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Decision support for blood glucose control in critically ill patients

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Publication date:
2010

Document Version
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Pielmeier, U. (2010). *Decision support for blood glucose control in critically ill patients: development and clinical pilot testing of the Glucosafe system*. Center for Model-based Medical Decision Support. Department of Health Science and Technology. Aalborg University.

Decision Support for Blood Glucose Control in Critically Ill Patients

Development and clinical pilot testing of the Glucosafe system

A thesis submitted in fulfilment of the requirements

for the degree of Doctor of Philosophy

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2010

"If you want to build a ship, don't drum up people together to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea . . . "

"How could drops of water know themselves to be a river? Yet the river flows on."

(Antoine de Saint-Exupéry)

Acknowledgements

I want to thank my supervisor, Professor Steen Andreassen, for his confidence in my work, his constant support and a never ending stream of ideas, but also for many valuable lessons of science and life over the course of three years.

Doctors Pernille Haure, Birgitte Nielsen, Ken Jensen, and the nursing staff at NOTIA at Aalborg Hospital. You have been a great help in all medical questions, and a constant source of inpiration to me. Thank you also for helping with the data collection and for your support in many practical issues on the clinical side of this project. For making me feel most welcome at your department, thank you.

I also want to express my gratitude to Professor Geoff Chase and colleagues from Canterbury University, New Zealand for a great cooperation and supervision on parts of this project. Even across this distance, replies seemed to come at the speed of light, any time of day. Thank you very much for all your help.

A great thanks to my family in Germany for moral support and back up, it meant a lot to me.

Thanks to all my friends, and to my colleagues from MMDS and AAU. I am grateful for all the motivation, the sense of humour and feeling of understanding, that you gave to me. Special thanks to Susanne Annikki, Tom and Mette Arleth, Petra and George Rössel, Sheena and Bram Smith, and Nicole Marheineke.

My gratitude goes to the companies Judex A/S and Radiometer Medical ApS for support of this project.

Most of all I want to thank my husband and my children, who have supported me all the way through this project. You gave me all the strength that I needed.

Aalborg, December 2010
Ulrike Pielmeier

This thesis is based on the following publications referred to in Chapters 2-6 by their roman numeral:

I Pielmeier U, Andreassen S, Nielsen BS, Chase JG, Haure P. **A simulation model of insulin saturation and glucose balance for glycemic control in ICU patients.** Comput Methods Programs Biomed. 2010; 97(3):211-22. Epub 2009 Jul 25. doi:10.1016/j.cmpb.2009.06.004

II Andreassen S, Pielmeier U, Chase JG. **Receptor-based models of insulin saturation dynamics.** ACTA Press, Proceedings of the 6th IASTED International Conference on Biomedical Engineering, BioMED 2008, Innsbruck, Austria, February 13-15, 2008; 182-186.

III Pielmeier U, Andreassen S, Nielsen BS, Hann CE, Chase JG, Haure P. **Comparison of identification methods of a time-varying insulin sensitivity parameter in a simulation model of glucose metabolism in the critically ill.** IFAC Proceedings Volumes (IFAC PapersOnLine), Proceedings of the 7th IFAC Symposium on Biological and Medical Systems, Aalborg, Denmark, August 12-14, 2009; 7(1):67-72. doi:10.3182/20090812-3-DK-2006.0061

IV Chase JG, Andreassen S, Pielmeier U, Hann CE, McAuley KA, Mann JI. **A glucose-insulin pharmacodynamic surface modeling validation and comparison of metabolic system models.** Biomedical Signal Processing and Control. 2009; 4(4): 355-363. doi:10.1016/j.bspc.2009.04.002

V Pielmeier U, Chase JG, Andreassen S, Nielsen BS, Haure P, Shaw GM. **Prediction validation of two glycaemic control models in critical care.** IFAC Proceedings Volumes (IFAC-PapersOnline), Proceedings of the 17th World Congress The International Federation of Automatic Control, Seoul, Korea, July 6-11, 2008; 17(1):8074-8079. doi: 10.3182/20080706-5-KR-1001.1773

VI Pielmeier U, Andreassen S, Juliussen B, Chase JG, Nielsen BS, Haure P. **The Glucosafe system for tight glycemic control in critical care: a pilot evaluation study.** J Crit Care, 2010; 25(1):97-104. doi:10.1016/j.jcrc.2009.10.003

VII Pielmeier U, Andreassen S, Chase JG. **When to measure blood glucose - Cohort-specific glycaemic control.** ACTA Press, Proceedings of the 6th IASTED International Conference on Biomedical Engineering, BioMED 2008, Innsbruck, Austria, February 13-15, 2008; 178-181.

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Summary

Hyperglycemia in intensive care patients is associated with increased mortality and prolonged illness. Tight blood glucose control reduces mortality and morbidity in some groups of critically ill patients, but increases the risk of hypoglycemia. Fear of hypoglycemia, and the required time and effort have yet prohibited tight blood glucose control to become a standard of care in intensive care units.

This thesis hypothesizes, that a decision support system can be built that improves blood glucose control in critically ill patients without increasing the risk of hypoglycemia. The thesis summarizes the design, development and clinical pilot testing of the model-based computerized decision support system 'Glucosafe'. This system recommends not only insulin dosing, but also nutrition for optimized blood glucose control. The system is based on a physiological multi-compartment model of insulin and glucose. Insulin resistance is modeled as a time-varying, patient-specific parameter, that reduces the maximal achievable insulin effect. The model also accounts for the saturation of insulin effect at high insulin concentrations, thus preventing the recommendation of insulin doses that lead to hypoglycemia. Recommendations are based on a set of penalty functions, that minimize the risks of hypo- or hyperglycemia, undernourishment or overfeeding. Recommendations include the route of feeding, giving early enteral feeding priority over parenteral nutrition. Finally, the system includes a feature to change the advice mode, in order for the system to recommend exclusively the dosing of insulin.

A retrospective evaluation of Glucosafe's accuracy to predict blood glucose concentrations showed a median error of less than 25% by the model for predicted values up to 270 minutes ahead in time. The prospective pilot testing of Glucosafe was carried out at the neuro- and trauma intensive care unit of Aalborg hospital in Denmark. Ten hyperglycemic patients were studied in an 'off-on-off' study design. Results showed that Glucosafe improved the blood glucose control significantly. Hypoglycemia did not occur during the trial. These results are preliminary and need to be confirmed by a large randomized clinical trial to reach a definite conclusion. The thesis concludes with outlining the workflow to include Glucosafe as a standard care tool for blood glucose control in intensive care units.

Chapter 1

Introduction

1.1 Hyperglycemia in critical care

Normal fasting blood glucose concentration ranges from approximately $4.0 - 6.0$ mmol/L in healthy adults [8]. Hyperglycemia is the commonly used term for abnormally high blood glucose concentrations; however, there are discrepancies with respect to the cut-off value by which the start of hyperglycemia is defined [9]. In patients with diabetes mellitus, high blood glucose is a chronic condition; measured values are used to diagnose the disease and to monitor the treatment course. However, hyperglycemia has also been observed in critically ill patients with no prior history of diabetes. The terms 'stress hyperglycemia' and 'transient hyperglycemia' have been proposed to describe this state [9; 10]. The content of this thesis focuses on hyperglycemia in critical illness, unless otherwise stated.

Severe traumatic injury is characterized by an initial hypometabolic response, followed by a longer-lasting, hypermetabolic phase [11]. These states are sometimes also referred to as 'ebb' and 'flow' phase of critical illness [11]. The ebb phase ceases after about 12 to 14 hours, while the duration of the flow phase depends on the severity of injury or infection; it typically peaks at around 3 to 5 days post-injury and subsides after 7 to 10 days [12]. Hyperglycemia is common during both phases, although for different causes. During the ebb phase, hyperglycemia is related to an increase in plasma epinephrine concentration which rises progressively with severity of injury shortly after the assault and causes an increase of hepatic glycogenolysis [13]. Another source for early hyperglycemia in this phase is the stress-induced activation of a feedback loop between two organ systems, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, that leads to increased levels of cortisol [14]. Cortisol is a counter-regulatory hormone that induces the biosynthesis of gluconeogenic enzymes and inhibits glucose uptake and metabolism in peripheral tissues. In the flow phase, hyperglycemia mainly results from a combination of glucagon-stimulated hepatic

gluconeogenesis [15] and peripheral and central insulin resistance [12]. Elevated glucagon levels in patients with hypermetabolic stress may reflect direct effects of tumor necrosis factor [16], a pro-inflammatory cytokine. Tumor necrosis factor and other cytokines, for example interleukin-1 and interleukin-6, also seem to be involved in the inhibition of insulin release [17] and in the impairment of insulin action on peripheral glucose disposal [18]. They are thus seen as important mediators of stress-induced insulin resistance. Other factors contributing to hyperglycemia during stress include total parenteral nutrition [19; 20], a history of diabetes mellitus, cirrhosis, pancreatitis, administration of certain drugs (for example corticosteroids), hypokalaemia and chromium deficiency [12].

The prevalence of hyperglycemia varies for different groups of critically ill patients, differently defined cut-off points and different diagnostic time points. In a study of children and adolescents attending paediatric emergency care, hyperglycemia occurred in 3.8% of screened patients and was defined as glucose concentration ≥ 8.3mmol/L at admission time [21]. Another retrospective study reported 4.9% prevalence of stress hyperglycemia in paediatric patients by the same definition criteria; however, as the study investigators noted, the prevalence was significantly higher in children affected by febrile seizures (12.9%) or traumatic injuries (11.7%), compared to other diagnoses [22]. Van den Berghe et al. [23] reported that 12% of critically ill adult patients had blood glucose levels exceeding 11.1 mmol/L shortly after surgery. In a study by Latham et al. [24], 21% of nondiabetic cardiothoracic surgery patients had developed postoperative blood glucose levels exceeding 11.1 mmol/L within 48 hours after surgery. The same authors showed that hyperglycemia occurred more often in patients with surgical site infections than in patients without surgical site infections; this observation was made for patients with and patients without a known history of diabetes [24]. Wide variations in hyperglycemia prevalence have been seen in nondiabetic patients after acute myocardial infarction, stress hyperglycemia having been reported in 3% to 71% of patients [25]. In hospitalized, severe sepsis patients without pre-diagnosed diabetes, 17.7% were found to have admission or fasting blood glucose levels exceeding 7 mmol/L [26]. Finally, in a study of trauma ICU[1] patients and different hyperglycemic cut-off points, blood glucose values exceeded 6.1 mmol/L in 93%, 8.3 mmol/L in 60% and 11.1 mmol/L in 17% of the patients, respectively [27].

A meta-analysis of 15 observational studies showed that among critically ill nondiabetic patients with myocardial infarction, those with glucose levels in the range of 6.1 - 8.0 mmol/L had an almost four-fold higher risk of death than patients with lower glucose values [25]. Similarly, acute hyperglycemia following stroke has been found to be associated with a two to threefold increased mortality and significant impairment in functional re-

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[1]Intensive Care Unit

covery [28; 29]. Leonidou et al. [26] reported a mortality rate of 43% in hospitalized hyperglycemic patients with severe sepsis, compared to 16% in normoglycaemic patients with severe sepsis. The relationship between the extent of hyperglycemia and mortality has been shown to be independent of injury characteristics and patient demographics in various groups of intensive care and hospital care patients [27; 30; 31]. Hyperglycaemia in critical illness has also been associated with increased severe infection [32], sepsis and septic shock [10] and multiple-organ failure [33].

In a multi-centre retrospective observational study, Egi et al. [34] demonstrated a significant positive association between reduced patient standard deviation ('variability') of blood glucose and decreased mortality risk for nondiabetic patients with different disease backgrounds. Surprisingly, the authors found that variability of glucose concentration was an independent and stronger predictor of mortality in the ICU than mean glucose concentration [34]. There is no clear understanding of the underlying mechanism to this finding. However, a study of type 2 diabetes patients demonstrated that fluctuations in glucose concentration may trigger adverse biologic events beyond those of chronic sustained hyperglycemia, and specifically and independently trigger oxidative stress [35]. Based on their findings, Egi et al. [34] hypothesized that glucose control should be aimed to reduce *both* absolute mean values and blood glucose variability in order to achieve survival benefits.

1.2   Glycemic control in the ICU

In a landmark randomized controlled trial of 1548 surgical intensive care patients, the outcomes of intensive insulin therapy with a glucose target of 4.4 to 6.1 mmol/L were demonstrated by van den Berghe et al. [23]. The mean morning blood glucose level ($\pm$ standard deviation) was 5.7 mmol/L (± 1.1 mmol/L) in the group receiving intensive insulin treatment, and 8.5 mmol/L (± 1.8 mmol/L) in the conventionally treated control group (controls receiving insulin treatment at blood glucose levels of 12 mmol/L or higher). Intensive insulin therapy reduced the risk of organ failure and ICU mortality by up to 45% [23]. The greatest survival benefits could be seen in patients who stayed five days or longer in the ICU. The in-hospital mortality was reduced by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red-cell transfusions by 50%, and critical-illness polyneuropathy by 44%. Patients in the intensive insulin treatment group were also less likely to require prolonged mechanical ventilation, and they were earlier discharged than controls. Severe hypoglycemia (blood glucose ≤ 2.2 mmol/L) occurred in 5.1% of patients in the intervention group compared to 0.8% in controls.

Some of the results by van den Berghe et al. [23] could be replicated in

clinical trials which used historic patient records as controls. One of the first studies was done by Krinsley [36] with a heterogeneous group of patients from a medical-surgical ICU. Intensive glucose management (the glucose target was < 7.75 mmol/L) reduced overall in-hospital mortality by 29% compared to a group of historic controls. The survival benefit was greatest for neurologic patients and for patients with septic shock, where mortality fell from 21.0% to 8.5% (P=.007), and from 60.4% to 33.3% (P=.02), respectively. Other significant improvements included reductions in the development of new renal insufficiency by 75%, in the number of patients requiring red-cell transfusion by 19%, and in the length of stay in intensive care by 11%. The median (interquartile range) blood glucose level for the historic control group was 7.3 mmol/L $(5.9 - 9.5$ mmol/L$)$. This value decreased to 6.6 mmol/L $(5.5 - 8.2$ mmol/L$)$ for the intervention group. Severe hypoglycemia (blood glucose ≤ 2.2 mmol/L) occurred in 0.34% among intensively treated patients with no significant change compared to controls.

In another single-centre study with historic controls, Chase et al. [37] reported a relative decrease of in-hospital mortality by 35%, from 31.9% to 20.6% (P=.02), for patients who had stayed in intensive care for at least five days. In their general ICU, strict blood glucose control was adopted as a clinical practice change. The frequency of severe hypoglycemia was 0.1% of all measurements with their SPRINT[2] protocol, which was a 50% reduction compared to the historic control group [37].

In contrast to studies with historic controls, randomized controlled studies were unable to replicate the mortality reduction and other results seen by van den Berghe and her team [23]. One well-reputated case is the VISEP study. This study was designed as multi-centre, two-by-two factorial trial, where patients with severe sepsis were assigned to one of two groups receiving intensive insulin therapy or conventional insulin treatment [38]. The trial was stopped early after a massive encounter of severe hypoglycemia (17% vs. 4.1%, P=.01) and an increase of the rate of serious adverse events (10.9% vs. 5.2%, P=.01) in the two intensive insulin groups, while there was no significant difference in the rate of death or the mean score for organ failure.

The results of the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation) trial [39] were even more contrary to the van den Berghe study. The primary outcome variable, 90-day mortality, was actually increased in patients randomly assigned to intensive insulin therapy, as compared with an intermediate target range for blood glucose. These findings, reflecting data collected in a set of more than 6,000 patients, contradicted the external validity of tight glucose control [40].

It has been hypothesized that the survival benefits of intensive insulin

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[2]Specialized Relative Insulin Nutrition Tables

therapy seen in the first van den Berghe study [23] may have been due to protective effects of insulin on the endothelium, mediating prevention of organ failure and death [33; 41]. A subsequent randomized controlled trial by van den Berghe et al. in medical ICU patients found similar organ protective effects; however, morbidity but not mortality was reduced in the intention-to-treat analysis [42]. Moreover, 18.7% of the intensively treated patients experienced at least one episode of severe hypoglycemia.

In a meta-analysis of 26 randomized controlled clinical trials by Griesdale et al., the authors concluded that intensive insulin therapy does not provide significant survival benefits, except in surgical patients [43]. The meta-analysis was based on results from intention-to-treat analyses and revealed a significant heterogeneity with respect to mortality results among the included trials. 16 of the studies used a glycemic target of ≤ 6.1 mmol/L for their intervention groups; 9 trials used a glycemic target of ≤ 8.3 mmol/L. The results did not reveal to which extent glycemic targets had been reached, or whether lack compliance correlated with their mortality findings. Based on a sub-analysis of 14 trials, the authors also found a six-fold higher risk of severe hypoglycaemia (blood glucose ≤ 2.2 mmol/L) among intensively treated patients compared to controls [43]. The correlation between increased risk of hypoglycemia and increased risk of death was however not tested.

Preiser et al. [44] showed in a multi-centre trial with medical and surgical intensive care patients that the occurrence of hypoglycemia induced a two-fold increased risk of death independent of the blood glucose target range. They also found that more severely ill patients were at a higher hypoglycemic risk, thus showing that the risk of hypoglycemia and the risk of death may be linked by severity of illness [44].

Another explanation for a higher mortality risk with severe hypoglycemia could be hypoglycaemia-induced oxidative stress and neuronal cell death during glucose reperfusion [45]. Irrespective of the cause is the minimization of the hypoglycemia risk of the greatest importance. However, current tight glycemic control protocols are primarily based on clinical experience. They require significant costs and efforts for their implementation and maintenance, however, results are highly variable with respect to achievement of targeted blood glucose levels and hypoglycemia [43; 46; 47; 48]. Therefore, they are not optimal for blood glucose control of critical care patients.

The degree of compliance to a protocol influences the outcome of tight glycemic control studies. The association between hyperglycemia and non-adherence to a tight glucose control protocol ($4.4 - 6.1$ mmol/L) was retrospectively investigated in an analysis of 1106 trauma and surgical intensive care patient records [49]. The investigators assessed, whether blood glucose measurements had been on schedule. It was found, that the timing had a significant impact on blood glucose control, and that late measurements were more often associated with severe hyperglycemia (> 8.3 mmol/L) or

hypoglycemia (< 3.3 mmol/L). Other studies found that protocol violations seriously compromise the effectiveness of a tight glycemic control strategy [50], and may even lead to its abandonment [44].

In addition to protocol compliance, the accuracy of blood glucose measurement devices is important for the success of tight glycemic control in intensive care. Arterial blood analysis has a significantly higher agreement with central laboratory measurements than capillary blood analysis [51; 52]. During hypoglycemia, agreement with central laboratory measurements was only 26.3% using capillary blood analysis in an observational study of point-of-care glucose measurement devices, and 55.6% and 64.9% for glucose meter and blood gas/chemistry analysis of arterial blood [51]. Glucose meters tend to overestimate whole blood glucose levels, whereas methods of arterial blood analysis tend to underestimate glucose values [51; 52; 53]. At high risk of hypoglycemia, blood gas/chemistry analysis of arterial blood should therefore be given priority over glucose meters, if laboratory measurements are not feasible.

Carbohydrate-rich nutrition and total parenteral nutrition exacerbate glucose levels [20; 54]. In contrast, low and moderate caloric intakes, preferably via the enteral route, have been associated with significantly lower incidences of hyperglycemia and improved patient outcomes [55; 56; 57]. However, prolonged hypocaloric enteral feeding should be avoided and parenteral nutrition should be added if caloric-protein targets cannot be achieved after several days [58]. Current research favours early initiation of enteral feeding if the gastrointestinal tract is functioning. According to a systematic review, early enteral feeding reduces the risk of hyperglycemia and reduces the need for insulin therapy [59]. Hence, nutrition provides an alternative control measure in addition to insulin.

1.3 Model-based glucose control

Conventional glycemic control methods respond to a measured blood glucose value with the prescription of a predefined insulin dose. Protocol implementations of such methods can be roughly divided into 'sliding scale' or 'dynamic' insulin titration protocols [46]. Sliding scale protocols prescribe standardized bolus sizes or insulin infusion rates for defined blood glucose ranges. Dynamic scale protocols combine a glucose target and for example the last two blood glucose values to determine the insulin infusion rate or bolus size [46]. Variants of these two basic types can be distinguished with regard to their complexity, their consideration of patient characteristics, the targeted blood glucose range, the degree of their automatization, the unambiguousness of their directives, and the allowed time to next measurement.

Model-based methods predict the outcome of a certain intervention, such as of a certain infusion size, and base their recommendation on the predicted

outcome that best matches a predefined target. Predictions are based on a model, which is representative of the glucose-insulin metabolism of the patient. The type of input to a model can vary, however, generally required are measured blood glucose concentrations and data regarding insulin therapy. Typically will the input of new data trigger the reassessment of one or more patient parameters, which are thereafter used by the model in the simulation of the outcomes of possible interventions.

Model-based methods are often implemented as computer programs, although adaptations to paper protocols have been successfully tried, such as with the SPRINT protocol [37]. Computer implementations of model-based control algorithms can graphically display the history or the future trend of a patient's clinical treatment, they may come with alarm functions, they may be capable of being integrated in electronic patient journals, or they can be designed to communicate with clinical information systems, for example in order to retrieve blood glucose values from electronic databases.

Models of glucose metabolism and insulin effect can be traced as far back as to the early 1970s [60; 61]. Computerized model-based control systems were introduced for educational purposes and for the improvement of insulin therapy in diabetes [62; 63; 64]. However, diabetes care models have been subsequently modified and tested in a critical care environment, since it can be argued, that the principles of pharmacokinetics and -dynamics work not differently in diabetes and in stress hyperglycemia [65; 66].

Of the clinically tested, computerized decision-support systems [67], only very few are model-based, while the majority are electronic versions of a dynamic or a sliding scale protocol. These are mostly 'carbohydrate-blind', i.e. they do not account for the carbohydrate intakes of patients. Nutritional advice is also not generally given, and is limited to include measures for counteracting hypoglycemia, for example by a glucose bolus [67]. In contrast, the model-based SPRINT protocol [37] makes use of a paper wheel to decide on insulin bolus sizes and nutrition intake. SPRINT was successfully implemented as a clinical practice change in a general medical ICU; however, a strict scheduling of blood glucose measurements (every 1-2 hours) is required, and none of the advantages of a computerized solution are offered.

1.4 Hypothesis

It is hypothesized, that model-based computer decision support can improve the blood glucose control of critically ill patients without increasing the risk of hypoglycemia.

1.5 Research Objectives

- Define the structure of a model that captures the relevant physiological processes involved, that can be identified from routine clinical data

- Find an appropriate method for making clinically relevant recommendations of insulin dosing and nutrition for treating hyper- or hypoglycemia

- Develop and test a computer decision support system based on the model and recommendation method in a clinical trial

- Find the means that enable this system to be incorporated into the routine management of ICU patients

Chapter 2

Model Structure

In this chapter the structure of the model will be described. The content is based on publications I and II.

The proposed model for the glycemic control system 'Glucosafe' is shown in Figure 2.1. It is a physiological compartment model of insulin kinetics and glucose metabolism [1].
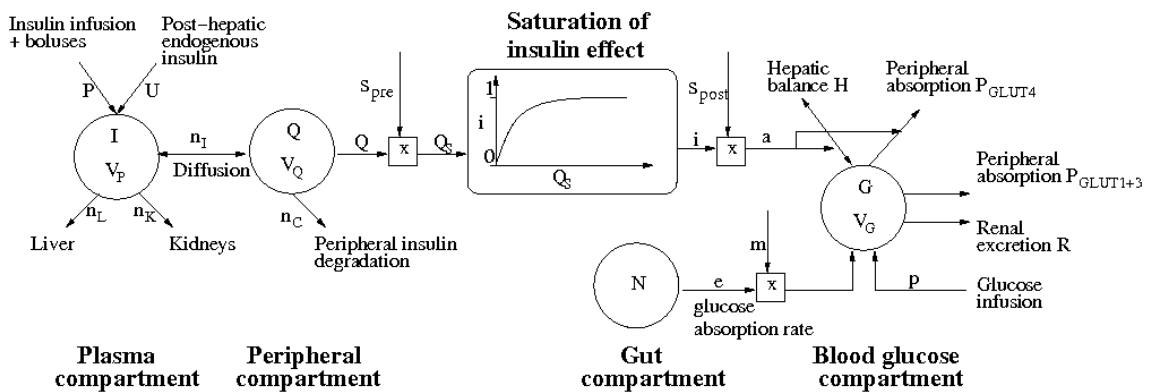
Figure 2.1: Glucosafe's compartment model structure (modified from [1])

The two compartments on the left of Figure 2.1 describe the insulin pharmacokinetics. The 'plasma' compartment I comprises plasma and hepatic space and the 'peripheral' compartment Q represents the distribution space of insulin in the extracellular interstitial fluid. Intravenous infusions and bolus injections are the exogenous input P, and pancreatic insulin appears (after first passing through the liver) as continuous input U in the plasma compartment. Insulin removal is modelled as the sum of hepatic and renal insulin clearance, n_L and n_K, and the net transport rate n_I from plasma to the peripheral compartment. In the peripheral compartment,

insulin molecules bind to receptors at the cell surfaces. The bound-insulin-receptor complex is endocytised and subsequently degraded within the cell. n_C denotes the intracellular degradation rate.

Volumes V_P and V_Q and fractional turnover rates of the compartments are calculated from demographic data (sex, age, height, weight, diabetic state) using standard equations for clearance of C-Peptide [68]. From the volumes and fractional turnover rates the net transport rate n_I is calculated and subsequently adjusted for the molecular mass difference between C-Peptide and insulin molecules. The insulin clearance rates, n_L and n_K, are calculated from steady-state assumptions in the model equations and experimental data from type 1 diabetic patients [1]. The endogenously produced insulin U is assumed to be a constant rate at a value of 42 mU/min for patients without type 1 diabetes. This value has been found to give optimal simulation results in a retrospective trial of 10 critical care patients [1]. Since this value is higher than reported ranges in healthy normal and obese subjects [69], in this model it is interpreted as a marker for an increased production of endogenous insulin in response to stress-induced hyperglycemia.
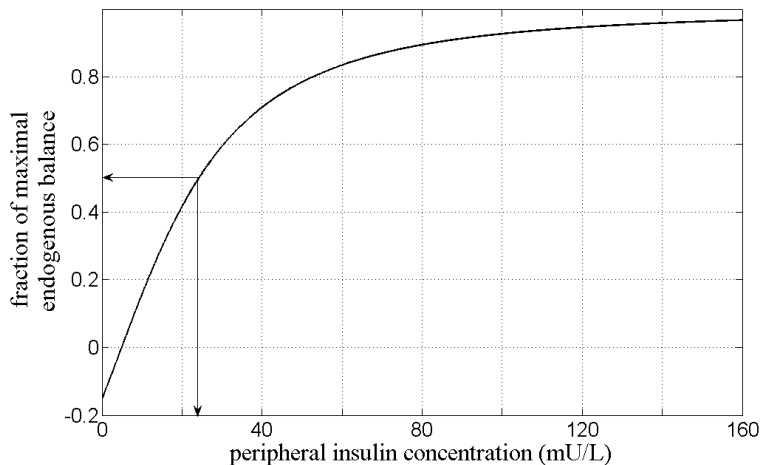
Figure 2.2: Endogenous glucose balance as function of peripheral insulin (modified from [2])

The box in the middle of Figure 2.1 is a description of the pharmaco-dynamic effect of insulin, i.e. the concentration-dependent effect on insulin-mediated glucose uptake. This effect is described as a non-linear transformation in Figure 2.2, where the maximal endogenous glucose turnover ('endogenous balance') is a function of the peripheral insulin concentration. The function values are normalized; a value of 1 thus represents the maximum insulin effect that is achievable on the endogenous balance. Saturation effects on glucose turnover at high insulin concentrations in the interstitium

have been shown in a number of studies [70; 71; 72; 73; 74].

Figure 2.2 marks the half-effect concentration, which is a concentration of about 24 mU/L in the interstitium, corresponding to about 40 mU/L in plasma, if it is assumed that the extracellular insulin concentration seen by the tissues is about 60% of the plasma concentrations in steady state [75]. From experiments performed by different groups in type 1 diabetes patients (see [74] for references) it was found that the average plasma insulin concentration $\bar{I}$ in response to the insulin infusion rate $INFR$ could be calculated as:

$$\bar{I} = INFR * C \tag{2.1}$$

where $C = 98.1$ (kg·min)/L. Thus, an infusion rate of 0.4 mU/(kg·min), i.e. a rate of 1.7 U/h in a 70 kg subject, is sufficient to reach half effect on insulin-mediated glucose turnover. From Figure 2.2 it can be seen that for a peripheral insulin concentration of 80 mU/L, the endogenous balance is about 90% and only marginal increases are achievable for higher concentrations. In a 70 kg subject, 90% endogenous balance is reached by continuously infusing 5.7 U/h, or 7.3 U/h in a 90 kg subject. This means that in protocols which permit much higher infusion rates, insulin therapy as the only measure to control blood glucose ceases to be an effective tool [2]. Quite the contrary, hypoglycemia can be aggravated by the relatively slow diffusion of insulin across the vascular bed, from the interstitial fluid into plasma. Modelling the saturation of insulin effects on endogenous balance is thus a very important feature of the model.
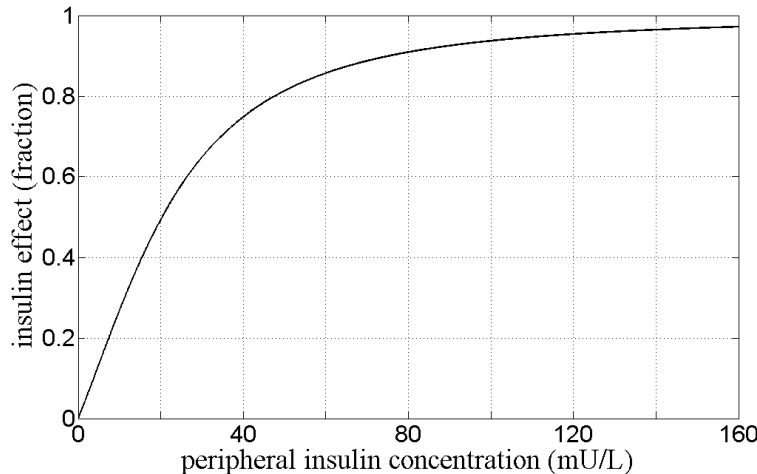

Figure 2.3: Maximal insulin effect as function of peripheral insulin concentration (modified from [1])

Values in Figure 2.2 lie in the range (-0.154; 1). For the parameter estimation it is more convenient to have a variable in the range (0; 1);

thus, the fraction of maximal endogenous balance is subjected to a linear transformation into that range and interpreted as fraction of maximal insulin effect, yielding the function shown in Figure 2.3.

Insulin resistance, or reduced insulin sensitivity is frequent in critical illness [12], meaning that the ability for insulin-mediated glucose uptake is constrained. The underlying mechanism is not entirely clarified, and the relationship to clinical outcomes remains to be explained [76]. In the Glucosafe model, insulin sensitivity is expressed as patient-specific parameter s. Values for s are estimated from simulations of the model with the clinical data of a patient, i.e. measured blood glucose concentrations, insulin therapy and nutrition. s is reassessed when new data becomes available. Thus, changes in values of s may reflect actual changes of a patient's insulin resistance state. s is approximately 1 for not insulin resistant subjects.
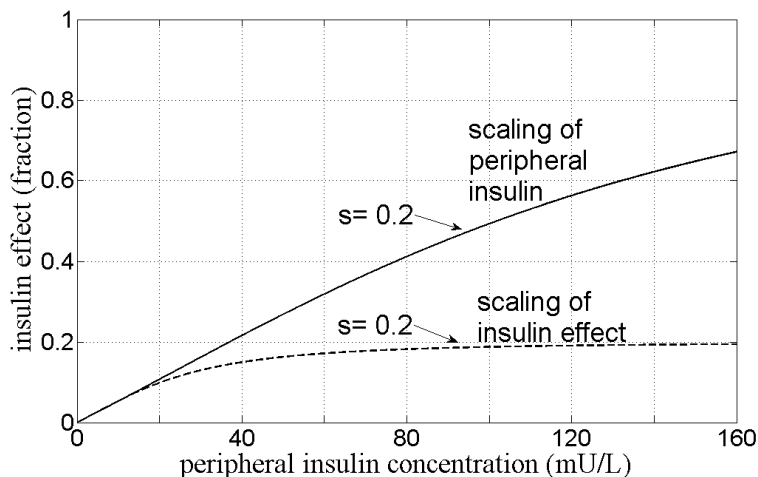
Figure 2.4: Effect of modelling insulin sensitivity s as scaling factor to either peripheral insulin or to insulin effect (modified from [1])

Two different assumptions concerning the site of reduced insulin sensitivity in the model were analysed [1]. One option is to model insulin sensitivity as a factor that scales the peripheral insulin concentration. This is schematically shown as arrow labelled s_{pre} in Figure 2.1, before the non-linearity. A physiological interpretation for this option could be the impairment of insulin delivery to skeletal muscle interstitium [77; 78], or a modification in the dynamics of the binding and unbinding of insulin to its receptor. Figure 2.4 shows that scaling of the peripheral insulin concentration shifts the concentration at which half insulin effect is reached to the right. Alternatively, the insulin sensitivity can be modelled as a scaling factor of fractional insulin effect, after the non-linearity. This option is schematically shown as arrow labelled s_{post} in Figure 2.1. A physiological interpretation of this op-

tion could be the down-regulation of the number of insulin receptors or a modification in the intracellular insulin signalling pathway [79; 80]. Figure 2.4 shows that modelling this option preserves the shape of the non-linearity function. A comparison of the two alternative approaches using retrospective data from 10 critically ill patients [1] favoured the second option. Thus, the insulin sensitivity parameter is used as a scaling factor to the fraction of maximum insulin effect i, yielding the (reduced) fractional insulin effect a, as schematically shown in Figure 2.1.

The right part of Figure 2.1 shows the total glucose balance, which is the sum of the endogenous glucose balance and the glucose appearance from enteral and parenteral nutrition. The rate of parenteral glucose uptake p is calculated directly from the infusion rate and glucose concentration of intravenous nutrition. The calculation of the rate of intestinal glucose absorption involves two steps. In the first step, the absorption rate e is calculated from the amount of carbohydrates N in the combined stomach and intestinal reservoirs [74]. The second step involves the modelling of a slower gastric emptying rate, like it is often found in enterally fed, critically ill patients [81]. Impaired gastric emptying has been associated with a slower absorption of nutrients [82]. Thus, the absorption rate e is scaled to a reduced value, as illustrated in Figure 2.5, with a scaling factor m that has been estimated for a mixed critical care population [1] .
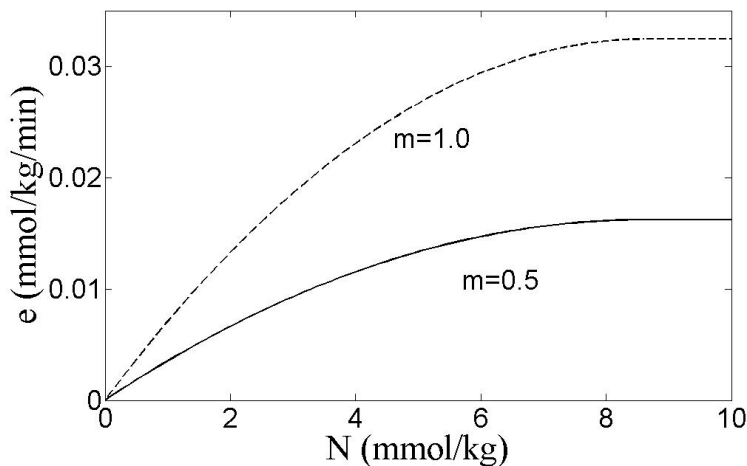
Figure 2.5: Intestinal glucose absorption rate e as function of the carbohydrate amount N. To model a slowed glucose absorption rate, e is scaled by m (from [1])

Finally, the endogenous glucose balance is calculated using the transporter model by Arleth et al. [74]. The endogenous glucose balance is described by four compartments, two representing the insulin-independent

glucose uptake and two representing the insulin-dependent glucose uptake. The hepatic balance H and the GLUT4-mediated peripheral glucose uptake P_{GLUT4} are functions of the blood glucose concentration G and of the fractional insulin effect a. The insulin-independent peripheral glucose uptake $P_{GLUT1+3}$ represents the transport mediated by GLUT1 and GLUT3 transporters and is non-linearly dependent on the blood glucose. The renal clearance R depends on the blood glucose and the glomerular filtration rate. Figure 2.6 shows the resulting endogenous glucose balance E as a function of blood glucose concentration and fractional insulin effect.

Figure 2.6: Endogenous glucose balance E as function of blood glucose G and insulin effect a (from [1])

Chapter 3

Parameter Identification Method

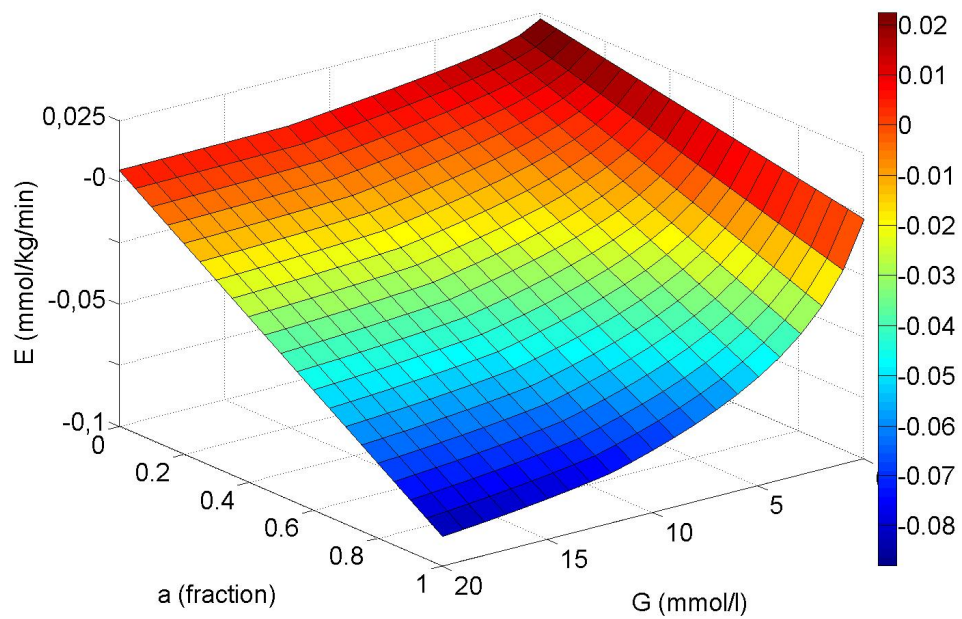*This chapter shortly presents different parameter identification methods of insulin sensitivity, and the results that were obtained from a comparison of the methods. The content is based on publication III.*

As shown in Chapter 2, the Glucosafe model has the patient-specific parameter s, whose value is estimated based on treatment data and blood glucose measurements. Thus, the estimated value of s varies over time and may reflect changing insulin resistance states of a patient. Values for s that are approximately 1 indicate a normal insulin response, whereas values that are lower than 1 indicate insulin resistance.

The course of the 'future' blood glucose is predicted based on the 'current' insulin sensitivity, assuming that deviations of insulin sensitivity from its current value will be small over the near future. Naturally, as the prediction time horizon increases, it becomes more likely that the future insulin sensitivity differs from its assumed 'current' value. From this, two conclusions can be drawn. First, predictions of blood glucose in the nearer future are more often more accurate than predictions with longer time horizon. This relationship can be described as function of mean prediction error over prediction time. Second, identification methods whose estimates of 'current' insulin sensitivity are on average more accurate than the estimates of other methods, should lead to a reduction of mean prediction error. Thus, a method comparison can be based on comparing mean prediction errors over prediction time, assuming that the method with smallest mean prediction error is the one whose estimates of insulin sensitivity are closest to the insulin resistance state of a patient.

Based on these assumptions, blood glucose predictions by the Glucosafe model were studied using retrospective clinical data from ten hyperglycemic critically ill trauma and neurosurgical patients with five different identifica-

tion methods of insulin sensitivity [3]. Compared were three least squares approaches, an integral based method [83] and a Bayesian-least squares approach. The evaluation was based on a comparison of root mean square of logarithmic prediction error for predictions with different time length, from short (1–2 hours) to longer (9–10 hours) time horizons.
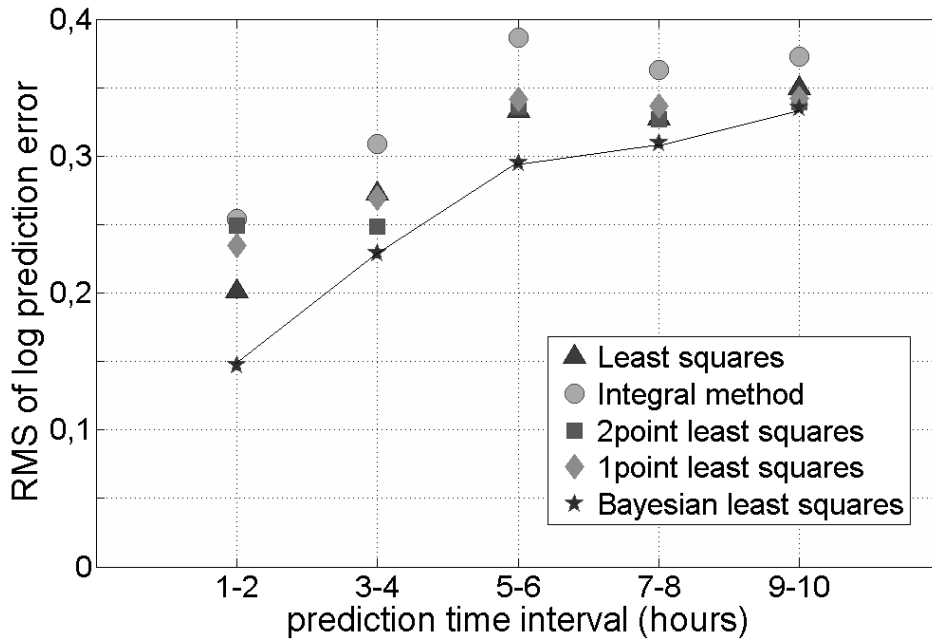

Figure 3.1: Root mean square (RMS) of log prediction error for five identification methods and varying prediction time lengths (modified from [3])

Figure 3.1 shows that the Bayesian least squares approach resulted in the smallest root mean square of logarithmic prediction error over all time intervals. This method also gave fewer and smaller outlying errors than the other methods [3]. A patient case is shown in Figure 3.2 as a representative example of the method comparison, that highlights the differences between these methods. Each panel of Figure 3.2 represents one method. The methods differed with respect to the criteria by which measurements in the past (up to 12 hours back) were included in the fit of the model-simulated blood glucose, and thus, in the estimation of s. Green dots in the panels represent measurements included for fitting, grey dots are excluded measurements. Red dots are measurements that lie in the predicted future of the patient.

On average, the Bayesian-least squares approach yielded smaller prediction errors than the other four methods. The Bayesian method is thus an effective identification method for the parameter s with this model. This result is preliminary; more patient cases will be necessary to verify this result.
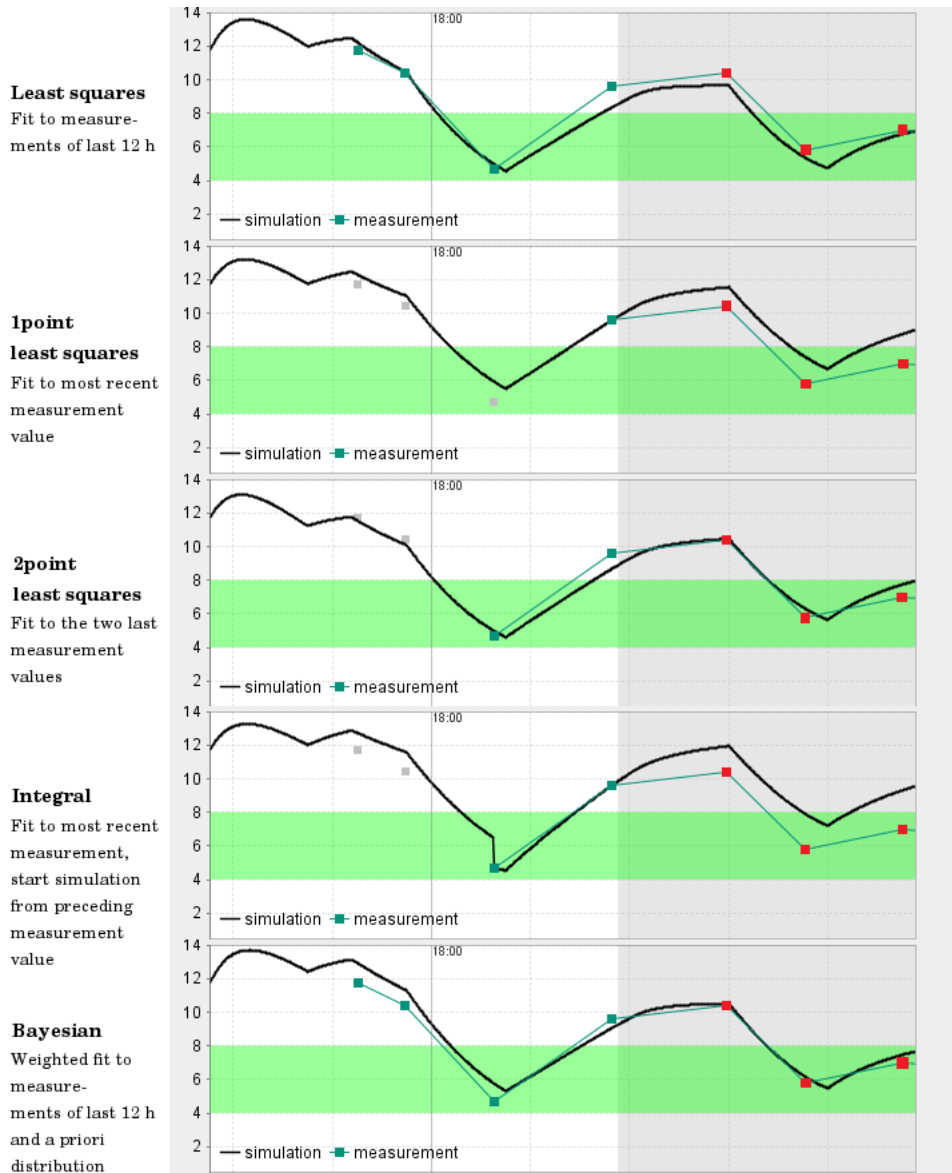
Figure 3.2: Case comparison of five parameter identification methods.

Chapter 4

Model Comparison

This chapter summarizes retrospective studies of the model, including a comparison to other relevant models of glucose metabolism. The content is based on publications IV and V.

Three-dimensional surfaces of plasma insulin, plasma glucose and resulting rate of change in endogenous glucose balance were developed for a quantitative comparison of four metabolic models [4]. The four models were the Glucosafe model (named 'Receptor model' or 'RM' in this publication), the minimal model ('MM') [61] and two variants of a non-linear glycaemic control model ('ND1' and 'ND2') [84], which has been studied retrospectively and in in the evaluation of the SPRINT protocol [37].

Each surface was the result of a model fit to a set of 77 glycemic clamp data points from hyperglycemic and normoglycaemic individuals with normal insulin sensitivity [74]. A grid search was used over physiological ranges of important model variables to fit the data to minimum error metrics, looking for a best error fit. The root mean square error and the frequency of error near zero were the error metrics used and the minimum error set of model variables was the same over both error metrics in each case. Note, that no fitting of model variables was needed in this study for the Glucosafe model whose endogenous glucose balance was already identified for the same 77 clamp data points [74]. Differences due to different saturation dynamics along the glucose and insulin axes can be clearly distinguished from the surface plots in Figure 4.1. The plots show that the Glucosafe model and the ND2 model very similarly account for saturation effects on glucose balance for high insulin and blood glucose concentrations, whereas both the minimal model and the ND1 model surface plots show steady increases of endogenous glucose balance.

In a second step, the model variables were left constant at the values identified with the first data set, and only insulin sensitivity was allowed to vary as a single parameter. In this setting it was assessed how well each
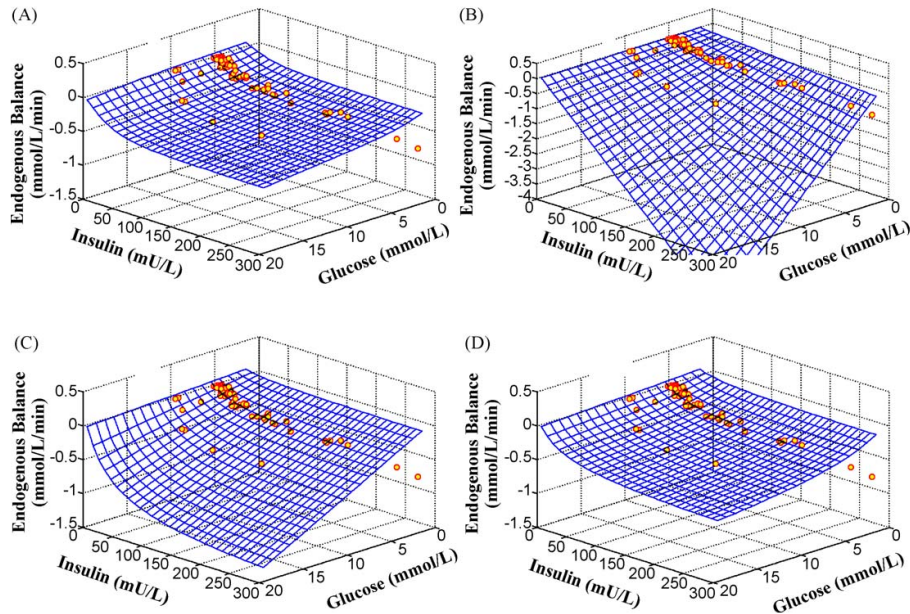
Figure 4.1: Glucose-insulin pharmaco-dynamic surfaces of four metabolic models, fitted to glycemic clamp data. A: Glucosafe model; B: Minimal Model; C: ND1 (non-linear glycemic control model variant 1); D: ND2 (non-linear glycemic control model variant 2) (from [4])

surface could fit another set of data. This second data set consisted of 146 glycemic clamps from a before-after intervention study of 73 normoglycemic individuals with relatively lower insulin sensitivity [85]. Assuming that the first and the second data were mainly set apart by a general reduction in insulin sensitivity in the second data set, it was hypothesized that the second set of data should be reasonably, although not optimally, fitted by reducing insulin sensitivity alone.

Results for both data sets and different error metrics showed similar results for the Glucosafe model, ND1 and ND2, though a trend could be seen for the Glucosafe model towards smaller error outliers compared to ND1 and ND2. All three models showed the expected reduction in insulin sensitivity with the fitting of the second data set. In contrast, the minimal model did not accurately predict the change in cohort insulin sensitivity. Particularly it was shown that the minimal model could fit only euglycemic regimens tolerably well, while the same constants did not capture data from the hyperglycemic regime. This finding emphasizes the importance of modelling insulin saturation dynamics as much as it highlights the minimal model's underperformance in states of hyperglycemic, insulin-resistant patients.

The prediction accuracy of the Glucosafe model and the ND1 model [84] was also compared in a retrospective study of 11 hyperglycemic patients from two ICUs [5]. The two cohorts were made up by six patients from a data pool of cross-sectional patients ('NZ' group) and by five patients from a neuro- and trauma ICU ('DK' group). The groups differed in admission diagnoses and in glycemic control methods. In the DK group, blood gas analyzers were used for arterial blood analysis, and hyperglycemic patients received continuous insulin infusions. In the NZ group, arterial blood was sampled using bedside point-of-care glucose meters, and insulin was given in the form of intravenous bolus injections. Due to those differences, the glycemic prediction accuracy was compared for each cohort separately.
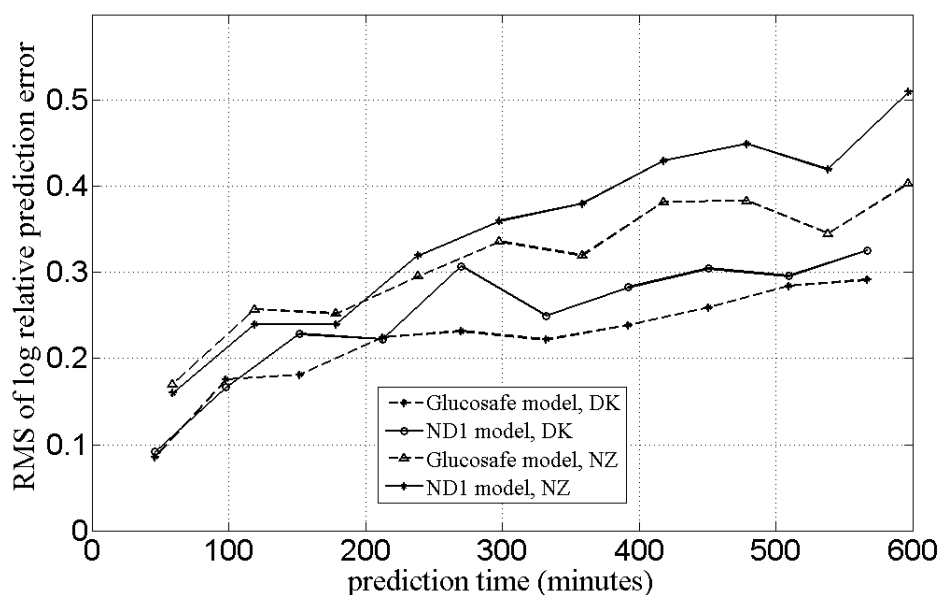
Figure 4.2: Root mean square (RMS) of log prediction error comparison of two cohorts and different prediction time lengths (modified from [5])

Prediction errors were similar for the two models, as seen in Figure 4.2. Both models predicted more accurately the blood glucose of patients from the DK group. Measures of median and interquartile ranges of blood glucose in these patients indicated better glycemic control and less fluctuation in that particular patient group which may explain this outcome. The maximum difference in root mean square of prediction error did not exceed $4-5\%$ in both cohorts. Outlying prediction errors were dominated by type 1 diabetic patients. Both models had a tendency to underestimate large glycemic changes.

Chapter 5

Pilot Evaluation of Glucosafe

This chapter explains the design of the decision support system and summarizes the results obtained from using the system in a clinical pilot trial. The content is based on publications VI.

The Glucosafe model was implemented in a new decision support system and tested in a prospective clinical trial [6]. Primary purpose of the study was to demonstrate the system's initial safety for tight glycemic control, particularly with regard to the prevention of an increase of hypoglycemic episodes that has been reported with other tight glycemic control studies [43]. The system was primarily used by the nurses of the ICU. The main system components were the model, an advice generator, an interactive graphical user interface and a database. Figure 5.1 schematically shows the main components and the main sequence of communication flows during operation of the system.
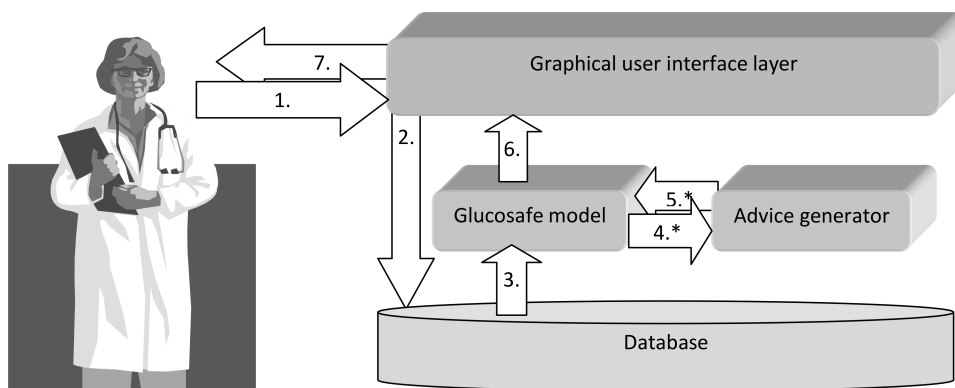

Figure 5.1: Main components and communication flows of the decision support system. Flows are represented as arrows. Communication loops during advice generation (marked by $*$)

1. The user enters a request over the graphical user interface. Possible requests include:

   (a) **Enter clinical data for getting therapeutic advice.** Clinical data comprise the time and rate of enterally/parenterally administered nutrition, time and rate of propofol and insulin infusions, time and amount of insulin boluses and time and values of blood glucose concentrations. This function is invoked when new data is available and triggers the generation of a new advice.

   (b) **Enter historic treatment or update the patient file.** This function is invoked to record the historic blood glucose measurements and course of treatment for the patient (without triggering advice generation). It is also invoked when a patient becomes newly registered with the system, or when the patient journal is updated (health evaluation scores, temperature, acquired infections, etc.).

   (c) **Accept/Reject/Modify advice.** This function may be invoked after advice generation to accept, reject or modify the therapeutic advice of the system.

2. Data and user request are stored in the database.

3. Data relevant to the user request are retrieved from the database. The patient's insulin sensitivity is identified using the Bayesian-least squares fitting method [3]. The 3-hour blood glucose outcome of the current treatment is predicted.

4. Suggest an intervention for parenteral and enteral nutrition, and insulin infusion and/or bolus.

5. Predict the 3-hour blood glucose outcome of the suggested intervention, compare to previously saved outcome and save the alternative with the better outcome. Loop back to step 4, until the global optimum has been found.

6. Communicate results of step 3 or final results of step 5 to the graphical user interface. Calculate the infusion pump rates of parenteral/enteral nutrition.

7. Display simulated and predicted blood glucose outcome to user. Show updated insulin sensitivity index. List current and historic insulin therapy and nutrition. Display advice (if applicable). Show schedule for next blood glucose measurement. Prepare for new user request.

The system was installed as a stand-alone application on a portable tablet PC with touch-sensitive screen. The interactive graphical user interface used during the pilot study is shown in Figure 5.2. The nurses were

instructed how to use the system in advance of the pilot study. During pilot testing, the nurses were encouraged to operate the system under supervision of one of the study investigators.
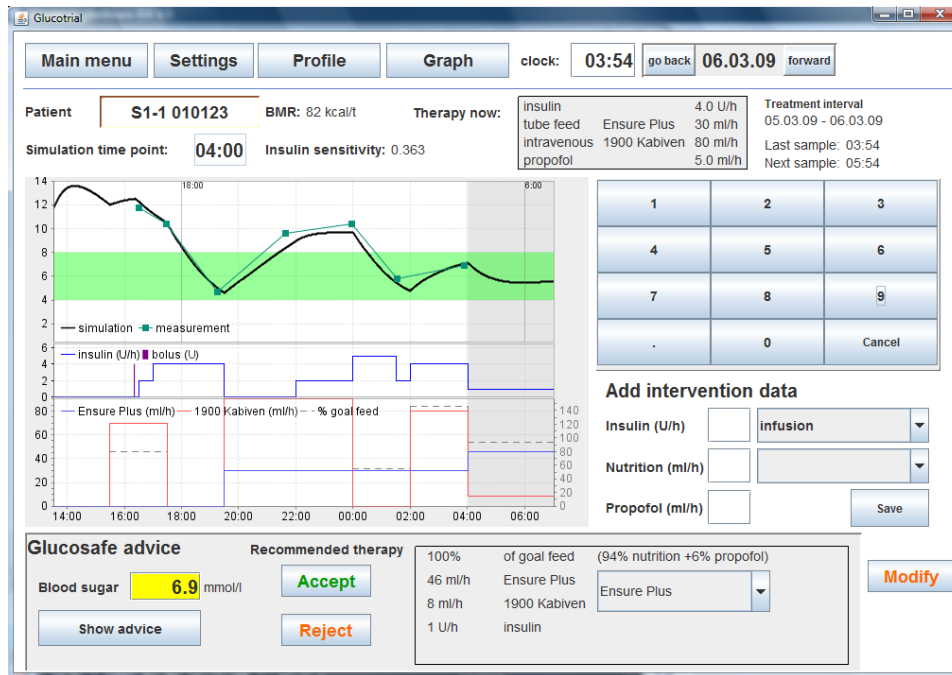

Figure 5.2: Graphical user interface of Glucosafe during the pilot trial of the system. Labels are translated to English (from [6])

Four penalty scoring functions were developed and used for generating the model-based advice. These functions assigned a penalty score to each possible therapeutic regimen and its predicted blood glucose outcome. A penalty score thus rated the undesirability of a particular choice or outcome relative to the 'most desirable' choice or outcome. Penalty scores rated (1) the predicted 3-hour blood glucose concentration, compared to the target range of $4.4 - 7.75$ mmol/L, (2) use of insulin, compared to no insulin therapy (and thus no hypoglycemic risk), (3) total caloric intake, as compared to a feeding rate corresponding to the patient's energy needs, and (4) use of parenteral nutrition, compared to using the enteral feeding route. The system advice resulted from the minimization of the sum of the penalty scores, over the total search space of regimens and predicted blood glucose outcomes.

10 hyperglycemic patients (median APACHE II: 12.5; interquartile range 7.5-16.3) from a neuro- and trauma intensive care unit at Aalborg hospital were included for pilot testing of the system. Each patient was treated according to Glucosafe advice for 12-14 hours. Outcomes and interven-

tion during Glucosafe control were compared to the 24-hour intervals before and after using Glucosafe ('off-on-off' study design). It was hypothesized that glycemic control would improve during Glucosafe usage compared to pre-intervention, and that glycemic control would worsen during post-intervention.

No mild (< 3.5 mmol/L) or severe (< 2.2 mmol/L) hypoglycemia was observed during the trial. The mean log-normal blood glucose during Glucosafe intervention (7.0 ± 1.1 mmol/L) was significantly lower compared to pre-intervention levels (8.6 ± 2.4 mmol/L; $P < 0.01$) and post-intervention levels (7.4 ± 1.5 mmol/L; P=0.03). Measurements of all three intervals are shown in the histogram in Figure 5.3. The lowest blood glucose measured during the intervention was 4.8 mmol/L. The mean time to reach target blood glucose range (4.4-6.1 mmol/L) was 5h. After exclusion of the initial 5h, mean log-normal blood glucose was 6.7 ± 1.2 mmol/L, and 40% of the measurements were in the 4.4-6.1 mmol/L range and 84% of the measurements were in the 4.4-7.75 mmol/L range. These results showed that Glucosafe improved the glycemic control in this patient cohort, and the system's initial safety from hypoglycemia was demonstrated.
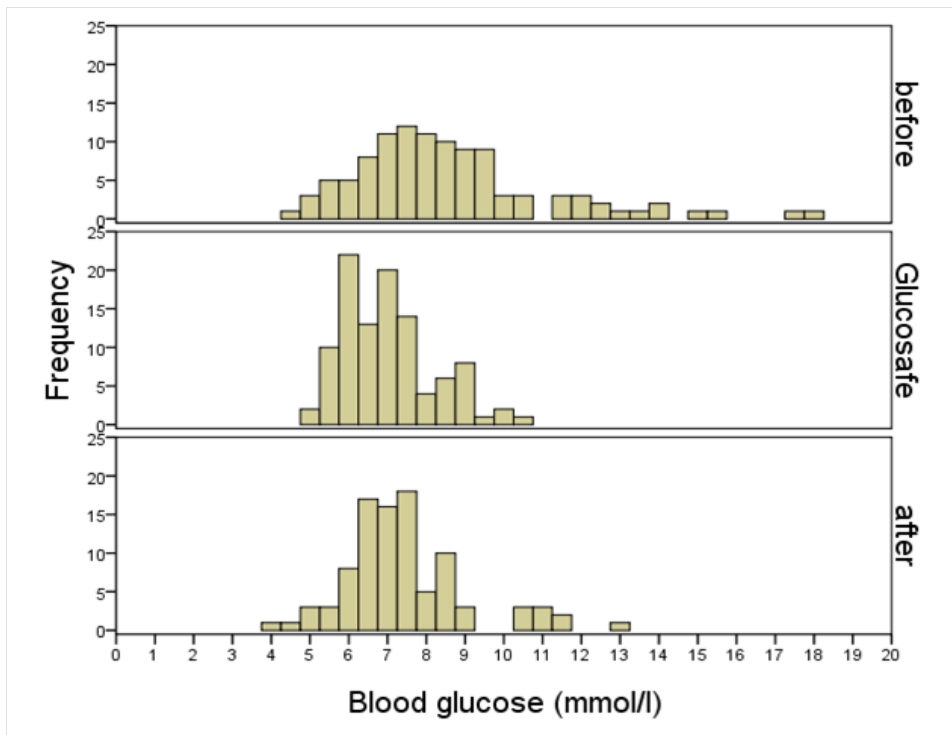

Figure 5.3: Blood glucose distributions during the Glucosafe study.

Chapter 6

Integration of Glucosafe

This chapter outlines how Glucosafe can be incorporated into the routine glycemic management of ICU patients. Part of the content is based on publication VII.

Integration of a new system into an established working routine raises questions of compatibility and user-acceptability by its intended users. The Glucosafe system has been designed to be used for glycemic control in intensive care units, and its intended users are primarily nurses. The system was implemented as stand-alone application for pilot testing. Installed on a single portable unit, the program needed to be carried from bedside to bedside. Data had to be entered manually and were saved on the local harddisk, with no means provided for data recovery, or data transmission to another unit or database. The scheduling of blood glucose measurements was unflexible. Outside the setting of a clinical trial, this system would be doomed to failure.

The installation of the Glucosafe program at the site of a centrally placed blood gas analyzer would be a first simple apprach towards integration of the system into clinical routine. Ideally, a new blood gas analysis would trigger an automatic advice by Glucosafe. A printout of the advice can be taken back by the nurse to the patient bedside to adjust the infusion pumps, and the printout can be saved to the patient journal.

Figure 6.1 shows a similar, although more advanced setup. Blood gas analysis triggers an advice by the system, which is subsequently sent to the hospital information system. From here the advice is accessible by users anywhere in the hospital, such as by a nurse viewing a terminal computer at the patient bedside. However, the system still needs to be updated manually with infusion pump settings and type of nutrition. These are additional work steps for the nurse and a potential source of error.

Alternatively, Glucosafe could be installed as a patient bedside monitoring system that receives the necessary information from the infusion pumps
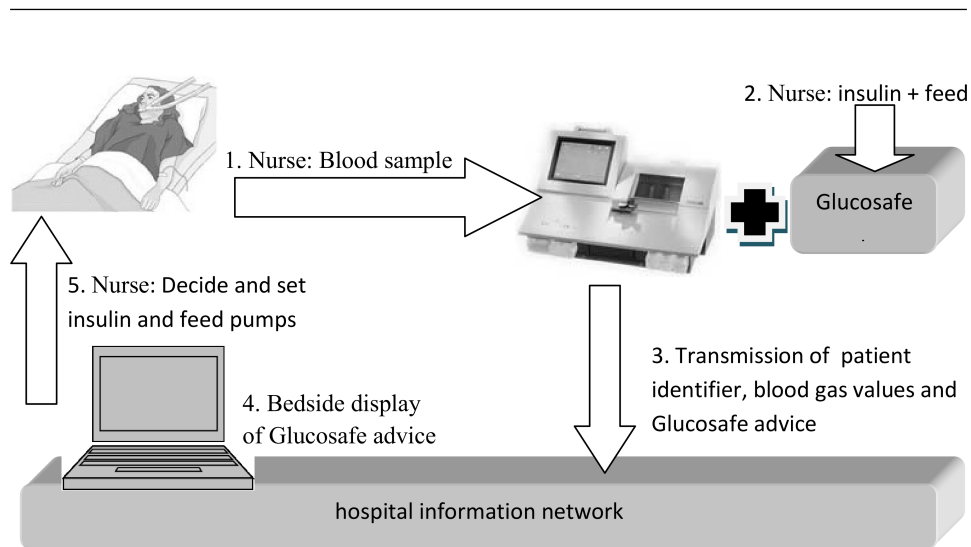
Figure 6.1: Central installation of Glucosafe with blood gas analyzer

over a cable network. This setup is schematically shown in Figure 6.2. Continuous polling of the settings of the infusion pumps eliminates the manual entering of timepoints and infusion rate changes. Only blood glucose measurements would have to be entered manually. However, in the case that these values are centrally stored and can be electronically accessed, a full automatization of glycemic control with the Glucosafe system can be realized, as shown in Figure 6.2.
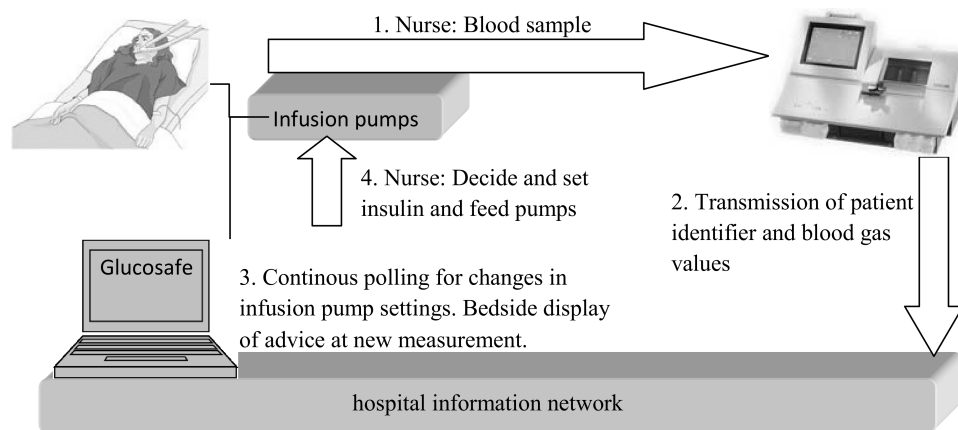
Figure 6.2: Fully automatized glycemic control process with Glucosafe

The user-acceptability of the system can be improved through added value by the system. Examples are monitoring functions, alarm functions, or automatic calculations. In the setup of Figure 6.2, an integrated Glucosafe

system may monitor the feeding rates and display updated information of accumulated caloric intake to the nurse. Another important safety issue can be solved by monitoring the insulin infusion pump. A feature can be built into Glucosafe that raises an alarm, if the pump continues to run at a rate for which Glucosafe predicts hypoglycemia. A continuously updated graph over changes of patient insulin sensitivity can assist in the health diagnosis of a patient.

Added value can also be provided by enabling the system to work with a flexible schedule of blood glucose measurements [7]. The accuracy of predictions is model-specific [7]. Based on the estimated model-prediction error, a graph of the expected error range for blood glucose predictions can be displayed along a time axis, as schematically shown in Figure 6.3. This range of error will have the shape of a funnel that widens with prediction time length [7]. Intersections of the upper and lower funnel edges with the target range define the next time point for measuring blood glucose. An alarm function can alert the user, if the calculated time point passed without action.
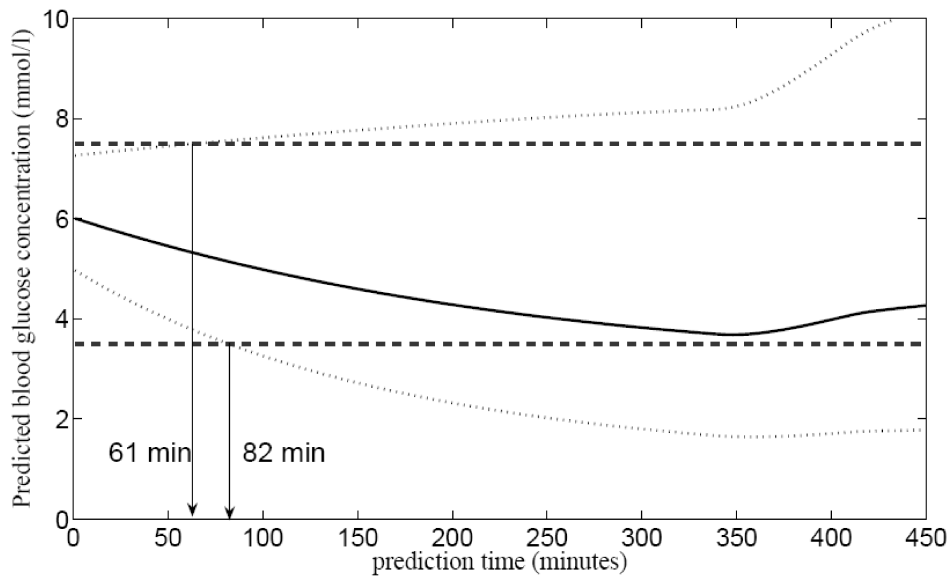

Figure 6.3: Flexible scheduling of measurements based on model prediction error. Solid line: predicted blood glucose course. Dotted line: 95% model prediction error range. Dashed lines: target range. In order to prevent hyperglycemia and hypoglycemia, the next measurement must be scheduled in 1-1.5 hours (modified from [7]).

Chapter 7

Discussion

This thesis summarizes the design, implementation and clinical pilot study of a multi-compartment model of insulin-glucose metabolism to be used for glucose control in critically ill patients. Based on this model, the computerized decision support system 'Glucosafe' significantly improved the glucose concentrations in ten hyperglycemic patients of a neuro- and trauma intensive care unit. In particular, hypoglycemia was not observed during control with Glucosafe. The hypothesis could therefore be proven. However, these results are preliminary in the sense that they were achieved in this subset of relatively homogeneous patients, and that the control time of each patient did not extend 14 hours. The clinical relevance and usefulness of the model in a highly heterogeneous population of 'critically ill' patients thus needs careful evaluation.

The Glucosafe model presented in this thesis is a physiologically based pharmacokinetic multi-compartment model for predicting the absorption, distribution and metabolism of insulin and glucose in humans. The Glucosafe compartments represent organs and tissue spaces and are parametrized with volumes, transport rates and diffusion rates. This modelling method has several strengths: (1) Parameter values can be estimated based on *a priori* available information from various sources (from in vitro or in vivo experiments, etc.). (2) The model gives also access to internal body concentrations of chemicals or their metabolites, and in particular at the site of their effects. (3) Finally, the physiologically based modelling approach leaves room for extrapolations. An example of a parametric extrapolation from healthy subjects to critically ill subjects in the Glucosafe model is the scaling of the rate of intestinal glucose absorption to simulate an impairment of gastric absorption function. A number of parametric extrapolation functions have been built into the computerized Glucosafe system. They allow adjustments of the model to treat subjects of different gender, age, height, weight, diabetic state, or gastric impairment. Glucosafe's decision support is also parametrized; the advice module takes an estimate of the

patient's required energy as input to generate a patient-specific recommendation. 'Nonparametric' extrapolations (requiring a change in the model structure) have the potential to make the model usable for a broader range of patients. For example, extending the model with an additional 'stomach' compartment could be a necessary element for the use of the system in patients who eat meals. However, extensions to the model increase its complexity, and the net benefit of adding structural information to the model should therefore be carefully quantified.

In critical illness, glycogenolysis and hepatic EGP[1] vary over time: the stores of glycogen are rapidly exhausted after injury, while EGP is mainly dependent on the amount of neoglucogenic substrates provided, and of the the hepatic function. A physiological adaptation of the model, using time from injury as a variable, should be analyzed. The data material from the pilot study is not suitable for such an analysis, as the data only capture the first days of patients in intensive care. Other events, such as febrile days or the administration of exogenous catecholamines and steroids, are associated with decreased insulin sensitivity. The capability of the model to capture these kinds of events by reduced estimates of insulin sensitivity should also be studied specifically.

Glucosafe's predictive accuracy has been retrospectively evaluated using data from observational studies. Parts of the data material have also been used for training the model. Since the predictive performance was maximized on the training data set, the model may have been overfit. A model which has been overfit will generally have poor predictive performance, as it can exaggerate minor fluctuations in the data. This possibility must be ruled out, by statistic tests (Chi-Square) and by testing predictive performance on unseen data. If overfitting has occurred, the training data set must be enlarged and supplemented with heterogeneous patient data, and the maximization of predictive performance must be repeated.

The pilot testing of the system included 10 hyperglycemic patients from a single-centre neuro- and trauma intensive care unit. Blood glucose levels were significantly reduced; after a mean of 5 h to reach the target range (4.4-6.1 mmol/l), the mean log-normal blood glucose concentration had been reduced to 6.7 ± 1.2 mmol/l and 40% of the measurements were in the 4.4-6.1 mmol/l range and 84% were in the 4.4-7.75 mmol/l range. These are initial results that compare well to results achieved by other computerized decision support systems for blood glucose control in intensive care units [67]. In a prospective 3-centre study of GRIP [86] in surgical, neurosurgical and cardiothoracic patients, the time to capture the target range (4-7.5 mmol/l) was 5.6 h, and 89% of measurements were within this range for the remaining time [67]. The achieved glucose variability was 1.2 mmol/l and was also similar to that achieved in the Glucosafe pilot study.

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[1]endogenous glucose production

Finally, the Glucosafe model and system needs to be tested in clinical trials to address a wider range of validation considerations, including those of usability, acceptability, reliability, etc. The clinical trials should be designed to assess the quality of glucose control with Glucosafe as compared to standard care and/or other clinical decision support systems using predefined glucose indicators for the comparison [87].

In conclusion: Preliminary results indicate significantly improved glycemic control with the model-based Glucosafe decision support system. Further studies are necessary to confirm these initial findings and to clarify the need for model improvements. Various solutions for system integration into routine management of critically ill patients have been outlined.

Chapter 8

Dansk Resumé

Hyperglykæmi observeres hyppigt hos patienter på intensivafdelinger og er blevet associeret med forringede behandlingsresultater. Stram glykæmisk kontrol har vist en reduktion i mortalitet og morbiditet in nogle grupper af kritisk syge patienter, dog er hypoglykæmi den primære bivirkning af stram glykæmisk kontrol. Den øgede risiko for hypoglykæmi samt den tid og indsats der er forbundet med intensiv insulin protokoller har startet en debat omkring fordele og ulemper ved stram glykæmisk kontrol på intensiv afdelinger.

Denne afhandling opsummerer arbejdet på design, implementering og et klinisk pilotforsøg af et modelbaseret computerprogram til beslutningsstøtte i glykæmisk kontrol hos intensiv patienter. Dette system, kaldet 'Glucosafe', giver anbefalinger angående insulinbehandling og ernæringsmæssig indtag til intensiv patienter med hyperglykæmi, til brug for det kliniske personale. Kernen af systemet er en kompartment model af insulin-glukose metabolismen. En plasma kompartment og en perifer kompartment i modellen beskriver farmakokinetiken tilknyttet insulin fra intravenøse infusioner eller boluser og fra den endogene insulinproduktion. Den farmakodynamiske effekt af insulin er beskrevet af det funktionelle forhold mellem insulin i det ekstracellulære rum og effekten på glukose optag i insulin-sensitivt væv. Modellen redegør for mætningen af insulineffekten ved høje koncentrationer, hvilket forhindrer behandlingsmæssige anbefalinger af for høje insulin doser, der kan øge risikoen for hypoglykæmi. Glukose metabolismen håndteres i modellen således at glukose absorptionen i mave-tarm systemet og den intravenøse glukoseinfusion er modelleret som inputs til blodglukose kompartmenten. Den endogene glukosebalance er beskrevet af en transportermodel af den hepatiske balance, nyrernes glukose optagelse og glukose optagelse på de perifere sites. Insulinfølsomheden er estimeret som en patient parameter, der er en indeks for patientens glykæmiske status. I modellen medfører formindsket insulinfølsomhed en reduceret maksimal opnåelig insulin effekt. Som parameter estimeringsmetode foreslås en bayesiansk fremgangsmåde

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på baggrund af en sammenligning af forskellige identifikationsmetoder. Til den rådgivende del af systemet blev der udviklet fire straffefunktioner, som straffer brug af for høje insulindoser, under- eller overernæring, brug af en parenteral ernæringsform og forudsagt hyper- eller hypoglykæmi som behandlingsresultat. Anbefalingerne er baseret på en minimering af summen af straffepoint, men systemet giver også mulighed for manuelt at ændre ernæringsanbefalingen.

Nøjagtigheden i Glucosafe's forudsigelser blev testet i et retrospektivt studie af ti hyperglykæmiske kritisk syge neuro- og traumepatienter. For hver patient var medianen af den absolutte procentfejl mindre end 25% for forudsigelsestider mindre eller lig med 270 min. Til prospektiv test af systemet blev der udviklet en interaktivt grafisk brugergrænseflade. Det prospektive pilotstudie af Glucosafe systemet blev udført på neuro- og traume intensiv afdelingen på Aalborg sygehus. Studiet viste en forbedret glykæmisk kontrol med anvendelse af Glucosafe, og der opstod ingen episoder med hypoglykæmi under studiet. Afhandlingen afsluttes med nogle betragtninger angående bruger acceptabilitet og systemintegration samt en skitsering af den kliniske arbejdsgang med Glucosafe som et praktisk værktøj til glykæmisk kontrol på intensiv afdelinger.

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