	0	3	167	89.5	1306	2.3	0.24	97.0
2	5.27	[4.30 6.30]	[4.79 5.78]	1	12	167	90.4	1362	1.6	0.27	92.8
3	6.59	[4.65 9.73]	[5.78 8.04]	0	6	167	80.1	1180	3.0	0.21	66.5
4	5.11	[4.38 5.67]	[4.74 5.67]	0	8	144	87.8	1323	1.4	0.27	92.4
5	5.98	[4.27 7.74]	[5.50 6.61]	0	11	167	97.7	1264	1.9	0.24	88.6
6	5.10	[4.05 6.08]	[4.74 5.42]	2	16	167	83.3	1244	1.4	0.27	90.4
7	6.03	[4.70 7.14]	[5.63 6.40]	0	0	158	103.1	1286	1.6	0.25	96.9
8	5.89	[4.30 7.60]	[5.30 6.64]	1	8	167	103.9	1320	1.7	0.25	92.2
9	6.78	[5.29 8.41]	[6.26 7.20]	0	1	167	89.6	1092	3.0	0.21	84.4
10	5.99	[4.17 7.73]	[5.29 6.53]	2	9	138	102.6	1337	1.8	0.25	88.4
11	6.51	[4.12 9.40]	[5.55 7.60]	2	15	167	82.0	1342	3.3	0.23	67.7
12	6.04	[4.39 7.34]	[5.57 6.59]	2	8	149	81.6	1201	2.1	0.24	93.3
13	6.45	[5.36 7.43]	[5.92 6.83]	0	1	167	59.3	1087	2.3	0.22	98.2
14	6.94	[5.31 9.71]	[6.32 7.94]	0	0	167	74.1	1086	3.3	0.20	70.1
15	5.70	[5.02 6.91]	[5.46 5.87]	0	1	167	96.7	1238	1.2	0.18	98.2
16	5.15	[4.31 6.13]	[4.86 5.47]	0	10	167	88.1	1441	2.0	0.20	94.0
17	5.12	[4.27 6.02]	[4.74 5.45]	0	13	167	80.6	1340	1.7	0.20	92.2
18	6.57	[5.03 9.39]	[6.08 7.03]	1	4	167	81.1	1199	3.0	0.22	85.0
19	6.92	[5.36 8.43]	[6.38 7.64]	0	1	167	77.2	1136	3.4	0.21	77.8
20	6.95	[5.92 8.14]	[6.52 7.25]	0	0	140	94.9	1206	2.6	0,22	88.5
Overall	6.05	[4.69 7.69]	[5.54 6.62]	1	6	3233	87.2	1250	2.2	0.23	87.7

TABLE II
RESULTS FOR ALL PATIENTS INCLUDED IN THE ADVICE VALIDATION WITH CLINICAL LIMITS IN CHRISTCHURCH HOSPITAL. IQR = INTERQUARTILE RANGE. THE NORMOGLYCAEMIA BAND IS DEFINED AS BLOOD GLUCOSE CONCENTRATION BETWEEN 4.4-7.75 MMOL/L. THERE WERE 0 HYPOGLYCAEMIC MEASUREMENTS (HYPOS) FOR ALL 20 PATIENTS. HYPOGLYCAEMIC IS WHEN BLOOD GLUCOSE CONCENTRATION IS BELOW 2.2 MMOL/L. THE OVERALL NUMBER OF ADVICES (3233) COUNTS THE TOTAL NUMBER OF ADVICE PERFORMED IN THIS STUDY

average nutrition rate, and the ability to keep the patients inside the range of normoglycaemia, are good examined in isolation. However, more importantly, in combination the compromise between nutrition given (87.17 % of DI), and the ability to keep patients normoglycaemic (87.7 % of measurements), can be hard to achieve with this general ICU cohort. The overall average calorie intake per day was 1250 kcal/day, and the overall average given insulin was 2.2 U/h, which makes the results from this study comparable to other similar studies. For example the SPRINT clinical implementation and evaluation study by Chase et al. [10], where the overall lognormal average calorie intake per day was 1283 kcal/day and overall average given insulin per hour was 2.8 U/h. This correlation to the SPRINT clinical results adds a further level of confidence in the virtual trials.

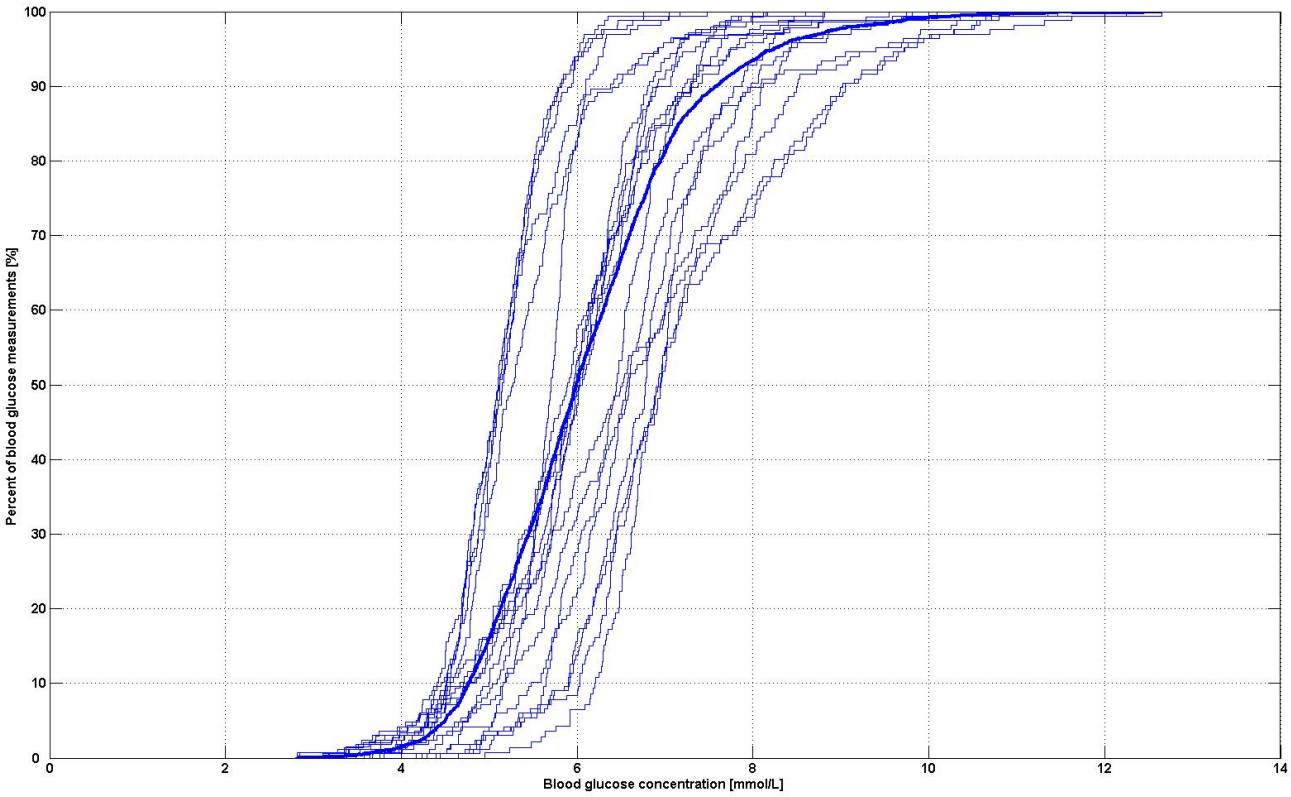

Fig. 6. *This figure illustrates the cumulative distribution of each virtual patients blood glucose values during glycaemic control. The thick line is the overall cumulative distribution of the blood glucose values for all 20 virtual patients. This figure represents all data including the original patientdata starting points.*

In later clinical scenarios, there maybe potential advice limitations in the glycaemic control. Some hospitals use fixed nutrition feeding rates (fx. 100 % of DI), so that insulin [U/h] is the only adjustable parameter to ensure patients are kept normoglycaemic. Observing Table II it can be seen that most of the average feeding rates for all 20 patients are in the 80-100 % of DI range. Hence, without modulating nutritional inputs many similar general ICU patients will have periods of hyperglycaemia (> 7.75 mmol/L) where insulin alone may not be fully effective.

V. Conclusion

This study presents and validates a glycaemic control system, utilizing the Glucosafe model [27] and an integral based parameter estimation method for fitting the patient specific insulin sensivity S_I [28]. The goal of validation is to prove the glycaemic control systems ability to keep 20 virtual patients (produced by patientdata using retrospective clinical data (SPRINT)) inside the range of normoglycaemia (4.4 - 7.75

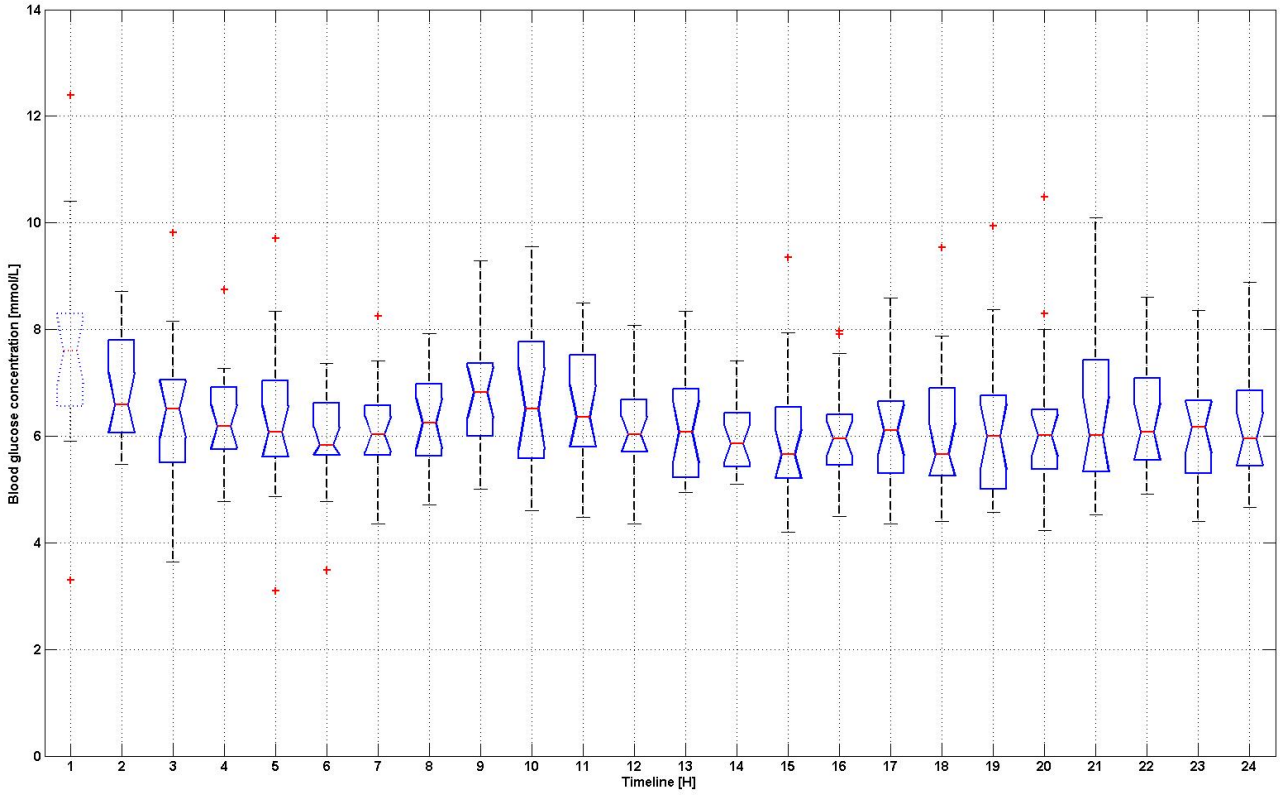

Fig. 7. *This figure shows the Box and whiskers plot (the smallest observation. lower quartile, median, upper quartile and largest observation for each hour) for all 20 patients blood glucose during the first 24 hours under glycaemic control. Points (outliers) beyond the whiskers are displayed using +. The dotted Box and whiskers plot at hour 1 represents original SPRINT blood glucose measurements, and are used as starting points for all virtual patients before going on the glycaemic control, these values are because of this not a result of the advice given.*

mmol/L).

The overall median and IQR blood glucose concentrations are, for all 20 virtual patients, within the range of normoglycaemia. This result is also achieved without any hypoglycaemic measurements below 2.2 mmol/L. Because of the low variation of average feeding given to the virtual patients, and that the overall average feeding is very close to estimated full calorie needs, the glycaemic control system is considered comparable to other similar studies [10], and acceptable for later use in control applications in a clinical setting.

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