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Summary (English)

Type 1 diabetes accounts for approximately 5% of the total diabetes population. It is caused by the destruction of insulin producing β-cells in the pancreas. Various treatment strategies are available today, some of which include advanced technological devices such as an insulin pump and a continuous glucose monitor (CGM). Despite these technological advances in the treatment of type 1 diabetes, the disease still poses an enormous and constant challenge for the patients. To obtain tight glucose control the patients are required to assess how much they will eat prior to the meal. They have to assess the timing, intensity and duration of physical exercise in advance, to adjust the insulin dose accordingly. Additionally, several uncontrollable and unpredictable factors such as stress, hormonal cycles and sickness changing the metabolic state make this task even more difficult.

The development of the insulin pump and the CGM has paved the way for a fully automatic treatment regime, the artificial pancreas. The idea is to connect the CGM with the insulin pump via a control algorithm running on e.g. the patients smart phone. The CGM observations are sent to the smart phone and based on this information, the control algorithm computes the optimal dose adjustment and sends instructions to the insulin pump.

To develop control algorithms, mathematical models of the physiological dynamics are needed. They attempt to describe the significant dynamics of the system and hence they approximate the system behavior. However, uncertainty in the model occurs due to the nature of physiological systems and due to the presence of unknown disturbances. An attractive approach to deal with this uncertainty is to use stochastic differential equations (SDEs). In a model based on

SDEs, the noise is separated into two terms: 1) a diffusion term occurring from model misspecifications, effects of unknown disturbances, or just true stochastic behavior of the system and 2) a measurement noise term representing the serially uncorrelated error occurring due to the imperfect analysing equipment. The diffusion term affects the evolution of the system directly.

The purpose of this PhD-project was to investigate the potential of SDEs in the artificial pancreas development. Especially, the emerging continuous monitoring of glucose levels makes SDEs highly applicable to this field. The current thesis aims at demonstrating and discussing the benefits and challenges by using SDEs compared to traditional methods on the basis of the results of the project.

First of all, we designed a clinical study to obtain high quality data from type 1 diabetes patients to identify the models from. The study included the main factors influencing the glucose level: insulin boluses, meals, and exercise. A modelling study showed that using SDEs in model development can be advantageous in several ways. We were able to pinpoint model deficiencies in a well-known model and to track parameter variation probably caused by a differences in meal type. This information could be added to the model to improve the fit. The study was limited by the lack of a software capable of handling SDE models of population effects instead of single-subject effects. A prototype of this type of software was developed parallel to the end of the project. Thus, we could finally identify a population model of the effect of exercise on the insulin absorption rate. The small amount of observations made it impossible to use SDEs to track parameter variation. Instead, we formulated a model structure with showed to be significantly better than the base model with a constant rate.

Two studies specifically related to the CGM observations were performed during the project. In the first study, we showed that SDEs could be used to tune a control algorithm for overnight glucose control on the basis of CGM observations. The tuned algorithm improved the controller performance in a subsequent clinical study. Further attempts to deal with the problems related to the CGM included a Bayesian estimation scheme. By incorporating prior knowledge about the uncertainty in the CGM observations into the estimation method, we succeeded in predicting the plasma glucose level with acceptable confidence from the CGM observations only.

Overall, the project confirms that SDEs have a large potential within this field. However, future modeling requires a robust software capable of handling the nonlinear population SDE models. When this is available, larger modeling studies can be initiated and the impact of SDEs would be expected to increase.

Summary (Danish)

Type 1 diabetes udgør ca. 5% af den totale diabetespopulation. Sygdommen skyldes en ødelæggelse af de insulin-producerende β-celler i bugspytkirtlen. Forskellige behandlingsstrategier er tilrådighed i dag, hvoraf nogle inkluderer avancerede teknologiske apparater, såsom en insulinpumpe og en kontinuert glukosemonitor (CGM). På trods af disse teknologiske fremskridt i behandlingen af type 1 diabetes, er sygdommen stadig en enorm og konstant udfordring for patienterne. For at opnå god glykæmisk kontrol, må patienterne på forhånd vurdere hvor meget de vil spise. De må vurdere tidspunkt for og intensitet og varighed af motion før start for at kunne justere doseringen af insulin derefter. Endvidere vanskeliggøres dette af flere ukontrollerbare og uforudsigelige faktorer såsom stress, hormonelle variationer og sygdom, som alle ændrer den metaboliske status.

Udviklingen af insulinpumpen og CGM'en har banet vejen for en fuldautomatisk behandlingsmetode - en såkaldt kunstig bugspytkirtel. Ideen er at forbinde CGM'en med insulinpumpen via en reguleringsalgoritme installeret på fx. patientens smartphone. CGM-observationerne bliver sendt til smartphonen og på basis af denne information, beregner reguleringsalgoritmen den optimale dosisjustering og sender instruktioner til insulinpumpen.

For at udvikle reguleringsalgoritmer er matematiske modeller af den fysiologiske dynamik nødvendige. De forsøger at beskrive de signifikante dynamikker i systemet og dermed approksimerer de systemets opførsel. Men modellerne indeholder usikkerheder på grund af fysiologiske systemers natur og på grund af ukendte forstyrrelser i systemet. En attraktiv metode til at håndtere denne usikkerhed er at bruge stokastiske differentialligninger (SD). I en model baseret

på SD er støjen opdelt i to separate led: 1) et diffusionsled, som opstår fra misspecifikationer i modellen, effekten af ukendte forstyrrelser, eller blot en reel stokastisk opførsel i systemet og 2) et målestøjsled, som repræsenterer de serielle ukorellerede fejl, som opstår på grund af uperfekt analyseudstyr.

Formålet med dette PhD-projekt var at undersøge potentialet af SD i udviklingen af den kunstige bugspytkirtel. Særligt brugen af CGM'en gør SD meget anvendelige indenfor dette felt. Denne afhandling forsøger at demonstrere og diskutere fordelene såvel som udfordringerne ved af benytte SD sammenlignet med traditionelle metoder på basis af resultaterne fra projektet.

Først og fremmest designede vi et klinisk studie for at indsamle data af høj kvalitet fra type 1 diabetikere til at identificere modellerne fra. Studiet indeholdte de faktorer med mest indflydelse på blodsukkeret: insulin, måltider og motion. Et modelleringsstudie viste at brugen af SD i modeludvikling kan være fordelagtig på flere måder. Vi kunne præcisere mangler i en velkendt model og spore variationen i et parameter, som sandsynligvis skyldes forskellige typer af måltider. Denne information kan indbygges i modellen og forbedre modellen. Studiet var begrænset af manglen af et software, som kan estimere SD-modeller af populationseffekter istedet for individuelle effekter. En prototype af denne type software blev henimod slutningen udviklet parallelt med projektet. Hermed kunne vi identificere en populationsmodel af effekten af motion på hastigheden af insulin-absorptionen. Den relativt lille mængde af data gjorde det umuligt at bruge SD til at spore parametervariationen. Istedet formulerede vi en modelstruktur, som viste sig at være signifikant bedre end en basismodel med en konstant hastighed.

To studier relateret til CGM'en blev udført under projektet. I det første studie, viste vi at SD kan bruges til at tune en reguleringsalgoritme til natlig blodsukkerkontrol på basis af CGM-observationer. Den tunede algoritme forbedrede reguleringsevnen i et efterfølgende klinisk studie. Videre forsøg på at håndtere problemerne relateret til CGM'en bestod i en Bayesiansk estimationsmetode. Ved at indbygge a priori viden om usikkerheden ved CGM-observationerne ind i estimationsmetoden, lykkedes det at prædiktere blodsukkerniveauet med acceptabel konfidens alene på baggrund af CGM-observationerne.

Alt i alt bekræfter projektet af SD har et stort potentiale indenfor dette felt. Men fremtidig modellering kræver et robust software, som kan håndtere disse ikke-lineære populationsmodeller baseret på SD. Når dette er klar, kan større modelleringsstudier blive påbegyndt og derved vil effekten af at benytte SD forventes at stige.

Preface

This PhD project was carried out at DTU Compute (former DTU Informatics) at the Section for Dynamical Systems in period from June 2009 until July 2013. It was financed by the Strategic Research council as a part of the DIACON project (NABIIT project 2106-07-0034). The DIACON project was founded by DTU Compute (DTU Informatics at that time), Hvidovre University Hospital and Novo Nordisk A/S to develop new treatment methods for type 1 diabetes.

The PhD project was supervised by Professor Henrik Madsen, DTU Compute and co-supervised by Professor Peter Ruhdal Jensen, DTU Systems Biology.

Lyngby, 13-August-2013

Anne Katrine Duun-Henriksen

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Thanks to my office mates, the PhD-students Roland Löwe and Julija Tastu - for contributing to my blood sugar level by making sure our storage of nuts, cookies, and chocolate was eternal. You made my days here joyful and in many ways interesting. My colleague PhD-student Philip Hvidthøft Delff Andersen for inspiring theoretical and practical discussions on mathematics and statistics. All the rest of my wonderful, funny, and intelligent colleagues at the section - for delightful coffee breaks and lunches that contributed to the broadening of my horizon. Furthermore, my colleague PhD-student Rune Juhl deserves a great appreciation for all the work you have put into improving CTSM – without these improvements this project would not have been the same.

Finally, I would like to thank my loving husband Jonas for always believing in me and for the endless support both on a professional and personal level. Without you, this thesis would never have made it to the printer. Thank you!

Contents

Chapter 1

Introduction

In 2008 the DIACON (DIAbetes CONtrol) project was founded by scientists from DTU Compute (at that time DTU Informatics), Department of Endocrinology at Hvidovre University Hospital and Novo Nordisk A/S. The overall aim was to improve the treatment of diabetes by developing semi- and fully-automatic insulin administration methods. This thesis focuses on the mathematical models related to the fully-automatic insulin administration. The semi-automatic methods will not be addressed, but are published elsewhere [11, 12]. The developed models and systems have the potential to improve the quality of life for patients with type 1 diabetes and to obtain tight glucose control to avoid the medical complications associated with improper glucose control.

Already in the 1960s mathematical models of the insulin-glucose system in diabetes made their entry [15]. During 1980s models were used to support diagnosis and treatment of diabetes [20]. As the therapy methods for type 1 diabetes have advanced, mathematical models have gained more attention and impact in relation to diabetes therapy.

Technology has likewise been a part of diabetes treatment for many years. The portable insulin infusion pumps were developed in London during the late 1970s [78]. In the same period, home monitoring of the glucose level from a finger stick sample became available for clinical practice [83, 95].

This chapter describes the background and motivation for the DIACON project as well as for this particular PhD-project. First, an introduction to type 1 diabetes is given followed by a description of the concept of an artificial pancreas - the ultimate goal for many researchers within the field of diabetes technology.

Examples of models used in the development of an artificial pancreas are shortly described. Furthermore, an introduction to the modelling approaches used in the PhD-project is presented. Finally, the objective of the PhD-project and the thesis outline is stated.

1.1 Type 1 Diabetes

Diabetes is one of the major health challenges of the 21st century. In 2011, 366 million people worldwide suffered from diabetes [96]. Type 1 diabetes accounts for approximately 5% of the total diabetes population [3]. Furthermore, the incidence of type 1 diabetes is increasing.

Type 1 diabetes is caused by the destruction of insulin producing cells in the pancreatic islets of Langerhans named β-cells. The selective destruction of the β-cells is in most cases an autoimmune reaction while the rest remain idiopathic. There is a strong genetic effect in the development of diabetes though not deterministic. No specific environmental factors are established as risk factors.

Insulin has an anabolic effect in multiple tissues. Those of importance for fuel homeostasis are skeletal muscle, adipose tissue, and the liver where insulin enhances the uptake and storage of glucose, fat and amino acids. At the same time, insulin counteracts the catabolism of the reserves. Variation in the insulin level is crucial to fuel homeostasis and to maintain the glucose level in plasma within a tight range. The net effect of insulin is a lowering of the plasma glucose level while counter-regulatory hormones, such as glucagon, raise the plasma glucose level. Thus, individuals with type 1 diabetes are constantly hyperglycemic if not treated.

The disease can occur at any age but the onset is typically seen in childhood. The symptoms are thirst, weight loss and polyuria, among others. Often the search for diabetes is motivated by these symptoms. In Denmark, the diagnosis is made by measuring the glucose level in a blood sample in fasting state. If the glucose level is above 7 mmol/l the individual is diagnosed with type 1 diabetes. In some cases an oral glucose tolerance test is necessary [26].

Prolonged hyperglycemia leads to a number of long term complications includ-

ing diabetic retinopathy, neuropathy, nephropathy, and cardiovascular diseases. As of today no cure exists and thus patients rely on exogenous insulin delivery for the rest of their lives. The goal of insulin therapy is to mimic the physiologic insulin profile. However, the insulin secretion from a normal pancreas is a strictly controlled process regulated by several factors including changes in circulating nutrients (glucose, amino acids and free fatty acids), hormones (e.g. glucagon, somastotatin), and neural control factors making the regulation extremely complex. Even though exogenous insulin is vital for the patients, dosing of insulin must done be with extreme care as too much insulin can cause hypoglycemia which in severe cases can be fatal.

Various treatment strategies are available today some of which include highly advanced technological devices. Most of the patients use insulin pens to inject long-acting insulin a few times daily and short-acting insulin boluses for every meal - a multiple daily injections (MDI) therapy. In addition, the patients are advised to check the glucose level with a glucose meter from finger stick samples several times a day and to take correction boluses or extra carbohydrates if needed.

An alternative to insulin pens, especially used by many children, is an insulin pump. An insulin pump delivers insulin continuously via a catheter placed in the subcutaneous layer often in the abdomen. Furthermore, the patient can manually dose insulin boluses via the pump in connection with a meal or for correction. This treatment method is called continuous subcutaneous insulin infusion (CSII) therapy. Combined with a continuous glucose monitor (CGM), this therapy method comprises the system used for sensor augmented pump therapy. A CGM uses a small sensor also placed in the subcutaneous layer. It monitors the interstitial glucose level and typically reports the value every five minutes. The CGM signal is shown in the display of the insulin pump. The rich information from the CGM combined with the insulin pump allow the patient to fine-tune the insulin delivery and obtain tight glucose control.

Despite the technological advances in the treatment of type 1 diabetes, the disease still poses an enormous and constant challenge for the patients. To obtain tight glucose control the patients are required to assess how much they will eat before the beginning of a meal to avoid a high postprandial plasma glucose level. They have to assess the timing, intensity and duration of exercise in advance to adjust the insulin dose accordingly. Additionally, several uncontrollable and unpredictable factors such as stress, hormonal cycles and sickness changing the metabolic homeostasis will make this puzzle even more difficult. While many of these disturbances occur during day time, the circadian rhythms in hormone levels demands the patient to check the glucose level even during night to avoid possible nocturnal hypoglycemia.

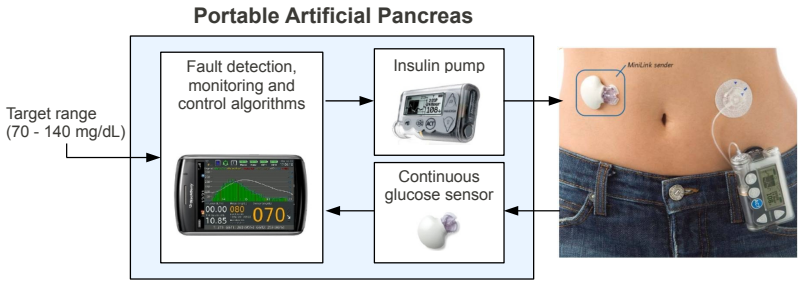

Figure 1.1: An illustration of the concept behind an artificial pancreas. The control algorithm could potentially be implemented on a smart phone as illustrated here. Modified from [75, 68]

Overall, it is obvious that patients with type 1 diabetes are required to have a rather non-spontaneous life style to keep the risk of longterm complications low and at the same time avoid severe hypoglycemia. Especially, children and adolescents with type 1 diabetes are challenged by this restriction.

For more details about type 1 diabetes and treatment thereof, see [44].

1.2 The Artificial Pancreas

The technological advances in diabetes treatment (the insulin pump and the CGM) have paved the way for a fully automatic treatment regime, the artificial pancreas. The idea is to connect the CGM with the insulin pump via a control algorithm running on e.g. the patients smart phone. The CGM observations are sent to the control algorithm and based on this information the control algorithm computes the optimal dose adjustment and send instructions to the insulin pump. The system is illustrated in Figure 1.1.

The ultimate goal is to free the patients from all decisions regarding management of their diabetes. The artificial pancreas should thus ideally be able to keep the plasma glucose level in the normal range 24 hours a day. This would decrease the risk of longterm complications due to hyperglycemia substantially and at the same time eliminate severe hypoglycemia events. However, taking into consideration the complex behavior of a physiological pancreas and the

number of unknown disturbances affecting the plasma glucose level this is not an easy task.

Currently, no commercial version of the artificial pancreas exists but the concept has been known for 50 years [51]. The area is heavily researched worldwide and each research group has its own strategy towards the system. Recent reviews are found in [22], [46], and [8].

An important issue to mention is the problem of inaccuracy and the time lag in the CGM signal with respect to the plasma glucose level. The time lag occurs because the CGM is placed in the subcutaneous layer (the interstitial volume) and is thus observing a lagged version of the plasma glucose level. The size of the time lag is reported to be between 12-20 minutes [92]. The inaccuracy is usually assessed by the mean absolute relative deviation (MARD) from a gold standard method. Currently available sensors have a MARD in the range of 11.8-20.2% [25]. The regulation of the plasma glucose level will be affected when the input to the control algorithm is inaccurate and unreliable. Even though many control algorithms are advanced enough to deal with this in some extent this problem is still recognized as one of the largest barriers to automatic control of the plasma glucose level [45, 85].

Furthermore, the subcutaneous delivery of insulin introduces a time delay from the time of injection to the time of appearance of insulin in plasma (the site of effect) due to the significant absorption time from subcutis to plasma. Therefore, it can take 90-120 minutes before the maximum effect on lowering of the plasma glucose level is reached even for rapid-acting insulins [46]. This delay should be handled carefully since once insulin is given there is no quick method to withdraw it again automatically. However, methods to take into account the previously delivered but still active insulin, the so-called "insulin-on-board" have been suggested [32]. Some groups use a dual pump system with an additional pump delivering glucagon to include a "brake" in the control algorithm [17, 80]. Glucagon counteracts the effect of insulin and can thus be used when too much insulin is dosed.

Inter- and intra-individual variability poses further obstacles on the way to a fully-automatic system. Insulin and meal absorption are both known to be subject to significant inter-variability which requires the control algorithm to be customized to each patient. However, the substantial intra-individual variability present in glucose metabolism due to stress, sickness, exercise, circadian rhythms etc. is difficult to handle from a control perspective.

Until now, the feasibility of the artificial pancreas has been proven by a number of research centers in a clinical setting [48, 18, 86, 31, 81, 4]. Within the last years, a number of groups have started to test an artificial pancreas outside the

clinic [19, 58, 56].

1.3 Physiological Models in Artificial Pancreas Modelling

The artificial pancreas development engages several research groups worldwide. A number of different approaches are being investigated. Different devices and different control strategies are used as well.

Mathematical models comprise the core of the engineering in the artificial pancreas field in a number of ways. They are employed in control, prediction, simulation of the glucose dynamics, and for investigating and quantifying pathophysiological phenomenas of the system.

Models for control range from black-box models of low order designed entirely on data, to larger nonlinear models based on physiological knowledge. The purpose of these models is to provide predictions of the plasma glucose level and insulin input within the time horizon that the regulation is concerned with. They can be tuned to the individual patient and device either by adjusting a single parameter or by estimating the entire model on data from that patient. Some models are estimated online, hence taking on an adaptive approach to deal with the significant intra-variability [33].

Simulation models are important for the researchers as they can give an indication of the performance of the control algorithms and strategies. The best candidates can then be tested further in clinical studies. The evaluation of control algorithms in a simulation environment has several advantages. First of all, simulations accelerate the development process as they can give an indication of the controller performance early in the process without the need of clinical or animal testing. They enable a comprehensive investigation of insulin treatments in near realistic conditions. Additionally, they allow the researchers to test various risk scenarios e.g. sensor/pump failures or parameter misspecification to analyse the controller robustness. All of these factors add to a substantial cost reduction.

In this thesis the focus is put on the physiological models of the insulin-glucose system in type 1 diabetes patients used within control and simulation.

The most well-known physiological model is the *minimal model* published in 1979 [9]. The original purpose of the model was to estimate insulin sensitivity – i.e. how sensitive the dynamics of glucose is to changes in insulin. The term

minimal refers to the fact that the model describes the key components of the system. In [64] a version of the minimal model is used in a control algorithm and the results are evaluated on a more complex physiological model acting as simulator. The minimal model has also been used as basis for a simulation model with extensions taking into account the meal response and the subcutaneous insulin delivery. This model is identified from data originating from studies testing an artificial pancreas on type 1 diabetes patients [52]. Recently, this model has been modified to include the effect of subcutaneous glucagon delivery as well [43].

In [34] a more complex model is presented. It is also based on the minimal model, however, the model takes into account circadian rhythm in the insulin sensitivity and the meal response depends on the type of carbohydrates in the meal.

Currently, one model (the Virginia/Padova model) is accepted by the FDA (Food and Drug Administration, USA) as a substitute of preclinical animal trials for testing of closed-loop strategies [57]. This model is a high order nonlinear model with a large number of parameters. The model describe the behavior of the plasma glucose level in several cohorts of type 1 diabetes patients (adults, adolescents and children). The model is estimated from data of approximately 200 healthy subjects and the parameter values are then adjusted to typical values for type 1 diabetes patients [24, 67].

Another popular simulation model is the one by Hovorka [49, 47, 97]. The model is characterised by the partitioning of the insulin effect on glucose into three separate terms. Some of the parameters attain an oscillatory behavior to include circadian rhythms. The model is formulated on the basis of clinical studies on healthy subjects [49].

Finally, the largest existing simulation model was published in [84]. This model divide the model into compartments representing the different organs. The parameter estimates are based purely on literature findings. In [99] a more detailed overview of some of the mentioned models are presented and discussed.

1.4 Modelling Approaches

Mathematical models of physiological systems attempt to describe the significant dynamics of the systems. Thus the models approximate the system to a certain degree. Even if the goal is to describe the total dynamical behavior, the model will never be able to explain all the variability as physiological systems

are influenced by stochasticity due to the nature of the systems.

Traditionally, models used for especially simulation of the insulin-glucose system in type 1 diabetes are based on ordinary differential equations (ODEs). While the parameters are estimated from real life data or literature, the structure of the models are based solely on knowledge about physiology. Solutions to ODEs are deterministic. Consequently, the future progression of the system can be predicted exactly from a set of initial values only. ODEs can be presented on state space form as:

$$\frac{d\boldsymbol{x}_t}{dt} = \boldsymbol{f}(\boldsymbol{x}_t, \boldsymbol{u}_t, \boldsymbol{\theta}, t) \tag{1.1}$$

$$\boldsymbol{y}_j = \boldsymbol{h}(\boldsymbol{x}_{t_j}, \boldsymbol{u}_{t_j}, \boldsymbol{\theta}, t) + \boldsymbol{\varepsilon}_j \tag{1.2}$$

Here (1.1) is the state equation describing the evolution of the system. $\boldsymbol{x}_t$ is the state vector, t is time, $\boldsymbol{u}_t$ is an input vector and $\boldsymbol{\theta}$ is a parameter vector. $\boldsymbol{f}(\cdot)$ is a known function - often nonlinear. Equation (1.2) is the observation equation describing how the system is observed. $\boldsymbol{y}_j$ is a vector of output variables, t_j is the sampling times, $\boldsymbol{h}(\cdot)$ is a known function and $\boldsymbol{\varepsilon}_j \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma})$ is a random error with mean zero and covariance $\boldsymbol{\Sigma}$.

It is seen from (1.1) and (1.2) that all the residual deviation between the model outcome and the observations is classified as measurement noise and does not affect the model evolution itself. This deterministic description of a physiological system does not take into account the influence of changes in the metabolism due to unknown disturbances, input uncertainties, or the true stochastic behavior of the system. Hence, it does not present a realistic trajectory.

Furthermore, as the measurement noise includes unmodelled disturbances and input uncertainties, the residuals will be correlated. This violates the assumption of independence required by many statistical tests such as students t-test, least squares and maximum likelihood. Consequently, the estimated model cannot be validated with standard statistical tools.

An alternative approach to overcome these critical issues is to use stochastic differential equations (SDEs) instead of ODEs. In a state-space model built upon SDEs the noise is separated into two terms:

1) a *diffusion* term occurring from model misspecifications, effects of unknown disturbances, or just true stochastic behavior of the system.

2) a measurement noise term representing the serially uncorrelated error occurring due to the imperfect analysing equipment.

A state-space model with SDEs can be formulated as:

$$d\boldsymbol{x}_t = \boldsymbol{f}(\boldsymbol{x}_t, \boldsymbol{u}_t, \boldsymbol{\theta}, t)dt + \boldsymbol{\sigma}_w(\boldsymbol{x}_t, \boldsymbol{u}_t, \boldsymbol{\theta}, t)d\boldsymbol{w}_t \tag{1.3}$$

$$\boldsymbol{y}_j = \boldsymbol{h}(\boldsymbol{x}_{t_j}, \boldsymbol{u}_{t_j}, \boldsymbol{\theta}, t) + \boldsymbol{e}_j \tag{1.4}$$

In (1.3) $\boldsymbol{\sigma}_w(\boldsymbol{x}_t, \boldsymbol{u}_t, \boldsymbol{\theta}, t)$ is the diffusion term. $\boldsymbol{w}_t$ is a Wiener process, i.e. it is a non-stationary continuous stochastic process that starts in 0 ($\boldsymbol{w}_0 = \boldsymbol{0}$) and has mutually independent Gaussian increments [65]. In (1.4) $e_j \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{\Sigma})$ is the independent measurement noise.

Solutions to SDEs are stochastic processes described by probability distributions. Thus simulations computed with SDE models include the uncertainty of the simulation. The segregation of the noise into two separate terms affecting the states and observations respectively, allows the noise to affect the states and obtain independent residuals to meet the requirements for the statistical tests.

Furthermore, SDEs are a strong tool for pinpointing model deficiencies and investigating the incorporation of additional information into the model to finally obtain an improved model [60, 91, 30]. In this way, model formulation can be data driven as opposed to ODEs where the influence of data is restricted to the parameter estimation. SDE models are often referred to as grey-box models as they combine the strengths of white- and black-box models. Hence, with grey-box models one can combine the information from data with prior physiological knowledge. The parameters are physiological interpretative while at the same time the information from data can be used to estimate and improve the model in a statistical framework.

In practice, model identification and parameter estimation in SDE models are not trivial - see [28] for a review. A specialized software program, CTSM (Continuous Time Stochastic Modelling), was developed to handle estimation of this type of models [59, 29, 61]. CTSM applies the likelihood principle to estimate the parameters in SDE models [66, 37]. To compute the prediction errors for a linear model, a continuous-discrete time Kalman filter is used. For non-linear models an extended Kalman filter is applied [59]. The current version of CTSM is a package for R which became available during the project [29].

SDEs have been applied to several areas within physiological and biological

modelling. A significant part of the work is done by former or present researchers in our department [91, 72, 54, 70, 77, 69, 76].

The large inter-individual variability in physiological systems requires to be handled specifically by the models. An attractive approach is to use hierarchical models to accommodate this variability. These models tend to estimate parameters based on data from several subjects instead of a single subject and take into account the inter- and intra-individual variability [5]. In these population models, parameters can be specified as

$$\boldsymbol{\phi}_i = \boldsymbol{g}(\boldsymbol{\theta}, \boldsymbol{Z}_i) \exp(\boldsymbol{\eta}_i) \tag{1.5}$$

where $\boldsymbol{\phi}_i$ is the parameter vector for individual i, $\boldsymbol{g}(\cdot)$ is a known function, $\boldsymbol{\theta}$ is overall population parameters and $\boldsymbol{Z}_i$ are fixed covariates e.g. age, weight, and gender. The random effects are introduced by $\boldsymbol{\eta}_i$, and are independent and multivariate normally distributed with mean zero.

A software that combines hierarchical modelling and modelling with SDEs was developed and implemented as a package for R [54] and in NONMEM [91]. The method has been demonstrated in several papers [69, 54, 91]. However, the population SDE models published until now are restricted in size and complexity.

1.5 Objectives of the PhD-Project

The purpose of this PhD-project was to investigate the potential of SDEs in artificial pancreas modelling. This area involves mathematical models spanning from simple low order linear models used for automatic control to complex non-linear models of high order used for simulation. Bridging from prior developed models we aimed at improving the predictive performance and simulation skills and include the effects of exercise and hormonal changes. Especially, the emerging continuous monitoring of glucose levels makes SDEs highly applicable to this field. First of all, the frequent sampling necessitates that the assumption of independence between observations is obeyed. The segregation of the error in SDEs helps to ensure this. Secondly, the inaccuracy of the CGMs requires careful modelling of the noise for which SDEs provides an excellent tool. Furthermore, the ability to pinpoint model deficiencies can be used to extend the state-of-the-art models to e.g. include effects of exercise in a data driven way.

The available software at the time of start of the project limited the possibilities. However, parallel to this project CTSM was improved and changed to an R-

package [29] making it much more efficient due to the possibility to do parallel computing and improved user-friendliness.

The current thesis aims at demonstrating and discussing the benefits and challenges by using SDEs compared to traditional methods on the basis of the results of the project.

1.6 Thesis Outline

The thesis consists of six chapters in total. The reader is referred to the papers and reports in the appendices for the full details about the work.

To develop mathematical models, clinical data from type 1 diabetes subjects was needed. Thus the first task in the project was to design a study to collect suitable data. In **Chapter 2**, the clinical study is described and the reflections on the study design are discussed.

In **Chapter 3** it is described how SDEs were used to pinpoint misspecification in a well-recognized model of the insulin-glucose dynamics and the study findings are discussed.

The next step was to incorporate the effect of exercise on the system. **Chapter 4** describes how a hierarchical model of the effect of exercise on the insulin absorption rate was identified and discusses the future improvements to the model.

Chapter 5 presents and discusses two studies specifically related the CGM where SDEs were used to tune a control algorithm based on real data and to estimate a predictive model with a Bayesian approach.

Finally, **Chapter 6** presents the main conclusions and suggestions for future work.

The papers and reports addressed in the thesis are presented in the appendices.

1.7 List of Publications

In this thesis, the following papers will be addressed (listed in order of appearance in the thesis):

- **Clinical Data for Advanced Glucose Modelling**
  Duun-Henriksen AK, Schmidt S, Nørgaard K and Madsen H
  Technical Report-2013-5, DTU Compute, Technical University of Denmark, 2013

- **Effects of Everyday Life Events on Glucose, Insulin, and Glucagon Dynamics in Continuous Subcutaneous Insulin Infusion–Treated Type 1 Diabetes: Collection of Clinical Data for Glucose Modeling**
  Schmidt S, Finan DA, Duun-Henriksen AK, Jørgensen JB, Madsen H, Bengtsson H, Holst JJ, Madsbad S and Nørgaard K
  Diabetes Technology & Therapeutics vol: 14, issue: 3, pages: 210-217, 2012

- **Model Identification Using Stochastic Differential Equation Grey-Box Models in Diabetes**
  Duun-Henriksen AK, Schmidt S, Røge RM, Møller JB, Nørgaard K, Jørgensen JB and Madsen H
  Invited paper for *Journal of Diabetes Science and Technology, March 2013, Volume 7, Issue 2: pages 431–440*

- **Modelling the Effect of Exercise on Insulin Pharmacokinetics in "Continuous Subcutaneous Insulin Infusion" Treated Type 1 Diabetes Patients**
  Duun-Henriksen AK, Juhl R, Schmidt S, Nørgaard K and Madsen H
  Technical Report-2013-13, DTU Compute, Technical University of Denmark, 2013

- **Tuning of Controller for Type 1 Diabetes Treatment with Stochastic Differential Equations**
  Duun-Henriksen AK, Boiroux D, Schmidt S, Skyggebjerg O, Madsbad S, Jensen PR, Jørgensen JB, Poulsen NK, Nørgaard K and Madsen H
  Proceedings of the 8th IFAC Symposium on Biological and Medical Systems, 2012

- **Predicting Plasma Glucose From Interstitial Glucose Observations Using Bayesian Methods**
  Hansen AH, Duun-Henriksen AK, Juhl R, Schmidt S, Nørgaard K, Jørgensen JB and Madsen H
  Submitted to *Journal of Diabetes Science and Technology, July 2013*

Additionally, the following papers were published during the PhD-project:

- **Control of Blood Glucose for People with Type 1 Diabetes: an in Vivo Study**
  Boiroux D, Schmidt S, Duun-Henriksen AK, Frøssing L, Nørgaard K, Madsbad S, Skyggebjerg O, Poulsen NK, Madsen H and Jørgensen JB
  Proceedings of the 17th Nordic Process Control Workshop, pages: 133-140, 2012, Technical University of Denmark, Kongens Lyngby

- **Overnight Control of Blood Glucose in People with Type 1 Diabetes**
  Boiroux D, Duun-Henriksen AK, Schmidt S, Nørgaard K, Madsbad S, Skyggebjerg O, Jensen PR, Poulsen NK, Madsen H and Jørgensen JB
  Proceedings of the 8th IFAC Symposium on Biological and Medical Systems, 2012

- **Psychosocial Factors and Adherence to Continuous Glucose Monitoring in Type 1 Diabetes**
  Schmidt S, Duun-Henriksen AK and Nørgaard K
  Journal of Diabetes Science and Technology, 2012 Jul 1;6(4):986-7

- **Model-based Closed-loop Glucose Control in Type 1 Diabetes – the DiaCon Experience**
  Schmidt S, Boiroux D, Duun-Henriksen AK, Frøssing L, Skyggebjerg O, Jørgensen JB, Poulsen NK, Madsen H, Madsbad S and Nørgaard K
  Accepted for publication in *Journal of Diabetes Science and Technology, June 2013*

- **Subdural to Subgaleal EEG Signal Transmission: The role of distance, leakage and insulating affectors**
  Duun-Henriksen J, Kjær TW, Madsen RE, Jespersen B, Duun-Henriksen AK, Remvig LS, Thomsen CE and Sørensen HBD
  Clinical Neurophysiology, Volume 124, Issue 8, August 2013, Pages 1570–1577

- **Clinical Evaluation of 3D/3D MRI-CBCT Automatching on Brain Tumors for Online Patient Setup Verification – A Step Towards MRI-based Treatment Planning**
  Buhl SK, Duun-Henriksen AK, Kristensen BH and Behrens CF
  Acta Oncologica, vol: 49, issue: 7, pages: 1085-1091, 2010

- **The Use of Stochastic Differential Equations with Multiplicative Noise in PK/PD Modelling**
  Røge RM, Møller JB, Duun-Henriksen AK and Madsen HM
  Manuscript for submission to Journal of Pharmacokinetics and Pharmacodynamics

Chapter 2

Data Acquisition

Behind a good and robust model lies at least one and preferably more good data sets. As stated in Section 1.3, some of the existing simulation models of the insulin-glucose system in type 1 diabetes patients are based on data from healthy subjects. To eliminate the risks of this physiological extrapolation we worked with data obtained from type 1 diabetes patients alone.

The clinical studies can be designed in various ways ranging from strictly controlled clamp and/or tracer studies to outpatient studies obtaining data from CGMs, and meal and bolus diaries.

Together with the clinical partner of the DIACON project, the Department of Endocrinology, Hvidovre University Hospital, we had the possibility to obtain data from type 1 diabetes patients of high quality.

The purpose of this clinical study was to collect data during situations resembling the everyday life of type 1 diabetes patients in a controlled environment. This chapter describes the experimental design of the study and the considerations behind it. Finally, a discussion follows about the applicability of the data set. The chapter is based on Technical Report I in Appendix A and Paper A in Appendix B.

2.1 Study Design

We based the design of the study on classical experimental factorial design [71]. However, in clinical studies involving human subjects some ethical and practical limitations naturally exists which need to be taken into the consideration when designing the study.

In total 12 type 1 diabetes patients were included in the study. All of them were treated with an insulin pump in their regular treatment. Each patient went through two study days separated by at least three weeks. Hence, the study consisted of 24 study days of which not two were identical.

The study investigated the effect of three factors on the plasma glucose level: Meals (carbohydrates), insulin boluses and exercise. The three factors are believed to be the everyday life factors with the most significant effect on the plasma glucose level in type 1 diabetes patients. Each factor was examined on two levels. The size of the levels were chosen to give a significant change in the plasma glucose level and on the same time resemble realistic values. See Table 2.1 for the definition and size of the levels.

One study day consisted of three events. An event corresponded to the introduction of one of the three factors on one of the two levels. The effect of each factor was observed for 150 min before the next event was initiated. Some of the study days included a snack in the afternoon as the third event. The overall design is depicted in Figure 2.1.

As mentioned, not two study days were identical. To avoid confounding the effect of a factor with the effect of the order of events, all possible combinations were included. However, as the patients had been fasting since the previous night, the first event was always a meal; either unbolused or underbolused as described in Table 2.1.

At least two hours prior to the start of the first event were spent on stabilizing the patients plasma glucose level to the normal range with insulin boluses or intravenously administrated glucose. The same happened after 150 min of observation of the third and last event before the patients left the clinic. Insulin was administrated via the insulin pump and the patients spent the day in bed except during exercise on a treadmill.

During the study day, plasma glucose values were obtained every ten minutes. Additionally, the patients wore a CGM measuring the subcutaneous glucose level every five minutes as well as an Actiheart device monitoring the activity level and heart rate [2]. Additionally, blood samples for analyses of insulin, glucagon,

Table 2.1: Description of event types. CHO: Carbohydrates, ICR: Insulin to carbohydrate ratio, HR: Heart rate, ISF: Insulin sensitivity factor

Event type	Levels	Description
Meal	Unbolused	Solid food with drink. 1 g of CHO/kg body weight. No meal bolus.
	Underbolused	Solid food with drink. 1 g of CHO/kg body weight. 50% of the insulin bolus matching the meal CHO content based on personal ICR.
Exercise	Mild	20 minutes on a treadmill with HR equal to 0.5 x (maximum HR - resting HR) + resting HR.
	Moderate	20 minutes on a treadmill with a HR equal to 0.75 x (maximum HR - resting HR) + resting HR.
Insulin bolus	Small	Insulin bolus estimated to lower plasma glucose level by 3 mmol/L based on personal ISF.
	Large	Insulin bolus estimated to lower plasma glucose level by 6 mmol/L based on personal ISF.
Snack	NA	Liquid. 0.4 g of CHO/kg of body weight.

cortisol, growth hormone, epinephrine and nor-epinephrine were obtained non-equidistantly 23 times during the study day. These hormones are all known to have an effect on the glucose dynamics under various circumstances [44].

2.2 Results

The obtained data set holds extensive information about the dynamics of the glucose metabolism in patients with type 1 diabetes. Plots of all the time series from the 24 data sequences are shown in Technical Report I in Appendix A.

2.3 Discussion

The purpose with this study design was to obtain a data set which included information about the system in the state we wished to simulate or predict i.e. everyday life conditions. However, we could not merely observe the patients in their everyday life as several uncontrolled disturbances would corrupt the data.

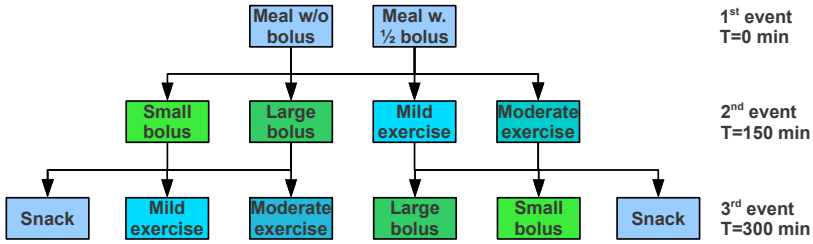

Figure 2.1: Illustration of the study design. T is the time since the start of the first event. The first event was always a meal followed by half the meal bolus or no bolus at all. The second event was either mild or moderate exercise or a small or large insulin bolus. The third event was either a snack, mild or moderate exercise or a small or large insulin bolus.

Instead, we collected the data in a controlled environment with a minimum number of disturbances to be able to isolate the effects of the factors of interest.

The selection of the time interval between two events was a trade-off between resembling the normal daily rhythm and our wish to separate each factor as much as possible to avoid masking the individual effects. Normally, patients with type 1 diabetes take an insulin bolus in connection with a meal to bring down the postprandial plasma glucose level. This is also the case for clinical studies testing control algorithms for an artificial pancreas – socalled closed loop studies. This correlated timing of inputs complicates the modelling as described in [36]. They showed that the separation of inputs has a quantitative effect on the prediction accuracy of the estimated models. Therefore, even though far from daily life treatment schemes we separated the effect of unbolused meals and insulin boluses.

Two of the simulation models published today are estimated on data originating from tracer and/or clamp studies [49, 24]. The advantage about clamp studies in relation to modelling is that by keeping the glucose level constant you obtain some kind of steady state condition. It is, however, an artificial steady state and the identifiable parameters from clamp studies do not relate to the transient behavior of the system but to the steady-state behavior.

Radioactive tracers can be used to observe the behavior of internal processes of the glucose metabolism. In [24] they use tracers to estimate the endogenous glucose production and in [49] they use them to estimate the effect of insulin on

distribution/transportation, disposal and the endogenous glucose production. We cannot from our data observe these processes directly and thus we restrict ourselves with respect to the models we can estimate. However, as will become clear later in this thesis, the SDEs allow us to identify some of this internal variation. Thus, to some extent, we might be able to model these processes by using prior physiological knowledge and the tools provided by the SDEs without expensive and complicated tracer studies.

The experimental design of this study is different from closed loop studies in several ways. First of all, not two study days were identical. We believe that this inhomogeneity is important to avoid confounding factor effects with "order" or "time of day" effects. However, the limitations due to the fact that we are dealing with human subjects could not be fully accomplished. Secondly, the events were separated by 150 minutes whereas in closed loop studies boluses are usually administrated together with a meal. Thus, as described earlier, the prediction accuracy of models estimated from this data set could be improved compared to models estimated from closed loop data. However, this hypothesis needs to be investigated in a comparative study before any conclusions can be made. Finally, we analysed several hormones not usually observed during closed loop studies enabling us to assess the influence from these on the plasma glucose dynamics.

Many of the hormones we analysed are related to the mental stress level. We did not monitor the patients mental stress level except indirectly via the heart rate. One could argue that the patients felt insecure in the beginning of the study day or just before exercise and as a consequence changes in the stress related hormones could be caused by this. The *human factor* in the study is a challenge when trying to isolate the effect of different inputs as neither they nor we can control the stress level. Furthermore, as we only collected data during the day from 7AM-17PM we cannot estimate the variation in hormone levels through a 24 hour period. Especially, the dawn phenomena would be important to include in a type 1 diabetes simulator and models for control [93]. Longer study days lasting more than 24 hours would have increased the value of this data set.

One major problem in the glucose modelling research field is the fact that the different research groups use their own data sets to estimate their models. This makes it hard to compare the performance of the models between groups. This has been pointed out by the world leaders within glucose modelling i 2009 in a report saying that *"A Web site describing different models and the data supporting them should be made publicly available, with funding agencies and journals requiring investigators to provide open access to both models and data"* [87]. Unfortunately, not much effort has been put into the realization of this website [85]. To our knowledge no general website currently exists. This reluctance to

share data and models slows the progress of the artificial pancreas development which unfortunately affects the patients. We fully recognize the importance of sharing data and wish to support the idea of availability of data sets by making it accessible to others. The technical report in Appendix A contains the full information about the study and is suppose to introduce researchers who want to work with the data to the study design and data files. We are in the progress of making the data set publicly available through the project website [74] together with the report. The data set could potentially serve as a general validation set for researchers to use for evaluating the model performance of future simulation and prediction models.

Even though we gained an information rich data set we must recognize the difficulties in transferring this information to everyday conditions. In real life, patients do not eat standardized meals. They do various types of sport at different intensities. They get sick and stressed. They drink alcohol and coffee. On top of all this, the response to these disturbances are subject to intra-individual variability. Thus, as pointed out in [88] it is important to remember that models based on data from an organized study obtained in a predetermined way will be much easier to control than real life patients.

Ideally, from the experience with this study we should have designed a new study but the time and money were not available. Several new studies could be suggested as there are many issues to investigate further. To fully understand the interplay between glucose absorption from a meal and the endogenous glucose production, tracers are necessary. Furthermore, to identify the relevant circadian rhythms in the system, future studies should last at least 24 hours. Finally, it is important to note that the observed effects of meals and exercise in this study cannot be generalized to other meal and exercise types. Specialized studies including several types of meal or exercise types are needed to identify general models.

Chapter 3

Pinpointing Model Deficiencies with Stochastic Differential Equations

As explained in Chapter 1, SDEs provide an excellent tool to identify model misspecifications and furthermore reveal how the model should be extended to deal with these misspecifications in theory. In this chapter, we describe how SDEs were used to identify misspecification in a previously published model [52]. The model identification was based on the data obtained from the clinical study described in Chapter 2. This chapter is based on Paper B in Appendix C.

3.1 Model Identification

The aim of this study was to investigate whether we could use SDEs to pinpoint deficiencies in an already published simulation model of the insulin-glucose system in type 1 diabetes patients based on the clinical data from the study described in Chapter 2. This was an invited paper and thus an additional purpose

was to introduce the use of SDEs to the research society within diabetes technology.

As base model we chose the identifiable virtual patient (IVP) model [52, 53]. It is also referred to as the Medtronic virtual patient as Medtronic uses this model in the development of their version of a artificial pancreas. The model is named identifiable virtual patient because of its identifiability from data normally available from clinical studies of artificial pancreas systems i.e. insulin and carbohydrate delivery, plasma glucose, CGM observations, and insulin observations. A simplified illustration of the IVP model is seen in Figure 3.1. The core of the model resembles the minimal model. Despite its simplicity, the model covers a more complex connection between insulin and glucose, and glucose effect on itself [9]. The insulin absorption from the pump and the meal absorption are modelled as linear three- and two-compartment models. The model is nonlinear due to the effect compartment describing the pharmacodynamic effect of insulin on glucose.

Initial attempts to estimate the parameters of the model showed that the part of the model related to the CGM sensor was not appropriate. One of the reasons for this inappropriateness is explained and dealt with in Chapter 5. Therefore, we excluded the CGM observations from the estimation and removed the state equations describing the dynamics between plasma and sensor glucose (Glucose (int.) in Figure 3.1).

The resulting base model consisted of six state equations and two observation equations (plasma insulin level and plasma glucose level). As the model does not include the effect of exercise, only data sequences from study days without exercise (in total four sequences from four patients) were used for model identification in this study. The modelling was done in the newly developed R package for continuous time stochastic modelling (CTSM) [29]. The current version only allows for single-subject modelling. Thus the model was fitted individually to each data sequence.

The first step was to identify an ODE version of the model og hence a model with no diffusion terms. This model served as base model for the subsequent SDE models. Identification was done with maximum likelihood estimation – see [59] for details about the estimation.

From this base model, we set out to identify the best SDE version of the model including one non-zero diffusion term. The ODE base model was extended to an SDE model including one diffusion term corresponding to a single state and again estimated with maximum likelihood. This was repeated for each of the six states of the system resulting in six SDE models in total.

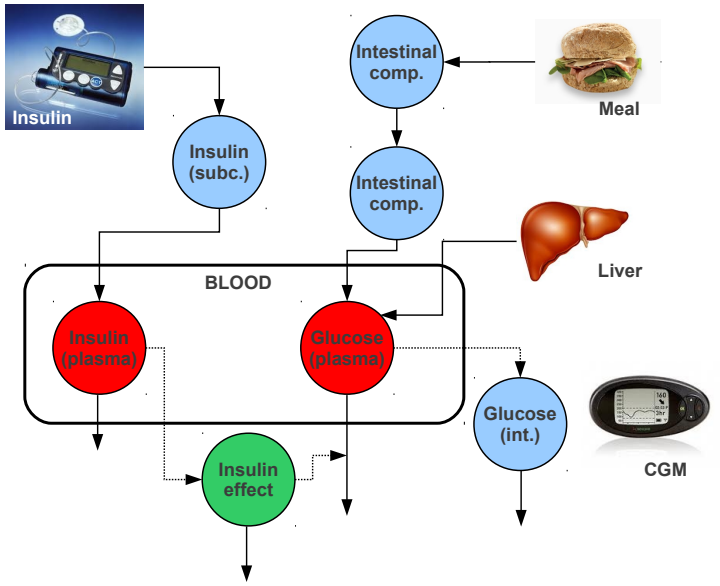

Figure 3.1: An illustration of the IVP model. In this study we did not estimate the parameters and states related to the CGM observations. Solid lines represent mass fluxes. Dotted lines represent effect fluxes.

The quality of the models were evaluated with a likelihood ratio test as the ODE base model is nested into all the SDE models. Thus, for each of the six SDE models with one diffusion term a test statistic was computed and evaluated. If we instead wanted to compare the SDE models directly, we could have used e.g. Bayesian Information Criteria. The SDE model resulting in the largest difference in likelihood estimate was appointed to be the best SDE version. As the models were estimated separately for each data sequence, the overall maximum likelihood estimate for each version of the model consisted of the sum of maximum likelihood estimates for each data sequence.

In the paper by Kanderian et al., they introduce intra-individual variability in some of the parameters to obtain an improved model fit [52]. They define three time windows in which the parameters are constant but at different levels for each window. With SDEs, we could instead use parameter tracking to avoid any subjective assessment of the intra-individual variability. Hence, in the paper we replaced the parameter related to the rate of meal absorption with a random walk to investigate the data driven variation of this parameter during the study day.

3.2 Results

First of all, we were able to show that adding a non-zero diffusion to the IVP model improved the maximum likelihood value significantly. The largest improvement was obtained when the non-zero diffusion term was added to the state equation describing the pharmacodynamic effect of insulin on the plasma glucose (Insulin effect in Figure 3.1). This indicates that this state equation is the most misspecified part of the IVP model according to our experimental results.

One-step predictions and autocorrelation functions of the residuals showed the improved model fit from the SDE model. It should be noted that all six SDE models were significantly better than the ODE base model (with no diffusion term) based on the maximum likelihood estimate.

By tracking the parameter related to the meal absorption rate we saw that this parameter varied according to the meal type. The data sequences included a standard solid meal (event 1) and a juice drink (event 3). The estimated rate of absorption was lower for the juice drink than for the solid meal.

3.3 Discussion and Future Work

This study showed that using SDEs in model development can be advantageous in several ways. We were able to pinpoint deficiencies and to track parameter variation probably caused by a differences in meal type. This information could be added to the model to improve the fit.

The state equation representing effect of insulin on the plasma glucose level was identified as the most misspecified part of the IVP model. From a physiological point of view this is reasonable as this simplification of the insulin effect is far from the real situation.

If we had been able to not only identify but also model the variation in the model parameters we could take into account the significant misspecification by e.g. ascribing this variation to outer factors or observed variation in other parts of the system. In this specific case, we identified the effect compartment representing the insulin effect as the most critical part of the model compared to the clinical observations. Thus an intuitive next step would be to track the related parameters - in this case the insulin sensitivity,S_i, and a rate parameter, p_2, controlling the speed of the effect. We attempted to replace these parameters with a random walk, but the estimation either failed before convergence or showed no variation. Reasons for this are probably that the data sequences were too short to estimate variation within the single data sequences. Longer sequences (at least 24 hours) are needed to fully evaluate this variation and its relation to circadian rhythms in one or more of the hormones we analysed in the clinical study.

From the autocorrelation function of the residuals we can evaluate whether the model is able to explain all systematic variation in the data. In this case, we saw a large decrease in autocorrelation for the best SDE model compared to the ODE model. However, any presence of residual correlation indicates that an extra state needs to be added to the model. The number of states needed can be determined from the *partial* autocorrelation function [73].

The choice of model showed to be reasonable as we were able to identify the model for all four data sequences. It has been criticized for not being suitable as simulation model [21], but as basis for model extension, this simple model was the most appropriate compared to the Hovorka and Virginia/Padova model [97, 24]. We did implement Hovorkas model as an SDE model but the size and complexity of the model together with the small amount of data per patient and the inflexibility of the old version of CTSM made it impossible to do rigorous model identification.

The varying rate of glucose absorption from the meal identified with a random walk is believed to be due to the type of meal. However, we cannot reject that the variation is simply due to the time of day - i.e. that the rate of absorption is higher in the afternoon than in the morning. In [94] they show that the glucose absorption at lunch and dinner is different from the absorption at breakfast. However, they find a higher absorption in the morning than at noon and evening contrary to our findings.

The results in this study suffers from the fact that the models were estimated on each data set separately and from four patients only. Thus we must be careful not to generalize the results to the underlying population. The statistical measure used for finding the best SDE model consisted of the sum of the individual maximum likelihood estimates. This measure has a drawback as we cannot guarantee that the significant improvements is caused by improvement in all four data sequences or if the finding originates from a major improvement in one data sequences only. We checked that all individual likelihood values had improved significantly, but we did not check if the best overall model was the best model for all individuals. Thus the findings may actually not be valid for all four data sequences. If we were to use all 24 sequences we would need an extension to the model including exercise effects. However, this extension would add to the number of parameters to be estimated which we believed to be non-identifiable and thus impossible to estimate from only a single data sequence.

In this study, we focused on short-term prediction. As the maximum likelihood estimation is based on one-step prediction errors the model is naturally optimized to make accurate predictions on the short term. However, it is important to note that the tools provided by SDEs could be used to identify a robust simulation model as well. It would require a different estimation criteria focusing on the parameters related to the steady-state behavior of the system. Furthermore, it would require that the degree of misspecification is low meaning that the diffusion terms are small. If however, the diffusion terms represent true random behavior in the system they should be a part of the model as they would reflect the uncertainty related to this stochasticity.

To build on this work the main obstacle needs to be overcome. An appropriate software capable of handling SDE model estimation from several subjects at the same time is needed. Fortunately, the development of an extension to CTSM for population models has recently begun. When this is ready, several approaches can be tested. First of all, the study described here could be repeated with a population model. This would overcome the problem of too few observations as the parameters could be estimated from the four data sequences simultaneously. All 24 data sequences could be included if they were cropped prior to exercise events. Alternatively, we could use this model to identify the significant effects of exercise in the data with, e.g, parameter tracking and hence use all the data

for estimation. In the next chapter, we describe our attempts to include exercise in the model.

Chapter 4

Exercise Effects in Type 1 Diabetes

Exercise poses a major challenge to fully automatic control of the plasma glucose level. The physiological responses of exercise are manifold and appear on short- and long-term scales. Mathematical models of these responses are relevant for both simulation models and control models.

In this chapter, a short description of the physiological responses to exercise and the models found in literature is given. Next, the methods and results from a modelling study related to exercise responses of the plasma insulin concentration is described. This study was motivated by the results of the clinical study described in Chapter 2, which showed that the plasma insulin concentration increased during a 20 minutes exercise bout – see Paper A in Appendix B. The modelling study was an initial step in the development of a population model (a hierarchical model) of the exercise effect on the plasma insulin concentration.

To our knowledge, no mathematical model of exercise effects on glucose dynamics take this increase in plasma insulin into account. Thus, the aim of this study was to identify a relevant model structure based on a hierarchical SDE model of this response. The chapter is based on the work in Technical Report II in Appendix D.

4.1 Physiological Responses of the Insulin and Glucose Dynamics to an Exercise Bout

Effects of single exercise bouts in type 1 diabetes patients are complex and dependent on many factors. Thus it is a difficult task for the patients to compensate for the exercise by eating carbohydrates or decreasing the insulin delivery prior to exercising. However, as well as healthy people, people with type 1 diabetes can benefit from regular exercise. But the benefits on plasma glucose control are not well established, illustrating the difficulties in managing diabetes while maintaining an active life style. A recent meta-analysis study showed however, that training (regular exercise) has a positive effect on glycemic control in type 1 diabetes [89].

Exercise increases insulin sensitivity both in healthy individuals and individuals with type 1 diabetes. In healthy individuals, the insulin secretion declines during moderate-intensity exercise to counteract the increased insulin sensitivity. However, as type 1 diabetes patients lack the ability to adjust the insulin secretion the result is hypoglycemia. Additionally, the endogenous glucose production is inhibited if the plasma insulin level is high which will amplify the hypoglycemia [44].

The meta-analysis in [89] showed that the response depends on exercise type, duration, nutritional status, time of insulin bolus delivery, and pre-exercise plasma glucose level. Whereas low-to-moderate exercise often results in hypoglycemia, less severe hypoglycemia or even hyperglycemia are seen after high-intensity exercise [39]. The latter is probably due to high counter-regulatory hormone action stimulating the endogenous glucose production [44]. After prolonged exercise, hypoglycemia may occur up to 6-15 hours after exercising [44, 89]. Not only the glucose level but also the plasma insulin levels changes during exercise. The latter depends on the time of bolus delivery, bolus size and injection site [44]. The effects on the plasma insulin level make the response to exercise even more unpredictable.

4.2 Models of Exercise Responses in Type 1 Diabetes

Several models have been suggested to take into account the acute (within hours) responses of exercise in type 1 diabetes. They use e.g. heart rate or the percentage of an individuals maximum oxygen consumption rate to quantify exercise. In

[27], an exercise extension to the minimal model is evaluated from simulations. The extension consists of three parameters related to the insulin sensitivity and utilization of glucose and insulin.

One study uses percentage of oxygen consumption rate and percentage of active muscle mass to quantify exercise. The model takes into account blood flow rate changes and redistribution, changes in muscle glucose uptake, and changes in liver glucose production and release. The model simulations are compared to glucose data from the literature [63]. An extended version of this model takes into account the glycogen depletion during exercise [62]. Furthermore, the study in [42] extend this model to heavy intensity exercise, however it is not compared to experimental data.

In [16], the minimal model is also used as basis to include the effects of exercise quantified by heart rate on longer lasting changes in insulin action and increased glucose uptake. The model is estimated on data from type 1 diabetes patients in a hyperinsulimic clamp study. A continuation of the work in [16] incorporated a stronger effect of intensity and the effect of the duration of the exercise bout[23].

Some of the models include the effect on the insulin concentration in plasma by assuming an increased insulin clearance rate during exercise [79, 63, 42].

4.3 Population Modelling of Plasma Insulin Changes During Exercise

In the clinical study described in Chapter 2, an increasing plasma insulin concentration was observed during the exercise bouts as a result of an increased absorption from the infusion site in the subcutaneous layer [82]. The reason to the increased absorption is not fully understood, but muscle contractions in the surroundings of the injection site have been suggested. However, this hypothesis does not agree with our results as the insulin pump was placed in the abdominal or lumbar area. Hence, other hypotheses could be that the response is related to an increased temperature or increased blood flow in the peripheral tissue.

The aim of this study was to identify a model capable of describing the changes in insulin absorption due to exercise. From the study described in the previous chapter, we realized that the current version of CTSM would not be adequate to identify a model for this effect due to the restriction to single-subject modelling. Thus, parallel to this project a prototype of a population modelling extension to CTSM was developed.

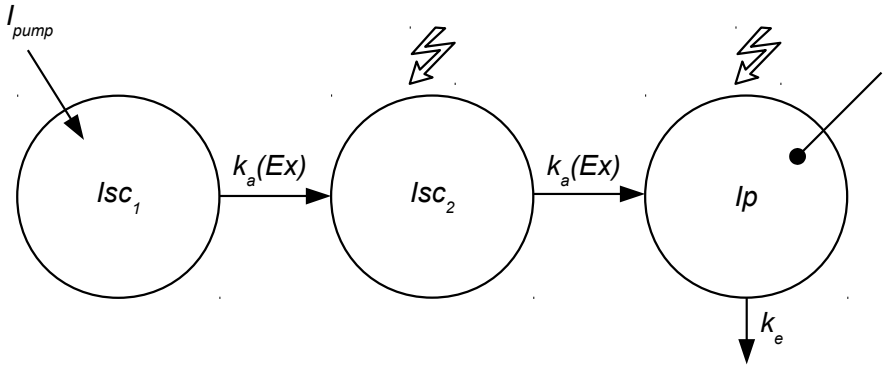

Figure 4.1: Illustration of the three-compartment SDE base model describing the pharmacokinetics of insulin delivered continuously from an insulin pump. Lightnings indicate diffusion terms.

Initially, a base model was identified. This was a linear three-compartment model suggested in [97]. The model was changed into an SDE by adding diffusion to two of the three compartments as indicated in Figure 4.1 by lightnings. Our hypothesis was that the absorption rate parameter, k_a, increased during exercise.

In total, we had 24 data sequences available from the clinical study. Due to unstable insulin plasma levels in the stabilization period prior to the first event, seven of the 24 sequences was disregarded in this study. Consequently, the model was identified from 17 sequences including approximately 23 observations each - see Appendix A for details on sampling scheme.

The insulin plasma concentration had to be strictly positive. As the state is influenced by diffusion, the only way to ensure that the state values remain positive is to make the diffusion state-dependent. However, the estimation method in CTSM cannot handle this state-dependency. To overcome this issue, the state was transformed with a Lamperti transformation to a state equation without state-dependent diffusion. Furthermore, the variance of the measurement error was forced to attain a minimum value as preliminary estimations showed that the parameter estimation brought it to zero. The minimum value was based on literature findings.

We used three approaches to model the effect of exercise on the insulin absorption rate. In the first approach, we attempted to track the variation in the absorption rate parameter with a random walk as with the meal absorption rate parameter in Paper B. However, initial attempts to estimate this variation showed that it was not feasible due to lack of observations. In the second

approach, the relationship between the insulin absorption rate parameter and exercise was modelled as a linear dependency without taking into account that the patients in the clinical study exercised on two levels - mild and moderate. Thus, the third approach was to separate the effect of mild and moderate exercise on the insulin absorption rate parameter. In this model formulation the absorption rate parameter, k_a was specified as a constant plus two terms related to mild and moderate exercise, respectively – see Technical Report II for details (Appendix D).

Parameters were estimated as for the model in Paper B with maximum likelihood estimation, however, the hierarchical structure of the model in this study requires a two-stage approach to estimate the parameters – see Technical Report II for more details. The models were compared to the base model with a likelihood-ratio test and with Akaike Information Criteria and Bayesian Information Criteria. Posterior identifiability was checked from the conditional likelihood profiles for each estimated parameter.

4.4 Results

From likelihood-ratio tests, Akaike Information Criteria, and Bayesian Information Criteria the model taking into account the exercise intensity showed to be the best model to describe the effect of exercise on the insulin absorption. The increase in absorption rate was largest for moderate exercise compared to mild exercise. In Figure 4.2, the one-step predictions from the model for one of the 17 data sequences are depicted. The increase in plasma insulin level related to exercise is captured by the model and the compliance with the observations is in general good. However, the associated uncertainty is large.

4.5 Discussion and Future Work

This study showed that the response of the plasma insulin concentration to exercise is significant and should be taken into account in future models of the exercise effects in type 1 diabetes patients. It is important to note that this model is estimated from data from patients using an insulin pump. Whether the model can explain the response in patients using insulin pens still has to be determined.

In the study, the two exercise intensities were represented separately by binary variables indicating whether the patient was exercising or not. A more general

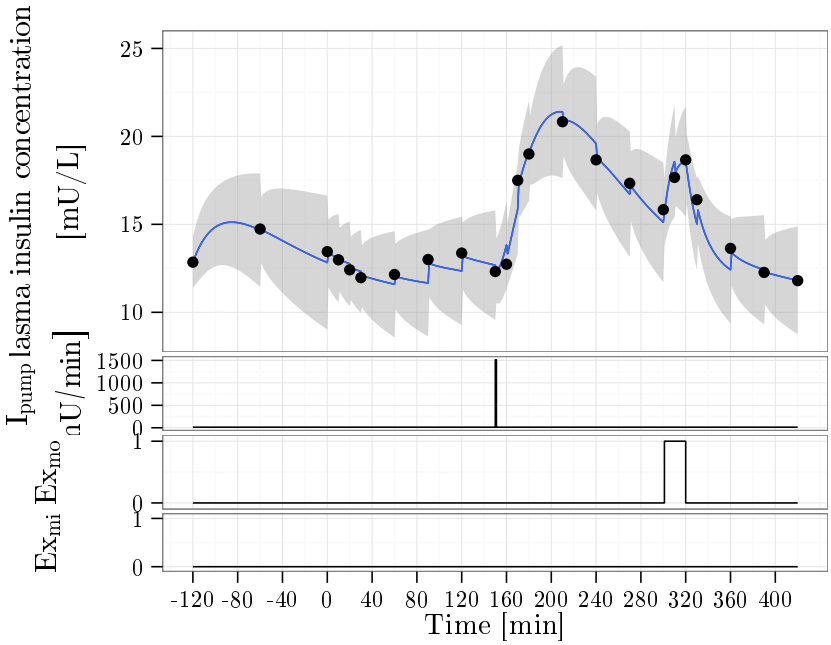

Figure 4.2: Data sequence no. 10. Top: One-step predictions from the model taking into account of different intensities (blue line). The observations are represented by dots. The grey area indicates 95% prediction interval. Middle and bottom: Insulin and exercise inputs.

way of quantifying exercise is as mentioned to use the heart rate as indicator of exercise. However, for some of the data sequences used in this study, the heart rate information was unavailable due to monitoring problems.

Undoubtedly, the development of a realistic model of the effects of exercise requires highly customized clinical studies. First of all, the sampling time during the exercise bout should be short. One suggestion is to extend the exercise bout to 30 minutes and analyse plasma insulin concentration every five minutes during and immediately after. Also, the effect of the timing between the exercise bout and the bolus injection has to be investigated.

The effect of exercise was not individualised in the model. However, it is reasonable to assume that the observed effect depends on the individual patients weight, level of fitness, pump placement etc. To incorporate this individualisation into the model also requires more clinical studies.

The next step could be to combine the optimal model from this study with e.g. the model used in Paper B to estimate the effect of this increased plasma insulin concentration on the plasma glucose level from the entire data set. If this combined model is not adequate to explain the data, SDEs could be used to identify additional effects of exercise e.g. on the insulin sensitivity or the glucose disposal. The optimal way of doing this would of course be to use the significance of the diffusion terms as a guide to identify those parameters influenced by exercise. If this is not possible, the same approach as the one used in this study could be used – i.e. define a structure of the dependency and estimate the different model candidates. A good candidate for this structure could be the model suggested by [16], due to its simplicity, the fact that it is based on the minimal model as the model in Paper B, and due to the fact that exercise is quantified by heart rate which is available for most of the data sequences in our data set. A critical prerequisite for these suggestions for future work, is that the prototype of the population extension to CTSM is further developed.

As this study was conducted at the end of the PhD-project, the results are preliminary. Further improvements to the model could be made by removing insignificant parameters from the model. The posterior identifiability check showed that the variance of the measurement error was unidentifiable – i.e. the profile did not show a minimum. This is probably due to the specification of the error model as additive instead of proportional or that the estimation method compensates for a bad prediction by relying fully on the observations. Thus other base models should be tested. In [98], they suggest to use a more complex model with two parallel absorption routes - one fast and one slow absorption route with saturable local degradation. With this structure, the influence of exercise could be added by increasing the fraction of insulin molecules traveling

through the fast absorption route during exercise and/or by decreasing the local degradation and thus increase the amount of insulin that appears in plasma.

The population modelling approach is crucial in these models. The variability between and within individuals is recognized as one of the major challenges to the realisation of the artificial pancreas. With this type of hierarchical models, this variability can be estimated, categorized as inter- or intra-individual variability, and to some extent be explained from demographic, pathophysiological or environmental factors that may influence the behavior of the insulin-glucose system. This extra information can be used to customize models for simulation or control to individuals. From the prior knowledge about the above mentioned factors, the parameters can be estimated from this information instead of expensive and time-consuming clinical studies. To improve the models compliance with the individual patient, a combination of prior knowledge and data could be used in a Bayesian context as suggested in [40]. However, for the population model to be robust and representative, it has to be based on a large number of representative subjects.

Chapter 5

SDEs in Automatic Control of the Glucose Level

Several strategies for automatic control of the plasma glucose level have been applied by the large number of research groups involved in artificial pancreas projects. The most often applied methods are proportional, integrative and derivative (PID) control, fuzzy-logic methods and Model Predictive Control (MPC) [46].

One of the aims of the DIACON project was to develop and test automatic control algorithms to regulate the glucose level in type 1 diabetes patients. For this purpose we used the MPC strategy.

As pointed out in Chapter 1, the inaccuracy of the CGMs is one of the major problems for the realization of the artificial pancreas. During the project, two studies related to CGMs were done. The first of them deals with tuning of a control algorithm designed for overnight glucose control based on CGM observations. The second one deals with prediction of the plasma glucose level from CGM observations alone using a nonlinear SDE model and a Bayesian estimation method. This chapter shortly describes the two studies and the results of them. Finally, the perspectives of the studies are discussed and future work is suggested. The chapter is based on the work in Paper C in Appendix E and Paper D in Appendix F.

5.1 The DIACON Artificial Pancreas

In the DIACON project we focused on MPC for several reasons. With MPC it is possible to implement constraints in a systematic way. In this case, it is very beneficial with a predictive controller due to the time delays related to insulin absorption and glucose diffusion from plasma to the subcutaneous layer. MPC has appointed as the most promising strategy for glucose control [21].

A key component of an MPC controller is the model used for prediction of the future output (plasma glucose values) and future input (insulin delivery). Whereas models for simulation are often non-linear and high dimensional, models used for control purposes are typically simpler and in most cases linear since they are derived from a linear system description.

5.1.1 Tuning of Controller with SDEs (Paper C)

This study deals with estimation of the optimal tuning of a Kalman Filter in an MPC controller for glucose control. The first version DIACON controller was based on a linear second order model with three patient specific parameters related to the effect of insulin on the plasma glucose level [14, 10]. These patient specific parameters are already used by the patients or their physician in the normal daily treatment. The controller was designed to stabilize the plasma glucose level overnight. This time of day was chosen due to the absence of disturbances such as meals, exercise, and stress.

We initially modelled the system by an ARIMAX model which includes an integrator to ensure off-set free tracking [65, 50]. The structure of the stochastic part of the models is a trade off between offset-free control and model-plant mismatch. The parameter governing the influence of the integrator was determined from initial simulations [13].

After a preliminary clinical pilot study it became clear that the stochastic part was misspecified – i.e. the gain of the build-in Kalman filter was not properly tuned. The controller was too sensitive to deal with the noisy signal from the CGM as the corresponding variance estimate was too small [7]. A situation from the pilot study is shown in Figure 5.1. When starting automatic control (at 22:00) the local trend was increasing whereas the global trend was decreasing. The model predicted an increase in plasma glucose from the local trend and thus suggested a large bolus as compensation.

The local trend was however not physiological in the sense that is was not

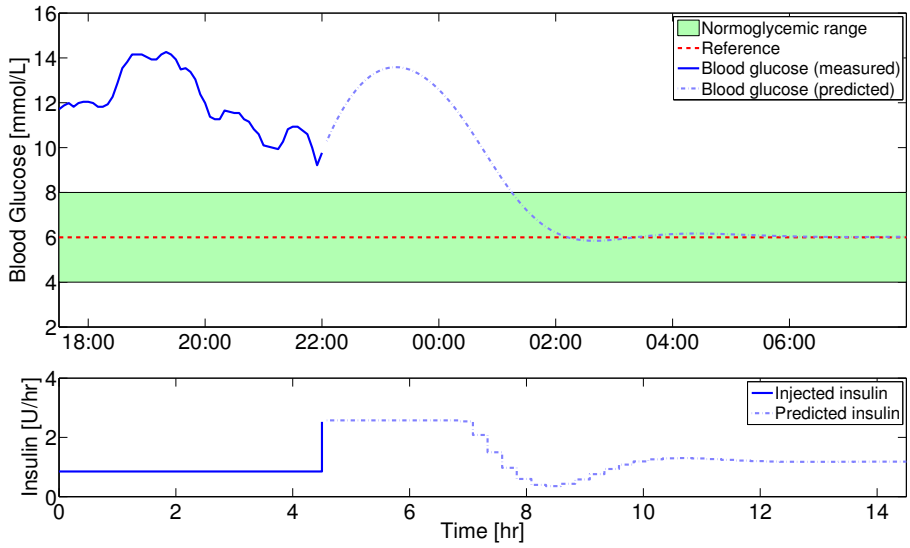

Figure 5.1: Top: CGM observations (solid line) and plasma glucose prediction at the start of automatic control (dashed line) from the first pilot study. As seen, the controller relies too much on the local trend. Bottom: Insulin delivered by the pump (solid line) and predicted insulin delivery (dashed line).

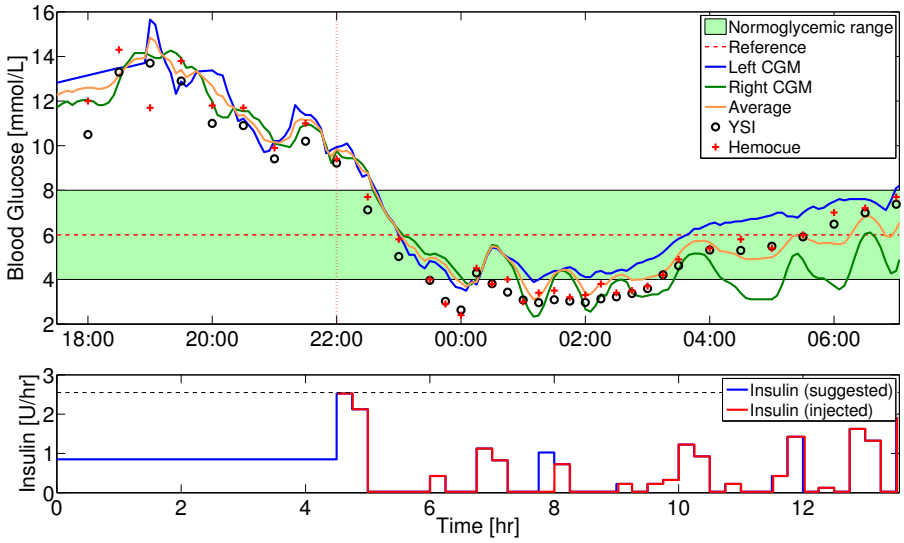

Figure 5.2: Result of the first pilot study. Top: Glucose observations, YSI: Plasma glucose values (gold standard), Hemocue: Glucose values [38]. The right CGM acted as feedback to the controller. Bottom: Insulin delivery from the pump.

caused by a disturbance in the plasma glucose level but simply variation in the CGM signal. The bolus suggestion from the controller (which was delivered to the patient) caused the plasma glucose to decrease into the hypoglycemic range and intravenously glucose had to be administrated at 00:00 to avoid severe hypoglycemia. The complete CGM and plasma glucose traces from the pilot study are plotted in Figure 5.2.

With CTSM we had the possibility to estimate the optimal Kalman filter gain directly from the data instead of from simulations. The model was implemented as a second order linear SDE model with two identical diffusion variances with zero covariance. Two CGM sensors monitored the glucose level every five minutes throughout the night. Data from both of them were used for the estimation (see Figure 5.2).

The structural parameters were fixed according to the patients specific values. The variance of the diffusion terms and of the normally distributed measurement noise were estimated with a modified maximum likelihood estimation. Normally, the maximum likelihood estimation is based on one-step predictions. However, in this case, the estimation was based on three-step predictions. The ratio between the system and measurement noise variances are directly related to the

Kalman filter gain in the controller.

5.1.2 Prediction of Plasma Glucose From CGM Observations Using SDEs and a Bayesian Estimation Method (Paper D)

In a later study, a more physiological approach was investigated [41]. In this study, the base model was the same nonlinear model as the one used in the study described in Chapter 3 (the IVP model). However, here we extended it with a submodel representing the transport of glucose from plasma to the interstitial space where the CGM sensor is placed. Insulin plasma, plasma glucose, and CGM observations were available. The meal input was disregarded as we used overnight data originating from the clinical feasibility study of the control algorithm studied in Paper C [81].

The focus was to investigate if the IVP model could be used as prediction model in an artificial pancreas - or more specifically if an SDE version of the IVP model could predict the plasma glucose level from the CGM observations alone. We took into account the fact that the CGM is not observing the plasma glucose level directly by adding an extra state representing the interstitial glucose level as described in [52]. Thus we included two separate observation equations - one observing the plasma glucose level and one observing the interstitial glucose level (and an extra one for plasma insulin).

Initially, the forward selection method based on maximum likelihood estimation was applied to identify the relevant diffusion terms as described in [30]. The CGM provided a new observation every five minutes and the plasma glucose level was analysed with a gold standard method (YSI) every thirty minutes. Consequently, the number of observations was unequally distributed between the two types of observations. Moreover, the two observation types are very different in terms of accuracy and observes two distinct glucose concentrations.

The fact that maximum likelihood estimation weights every single observation equally poses a problem when dealing with models including two observation processes with different accuracy and number of samples. The initial model identification resulted in a very accurate prediction of the dense CGM observations but an inaccurate prediction of the YSI observations (see Figure 5.4). This is due to the equally weighting of the observations in the maximum likelihood estimation. To some extent, the likelihood will increase when the observation type with the highest number of observations can be predicted accurately by the model.

By including prior knowledge about the inaccuracy of the CGM and thus employing a Bayesian estimation method, the problem of equally weighting was overcome and the plasma glucose predictions were improved.

5.2 Results

Both studies involved data from one patient only. However, the results in Paper D using the Bayesian method was cross-validated on a second data set from another study night.

5.2.1 Tuning with SDEs, Paper C

In Figure 5.3, the situation from the beginning of automatic control in the first pilot study is shown – now with the Kalman gain found from data with the SDE model. The prediction is now more realistic compared to the actual overall behavior of the glucose level.

Another pilot study was conducted and showed an improved controller performance - see Appendix E for the plot. Finally, we went into the real clinical study to evaluate the feasibility of the DIACON controller in overnight control. The results of the study are described in [81].

5.2.2 Bayesian Estimation Method, Paper D

The predictions of the plasma and interstitial glucose level with the maximum likelihood estimate are shown in Figure 5.4. It is clear that the optimal likelihood estimate is not optimal in this case as the aim is to predict the plasma glucose level with acceptable confidence.

With the Bayesian approach including prior information regarding the accuracy of the CGM and the YSI analysis methods, the predictions are improved as shown in Figure 5.5. The plasma glucose level is predicted more accurately and with less uncertainty whereas the opposite holds for the interstitial glucose observations.

To test the predictive performance of the model based on the Bayesian approach, the predictions were recomputed - this time excluding the insulin and YSI data

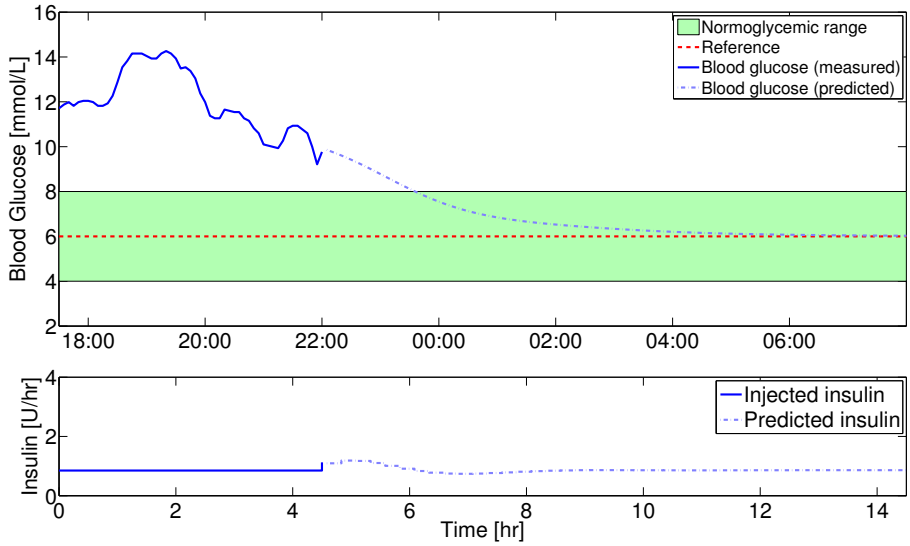

Figure 5.3: Top: CGM observations (solid line) and plasma glucose prediction (dashed line) from the first pilot study at the time of start of automatic control if the data tuned Kalman gain had been used. The normal range is indicated as the green area. Bottom: Insulin delivered by the pump (solid line) and suggested insulin supply (dashed line).

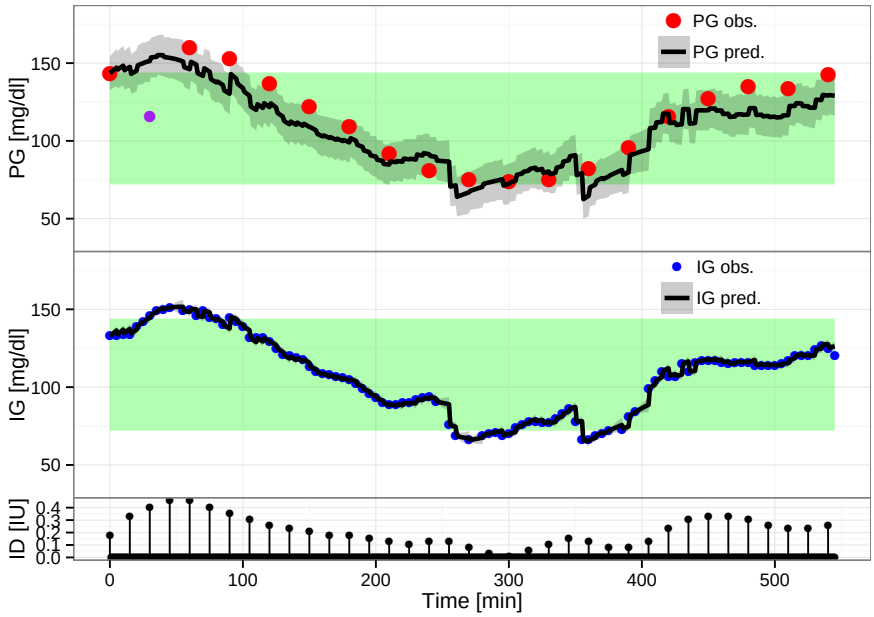

Figure 5.4: Prediction of plasma glucose (PG) and interstitial glucose (IG) observations using maximum likelihood estimation. The green ribbon reflects the normoglycaemic range. The purple observation is an outlier not used in the estimation nor prediction. Top: One-step prediction and 95 % prediction band of the plasma glucose observations. The prediction is not in agreement with the observations. Steep transitions are seen when there is a change in the interstitial glucose observations. Middle: One-step prediction of the interstitial glucose observations and 95% prediction band. The prediction band is unrealistically narrow, reflecting the fact that the model seeks to explain the sensor error exactly, not reflecting that the plasma glucose observations are analysed with a gold standard method. Bottom: Insulin delivery (ID) as boluses.

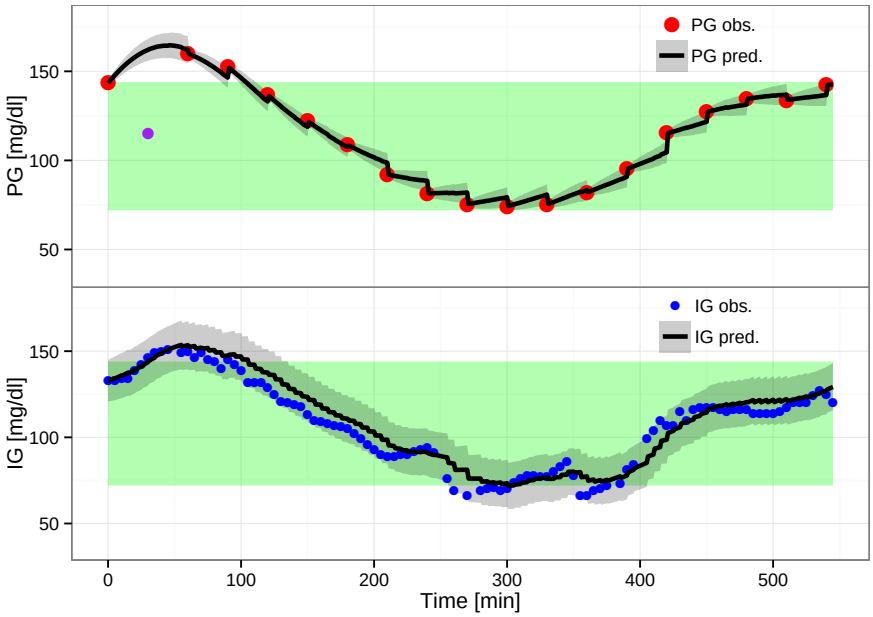

Figure 5.5: Prediction of plasma glucose and interstitial glucose observations using Bayesian estimation. Green ribbon reflects the normoglycaemic range. The purple observation is an outlier not used in the Bayesian estimation nor prediction. Top: One-step prediction and 95% prediction band of the plasma glucose observations. Small adjustments are seen when a new plasma glucose observation is obtained, but the prediction is in general agreement with the observations. Bottom: One-step prediction of interstitial glucose observations and 95% prediction band.

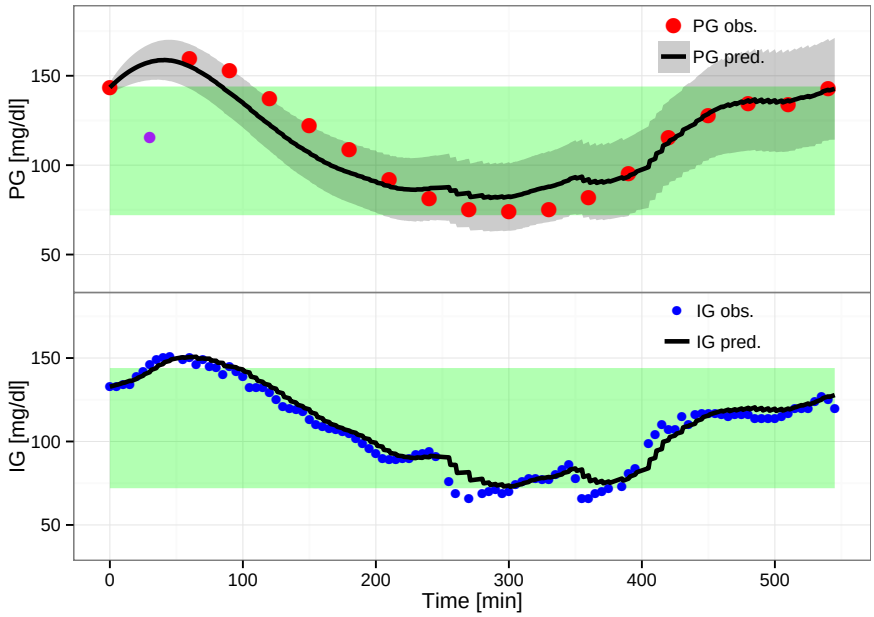

Figure 5.6: Prediction of plasma glucose and interstitial glucose using only interstitial glucose observations. Green ribbon reflects the normoglycaemic range. The purple observation is an outlier not used in the Bayesian estimation nor prediction. Top: One-step prediction of plasma glucose and 95% prediction band. The dynamics of plasma glucose are captured in the prediction and the prediction band covers all but two plasma glucose observations. Bottom: One-step prediction of interstitial glucose.

except the initial YSI observation. To some extent, this resembles the real life situation where the only available information about the plasma glucose level is the CGM observations and a few daily calibrations.

The predictions were cross-validated on data from the same patient on another study night. Hence, Figure 5.6 shows the prediction of the same study night as in Figure 5.5, but with a model estimated with data from the other study night. As seen, the model is capable of predicting the plasma glucose level with a quite good level of confidence. However, towards the end of the study night the uncertainty increases. This would interfere with the performance of a potential controller. Thus, if a second YSI observation was used a calibration at a later point, the confidence at this time would improve.

5.3 Discussion and Future Work

The studies show two distinct applications of SDEs in automatic control of the glucose level and two different approaches handled the inaccuracy of the CGM. The models are two different candidates for MPC representing each end of the range of models. The model in Paper C is simple and linear, though it is still based on physiological knowledge as the model in Paper D. The latter exploits the fact that the CGM sensor does not directly observe the state we wish to control (the plasma glucose level) whereas the first model assumes that the output is the plasma glucose level and all differences are classified as noise. Incorporating the explicit physiological difference between the plasma glucose and the interstitial glucose in the model has previously shown to be advantageous [55, 35].

The deterministic parameters of the simple model in Paper C was not estimated from data but based on prior knowledge. If the parameter values are not known by the patient it could be beneficial to use the same approach as in Paper D with a Bayesian (or maximum likelihood) estimation of these parameters. However, the two methods require different types of data and information to be estimated and calibrated. The model in Paper D needs plasma glucose observations and plasma insulin observations to be fully estimated while the model in Paper C only needs a series of CGM observations, the known patient specific parameters, and information about the insulin input.

The Kalman filter tuning in Paper C was based on data from only one patient and only one study night. The second pilot study on the same patient showed an improvement in robustness and was less affected by non-physiological disturbances, indicating that the intra-variability was non-significant in this case. For the sake of simplicity, the same Kalman gain value was used throughout the entire clinical study involving several patients following the second pilot study. In general however, we would except the gain to be influenced by both inter- and intra-variability caused by physiological variation and device related variation [6]. To accommodate the inter-individual variability, the Kalman filter gain should be tuned for the individual patient prior to the start of automatic control.

The controller should ideally be able to adapt to both kinds of variability and thus an adaptive approach is needed. Both models could in principle be implemented in an adaptive algorithm where model parameters were estimated on-line to take into account the intra-variability. The intra-variability occurs due to the physiological changes that occur over time (exercise, stress or medication) and due to the fact that the CGM sensor is exposed to biofouling [92]. During the DIACON project, we showed that adaptive tuning with recursive

least squares for a similar model to the one in Paper C, improves overnight control in a simulation study [13]. For the model in Paper D, the parameters related to the interstitial glucose level and the CGM observations could be estimated adaptively. Estimation of all the parameters would require insulin and plasma glucose observations which are not available outside the clinic.

One of the direct advantages of using SDEs to estimate this type of models is that we obtain an estimate of the prediction uncertainty. With respect to control, this is important as pointed out in [1]. The extra information in terms of uncertainty can be used to include extra safety constrains based on the probability density. The constraints can be asymmetric taking into account the severity of acute hypoglycemia versus the long-term risks related to hyperglycemia.

From the initial estimations in Paper C based on one-step predictions we concluded that a step-size of one (corresponding to 5 minutes) resulted in a too sensitive Kalman gain. This assessment was done on the basis of the prediction by the MPC model with the corresponding estimated Kalman filter gain. By reorganizing the dataset, we were able to force CTSM to base the maximum likelihood estimation on the three-step prediction which showed to improve the relevant prediction. Three steps (15 minutes) correspond to the controller actuation rate. This accordance between controller actuation rate and estimation criteria could be causing the observed improvement. However, more data is needed to document the validity of this hypothesis. Ideally, the estimation could be based on multiple prediction horizons corresponding to the length of the prediction horizon used by the controller (0-15 minutes).

In Paper D, we use the initial YSI observation to calibrate the model. In real life, CGMs are calibrated from finger stick measurements analysed with a glucose meter. The glucose meters are less accurate than the YSI analysis which off course would interfere with the prediction accuracy of the model. Thus the real life performance of the model would be expected to be less good than what we obtained. The differences between YSI analysis and glucose meters are not only due to the different technical specifications and methods but also due to the fact that glucose meters are used with capillary blood whereas the YSI analysis in our study is done on venous blood. The glucose concentration can vary significantly between the two pools under certain circumstances [90].

These studies illustrate that SDEs have a large potential in the development of models for MPC of the glucose dynamics when it comes to handling the CGM problems. The studies are based on results from a single subject and thus more studies are needed to validate the models and their applicability. Future studies should include clinical testing of an adaptive version of the model in Paper C. For the model in Paper D, the next step would be to estimate the model on data from several patients to confirm the present results. Furthermore, the

model could be extended to include meals as the model presented in Paper B in Appendix C.

Chapter 6

Conclusions

A fully automatic dosing system for type 1 diabetes would lighten the patients from the constant burden of managing their diabetes. However, many obstacles have to be overcome before the artificial pancreas becomes a reality. In this project we investigated how SDEs can aid in the process of reaching this goal. Several areas within the field was investigated.

First of all, we designed a clinical study to collect information rich data for model identification. This was motivated by the fact that data obtained during clinical studies testing artificial pancreas systems does not show an adequate excitation as the aim of this type of studies is to keep the glucose level in target. Furthermore, the inputs are often correlated in time. As an alternative to this method, we developed a study design where events were separated by 150 minutes and the order of events was different between study days. The study included meals, insulin boluses and exercise bouts. Plasma glucose, insulin observations and CGM observations were obtained. Furthermore, we analysed a number of hormones known to be important for glucose metabolism. Thus, the data set holds a lot of information about the counter-regulatory responses. This information still has to be fully utilized. The data set is fully documented and will become available for other researchers from the DIACON webpage.

Future clinical studies should provide us with 24 hour profiles of the insulin-glucose dynamics to be able to fully identify diurnal variation. Additionally,

tracer studies would be necessary to estimate the endogenous glucose production.

In a modelling study, we showed that by using SDEs we could identify the most misspecified part of a well known model of the insulin-glucose dynamics in type 1 diabetes. This part was the pharmacodynamic part of the model representing the insulin effect on plasma glucose. Furthermore, we identified variation in the glucose absorption from a meal probably due to different meal types. However, the study was limited by the lack of a robust software capable of handling population SDE models and by too short data sequences. Thus, the findings need to replicated in a larger study when the required software is available, before using them for further model development either towards a predictive model for control, alarm purposes, or for a simulation model.

As a first step towards a model including the effects of exercise on insulin and glucose dynamics we modelled the increase in insulin absorption during exercise as observed in our clinical study. Parallel to this study a prototype of a population modelling extension to CTSM was developed which allowed us to build a population model including fixed and random effects. Ideally, we should have used parameter tracking to estimate changes in the absorption rate, but the data set included only two observations during the exercise period which is inadequate to drive the tracking. Instead, we assumed a model structure for this relationship which showed to be significantly better than a base model with constant absorption rate. Future studies should include more clinical data to understand the relationship better and testing whether more advanced models are needed.

CGMs plays an important role in the artificial pancreas system and have been identified as one of the major obstacles to automatic control due to the associated inaccuracy and delay. This was confirmed by initial attempts to model the CGM signal and by a clinical pilot study testing an algorithm for overnight glucose control. Two studies related to the CGMs were performed during the project. In the first study, we showed that SDEs could be used to tune a control algorithm for overnight glucose control on the basis of CGM observations from the initial pilot study. The tuned algorithm improved the controller performance in a subsequent clinical study. The improvement would expect to increase if the algorithm is tuned in an individual and even device specific way. Furthermore, if the tuning is incorporated into an adaptive scheme the results would expect to improve even further due to the inherent presence of diurnal variation in the human metabolism and the fact that the CGM sensor is exposed to biofouling.

Further attempts to deal with the problems related to the CGM included a Bayesian estimation scheme. The approach can take into account the problem in maximum likelihood estimation of insulin-glucose dynamics, namely that the

number of observations from the CGM is usually much higher than the number of observations of the plasma glucose level analysed with a gold standard method. By incorporating prior knowledge about the uncertainty in the CGM observations into the estimation method, we succeeded in predicting the plasma glucose level with acceptable confidence based on the CGM observations alone.

Overall, the results in this project confirm that SDEs have a large potential within artificial pancreas modelling. However, as pointed out earlier, future modelling requires a robust software capable of handling the nonlinear population SDE models. When this is available larger modelling studies can be initiated and the impact of SDEs would be expected to increase.

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Appendices

Appendix A

Technical Report - I

Clinical Data for Advanced Glucose Modelling

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Clinical Data for Advanced Glucose Modeling

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Abstract

Keywords: Type 1 diabetes, Blood glucose modelling, PK-PD modelling, Experimental design

1 Introduction

This report is a supplement to a data set from a clinical study performed at Hvidovre University Hospital, Denmark as a part of the DIACON (Diabetes in Control) project in 2009-2010. The DIACON project is an interdisciplinary team situated in Denmark with both clinicians and scientist involved in the project. The aim of the DIACON project is to develop automatic treatment methods for type 1 diabetes and thereby improve the quality of life for the patients. The ultimate goal is to obtain fully closed loop control of the blood glucose level. This is known as the artificial pancreas and consists of continuous subcutaneous insulin infusion (CSII) from a pump, a continuous glucose monitor (CGM) obtaining the blood glucose level and finally, a control algorithm regulating the insulin pump based on feed back from the CGM. The controller determines the optimal amount of insulin to keep the blood glucose in the target range. An illustration of the components of an artificial pancreas is seen in Figure 1.

In the development of control algorithms for an artificial pancreas, virtual type 1 diabetes patients are a useful tool for pre-clinical testing and verification. The advantages are several: acceleration of the development process, lower costs, and the possibility of testing extreme treatment strategies without having to deal with the ethical aspects.

One of the purposes of the DIACON project is to develop a robust and reliable model of the insulin-blood glucose dynamical system. To be able to do this we needed a data set including observations of the system in type 1 diabetes patients.

Since the insulin-blood glucose system is a very complex system affected by many different factors such as meals, physical exercise and changes in stress level etc., the study had to be quite controlled. Further, a previous ambulant study had shown that out clinic data is too noise corrupted and unreliable due

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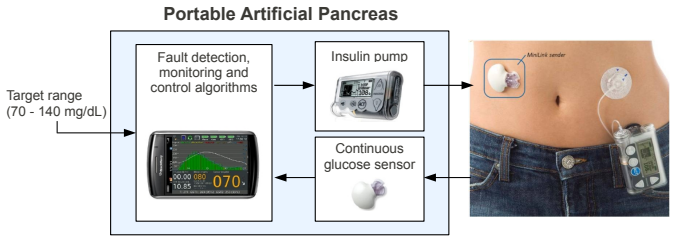

Figure 1: *Illustration of the artificial pancreas.*

to unknown disturbances and incorrect reportings by the involved patients. For these reasons the data collection was performed in clinic and designed to mirror the every day life of type 1 diabetes patients.

Meals, insulin boluses, and physical exercise were included as factors (controlled inputs) since they are believed to be have the greatest effect on the blood glucose level. By separating the occurrence of the factors and initiate them in changing order a total of 24 different sequences were constructed. The obtained data set is extensive and hence use full for many different modeling purposes.

The present report can be seen as an introduction to the study design and a guide to the data files including all data. It is intended for students, researchers or clinicians who wish to use the data for modeling purposes or get insight in to the insulin-blood glucose dynamics.

Furthermore, the majority of the results of this study has been published in the paper "Effects of Everyday Life Events on Glucose, Insulin, and Glucagon Dynamics in Continuous Subcutaneous Insulin Infusion-Treated Type 1 Diabetes: Collection of Clinical Data for Glucose Modeling" in the journal "Diabetes Technology and Therapeutics", see [2] for details.

The following sections will explain the study design in detail including subject statistics followed by a presentation of all the data observed and a guide to the data files following this report.

2 Description of the study design

As mentioned in the introduction, to collect data suitable for advanced modelling of type 1 diabetes is it advantageuos to do a controlled in-clinic study to avoid disturbances by uncontrolled factors. This section describes the study design.

2.1 Study design

The clinical study was designed from the theory of classical design of experiments. The basis was a factorial design with three main factors, each investigated on two levels. The factors and the defined levels are described in detail in section 2.2. The study consisted of 24 different sequences (study days) in which the three factors were combined differently.

In every day life the factors affecting the blood glucose level are often confounded, e.g., a meal is usually accompanied by a insulin bolus. Hence it can be difficult to estimate the true effect of each factor. To avoid problems with unidentifiability due to confounding factors, the occurrence of the events was separated in time by 150 minutes. A study day included three different events in total.

The combination and order of event types is seen in Figure 2. The first event was always a meal since the patients had been fastening for at least 10 hours before start. The second and third event was either

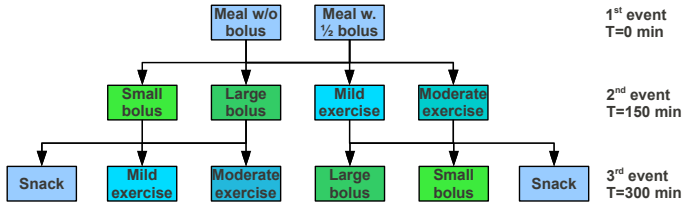

Figure 2: *Schematic overview of the study design. In total the study included 24 different sequences. T is study time.*

a bolus, exercise or a snack. Prior to the first event was a stabilization period from 8AM to 10AM (T=0 min) to bring the blood glucose level in the normal range. Likewise, was the last event (T=300 min) followed by a stabilization period to make the patient ready to leave the clinic.

2.2 Event types

In this study the three events investigated was: Meal including fast-acting carbohydrates, exercise on a treadmill and insulin boluses. Each event type was studied at two levels. Additionally, some study days included a liquid snack. A description of the levels is seen in table 1.

The meal was either given with half the meal bolus or with no bolus at all. The size of the meal bolus was determined from the subjects weight and personal insulin-to-carbohydrate ratio (ICR). ICR is defined as the amount of carbohydrate in milligrams one unit of insulin can counterbalance. The energy composition of the meal was 52% carbohydrates, 18%protein and 30% fat. It included simple carbohydrates form white bread, ham, cheese, margarine, marmalade, milk and juice. The snack was a protein drink with an energy composition of 89% carbohydrates and 11% protein. The size of the meal and snack was determined from the body weight as seen in Table 1.

Exercise was separated in a mild and moderate level, the former defined as 50% of interval between resting heart rate and maximum heart rate and the latter as 75%. An insulin bolus was separated into a small and large bolus, a small bolus was defined to lower blood glucose by 3 mmol/L based on the personal insulin sensitivity factor (ISF) and a large bolus was defined to lower blood glucose by 6 mmol/L based on personal ISF. ISF is defined as point drop in plasma glucose (mmol/L) per unit of insulin.

Table 1: *Description of event types*

Event type	Levels	Description
Meal	Unbolused	Solid food with drink. 1 g of CHO/kg body weight. No meal bolus.
	Underbolused	Solid food with drink. 1 g of CHO/kg body weight. 50% of the insulin bolus matching the meal CHO content based on personal ICR.
Exercise	Mild	0.5 x (maximum HR - resting HR) + resting HR.
	Moderate	0.7 x (maximum HR - resting HR) + resting HR.
Bolus	Small	Insulin bolus estimated to lower blood glucose level by 3 mmol/L based on personal ISF.
	Large	Insulin bolus estimated to lower blood glucose level by 6 mmol/L based on personal ISF.
Snack	NA	Liquid. 0.4 g of CHO/kg of body weight.

2.3 Data collection

During the study day blood glucose level was analyzed every ten minutes. Insulin level was analyzed every ten minutes 30 minutes after an event otherwise every 30 minutes. Additionally, glucagon, cortisol, growth hormone, and epinephrine and norepinephrine levels were analyzed according to the same scheme as insulin. The CGM recorded the sensor glucose level every 5 minutes. The Actiheart recorded activity and heart rate every minute.

3 Description of patients and equipment

This section present physiological details about the patients and details regarding the equipment used for monitoring and analysis.

3.1 Patients

Twelve type 1 diabetes patients participated in the study. They were all recruited from the diabetes clinic at Hvidovre Hospital. All were treated with insulin aspart (Novo Nordisk, BagsvÃ¦rd, Denmark) using a pump (Paradigm 522/722 from Medtronic, Northridge, CA) for at least six months before the first visit. The patient characteristics are shown in table 2.

Table 2: *Patient Characteristics*

Female sex	75%
Age	34.3±9.1 years
Body mass index	25.1±4.3 kg/m^2
Diabetes duration	16.5±10.2 years
C-peptide	0.097±0.078 nmol/L
Hemoglobin A1c	6.7±0.4%
Total daily insulin	0.63±0.11 U/kg/day

3.2 Equipment for blood analysis

The blood samples drawn during the study where analyzed for different hormone concentrations and blood glucose concentration. This section describes the methods and equipment used for these analysis.

Blood glucose was analyzed with gold standard equipment (YSI2300 STAT Plus, Yellow Springs Instruments, Yellow Springs, OH).

Insulin aspart was analyzed with a specific immunoassay using the LOCI-technology at Novo Nordisk A/S, Måløv, Denmark.

The glucagon analysis was made with a pancreas specific glucagon assay with a low detection limit at the Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. The glucagon assay was directed against the C-terminal of the glucagon molecule (antibody code no. 4305) and therefore measures glucagon of mainly pancreatic origin

Cortisol was analyzed with Solid-phase chemiluminiscense competitiv immunometric assay and growth hormone was analyzed with Solid-phase two-site chemiluminiscense immunometric assay both on Immulite 2000 (Siemens Healthcare Diagnostics) at Department of clinical biochemistry, Hvidovre Hospital, Denmark.

For the plasma catecholamine extraction procedure the The concentration of epinephrine and norepinephrine was determined by HPLC with electrochemical detection (Pcat extraction kit part no: 45-0141,

Thermo Fisher Scientific, California, USA). The column was a Prodigy 3u ODS (3) C18 (2 mm x 100 mm, particle size 3 μm, phenomenex). The mobile phase consisted of 55 mM sodium acetate, 1 mM octanesulfonic acid, 0.1 mM Na2EDTA and 8% Acetonitrile, adjusted to pH 3.2 with 0.1M acetic acid, and was degassed using an on-line degasser. Twenty μl of the samples were injected and the flow rate was 0.15 mL/min. The electrochemical detection was accomplished using an amperometric detector (Antec Decade from Antec, Leiden, The Netherlands) with a glassy carbon electrode set at 0.8 V, with an Ag/AgCl as reference electrode.

3.3 Activity monitor and continuous glucose monitor

To monitor the activity level of the patients, the Actiheart (CamNtech Ltd., Cambridge,UK) was used. The Actiheart monitors heart rate and activity from an accelerometer. During the study the patients also wore a CGM (Paradigm Real-Time, Medtronic) observing the glucose level in the subcutaneous layer.

4 Description of data files

For each study day a .csv file with all the data exits. All types of outputs and covariates are included. The time resolution is in minutes. Furthermore, an info file and comments file are included for each sequence.

Some of the data files includes missing observations. Look in the comments file for information about missing observations and other discrepancies between the planned sequence and what was performed.

In the table below all the input and outputs are stated in the order they appear in the data file. First column is a time vector which is followed by four inputs vectors corresponding to carbohydrates, insulin delivery, IV glucose administration and prescribed exercise level determined from the beats per minute (BPM). Hereafter blood glucose (YSI) and sensor glucose (CGM) values are stated followed by insulin plasma concentration and the remaining hormones stated in section 2.3. Finally, data and information from the Actiheart are listed.

The content of the info file can be seen in table 4. It contains information about the study: date, and sequence no., and information about the patient, e.g., age, weight, resting heart rate (HR), and basal insulin rate settings for the pump.

The comments files include a time vector corresponding to the one in the data files and the comments from the physician in charge of the study. They also include blood pressure observations obtained during the study day.

The data files are named with a number representing the participant and the letter 'a' or 'b' indicating whether it is the first or the second study day for that participant. E.i. the data file for participant no. 3's second event is named 03b_data.csv. The info and comments files are named 03b_info.csv and 03b_comments.csv respectively.

4.1 Conversion of units

In glucose modelling and diabetes research, different units are used for blood glucose and sensor glucose level. The most often used unit for insulin is units. In table 5 is the different conversion factors for glucose and insulin stated. For the plots presented later in this report, the unit for cortisol was changed from nmol/L to ng/mL. This conversion is also included in the table.

Table 3: *Data file content*

Variable	Unit	Description
TT	[min]	Trial time
CHO	[g]	Carbohydrate intake
I_{in}	[U]	Insulin delivery from the pump
G_{in}	[g]	I.V. Glucose delivery
EX	[BPM]	Prescribed exercise level
YSI	[mmol/L]	Plasma glucose level
CGM	[mmol/L]	Subcutanoues glucose level
I_{out}	[pM]	Insulin concentration in plasma
GG	[pM]	Glucagon concentration in plasma
CS	[nmol/L]	Cortisol concentration in plasma
GH	[ng/mL]	Growth hormone concentration in plasma
AL	[ng/mL]	Adrenaline concentration in plasma
NL	[ng/mL]	Noradrenaline concentration in plasma
ACT	[Counts]	Activity level
CL_BPM	[BPM]	Observed heart rate (cleaned)
Raw_BPM	[BPM]	Observed heart rate (raw)
OK/Rec	[-]	Index indicating whether the BPM recording is properly recorded (OK) or had to be recovered (Rec)
ECG (μV)	[μV]	Eccocardiogram observations used to calculate ACT
Lt s	[s]	Amount of lots seconds in the current minute in the Actiheart
J/ep	[Joule]	Joules per epoch
J/ep/kg	[Joule]	Joules per epoch per kilo body weight

5 Plots of data

This section presents plots of the entire data set. In Table 6 an overview of the entire study is presented.

Each plot presents the specific sequence and timing and size of inputs: Meals, insulin boluses and intravenously administrated glucose. Furthermore, all the analyzed observations are plotted, e.g., YSI, CGM, Insulin aspart, glucagon, heart rate, activity, norepinephrine, epinephrine, cortisol and growth hormone. The title of the plots is participant no. and a or b referring to the first or second study day for that participant. Note that for participant no. 01 they are named 01b and 01c since we performed a pilot study on this participant which is not included. Participant no. 9 was excluded from the study due to pregnancy and no data exists from this participant. An additional participant was included instead (no. 13).

Table 4: *Info file content*

Variable	Description
Date	Date of the study day
Sequence no.	1:24
Patient ID	Initials and date of birth
Patient trial no.	States the patients no. of visit.
Age	Age in years
Sex	M/F
Weight	Body weight in kg
Height	Height in meters
Norm. ICR	The patient's normal insulin-to-carbohydrate ratio
Norm. ISF	The patient's normal insulin sensitivity factor
Basal insulin rate	Time interval: Basal rate
Target BG	The target blood glucose
Resting HR	Resting heart rate
Maximum HR	Maximum heart rate
Actiheart	Device A or B
Sensor placement	States the placement of the sensor on the body
Pump placement	States the placement of the pump on the body
Diabetes debut	Year of diabetes debut
Medication	List of the patient's medication (if any)

Table 5: *Conversion of units*

Glucose [1]	1 mmol/L	18.0182 mg/dL
Insulin[1]	6 pM	1 mU/L
Cortisol [1]	1 nmol/L	2.759 ng/mL

Table 6: *Overview of the clinical DIACON study 2009-2010*

Patient #	Event 1	Event 2	Event 3	Short code
01_b	Meal w/o bolus	Moderate exercise	Large bolus	0bMOeLb
01_c	Meal w $\frac{1}{2}$bolus	Moderate exercise	Small bolus	$\frac{1}{2}$bMOeSb
02_a	Meal w $\frac{1}{2}$bolus	Small bolus	Mild exercise	$\frac{1}{2}$bSbMIe
02_b	Meal w $\frac{1}{2}$bolus	Mild exercise	Small bolus	$\frac{1}{2}$bMIeSb
03_a	Meal w/o bolus	Large bolus	Mild exercise	0bLbMIe
03_b	Meal w $\frac{1}{2}$bolus	Large bolus	Moderate exercise	$\frac{1}{2}$bLbMOe
04_a	Meal w $\frac{1}{2}$bolus	Small bolus	Snack	$\frac{1}{2}$bSbSn
04_b	Meal w $\frac{1}{2}$bolus	Mild exercise	Large bolus	$\frac{1}{2}$bMIeLb
05_a	Meal w $\frac{1}{2}$bolus	Moderate exercise	Snack	$\frac{1}{2}$bMOeSn
05_b	Meal w/o bolus	Small bolus	Snack	0bSbSn
06_a	Meal w $\frac{1}{2}$bolus	Large bolus	Mild exercise	$\frac{1}{2}$bLbMIe
06_b	Meal w $\frac{1}{2}$bolus	Moderate exercise	Large bolus	$\frac{1}{2}$bMOeLb
07_a	Meal w/o bolus	Mild exercise	Small bolus	0bMIeSb
07_b	Meal w/o bolus	Moderate exercise	Small bolus	0bMOeSb
08_a	Meal w/o bolus	Mild exercise	Snack	0bMIeSn
08_b	Meal w/o bolus	Large bolus	Moderate exercise	0bLbMOe
10_a	Meal w $\frac{1}{2}$bolus	Moderate exercise	Small bolus	$\frac{1}{2}$bMOeSb
10_b	Meal w $\frac{1}{2}$bolus	Mild exercise	Snack	$\frac{1}{2}$bMIeSn
11_a	Meal w $\frac{1}{2}$bolus	Large bolus	Snack	$\frac{1}{2}$bLbSn
11_b	Meal w/o bolus	Mild exercise	Large bolus	0bMIeLb
12_a	Meal w/o bolus	Small bolus	Moderate exercise	0bSbMOe
12_b	Meal w/o bolus	Moderate exercise	Snack	0bMOeSn
13_a	Meal w/o bolus	Small bolus	Mild exercise	0bSbMIe
13_b	Meal w/o bolus	Large bolus	Snack	0bLbSn

The code in the last column is combined of the three event during the study day. 0b corresponds to a meal w/o bolus and $\frac{1}{2}$b corresponds to a meal w/ half bolus. Lb corresponds to at large bolus. Sb corresponds to a small bolus. MOe corresponds to moderate exercise. MIe corresponds to mild exercise. Sn corresponds to a snack.

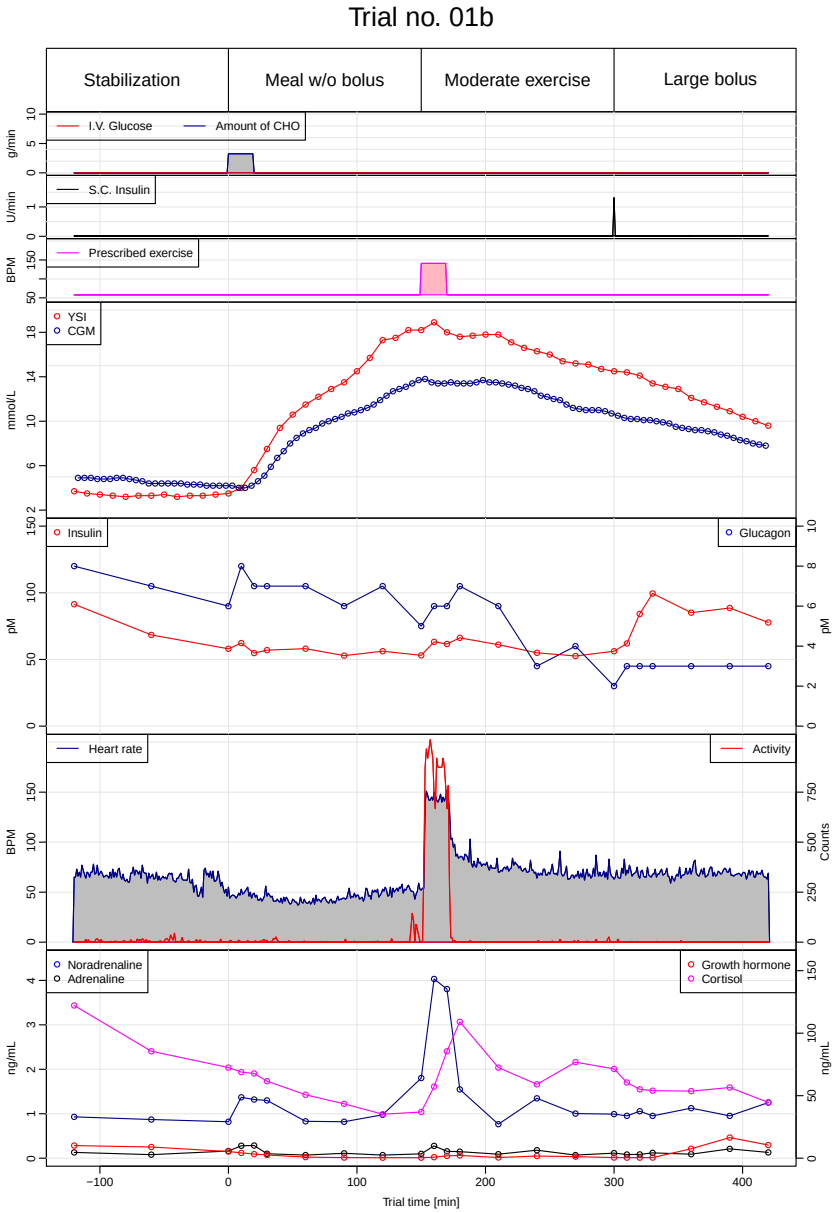

Figure 3: *Results from trial 01b. Note that the S.C. insulin is above zero according to table ll at all times even though it is hard to see.*

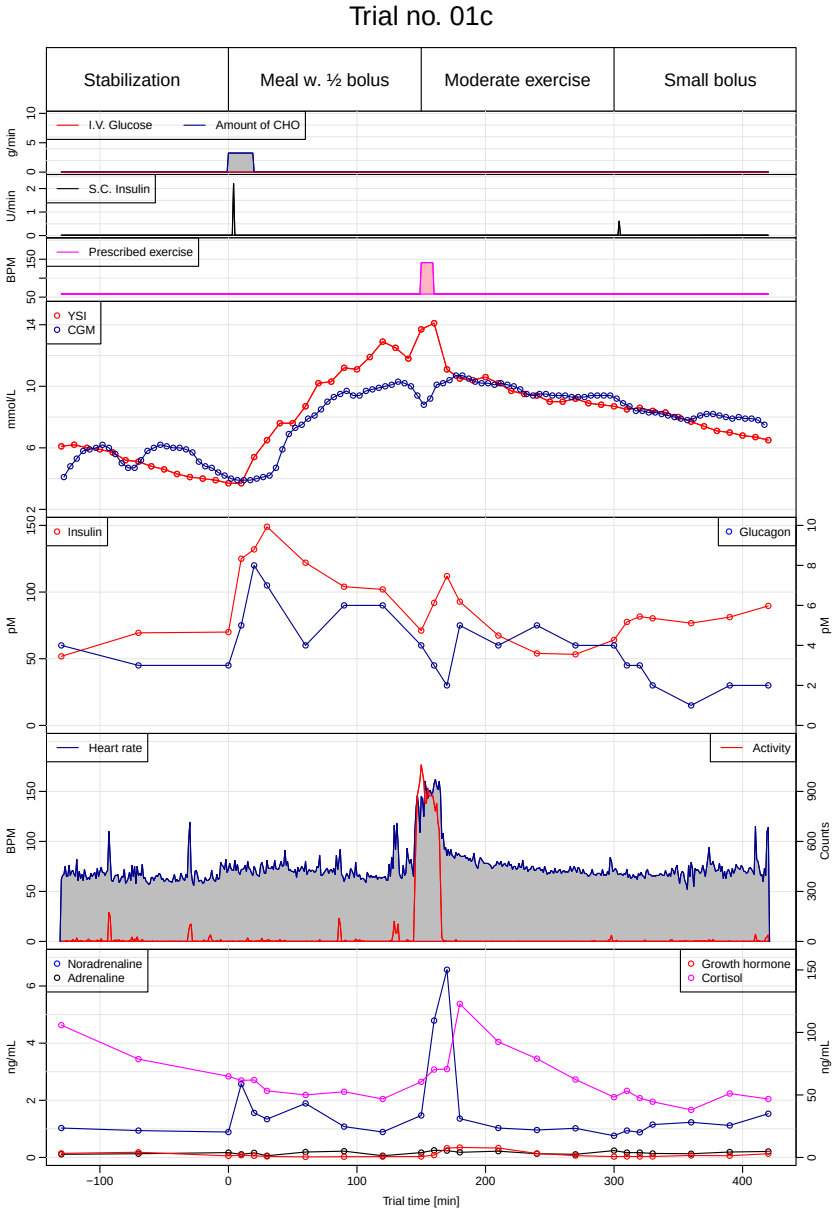

Figure 4: *Results from trial 01c. Note that the S.C. insulin is above zero according to the info file.*

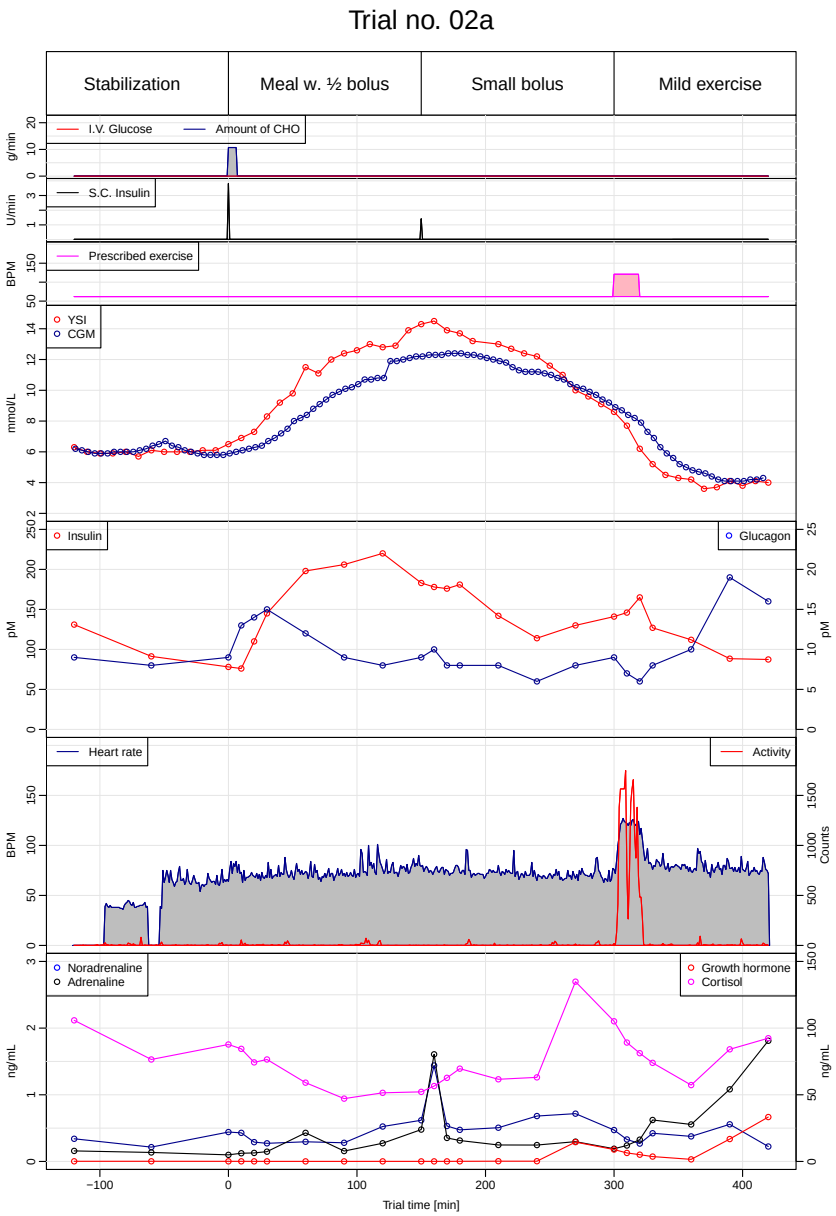

Figure 5: *Results from trial 02a. Note that the S.C. insulin is above zero according to the info file.*

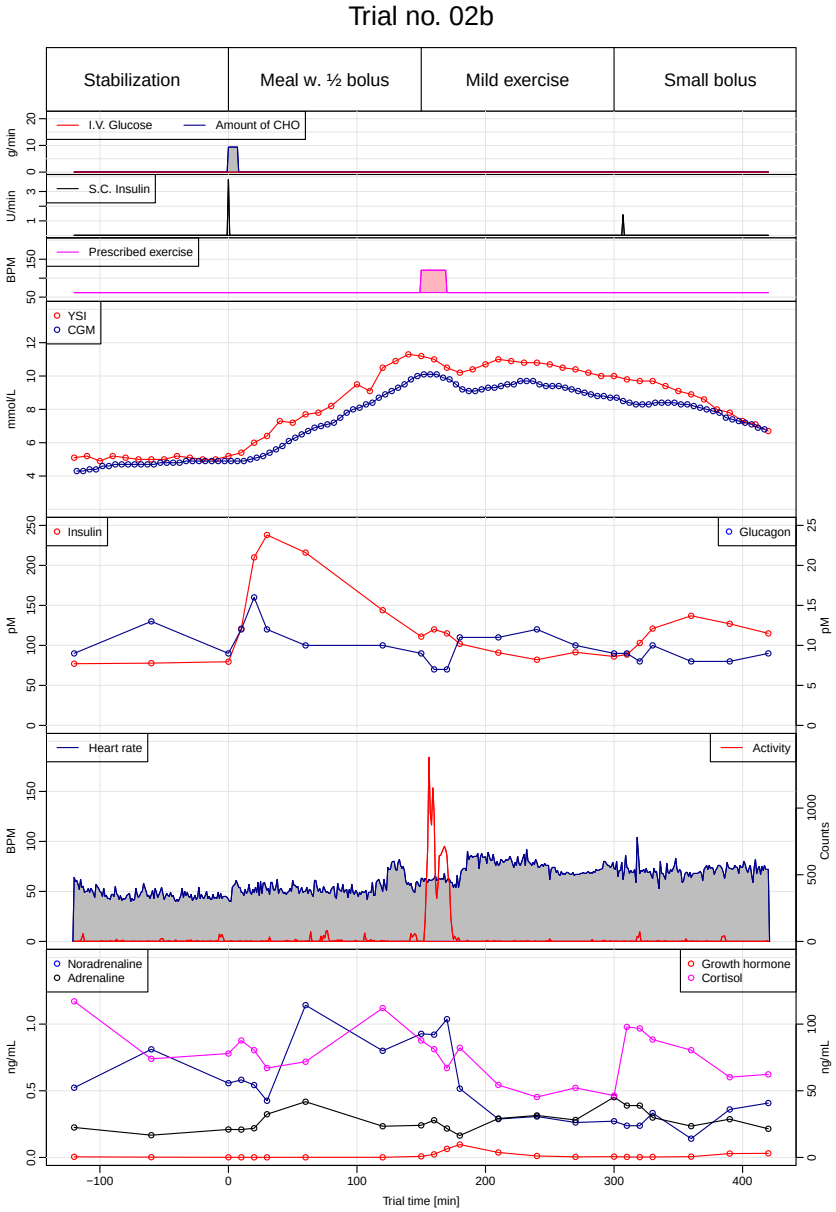

Figure 6: *Results from trial 02b. Note that the S.C. insulin is above zero according to the info file.*

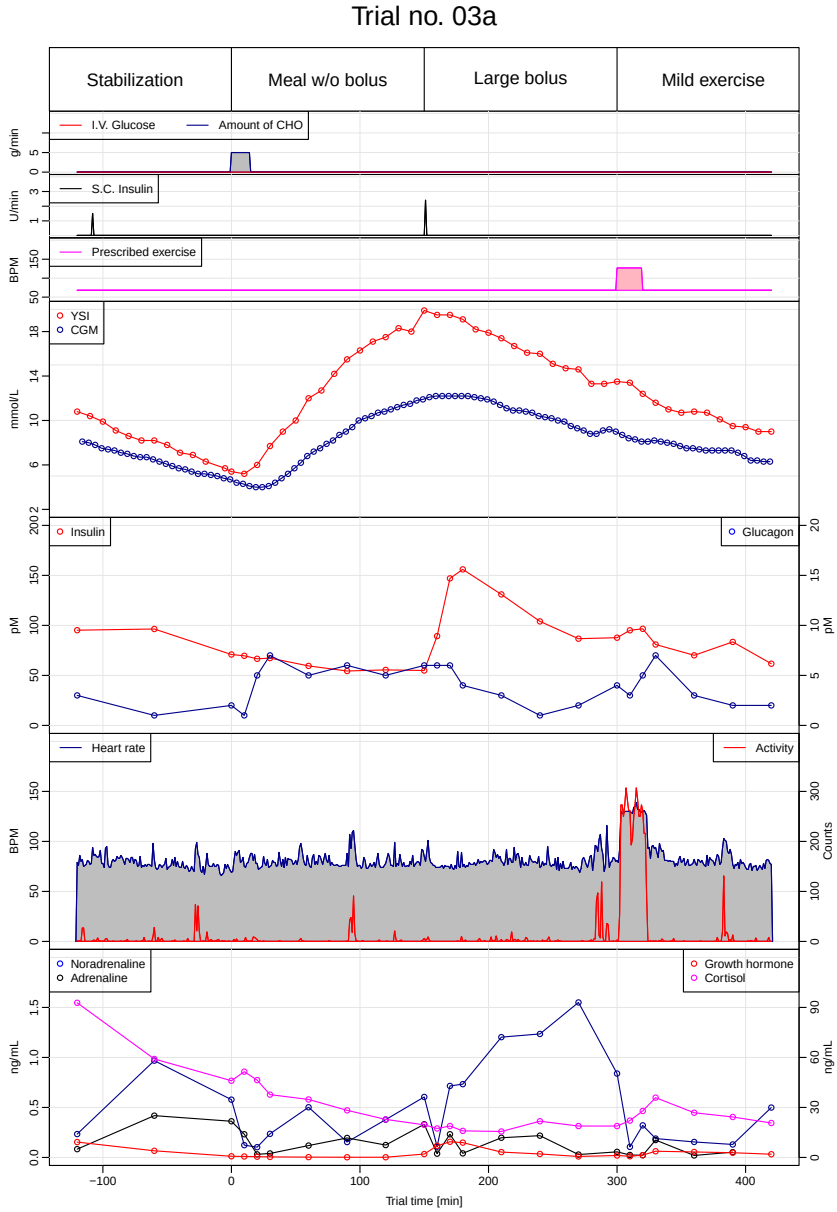

Figure 7: *Results from trial 03a. Note that the S.C. insulin is above zero according to the info file.*

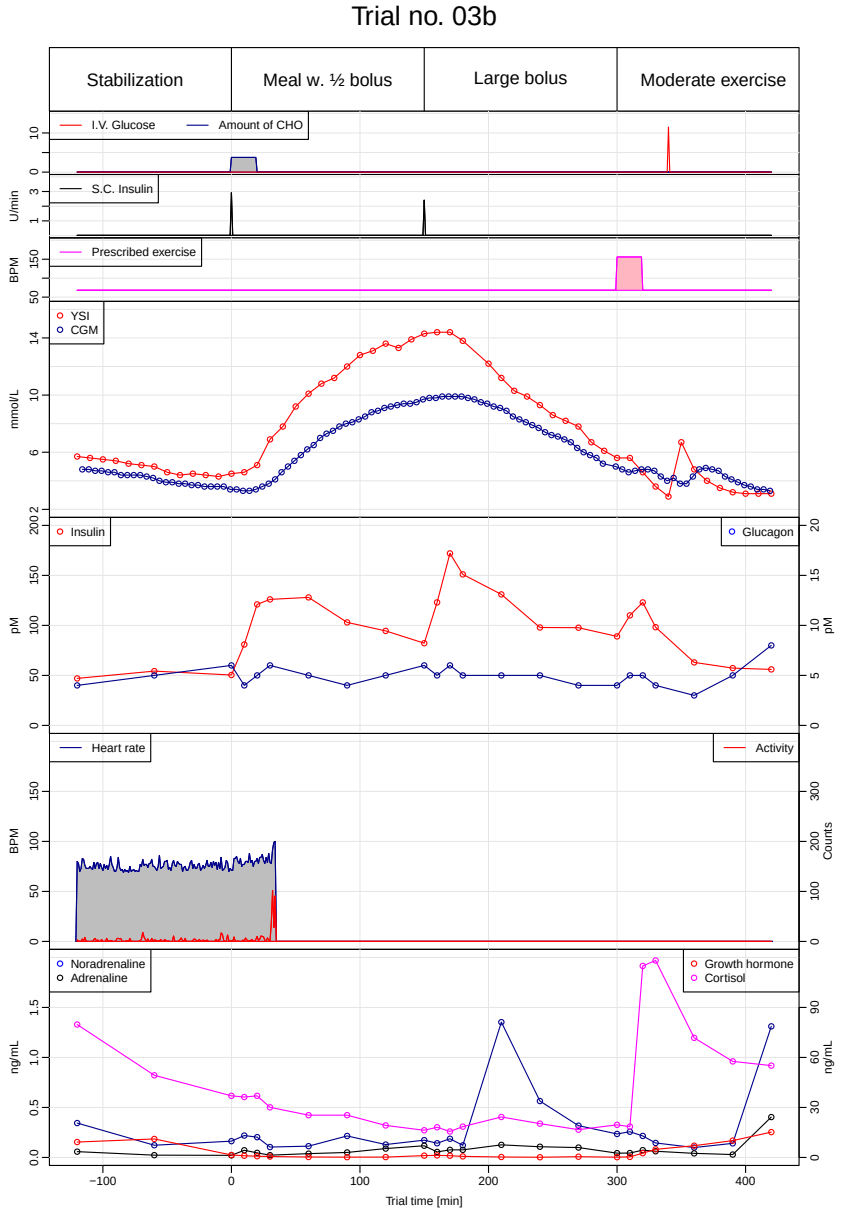

Figure 8: *Results from trial 03b. Note that the S.C. insulin is above zero according to the info file.*

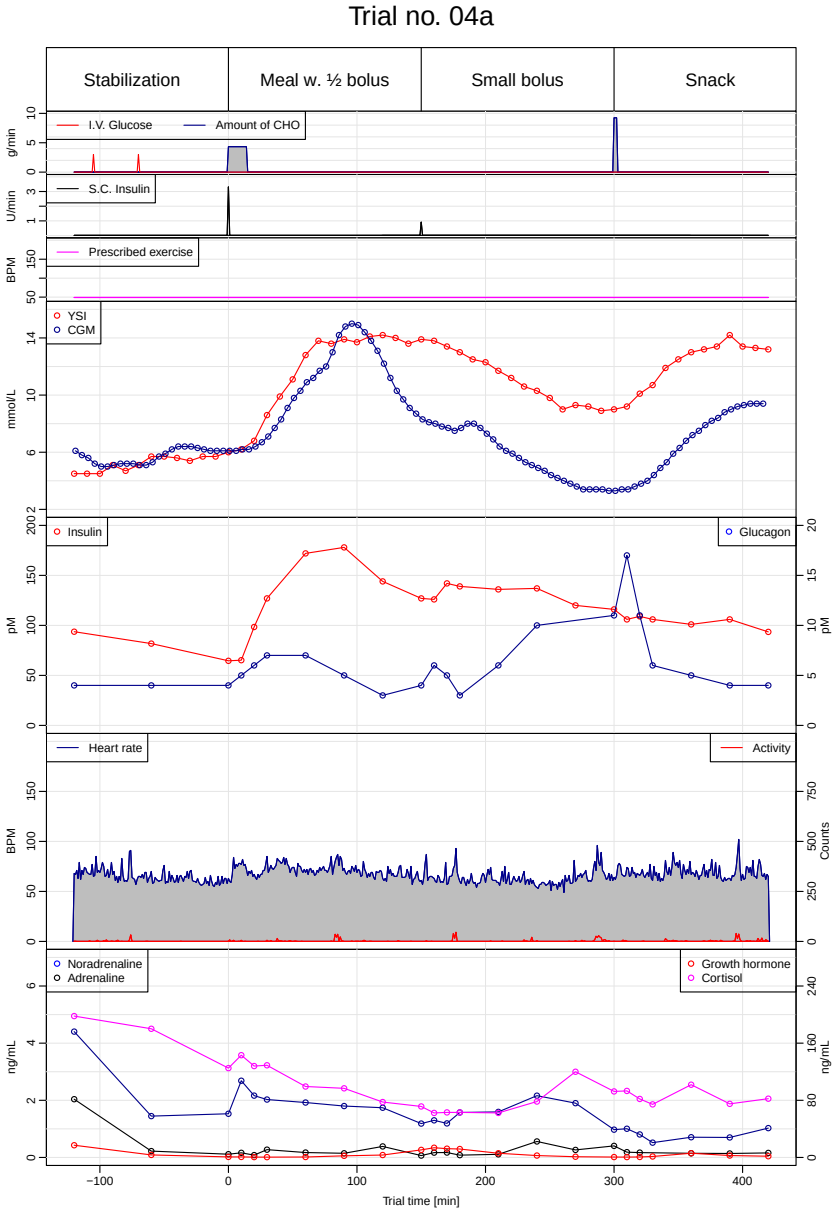

Figure 9: *Results from trial 04a. Note that the S.C. insulin is above zero according to the info file.*

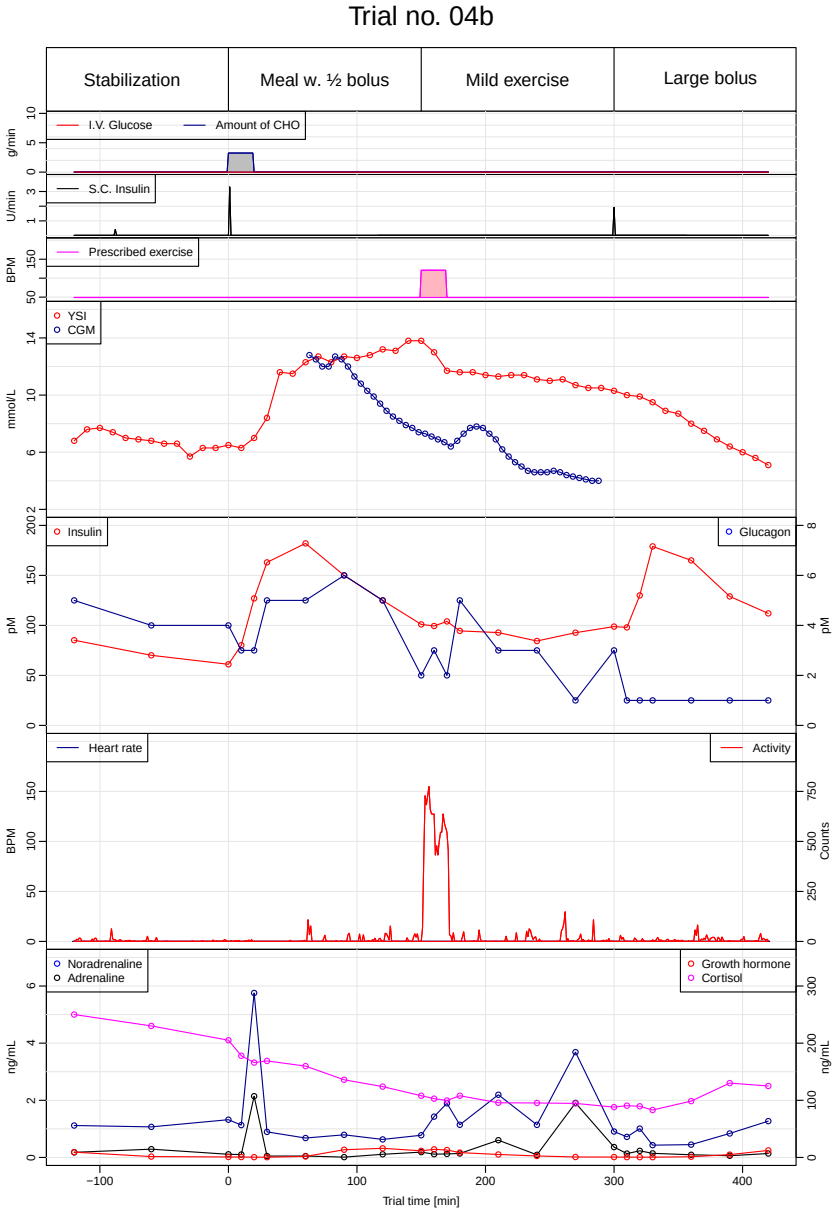

Figure 10: *Results from trial 04b. Note that the S.C. insulin is above zero according to the info file.*

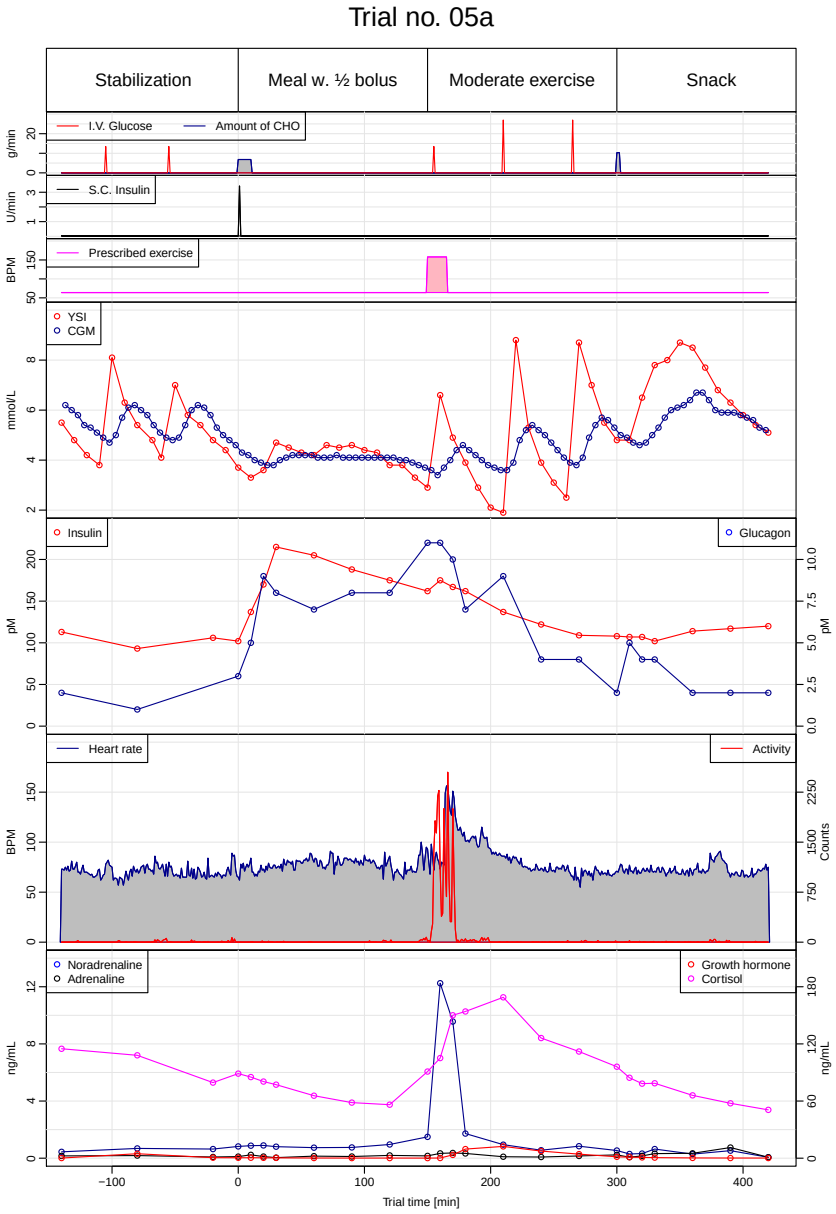

Figure 11: *Results from trial 05a. Note that the S.C. insulin is above zero according to table ll at all times even though it is hard to see.*

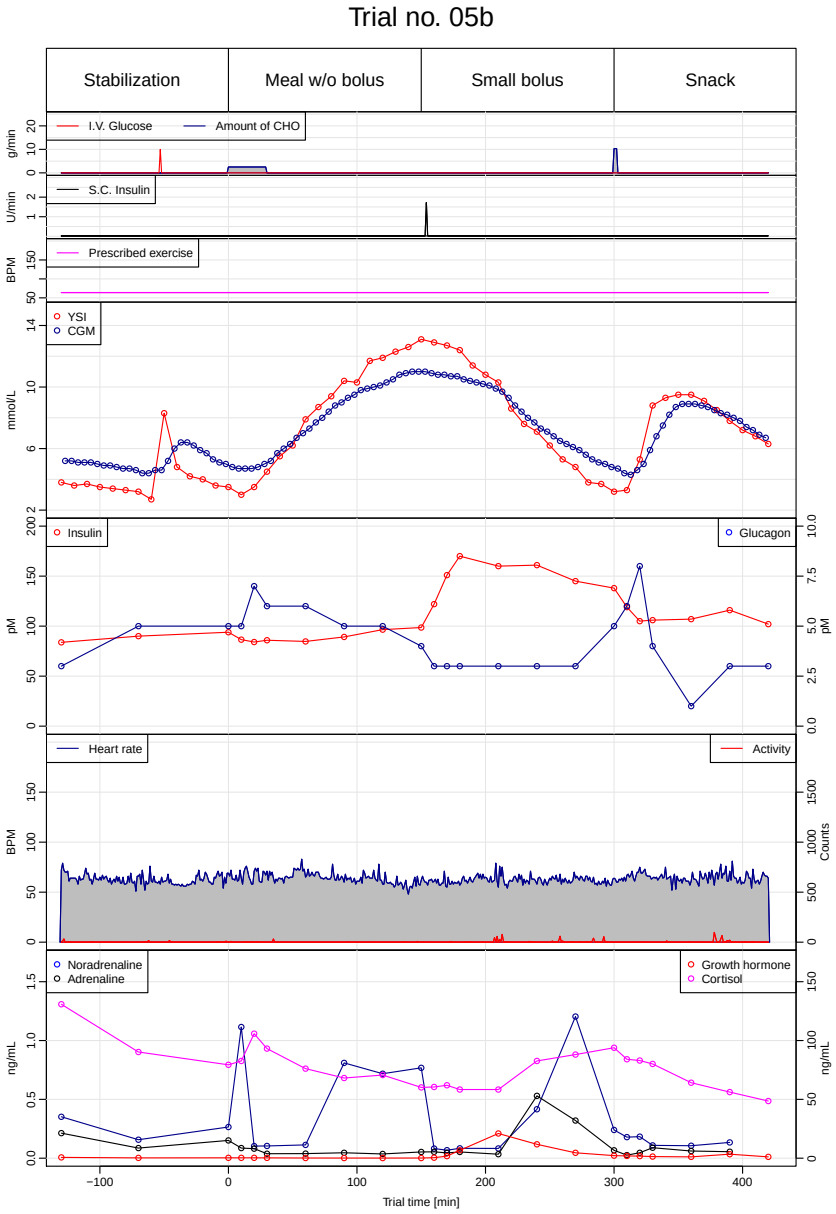

Figure 12: *Results from trial 05b. Note that the S.C. insulin is above zero according to table ll at all times even though it is hard to see.*

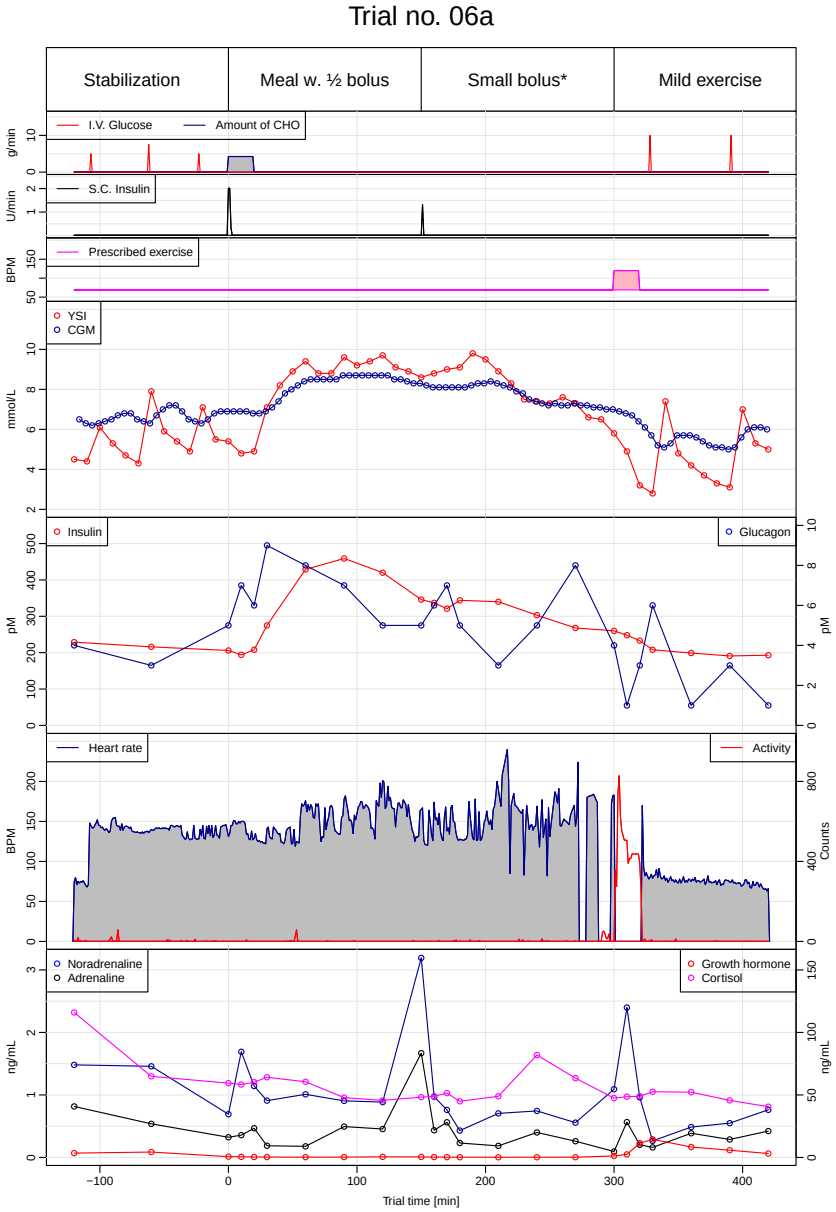

Figure 13: *Results from trial 06a. Note that the S.C. insulin is above zero according to the info file.*

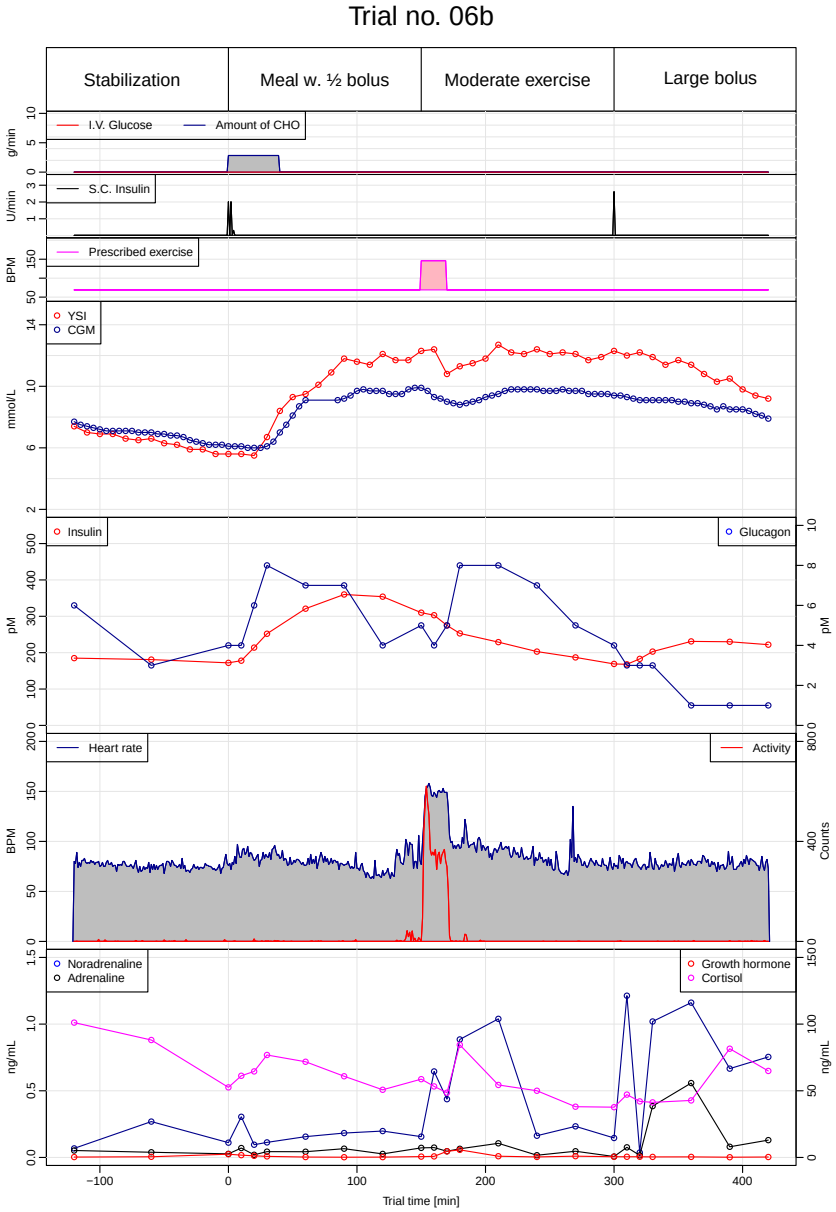

Figure 14: *Results from trial 06b. Note that the S.C. insulin is above zero according to the info file.*

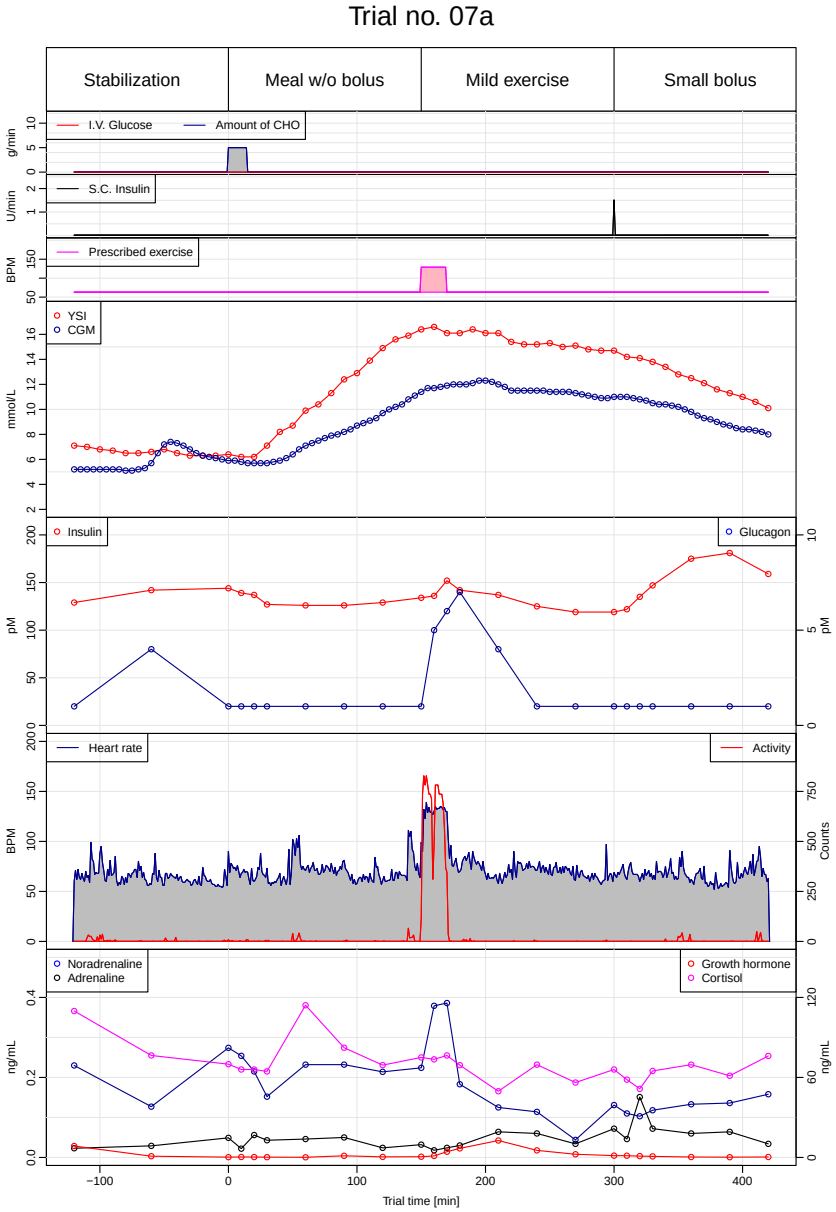

Figure 15: *Results from trial 07a. Note that the S.C. insulin is above zero according to the info file.*

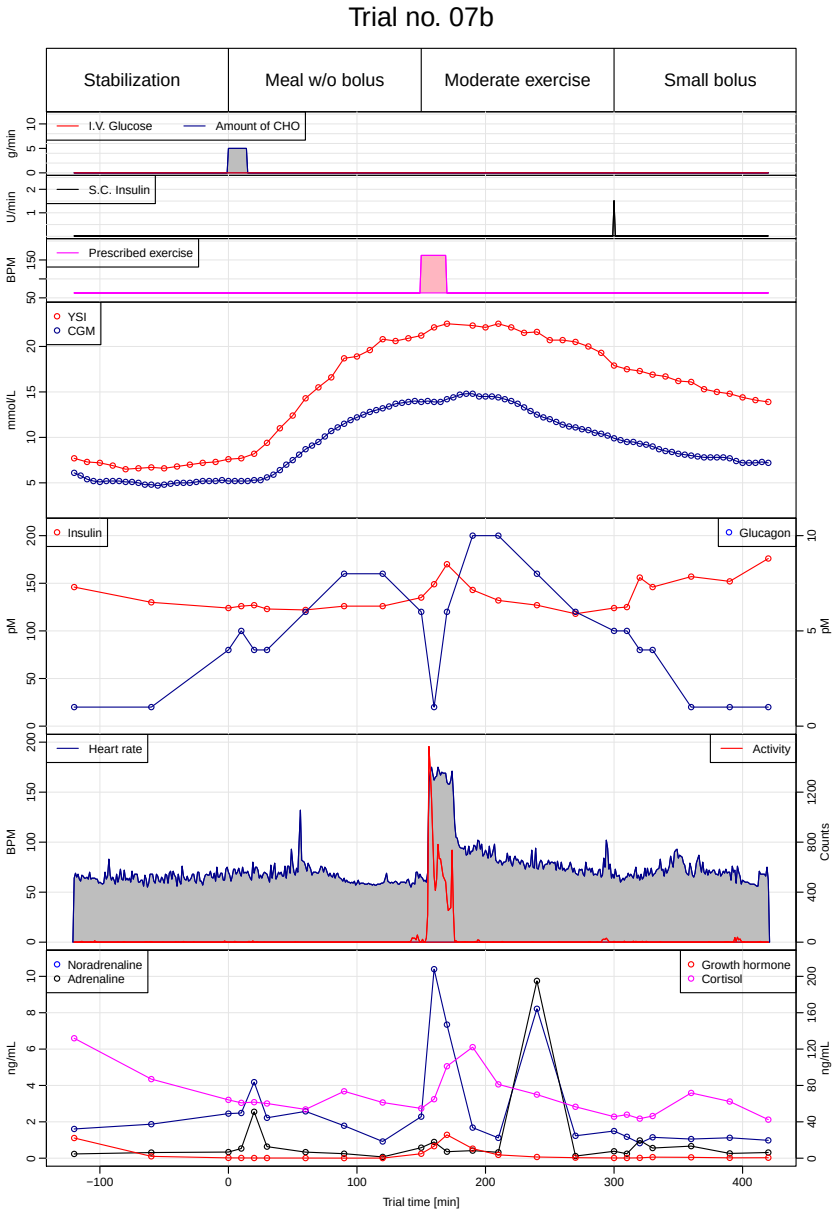

Figure 16: *Results from trial 07b. Note that the S.C. insulin is above zero according to table ll at all times even though it is hard to see.*

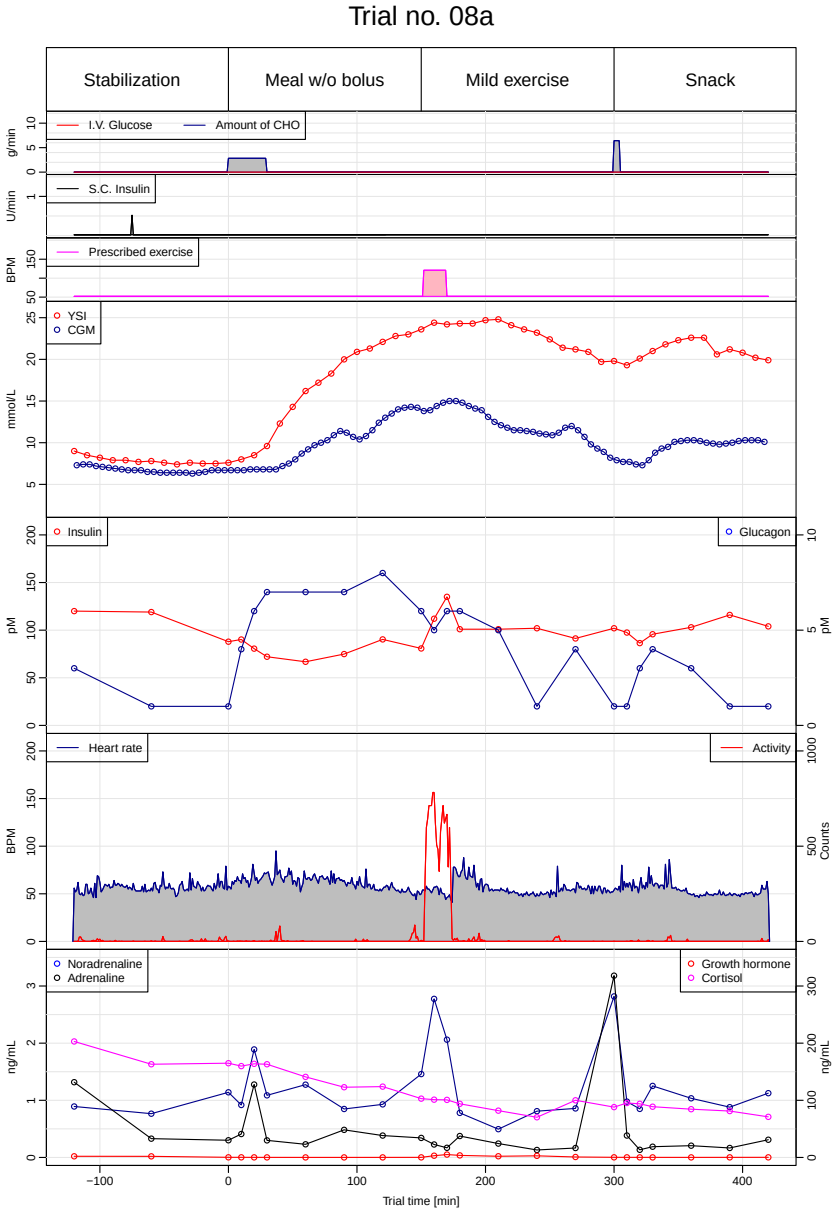

Figure 17: *Results from trial 08a. Note that the S.C. insulin is above zero according to the info file.*

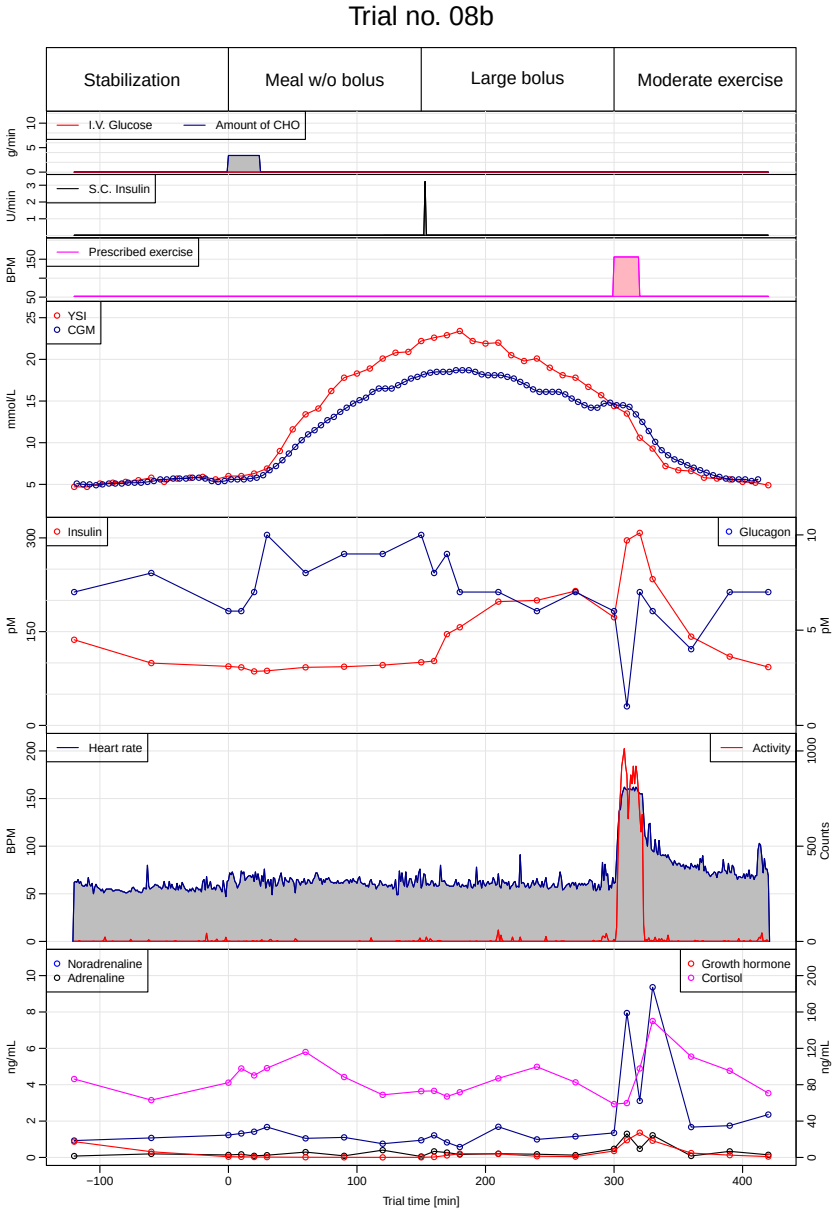

Figure 18: *Results from trial 08b. Note that the S.C. insulin is above zero according to the info file.*

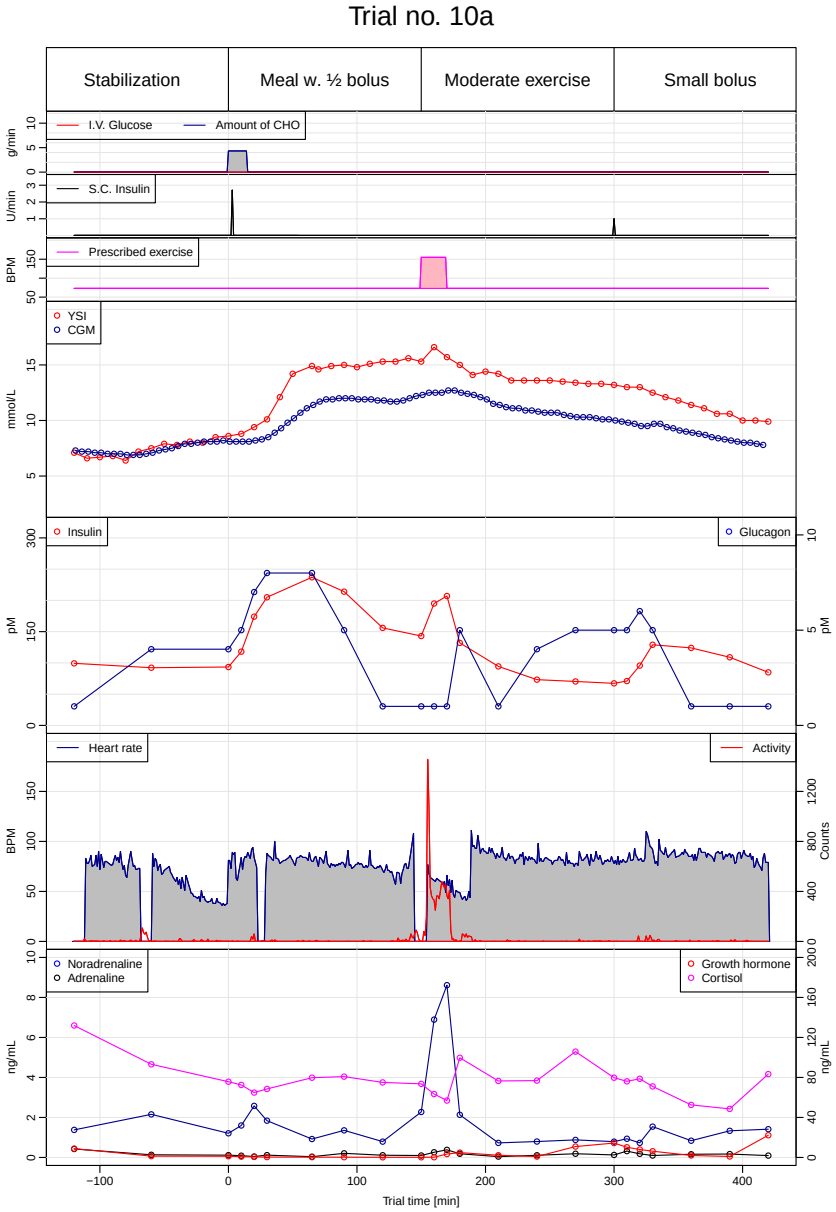

Figure 19: *Results from trial 10a. Note that the S.C. insulin is above zero according to the info file.*

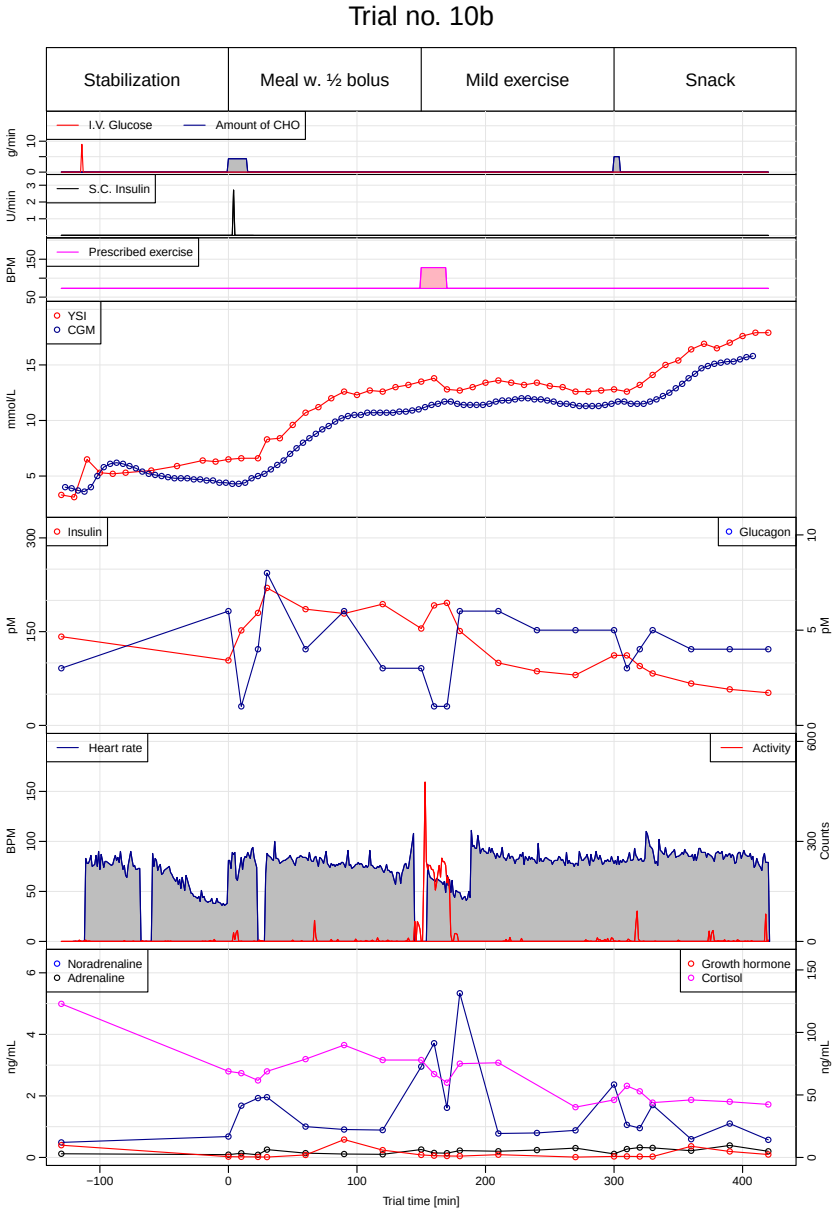

Figure 20: *Results from trial 10b. Note that the S.C. insulin is above zero according to the info file.*

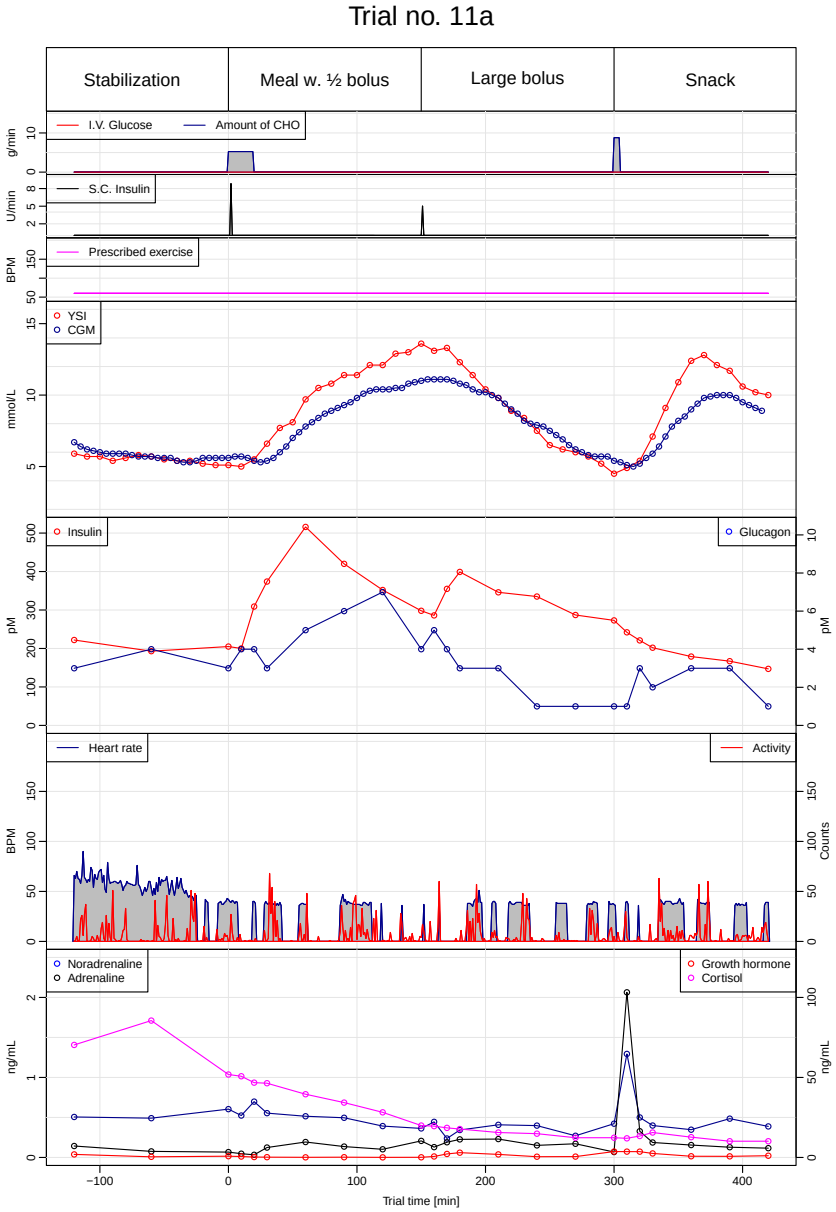

Figure 21: *Results from trial 11a. Note that the S.C. insulin is above zero according to the info file.*

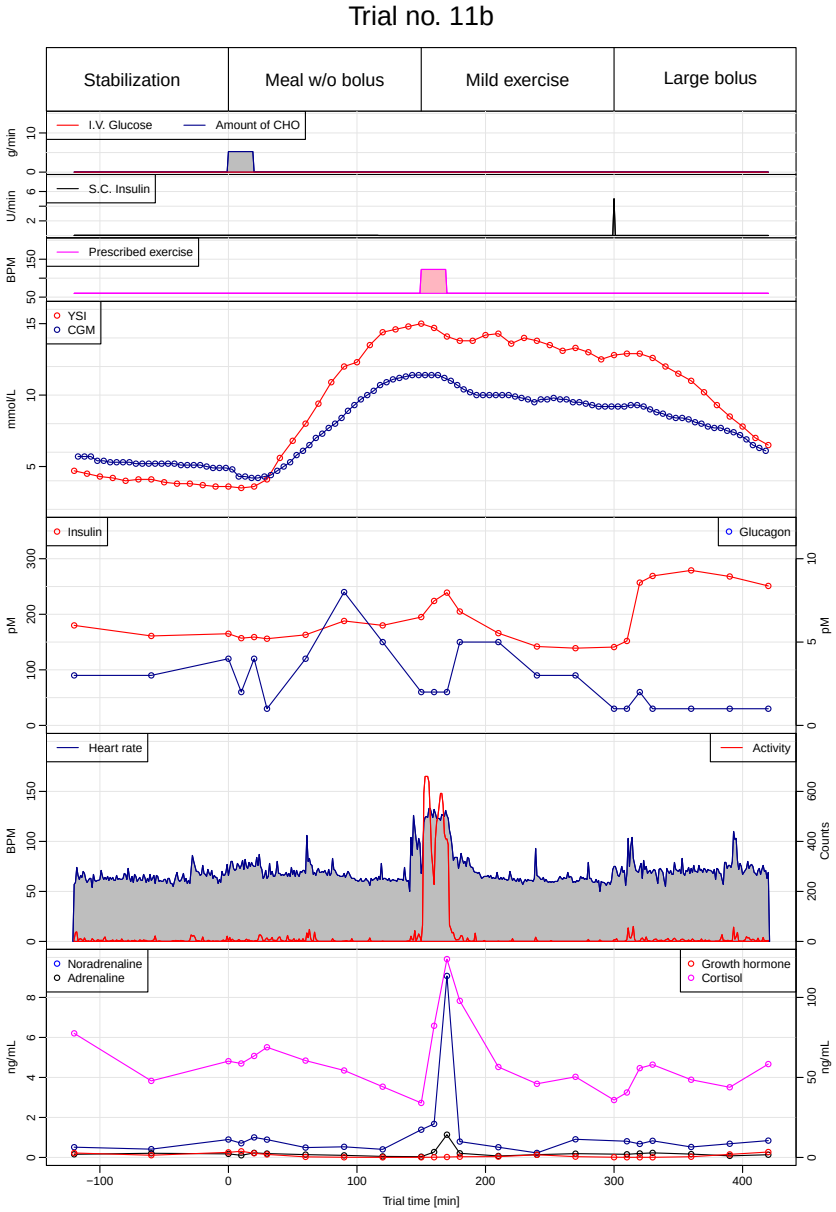

Figure 22: *Results from trial 11b. Note that the S.C. insulin is above zero according to the info file.*

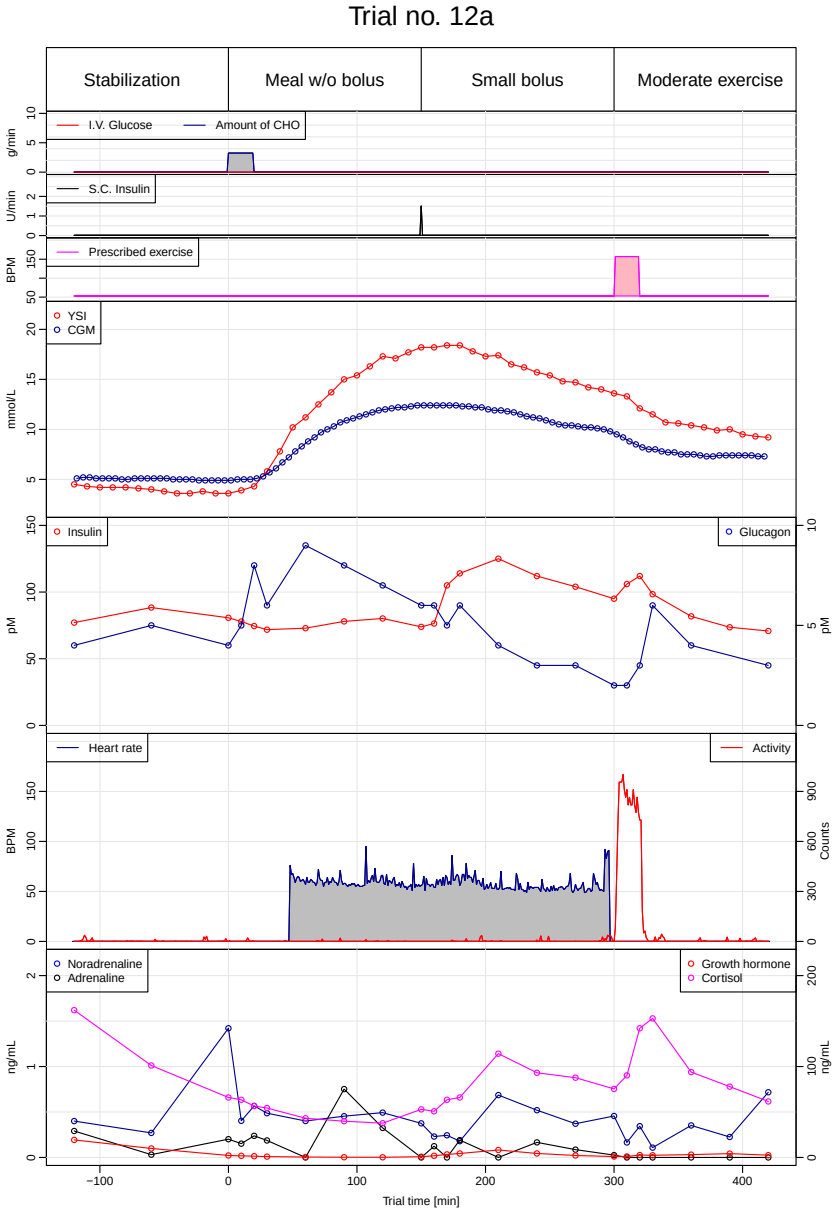

Figure 23: *Results from trial 12a. Note that the S.C. insulin is above zero according to the info file.*

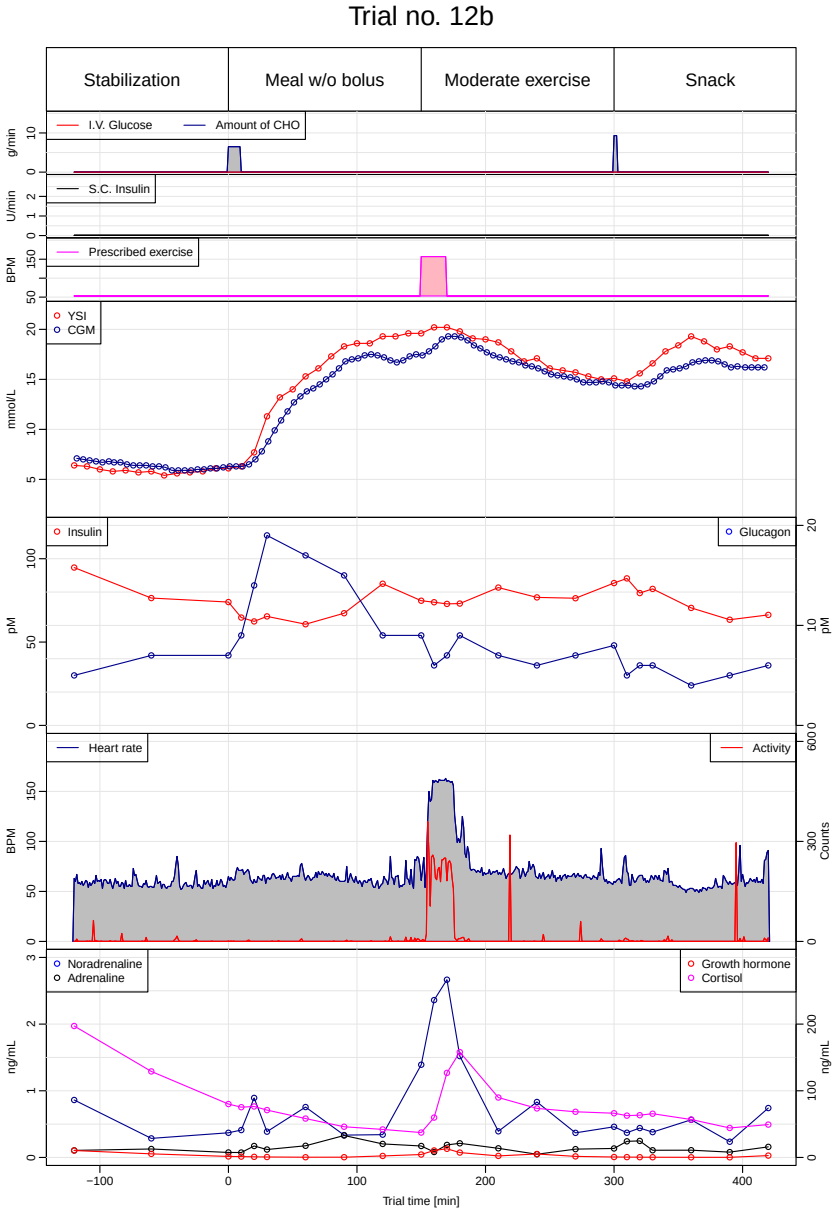

Figure 24: *Results from trial 12b. Note that the S.C. insulin is above zero according to the info file.*

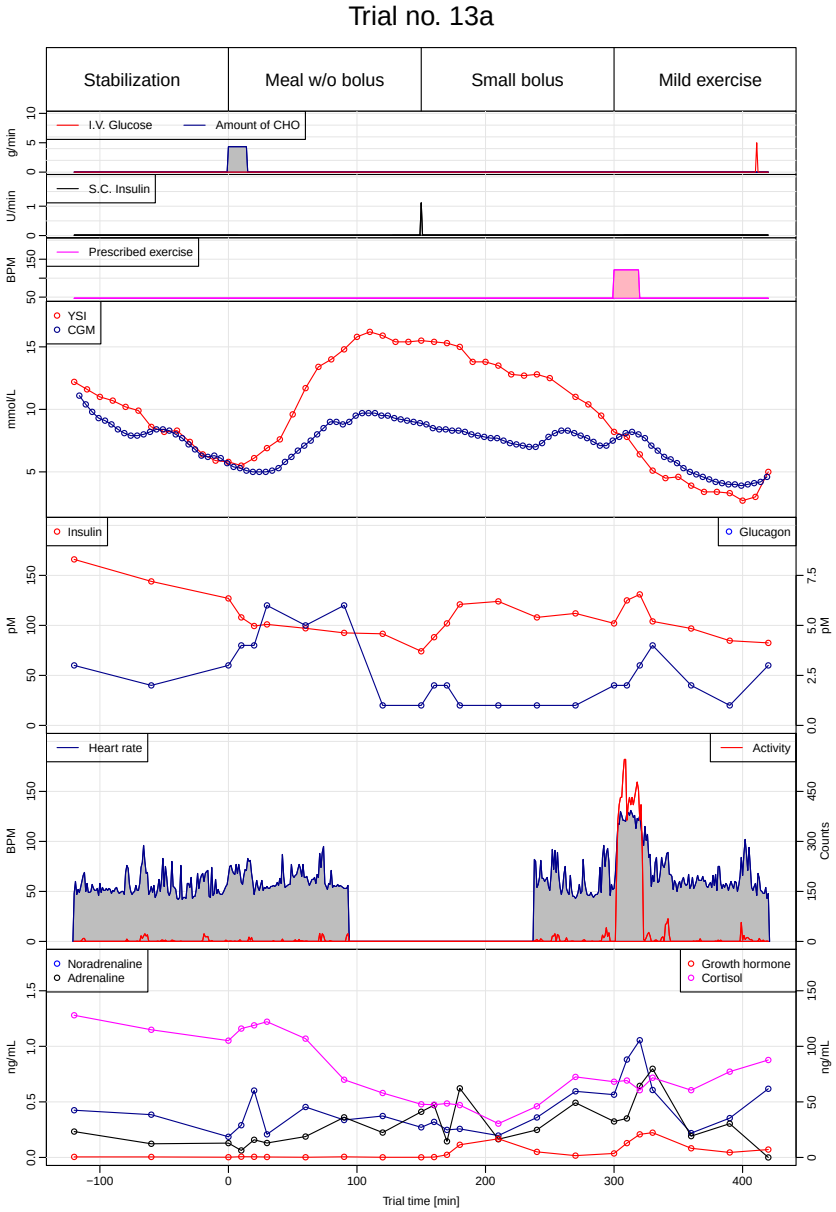

Figure 25: *Results from trial 13a. Note that the S.C. insulin is above zero according to the info file.*

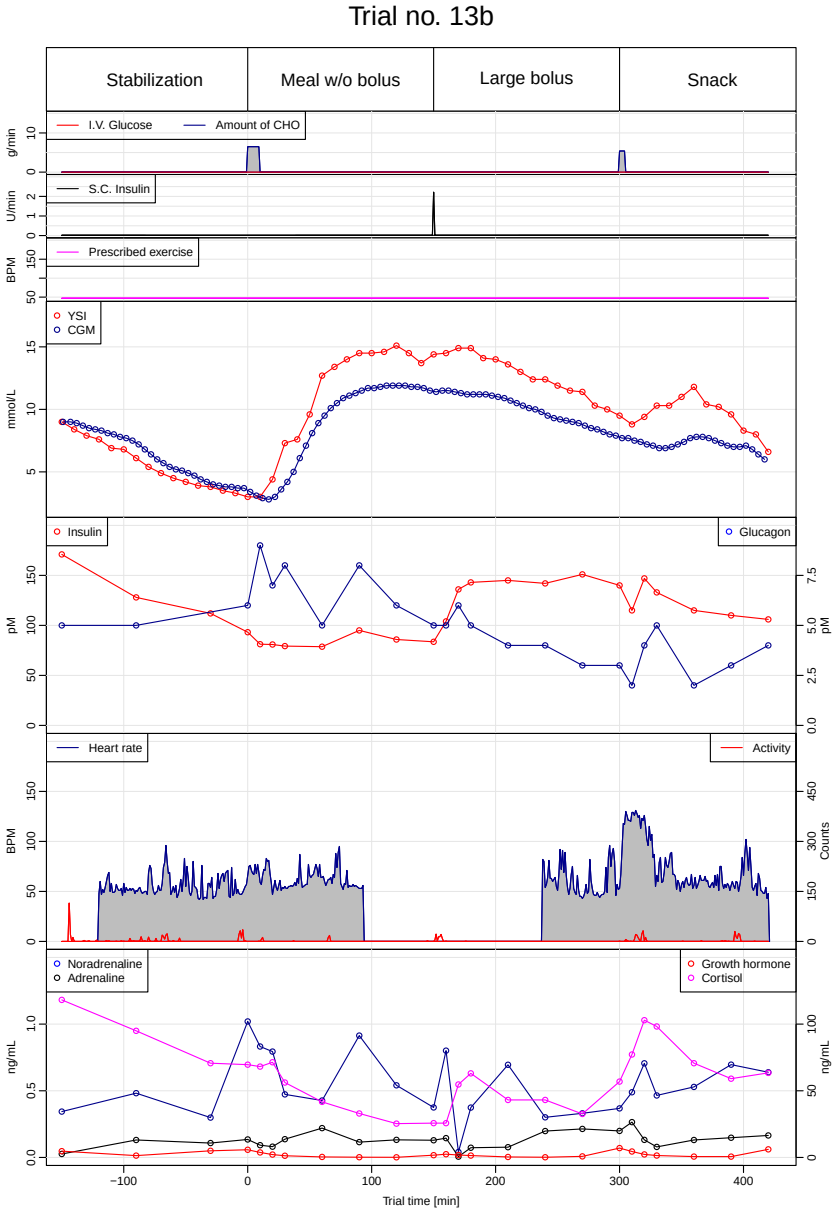

Figure 26: *Results from trial 13b. Note that the S.C. insulin is above zero according to the info file.*

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[2] S. Schmidt, D. Finan, A. Duun-Henriksen, J. Jørgensen, H. Madsen, H. Bengtsson, J. Holst, S. Madsbad, and K. Nørgaard. Effects of everyday life events on glucose, insulin, and glucagon dynamics in continuous subcutaneous insulin infusion–treated type 1 diabetes: Collection of clinical data for glucose modeling. *Diabetes technology & therapeutics*, 14(3):210–217, 2012.

Appendix B

Paper A

Effects of Every Day Life Events on Glucose, Insulin, and Glucagon Dynamics in Continuous Subcutaneous Insulin Infusion-Treated Type 1 Diabetes: Collection of Clinical Data for Glucose Modeling

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Original Article

Effects of Everyday Life Events on Glucose, Insulin, and Glucagon Dynamics in Continuous Subcutaneous Insulin Infusion–Treated Type 1 Diabetes: Collection of Clinical Data for Glucose Modeling

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Abstract

Background: In the development of glucose control algorithms, mathematical models of glucose metabolism are useful for conducting simulation studies and making real-time predictions upon which control calculations can be based. To obtain type 1 diabetes (T1D) data for the modeling of glucose metabolism, we designed and conducted a clinical study.

Methods: Patients with insulin pump–treated T1D were recruited to perform everyday life events on two separate days. During the study, patients wore their insulin pumps and, in addition, a continuous glucose monitor and an activity monitor to estimate energy expenditure. The sequence of everyday life events was predetermined and included carbohydrate intake, insulin boluses, and bouts of exercise; the events were introduced, temporally separated, in different orders and in different quantities. Throughout the study day, 10-min plasma glucose measurements were taken, and samples for plasma insulin and glucagon analyses were obtained every 10 min for the first 30 min after an event and subsequently every 30 min.

Results: We included 12 patients with T1D (75% female, 34.3 ± 9.1 years old [mean ± SD], hemoglobin A1c 6.7 ± 0.4%). During the 24 study days we collected information-rich, high-quality data during fast and slow changes in plasma glucose following carbohydrate intake, exercise, and insulin boluses.

Conclusions: This study has generated T1D data suitable for glucose modeling, which will be used in the development of glucose control strategies. Furthermore, the study has given new physiologic insight into the metabolic effects of carbohydrate intake, insulin boluses, and exercise in continuous subcutaneous insulin infusion–treated patients with T1D.

Background

Mathematical models of glucose metabolism are useful in developing glucose control algorithms for patients with type 1 diabetes (T1D); they are invaluable in performing preclinical simulation research, and they may be used online to make predictions of future glucose values.[1] Quantitative knowledge about the metabolic effects of continuous subcutaneous insulin infusion (CSII) therapy with short-acting analog insulin in patients with T1D, however, is sparse. To date, most glucose modeling data have been derived from short-term observation of type 2 diabetes populations under fasting conditions.[2] These studies do not reflect intraday variability, and it is unclear whether the results can be extrapolated to a heterogeneous T1D population. Another approach to the modeling of glucose metabolism is to use insulin and continuous glucose monitoring (CGM) data from previous closed-loop studies.[3] Unfortunately, access to such data is often restricted. More easily accessible are ambulatory data from patients using CGM; however, ambulatory data are not amenable to model development because the system inputs are not introduced in a predetermined, organized order, and uncertainty in the data is high because of unmeasured or inaccurately recorded influences resulting in limited accuracy

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of the models, as evidenced by metrics such as root mean squared error values and mean square prediction error.[4,5] To collect high-quality T1D data suitable for developing accurate models of glucose metabolism, we designed an in-clinic study addressing inter-individual variability in everyday situations in adults with CSII-treated T1D. Data will be used in the construction of a virtual T1D clinic for preclinical simulations of different glucose control strategies including a closed-loop system. The DiaCon Study Group is working for better diabetes control in general, and glucose modeling is one of the group's main research areas. The aim of this article is to present the study protocol, design considerations, and results of the clinical study.

Subjects and Methods

Participants

We recruited 12 patients with T1D from the outpatient diabetes clinic at Hvidovre University Hospital, Hvidovre, Denmark. Patient characteristics were as follows: female sex, 75%; age, 34.3 ± 9.1 years (mean ± SD); body mass index, 25.1 ± 4.3 kg/m^2; diabetes duration, 16.5 ± 10.2 years; C-peptide, 0.097 ± 0.078 nmol/L (C-peptide was measured 2 h after meal simulation); hemoglobin A1c, 6.7 ± 0.4%; and total daily insulin, 0.63 ± 0.11 U/kg/day. For a minimum of 6 months, patients had been treated with insulin aspart (Novo Nordisk, Bagsværd, Denmark) using the Paradigm® 522/722 insulin pump (Medtronic, Northridge, CA). During the study, patients also used a CGM device (Paradigm Real-Time) from Medtronic and an Actiheart® (CamNtech Ltd., Cambridge, UK), which estimates activity energy expenditure based on heart rate (HR) and accelerometer measurements. Insulin was infused, and CGM devices were inserted into the subcutaneous tissue on the lower abdomen or the lower back. Patients who reported uncertainty about the accuracy of their insulin pump settings performed basal rate and bolus guide testing and optimized pump settings accordingly the first in-clinic study day.[6]

The study protocol was approved by the regional ethics committee, and the patients gave informed consent to participation. No remuneration was given.

Experimental design

We devised a modified factorial design study with 24 different study days with predetermined daily life events influencing blood glucose (BG). Each study day consisted of three different events. The event types and sequences of events are described in Tables 1 and 2. Patients were randomly assigned to complete two different study days separated by at least 3 weeks. Except for the duration of the events, the patients spent the day reclining in bed. Study days started at 8:00 a.m. The first 2 h were free of events, designed to stabilize the BG and the effects of transportation to the hospital. The first event of the day was at 10:00 a.m. and was always a meal. The second event was at 12:30 p.m. and was either an insulin bolus or a 20-min bout of exercise, and the third event was at 3:00 p.m. and was an insulin bolus, an exercise bout, or a snack. The events at 12:30 p.m. and 3:00 p.m. were never of the same type on the same study day. At 5:00 p.m. patients' BG was stabilized, and they were subsequently discharged.

The meal, insulin bolus, and exercise events had two levels as described in Table 1. The meal came either with no insulin or with an insulin bolus corresponding to 50% of the bolus needed to cover the carbohydrate (CHO) content of the meal estimated from the patient's insulin to CHO ratio. The meal bolus was given when the patient started eating. The size of the meal was determined by the weight of the patient (1 g of CHO/kg of body weight) with a composition by energy of 52% CHO, 18% protein, and 30% fat. The CHOs were simple, and the meal included white bread, ham and cheese, margarine, marmalade, milk, and juice. The snack was a juice drink (ProvideXtra, Fresenius Kabi, Bad Homburg, Germany) with 89% of the energy coming from CHO and 11% from fat. The snack size was determined by the patient's weight (0.4 g of CHO/kg of body weight). Meals were ingested over approximately 15 min, and snacks over 5 min.

The exercise event was running, performed on a treadmill. Mild and moderate exercise was quantified by HR and defined as 50% and 75% of the HR reserve, respectively. HR levels were calculated using the formula of Karvonen et al.:[7]

$$HR_{study} = \%\ \text{intensity} \times (HR_{max} - HR_{rest}) + HR_{rest}$$

The patient's HR was measured online, and the speed of the treadmill was adjusted to achieve the prescribed HR. As a safety precaution, we measured blood ketones before exercise if the plasma glucose (PG) was >252 mg/dL.

The "small" and "large" insulin boluses were estimated to lower PG by 54 and 108 mg/dL, respectively, based on the patient's insulin sensitivity factor.

We instructed patients not to exercise or consume alcohol on the day before the in-clinic study and to fast starting at 10:00 p.m. On the morning of the study day, patients calibrated their CGM devices at home with capillary blood. Upon arrival at the hospital a sampling cannula was placed in an antecubital vein. If PG was <54 mg/dL at any time, another cannula was placed in the other arm, and intravenous glucose was give to raise PG to 94 mg/dL.

We performed 10-min PG measurements throughout the experiment (YSI2300 STAT Plus, Yellow Springs Instruments, Yellow Springs, OH). Blood samples for insulin and glucagon analysis were obtained every 10 min for the first 30 min after an event and subsequently every 30 min. Sensor glucose (SG) values (i.e., CGM measurements) were obtained at 5-min intervals and automatically stored in the insulin pump. After the end of the study day, insulin infusion data, CGM data, and activity and HR data were downloaded from the respective devices. To further improve the physiological understanding of glucose dynamics during CSII treatment, samples for growth hormone, cortisol, epinephrine, and norepinephrine analysis were drawn at the same intervals as insulin and glucagon; however, these data will be reported separately elsewhere.

Changes in concentrations are reported instead of specific values because the baseline values of each event differed markedly as a result of subject-to-subject physiological variability as well as the different sequences of events on different study days. If not otherwise specified, results in the text are mean ± SD values. A 5% level is used for significance testing. These significance tests are assuming mutually independent data points; however, future modeling studies should contain parametric descriptions of the autocorrelation structure of data.[8] Area under the curve (AUC) was calculated using the trapezoid rule to quantify the effects of the events.

Table 1. Event Type and Sequence Descriptions

Description of event types		
Meal	Unbolused	Solid food with drink. 1 g of CHO/kg of body weight. No meal bolus
	Underbolused	Solid food with drink. 1 g of CHO/kg of body weight. 50% of the insulin bolus matching the meal CHO content based on personal ICR
Exercise	Mild	0.5 × (maximum HR − resting HR) + resting HR
	Moderate	0.7 × (maximum HR − resting HR) + resting HR
Bolus	Small	Insulin bolus estimated to lower PG by 54 mg/dL based on personal ISF
	Large	Insulin bolus estimated to lower PG by 108 mg/dL based on personal ISF
Snack	NA	Liquid. 0.4 g of CHO/kg of body weight.

Description of sequences			
1st event	*2nd event*	*3rd event*	*Sequence no.*
Meal unbolused	Bolus, small	Exercise, mild	1
		Exercise, moderate	2
		Snack	3
	Bolus, large	Exercise, mild	4
		Exercise, moderate	5
		Snack	6
	Exercise, mild	Bolus, small	7
		Bolus, large	8
		Snack	9
	Exercise, moderate	Bolus, small	10
		Bolus, large	11
		Snack	12
Meal underbolused	Bolus, small	Exercise, mild	13
		Exercise, moderate	14
		Snack	15
	Bolus, large	Exercise, mild	16
		Exercise, moderate	17
		Snack	18
	Exercise, mild	Bolus, small	19
		Bolus, large	20
		Snack	21
	Exercise, moderate	Bolus, small	22
		Bolus, large	23
		Snack	24

CHO, carbohydrate; HR, heart rate; ICR, insulin to carbohydrate ratio; ISF, insulin sensitivity factor; NA, not applicable; PG, plasma glucose.

Results

We present mean changes in PG, SG, plasma insulin, and glucagon concentrations for the three event types: CHO intake, exercise, and insulin bolus. These data are shown in Figures 1–3.

CHO intake

Three event types included CHO intake: the unbolused meal, the underbolused meal (50% meal bolus), and the unbolused snack. The unbolused meal was served on 12 study days, and the underbolused meal was served on another 12 study days. Eight patients were randomized to have the same type of meal on both study days; four patients had the unbolused meal on one study day and the underbolused meal on the other. Six subjects had one of the eight snack events, and one subject completed two study days including a snack event (Tables 1 and 2).

After the meals, PG increased throughout the observation period (Fig. 1). Peak values at 150 min were 232.8 ± 43.4 mg/dL and 120.2 ± 53.1 mg/dL ($P = 10^{-5}$) above baseline for the unbolused and the underbolused meals, respectively. After 60 min, mean PG and AUC for the two meal event types were significantly different; SG values did not statistically differ until 110 min, and SG AUC differed only the last 20 min of the observation period. PG after the snack peaked at 60 min (78.3 ± 33.5 mg/dL) and then decreased again. In the first 60 min after the underbolused meal, plasma insulin rose to 135.5 ± 70.2 pmol/L above baseline and then fell again. After the unbolused meal, plasma insulin remained stable, but after the snack event there was a slight decrease in plasma insulin to 35.4 ± 42.9 pmol/L at 120 min. Glucagon concentrations and AUC after the meals were not significantly different.

Exercise

Nine subjects performed mild exercise on 10 study days. Eight subjects performed moderate exercise on 10 study days (Tables 1 and 2). One moderate exercise event was excluded from the analysis because the subject received intravenous glucose at the beginning of the event. There were no significant differences in mean concentrations or AUC for PG, SG, plasma insulin, or glucagon following mild and moderate

Table 2. Patient Characteristics and Study Day Event Sequences

Patient	Sex	Age (years)	BMI (kg/m^2)	Diabetes duration (years)	HbA1c (%)	Total daily insulin (U/kg/day)	Study day	Event 1 (CHO/ insulin)	Event 2	Event 3
1	F	51	23.1	43	6.4	0.45	1	65 g/—	Moderate exercise	1.3 U of insulin[a]
							2	65 g/2.2 U	Moderate exercise	0.6 U of insulin[b]
2	M	41	22.2	8	6.9	0.61	1	75 g/3.8 U	1.4 U of insulin[a]	Mild exercise
							2	75 g/3.8 U	Mild exercise	1.4 U of insulin[a]
3	F	35	26.9	26	6.9	0.50	1	75 g/—	2.4 U of insulin[b]	Mild exercise
							2	75 g/2.9 U	2.4 U of insulin[b]	Moderate exercise
4	F	26	21.4	13	6.7	0.72	1	65 g/3.3 U	0.9 U of insulin[a]	Snack 28 g of CHO
							2	65 g/3.3 U	Mild exercise	1.9 U of insulin[b]
5	M	31	23.5	23	5.8	0.73	1	75 g/3.4 U	Moderate exercise	Snack 31 g of CHO
							2	75 g/—	1.7 U of insulin[a]	Snack 31 g of CHO
6	M	49	25.1	7	6.1	0.47	1	85 g/4.3 U	1.3 U of insulin[c]	Mild exercise
							2	85 g/4.3 U	Moderate exercise	2.6 U of insulin[b]
7	F	25	23.8	8	6.9	0.76	1	75 g/—	Mild exercise	1.5 U of insulin[a]
							2	75 g/—	Moderate exercise	1.5 U of insulin[a]
8	F	29	32.6	19	7.0	0.67	1	85 g/—	Mild exercise	Snack 32 g of CHO
							2	85 g/—	3.2 U of insulin[b]	Moderate exercise
9	F	38	20.3	13	6.8	0.57	1	65 g/2.7 U	Moderate exercise	1.0 U of insulin[a]
							2	65 g/2.7 U	Mild exercise	Snack 25 g of CHO
10	F	34	34.7	12	7.1	0.78	1	105 g/—	Mild exercise	5 U of insulin[b]
							2	105 g/8.8 U	5 U of insulin[b]	Snack 44 g of CHO
11	F	29	24.4	14	6.6	0.66	1	65 g/—	1.5 U of insulin[a]	Moderate exercise
							2	65 g/—	Moderate exercise	Snack 28 g of CHO
12	F	23	23.3	12	7.1	0.62	1	65 g/—	1.1 U of insulin[a]	Mild exercise
							2	65 g/—	2.2 U of insulin[b]	Snack 27 g of CHO

[a]Large insulin bolus.
[b]Small insulin bolus.
[c]The subject should have had a large insulin bolus (2.6 U) according to the randomization; however, as this amount of insulin would likely have caused severe hypoglycemia, it was decided to overrule the planned sequence and administer a small insulin bolus instead.
CHO, carbohydrate; HbA1c, hemoglobin A1c.

exercise. PG levels decreased by 43.4 ± 27.4 mg/dL and 63.2 ± 52.5 mg/dL after mild and moderate exercise, respectively (Fig. 2). Plasma insulin displayed a biphasic pattern: peak values after 20 min of mild and moderate exercise were 26.0 ± 17.1 pmol/L and 26.3 ± 51.6 pmol/L above baseline, respectively, followed by a decline to 29.5 ± 25.3 pmol/L and 44.5 ± 42.8 pmol/L below baseline values at 120 min. A slight decrease in glucagon concentrations was observed after initiation of exercise followed by an increase and peak at the 30-min mark of 2.1 ± 2.0 pmol/L for mild exercise and 2.0 ± 1.5 pmol/L for moderate exercise. Mean energy expenditure was 64 ± 33 kcal and 117 ± 42 kcal during mild and moderate exercise, respectively ($P = 0.01$). There was no correlation between the decrease in BG concentration and activity energy expenditure.

Insulin bolus

A small insulin bolus was given to nine patients and a large bolus to seven patients (Tables 1 and 2). Following the injection of small (1.3 ± 0.2 U) and large (2.8 ± 1.4 U) insulin boluses, PG decreased by 71.8 ± 31.9 mg/dL and 92.6 ± 27.5 mg/dL, respectively, after 120 min ($P = 0.14$) (Fig. 3). PG AUCs did not significantly differ. Plasma insulin peak times were 30 min for both small and large boluses, and the respective peak values were 29.9 ± 24.0 pmol/L and 74.6 ± 30.7 pmol/L above baseline ($P = 0.002$). Glucagon concentrations were lower at all times after the large insulin bolus event compared with the small, but the difference was statistically significant only at 10 and 30 min.

CGM accuracy

The mean absolute difference between paired SG and PG for all study days in total was 28.9 mg/dL (95% confidence interval, 17.6–42.0 mg/dL), and the mean absolute relative difference was 21.6% (17.9–25.2%). When patients were fasting, reclining in bed, and only receiving their basal insulin infusion (8:00–10:00 a.m.), mean absolute difference for all study days in total was 8.9 mg/dL (5.3–12.5 mg/dL), and mean absolute relative difference was 11% (6.5–15.5 %). CGM accuracy decreased during rapid changes in PG. On all study days, CGM values were lower than the actual PG values when PG was increasing but also when PG was stable in the hyperglycemic ranges (< 198 mg/dL). Only during sharp decreases in PG and when PG was stable in the normoglycemic range did CGM values correspond to or exceed YSI measurements.

Discussion

We devised a new in-clinic protocol based on daily life events including meals, snacks, insulin boluses, and exercise to obtain T1D data for glucose modeling. CHO intake and changes in insulin delivery are the two most important variables in glucose control in T1D. We designed the study such that these two variables on 12 of the 24 study days were introduced simultaneously, as they often are in real life. On

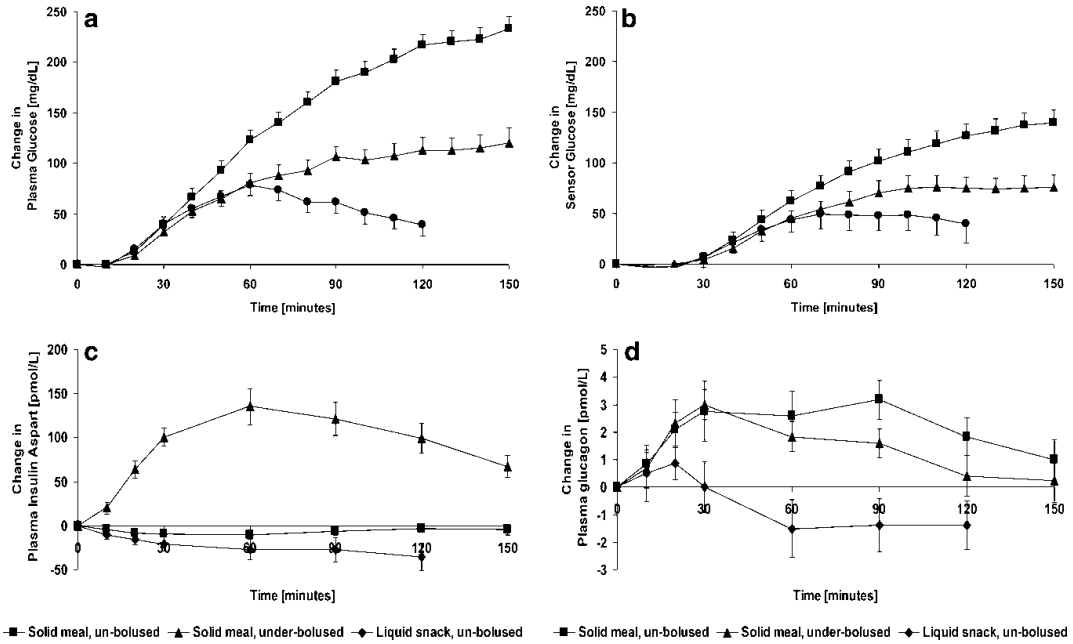

FIG. 1. Changes in (**a**) plasma glucose, (**b**) sensor glucose, (**c**) plasma insulin aspart, and (**d**) glucagon after ingestion of an unbolused liquid snack (0.4 g of carbohydrate/kg of body weight), after an unbolused solid meal (1.0 g of carbohydrate/kg of body weight), and after a solid meal with 50% of the insulin bolus needed to cover the carbohydrate content of the meal based on the patients' insulin to carbohydrate ratios. Data are mean ± SEM values.

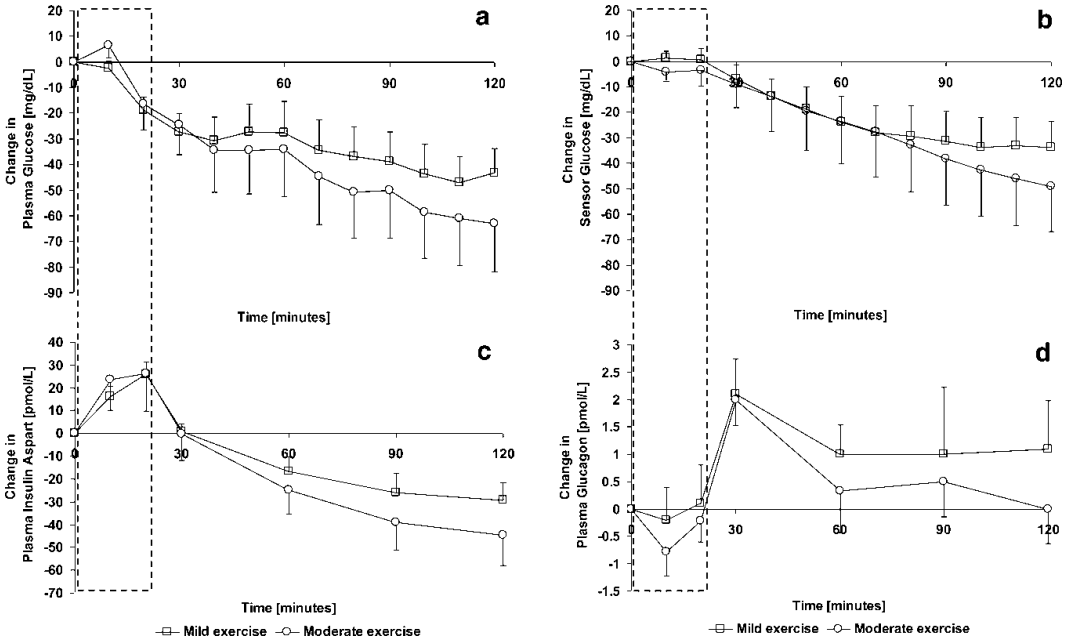

FIG. 2. Changes in (**a**) plasma glucose, (**b**) sensor glucose, (**c**) plasma insulin aspart, and (**d**) glucagon during and after a 20-min bout of mild and moderate exercise ona treadmill. The dotted boxes indicate the exercise period. Data are mean ± SEM values.

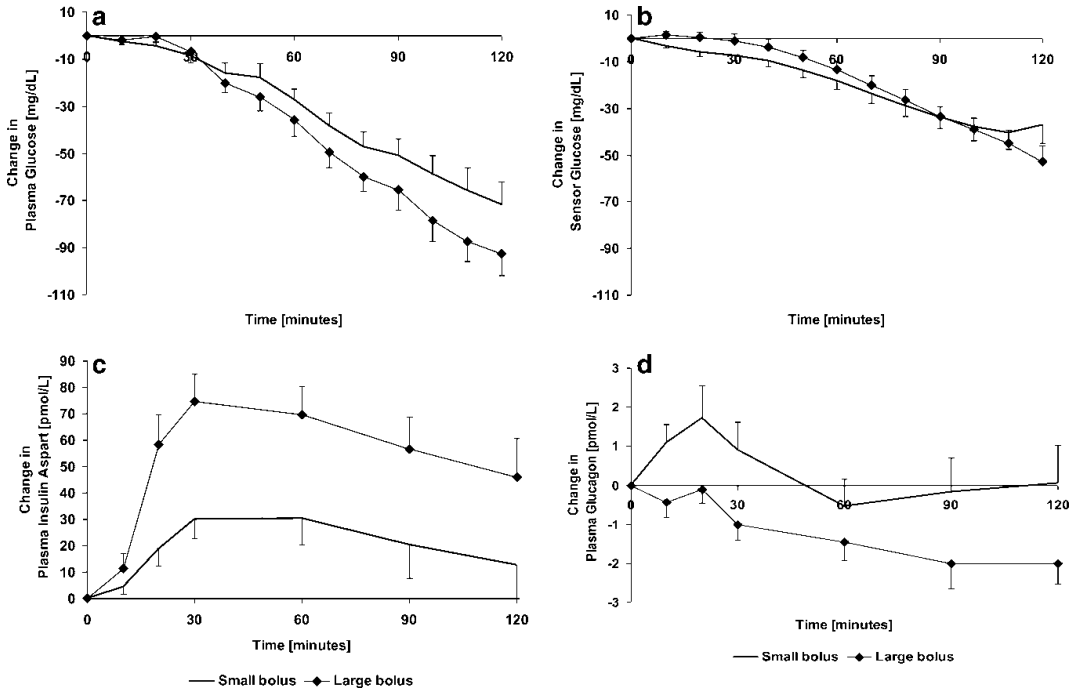

FIG. 3. Changes in (**a**) plasma glucose, (**b**) sensor glucose, (**c**) plasma insulin aspart, and (**d**) glucagon after a small and a large insulin bolus. The sizes of the small and large insulin boluses were based on the patients' insulin sensitivity factors and an intended decrease in plasma glucose of 54 mg/dL and 108 mg/dL, respectively. Data are mean ± SEM values.

other study days we separated CHO intake and insulin bolus temporally to be able to observe the responses to each system input. Practical T1D measurement heruristics involve a simultaneity between CHO intake and insulin boluses. Unfortunately, this simultaneity disadvantages some useful dynamic modeling strategies that cannot satisfactorially distinguish the very different effects of these two system inputs. It has been shown quantitatively in simulation studies that there is a substantial positive correlation between the prediction accuracy of models and the degree of separation of the inputs from which they were identified.[9]

Different levels of CHO intake and insulin boluses were also applied to the protocol. The levels were chosen to gain both fast and slow changes in PG and to challenge the system as much as possible while maintaining realistic values.

Exercise can induce decreases in PG with risk of hypoglycemia during, immediately after, or hours after finishing the activity. However, exercise can also induce hyperglycemia depending on insulin concentration and the type and intensity of exercise.[10] We incorporated into our study protocol both mild and moderate exercise to study these effects.

Each of the 12 subjects was studied on two separate days performing two different sequences of events. In some cases the two study days contained identical events, but in different order; in other cases the events were different. This makes it possible to test the inter-individual performance of the models under identical and dissimilar experimental conditions and to some extent also the intra-individual performance, although a 2-day study does not fully reflect the intra-individual variability. From a clinical perspective, the effects of the different study events are not fully separated; nevertheless, with advanced statistics, such as mixed effects modeling,[11] it is possible to further separate the events and obtain more information across the study population.

One of the DiaCon Study Group's aims is to develop a closed-loop system to improve glucose regulation in T1D. We have based our closed-loop system on the subcutaneous–subcutaneous approach, which has the greatest potential for commercialization in the near future.[12] High-quality insulin pumps are readily available, and sensor performance is steadily improving. The Actiheart used in this study records data for energy expenditure estimations that have to be performed retrospectively. Devices providing the information in real-time are, however, available, which makes it possible to integrate activity in a control algorithm.

We prioritized to perform glucagon analyses to gain insight into the glucagon dynamics in patients with T1D treated with CSII, but also to collect data for potential modeling purposes. Although we intend to develop an algorithm controlling glucose solely by insulin delivery, other groups are working on bihormonal closed-loop solutions based on dual pumps delivering both insulin and glucagon.[13,14] It remains to be determined how the strategies will ultimately perform in an integrated system.

Plasma insulin increased, as anticipated, following the infusion of a half-size meal bolus and remained stable during

the unbolused meal. The slight, unexpected decrease in plasma insulin after the unbolused meal was most likely a result of the preceding exercise and insulin bolus events and not an effect of the meal itself. The greater increase in glucagon concentration after the meals compared with after the snack reflects the foods' differing protein content.

During the 20-min bouts of mild and moderate exercise plasma insulin increased. This observation is consistent with the results of one study of exercise in T1D insulin pump users.[15] In contrast, other studies concluded that exercise did not induce increases of insulin concentrations in CSII-treated patients.[16–18] The observed increase in plasma insulin could be explained physiologically by increases in skin blood flow during exercise for thermoregulatory purposes.[19]

The difference in mean energy expenditure during mild and moderate exercise was statistically significant. Nevertheless, changes in PG, SG, plasma insulin, and glucagon during and after exercise did not significantly differ during the 2-h observation period. A tendency toward a greater decrease in PG following moderate exercise was, however, observed, and statistical significance may have been achieved with a larger patient sample. Glucose control in relation to exercise in T1D is complex, and the results of our study should not be extrapolated to other intensities or durations of exercise or exercise performed under different conditions, at different hours of the day, at different time intervals from meals, or with different levels of plasma glucose, insulin, and glucagon. Although there was no simple linear association between activity energy expenditure and decrease in PG during exercise, data analysis might reveal a more complex relation including the counterregulatory hormones that can be modeled and used in a control algorithm.

The decrease in PG after infusion of the large insulin bolus was less than estimated; however, if the observation period had been of the same length as the insulin action time the estimated value might have been achieved. The decrease in PG after infusion of the small bolus, on the other hand, was even larger at 120 min than the estimated total decrease. One explanation for this could be a carryover effect from previous events (e.g., exercise or the meal with the half-size meal bolus).

Accuracy of the CGM was also studied. Mean absolute relative difference for all study days was higher than reported data (21.6% vs. 15.2%).[20] The reason for this divergence could be that these previous studies were performed during eu- and hypoglycemia, whereas most subjects in our study spent a considerable amount of time in the hyperglycemic ranges. Furthermore, the study subjects experienced rapid changes in BG, and CGM values are known to differ from YSI values in these situations.

A limitation of multi-event study days is that PG will vary from the beginning of one event to the next. In our study the different sequences of events further resulted in different baseline values within the same event type, which is why only changes in baseline values are reported in the text and figures. From a strict physiologic point of view it is impossible to draw firm conclusions based on this type of data. On the other hand, these data are highly suited for the intended modeling purposes using advanced pharmacokinetic/pharmacodynamic modeling methods.[21–23] The patients spent the study day reclining in bed, which may not be representative of outpatient life. The reason for choosing this setup and introducing the events temporally separated was to eliminate the confounding effects of other activities (e.g., the catecholamine response elicited from physical activity).

In conclusion, we have conducted a clinical study based on a novel protocol whereby we have gathered information-rich T1D data for glucose modeling. The next steps will be to develop models of glucose metabolism to be implemented in a virtual T1D clinic. The virtual clinic will be used for simulations of different glucose control strategies including a closed-loop glucose control system.

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Appendix C

Paper B

Model Identification Using Stochastic Differential Equation Grey-Box Models in Diabetes

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ORIGINAL ARTICLE

Model Identification Using Stochastic Differential Equation Grey-Box Models in Diabetes

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Abstract

Background:

The acceptance of virtual preclinical testing of control algorithms is growing and thus also the need for robust and reliable models. Models based on ordinary differential equations (ODEs) can rarely be validated with standard statistical tools. Stochastic differential equations (SDEs) offer the possibility of building models that can be validated statistically and that are capable of predicting not only a realistic trajectory, but also the uncertainty of the prediction. In an SDE, the prediction error is split into two noise terms. This separation ensures that the errors are uncorrelated and provides the possibility to pinpoint model deficiencies.

Methods:

An identifiable model of the glucoregulatory system in a type 1 diabetes mellitus (T1DM) patient is used as the basis for development of a stochastic-differential-equation-based grey-box model (SDE-GB). The parameters are estimated on clinical data from four T1DM patients. The optimal SDE-GB is determined from likelihood-ratio tests. Finally, parameter tracking is used to track the variation in the "time to peak of meal response" parameter.

Results:

We found that the transformation of the ODE model into an SDE-GB resulted in a significant improvement in the prediction and uncorrelated errors. Tracking of the "peak time of meal absorption" parameter showed that the absorption rate varied according to meal type.

Conclusion:

This study shows the potential of using SDE-GBs in diabetes modeling. Improved model predictions were obtained due to the separation of the prediction error. SDE-GBs offer a solid framework for using statistical tools for model validation and model development.

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Abbreviations: (ACF) autocorrelation function, (BG) blood glucose, (BW) body weight, (CHO) carbohydrate, (CSII) continuous subcutaneous insulin infusion, (IVP) Identifiable Virtual Patient, (ODE) ordinary differential equation, (PD) pharmacodynamic, (PK) pharmacokinetic, (SDE) stochastic differential equation, (SDE-GB) stochastic-differential-equation-based grey-box model, (T1DM) type 1 diabetes mellitus

Keywords: autocorrelation, blood glucose dynamics, statistical model building, stochastic differential equations, stochastic grey-box modeling, type 1 diabetes mellitus

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Introduction

Several studies have shown promising potential for automatic insulin delivery in the treatment of type 1 diabetes mellitus (T1DM) patients. In the development of control algorithms for an artificial pancreas, virtual T1DM patients are a useful tool for preclinical testing and verification. The advantages are several: acceleration of the development process, lower costs, and the possibility of testing extreme treatment strategies without having to deal with the ethical aspects. The acceptance of virtual preclinical testing is growing and thus also the need for robust and reliable models for simulation. Currently, several dynamic models of the blood glucose (BG)–insulin system in T1DM patients exist.[1–4] The simplest models are used for simulating BG response after an intravenous glucose tolerance test, and the most advanced and complex models are used for simulating BG response to a meal [in terms of amount of ingested carbohydrates (CHOs)] and to continuous subcutaneous insulin infusion (CSII) from a pump. One of the most complex models has been approved for preclinical *in silico* testing of control algorithms by the U.S. Food and Drug Administration.[5]

The existing models can be categorized as white-box models based on ordinary differential equations (ODEs). White-box models are mainly constructed on the basis of physiological knowledge about the system. Solutions to ODEs are deterministic functions of time, and hence these models are built on the assumption that future concentrations and effects can be predicted exactly.

An essential part of model validation is the analysis of the residual errors (the deviation between the true observations and the one-step predictions provided by the model). This validation method is based on the fact that a correct model leads to uncorrelated residuals. This is rarely obtainable for white-box models. Hence, in these situations, it is not possible to validate ODE models using standard statistical tools. However, by using a slightly more advanced type of differential equations, this problem can be solved. By replacing ODEs with stochastic differential equations (SDEs), we can obtain uncorrelated residuals both by systematically improving the model and because of the way the stochasticity enters the system.

Stochastic-differential-equation-based models are referred to as grey-box models because the structure of the model is built on a combination of physiological knowledge, as white-box models, and on statistical information based on the observations, as black-box models, which are entirely built on data. Hence, stochastic-differential-equation-based grey-box models (SDE-GBs) can be seen as a mix of white-box and black-box models as sketched in **Figure 1**. An SDE-GB can be written as

$$dx_t = f(x_t,u_t,t,\theta)dt + \sigma(u_t,t,\theta)d\omega \quad (1)$$

$$y_k = h(x_k,u_k,t_k,\theta) + e_k \quad (2)$$

The equations describing the dynamics of the states of the system, x_t, are formulated in continuous time and are separated in a drift term, $f(x_t,u_t,t,\theta)$, and a diffusion term, $\sigma(u_t,t,\theta)d\omega$. The observations, y_k, are linked to the states through the observation equations, **Equation (2)**, which are typically formulated in discrete time and include the measurement error, e_k. u_t represents the inputs and θ the parameters of the system.

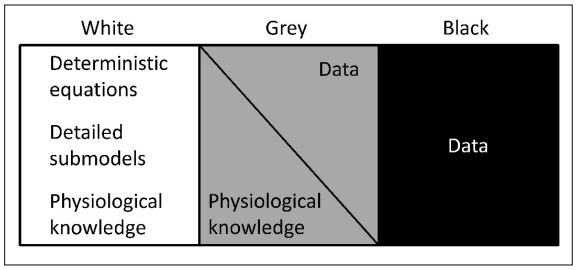

Figure 1. Illustration of the concept of grey-box modeling. White-box models are based mainly on knowledge about the system. Black-box models are built on statistical information from the data. Grey-box modeling combines the two approaches.

As seen in **Equations (1)** and **(2)**, the SDE-GB separates the residual error into two separate error terms:

- The diffusion, $\sigma(u_t,t,\theta)d\omega$, representing model approximations and noise originating from unknown disturbances to the system, e.g., changes in metabolism due to physical activity, altered stress level, hormone cycle, or simply true stochastic behavior and

- The measurement noise, e_k, representing the serially uncorrelated error occurring due to imperfect accuracy and precision of the analyzing equipment.

Solutions to SDEs are stochastic processes that are described by probability distributions. This property allows for maximum likelihood estimation.[6]

In physiological modeling, SDE-GBs are obvious choices from a theoretical point of view due to their ability to describe the stochastic, complex, and unpredictable nature of these systems. The separation of the residual error into diffusion and measurement noise results in a more correct description of the prediction error. If the model is describing the data properly, this formulation will lead to uncorrelated residuals.

Inclusion of the diffusion has another advantage, mainly related to the model building itself. By investigating the diffusion terms, one can retrieve information about how to improve an insufficient model. Diffusion terms that are estimated to be relatively large indicate a model mismatch for the relevant part of the model. Accordingly, the diffusion terms can help in the search for a more reliable model.[7] SDE-GBs have been found to be useful within many areas of mathematical modeling of biological and physiological systems.[8–12]

This article focuses on the advantages of using SDE-GBs when modeling the glucoregulatory system in T1DM patients. We start out from a previously published ODE-based model[3] and use SDEs and statistical analysis to extend the model by adding significant diffusion terms.

Methods

Data

Data from a clinical study conducted at Hvidovre University Hospital as a part of the DIACON project were used.[13] Four CSII-treated T1DM patients performed four different study sequences, including standardized meals and insulin boluses. During each study day, three events took place. The first event took place after at least 120 min of BG stabilization. It consisted of a standardized solid meal [1 g CHO/kg body weight (BW)] with either a half-meal-size insulin bolus calculated on the basis of the patient's insulin sensitivity factor and insulin-to-carbohydrate ratio or with no bolus at all. The second event was introduced 150 min after the meal and was a small or large bolus defined as a bolus that would lower BG by 54 or 108 mg/dl, respectively. Finally, after another 150 min, the patient was given a standardized liquid snack (event 3; 0.4 g CHO/kg BW). The combination of events on the four study days is depicted in **Table 1**. Patients spent the day in bed and received their normal basal rate of insulin during the whole study day. Blood glucose samples were obtained every 10 min (YSI2300 STAT plus, Yellow Springs Instruments, Yellow Springs, OH) and plasma insulin concentration was sampled nonequidistantly 23 times during the trial day.

The Initial White-Box Model

We used the Identifiable Virtual Patient (IVP)[3,14] as an initial white-box basis for formulating our grey-box model. The IVP model is an extended minimal model, including meal absorption and CSII. This initial model will be presented as an SDE-GB with diffusion. The insulin pharmacokinetic (PK) model is a two-compartmental model:

$$dI_{subc} = \frac{1}{\tau_1}\left(\frac{ID}{C_I} - I_{subc}\right)dt + \sigma_{Isubc}d\omega_1 \quad (3)$$

$$dI_p = \frac{1}{\tau_2}(I_{subc} - I_p)dt + \sigma_{Ip}d\omega_2 \quad (4)$$

Table 1.
Description of the Four Study Sequences

Patient	Event 1	Event 2	Event 3
1	Meal + ½ bolus 65 g CHO + 3.3 U	Small bolus 0.9 U	Snack 28 g CHO
2	Meal without bolus 75 g CHO	Small bolus 1.6 U	Snack 31 g CHO
3	Meal + ½ bolus 105 g CHO + 8.8 U	Large bolus 5.0 U	Snack 44 g CHO
4	Meal without bolus 65 g CHO	Large bolus 2.2 U	Snack 27 g CHO

where I_{subc} represents the subcutaneous concentration of insulin (mU/liter) and ID is the input from CSII (mu/min) representing the insulin basal delivery rate and boluses. I_p represents the plasma insulin concentration (mU/liter). In this

study, the diffusion term parameterized as $\sigma d\omega$. σ is a scaling parameter for the diffusion, and $d\omega$ is assumed to be a Wiener process for which the increments are normally distributed.[15] The remaining parameter definitions are given in **Table 2**. The glucose–insulin dynamics are described as

$$dI_{eff} = p_2(S_I I_p - I_{eff})dt + \sigma_{I_{eff}} d\omega_3 \tag{5}$$

$$dG_p = \left(-(GEZI + I_{eff})G_p + EGP + \frac{D_2}{\tau_m} + \frac{G_{IV}}{\tau_g V_g} \right) dt + \sigma_{Gp} d\omega_4 \tag{6}$$

where I_{eff} is the pharmacodynamic (PD) effect of insulin (min^{-1}) on the BG level, G_p (mg/dl). G_{IV} is the intravenous glucose input (mg) administrated during the stabilization period if needed and is modeled as a vector of zeros except at the time instants where glucose was given during the clinical study. The meal absorption is described as a two-compartment model:

$$dD_1 = \left(\frac{AgCHO}{V_g} + \frac{D_1}{\tau_m} \right) dt + \sigma_{D1} d\omega_5 \tag{7}$$

$$dD_2 = \frac{1}{\tau_m}(D_1 - D_2)dt + \sigma_{D2} d\omega_6 \tag{8}$$

where CHO is the rate of ingestion of carbohydrates (mg/min). D_1 (mg) and D_2 (mg) represent the digestive system.

Table 2.
Identifiable Virtual Patient Model Parameters

Name	Unit	Description	Nominal value[a]
τ_1	min	Time constant related to the insulin movement between the subcutaneous layer and plasma	40–131
τ_2	min	Time constant related to the insulin movement between the subcutaneous layer and plasma	10–70
C_l	liter/min	Insulin clearance	0.54–2.01
p_2	1/min	Delayed insulin action on BG level	8.14×10^{-3}–2.33×10^{-2}
S_I	liter/(mU × min)	Insulin sensitivity	9.64×10^{-5}–1.73×10^{-3}
$GEZI$	1/min	Glucose effectiveness at zero insulin	1.00×10^{-8}-6.39×10^{-3}
EGP	mg/(dl × min)	Endogenous glucose production rate at zero insulin	0.6–3.45
τ_m	min	Peak time of meal absorption	27–107
τ_g	min	Time constant for the intravenous glucose administration	1
Ag	Dimensionless	Bioavailability for carbohydrates	0.9
V_G	dl/kg BW	Volume of distribution for glucose	1.93–4.14

[a] The values are obtained from Kanderian and coauthors[3] except Ag and τ_g, which were fixed during the estimation.

To specify which states we observe and to introduce measurement error, we construct two observation equations linking the observations to the actual state—one for each type of observation: YSI (representing the BG level) and I_A (representing the insulin level in plasma). For our model, the set of observation equations can be written as

$$YSI = G_p + \exp(e_{YSI}), \quad \exp(e_{YSI}) \in N(0, S_{YSI}) \tag{9}$$

$$I_A = I_p + \exp(e_{I_A}), \quad \exp(e_{I_A}) \in N(0, S_{I_A}) \tag{10}$$

where S represents the variance of the measurement noise for each of the two types of observations. The sequence of measurement errors, e, is assumed to be independent and identically distributed. If we expect time correlated errors,

e.g., if we used observations from a continuous glucose monitor, the correlated noise could be implemented in the model as a state.

Stochastic Differential Equation Grey-Box Model Construction

Because of the complex structure of SDEs, estimation of parameters in an SDE-GB is not trivial except for some simple cases. Instead, a maximum likelihood method in combination with an extended Kalman filter is used to estimate the parameters.[12,15] The likelihood function is formulated using the one-step prediction errors, $\varepsilon_{k,}$ and the associated variances, $R_{k|k\text{-}1}$:[15]

$$L(\theta;Y_N) = p(Y_N|\theta) \tag{11}$$

$$= \left(\prod_{k=1}^{N} \frac{\exp(-\frac{1}{2}\varepsilon_k^T R_{k|k-1}^{-1}\varepsilon_k)}{\sqrt{\det(R_{k|k-1})}(\sqrt{2\pi})^{\dim(Y_N)}} \right) p(y_0|\theta) \tag{12}$$

Y_N is the set of observations, and y_0 is the initial conditions. For a given set of parameters and initial states, ε_k and $R_{k|k\text{-}1}$ are computed by a continuous-discrete extended Kalman filter as described previously.[8,15] The parameter estimates are found by maximizing the log-likelihood:

$$\hat{\theta} = \text{argmax}\{\log(L(\theta;Y_N|y_0))\}. \tag{13}$$

The corresponding value of the log-likelihood is the observed maximum likelihood value for that data set and model. All computations were done using the free statistical software, R (version 2.15.1), and the "CTSMR-package" (Continuous Time Stochastic Modeling in R).[16]

To improve the IVP model using SDEs, the following forward selection strategy was used:

Step 1: The parameters of the ODE version of the model were estimated for each data set. The following parameters were fixed: $Ag = 0.9$ as in Dalla Man and coauthors,[1] $\tau_g = 1$ min, and all diffusion terms were fixed to zero. All initial conditions were fixed except for I_{eff}.

Step 2: One diffusion term at a time was now estimated together with the parameters estimated in step 1 for each data set. This was done six times corresponding to the six diffusion terms in **Equations (3)–(8)**.

Step 3: A likelihood-ratio test was used to identify the SDE-GB resulting in the most significant improvement compared with the ODE. The test statistic is[6]

$$D = 2(\log(\sum_i L) - \log(\sum_i L_0)) \tag{14}$$

where $i = 1$–4, corresponding to each of the four data sets. L and L_0 are the likelihood values obtained in **Equation (13)** for the SDE-GB and ODE model, respectively. D is $\chi^2(f)$ distributed, where f is the difference in number of parameters between the two models—in this case, $f = 1$.

Step 4: The model found in step 3 was extended by repeating the procedure in step 2. This time, yet another diffusion term was estimated. Hereby, the procedure was repeated five times. The best model now including two nonzero diffusion terms was identified with a likelihood-ratio test against the best SDE-GB identified in step 3. Analysis showed that it was not feasible to estimate more than two diffusion terms in the IVP model, given the limited size of each data set.

Step 5: In order to illustrate another method for systematic model improvement, we performed parameter tracking to pinpoint model deficiencies.[8] Parameter tracking can be used to identify parameters with systematic variation due to factors or disturbances not included in the model, e.g., changing hormone levels or other unknown factors influencing

the system. By changing the parameter of interest into a state and by setting the drift term to zero, the parameter is allowed to vary as a random walk as dictated by the data. This will reveal any presence of a systematic structure that can be included in the model subsequently.

Results

Model Evaluation

The performance of the models is evaluated from the likelihood-ratio tests and by examining the one-step predictions and the autocorrelation function (ACF) for the standardized residuals. One step corresponds to the time between two samples. The ACF of the residuals shows whether the residuals are correlated.[9,17] The standard deviations given in the following figures are equal to $\sqrt{diag(R_{k|k-1})}$.

A one-step prediction of the BG level from the ODE model and the ACF for the YSI residuals are seen in **Figure 2**. The one-step prediction is inaccurate, and especially after the bolus at 150 min, the predictions clearly deviate from the observations. The ACF shows that the YSI residuals are highly correlated and thus cannot be considered as independent. The same holds for the three other patients. The prediction of the insulin level from the ODE model and the corresponding ACF for the insulin residuals are shown in **Figure 3** for patient 1. The prediction seems acceptable, although the limited number of observations (n = 23) makes it hard to assess. Based on the corresponding ACF, the residuals appear to be correlated. The next step in the model development was to estimate the model parameters, including one nonzero diffusion term. **Table 3** shows the results from the likelihood-ratio test performed in steps 3 and 4. As seen from the six likelihood-ratio tests in step 3, we found that the largest improvement was achieved with a nonzero diffusion term on the PD effect of insulin on the BG level, I_{eff} in **Equations (5)** and **(6)**.

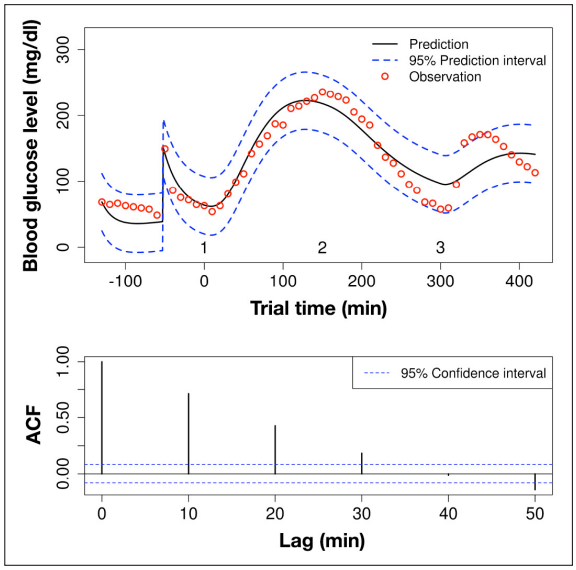

Figure 2. (Top) One-step prediction and 95% prediction interval from the ODE model and YSI observations for patient 2. The starting time of each event is indicated by 1, 2, and 3. The prediction is not in total agreement with the observations, particularly after the bolus at 150 min. **(Bottom)** The ACF for the YSI residuals from the ODE model. The sketched 95% confidence interval corresponds to an uncorrelated process. If more than 5% is outside this region, the process cannot be assumed to be uncorrelated. The residuals are strongly correlated in this case.

In the following, we define this model as SDE-GB 1. The one-step prediction of the BG level from SDE-GB 1

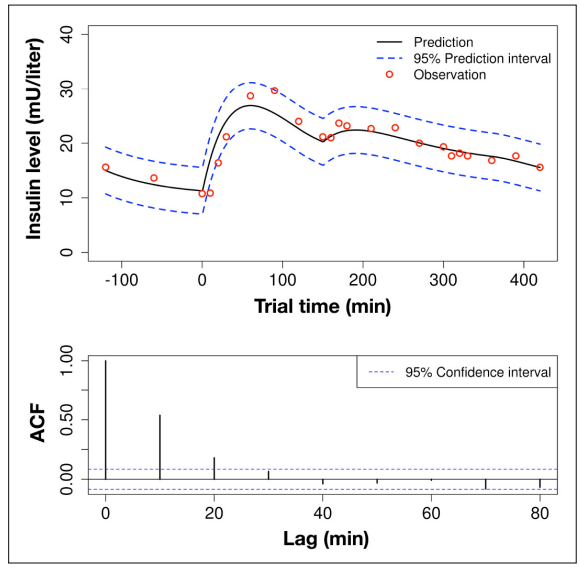

Figure 3. (Top) One-step prediction and 95% prediction interval from the ODE model and observations of the insulin plasma level for patient 1. The prediction is acceptable. **(Bottom)** The ACF for the insulin residuals from the ODE model. Despite the acceptable fit, the residuals are correlated.

for patient 4 is seen in **Figure 4**. The prediction has improved markedly, and the prediction uncertainty has also decreased substantially.

The ACF for the YSI residuals in **Figure 4** shows that the residuals now can be considered as almost independent only by the inclusion of a single nonzero diffusion term in the state representing I_{eff} in **Equations (5)** and **(6)**. Subsequently, SDE-GB 1 was extended as described in step 4. From the sequence of likelihood-ratio tests, we concluded that the largest improvement was achieved with an additional nonzero diffusion term on the state describing the insulin plasma level, I_p in **Equations (3)** and **(4)** as stated in **Table 3**. This model is named SDE-GB 2 and includes two nonzero diffusion terms in total. Based on the individual likelihood values (for each data set) found in **Equation (13)**, we saw that the obtained likelihood value had improved significantly only for patients 1 and 2. Thus we consider this model only for these two patients.

To illustrate the effect of the additional diffusion term, **Figure 5** shows the one-step prediction of the insulin level from SDE-GB 1 and the ACF for the residuals for

Table 3.
Estimated Log-Likelihood Values and Test Statistics and *P* Values from the Likelihood-Ratio Tests

	log(∑*L*)	*D*[a]	*P* value[b]
ODE model	-510.3	—	—
SDE-GB σ_{Ip}	-494.0	32.6	1.13×10^{-8}
SDE-GB σ_{Isc}	-494.3	32	1.54×10^{-8}
SDE-GB σ_{Ieff}	-326.9	366.8	0
SDE-GB σ_{G}	-357.7	305.2	0
SDE-GB σ_{D1}	-331.1	358.4	0
SDE-GB σ_{D2}	-337.1	346.4	0
SDE-GB $\sigma_{Ieff+}\sigma_{Ip}$	-319.9	14	0.00018
SDE-GB $\sigma_{Ieff+}\sigma_{Isc}$	-324.6	4.6	0.032
SDE-GB $\sigma_{Ieff+}\sigma_{G}$	-326.9	0	1
SDE-GB $\sigma_{Ieff+}\sigma_{D1}$	-326.9	0	1
SDE-GB $\sigma_{Ieff+}\sigma_{D2}$	-326.9	0	1

[a] The test statistic *D* is computed from **Equation (14)** as the likelihood ratio between the ODE model and the following six models in the table (SDE-GB $\sigma_{Ip\text{-}D2}$), and between SDE-GB σ_{Ieff} and final five models in the tables (SDE-GB $\sigma_{Ieff+Ip\text{-}Ieff+D2}$).

[b] Based on a $\chi^2(1)$ distribution.

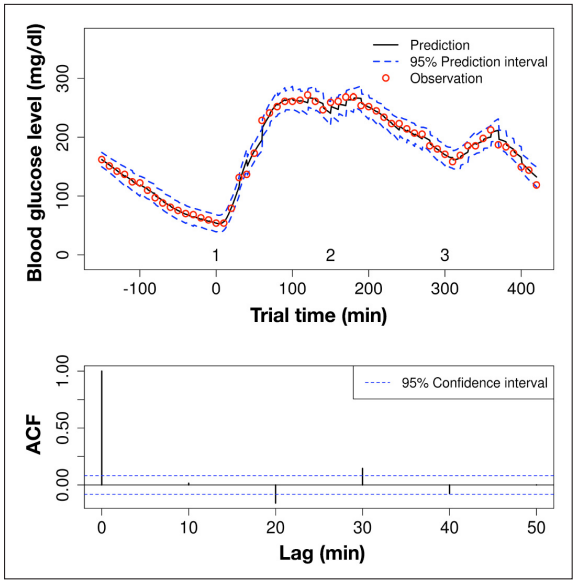

Figure 4. (Top) One-step prediction and 95% prediction interval from the SDE-GB 1 and YSI observations for patient 4. The prediction has improved from the ODE model prediction. The starting time of each event is indicated by 1, 2, and 3. **(Bottom)** The ACF for the YSI residuals from the SDE-GB 1. Almost no significant correlation is left.

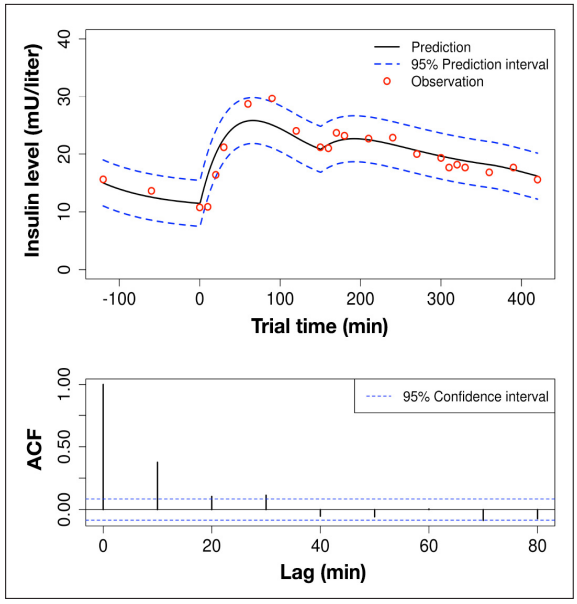

Figure 5. (Top) One-step prediction and 95% prediction interval from SDE-GB 1 and observations of the insulin plasma level for patient 1. The prediction is acceptable. **(Bottom)** The ACF for the insulin residuals from SDE-GB 1. Some correlation is still present.

patient 1. The ACF has improved from the ODE model, but some correlation is still present. **Figure 6** shows the one-step prediction of the insulin level from SDE-GB 2 together with the ACF for the residuals. The extra nonzero diffusion term removes the correlation between the residuals.

Parameter tracking

Kanderian and coauthors[3] introduced intraday variation by separating data in time windows and estimating some of the parameters within these windows. The time windows are found on the basis of subjective predefined criteria for the model fit. Using the SDE-GB approach, we do not need to define such criteria to be able to investigate parameter variation. By changing a parameter into a state, we allow the parameter to vary over time. We can then track the variation in the parameter value.

As the patients are served two types of meals (solid and liquid), we would expect the peak time of meal absorption, τ_m, to differ for the two meals. We expanded SDE-GB 1 by adding a state representing τ_m. The state was modeled as a random walk:

$$d\tau_m = \sigma_{\tau_m} d\omega_7 \tag{15}$$

With this formulation, we could track τ_m and identify the possible factors affecting the variation of this parameter. In **Figure 7**, a result of this tracking is seen. As expected, τ_m is estimated to be shorter after a liquid snack than after a solid meal. A future step would be to replace the random walk with an equation including meal type as the explanatory variable. We were not able to do this due to the limited size of the data sets. However, another case using parameter tracking for model expansion is presented elsewhere.[8]

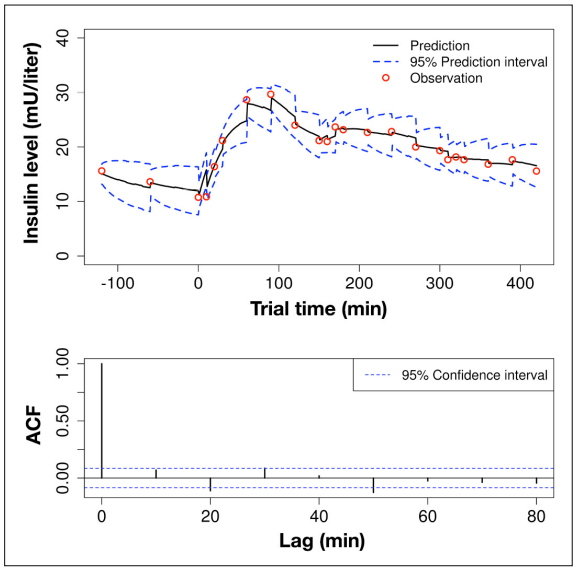

Figure 6. (Top) One-step prediction and 95% prediction interval from SDE-GB 2 and observations of the insulin plasma level for patient 1. The prediction has improved from the ODE model and SDE-GB 1. **(Bottom)** The ACF for the insulin residuals from SDE-GB 2. No significant correlation is left.

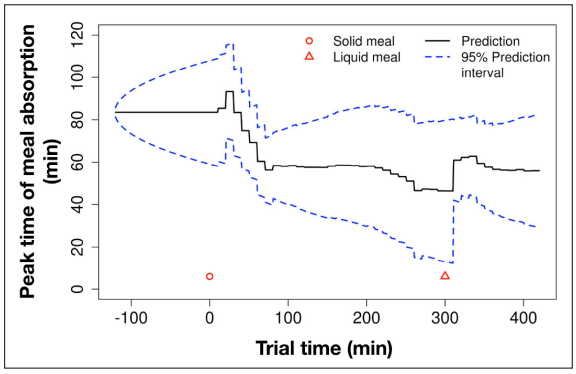

Figure 7. A result of parameter tracking. The one-step prediction and 95% prediction interval of the peak time of the meal absorption shows that the peak time is shorter for the liquid meal than the solid meal as expected.

Discussion

In this article, a systematic approach for formulating SDE-based glucoregulatory grey-box models has been described. Using an ODE-based model as basis, the approach consists of a sequential method for obtaining a statistical validated SDE-based model. The steps include identification of the needed diffusion terms from a combination of forward selection, model testing, and model validation. The final model provides a robust and validated description of the data and provides much more accurate and realistic predictions.

We have focused on short-term prediction, which is relevant if the model is to be used for prediction in model predictive control of T1DM. In this case, the prediction is updated every time a new observation is available and cannot drift far away. SDE-GBs will be superior to ODE models for pure simulation as well, although this requires a careful investigation of the diffusion, which is out of the scope of this article.[18]

The fact that the diffusion term was found to be significant for the state describing the PD effect of insulin on the BG level could indicate that the drift term of this part of the model is too simple to explain the true physiological relation. It might, however, also indicate that this part of the system is exposed to true physiological variation.

The advantages of SDE modeling are several. The most important is the possibility to use statistical tools for model selection and validation. Very few physiological systems, if any, contain states that can be predicted exactly. Since most statistical test principles rely on a full description (probabilistic distribution) of the future state values of the system, such statistical test procedures will lead to wrong conclusions about parameters and effects if they are based on an ODE model. The fact that SDE-GBs provide improved parameter estimates for models describing systems influenced by disturbances, i.e., nondeterministic states, has been shown elsewhere.[19]

Another advantage is the ability to pinpoint model deficiencies and to explore where and how to improve the model, as shown here with the peak time of meal absorption parameter τ_m. Parameter tracking with SDE-GBs is a strong tool in investigating how physiological variation influences the parameters of the models. This is recognized as the largest technical challenge in the development of simulation models.[20] A systematic method for SDE-GB development is described by Kristensen and coauthors.[7]

The main disadvantage with SDE modeling is that it requires more complex estimation methods, which are not a part of standard modeling software tools. A full establishment of SDEs in diabetic modeling requires, first of all, an implementation of the estimation algorithms in commonly used software. Additionally, the computational burden is significantly larger for SDE-GBs, which puts demands on the researcher's computer capacities. A first step toward fully recognizing the potential of SDE models is to use the ACF of the residuals as model validation as we have shown here. This is a fruitful way to test for independence.

The presence of the diffusion term in a state representing, e.g., a concentration can make the concentration drop below zero and thereby conflict with the physical understanding. To avoid this, a state-dependent diffusion term can be used to force the noise to decrease to zero when the concentration decreases to zero.[10]

To construct a reliable and robust virtual T1DM patient, the underlying model should not only represent an individual patient; it should ideally be a population SDE model based on clinical data from a large population. Population models include population parameters and random effects representing the intersubject variability in the parameter values.[21,22] This type of model has shown great potential within PK/PD modeling.[9]

Conclusion

The aim of this article was to use clinical data and an existing ODE model of a T1DM patient to illustrate the most important aspects and advantages of SDE-GB modeling. Data from four patients were used to estimate parameters in an ODE model and two SDE-GBs. Addition of a single diffusion term resulted in significant improvements in the ODE model in terms of predictions and prediction uncertainty. The ACF of the residuals confirmed that the SDE-GBs were statistically valid as opposed to the ODE model.

We have shown that SDE-GBs offer a solid framework for using statistical tools for model building and validation. Parameter tracking proved to be a useful tool to reveal the variation in the parameter describing the time to peak absorption of the meal. More reliable model predictions and the possibility to evaluate the uncertainty of the predictions as provided by the SDE-GBs will improve the reliability and potential of virtual T1DM patients.

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Appendix D

Technical Report - II

Modelling the Effect of Exercise on Insulin Pharmacokinetics in "Continuous Subcutaneous Insulin Infusion" Treated Type 1 Diabetes PatientsXXX

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Modelling the Effect of Exercise on Insulin Pharmacokinetics in "Continuous Subcutaneous Insulin Infusion" Treated Type 1 Diabetes Patients

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Abstract

Introduction: The artificial pancreas is believed to ease the burden of constant management of type 1 diabetes for the patients substantially. An important aspect of the artificial pancreas development is the mathematical models used for control, prediction or simulation. A major challenge to the realization of the artificial pancreas is the effect of exercise on the insulin and plasma glucose dynamics. In this report, we take the first step towards a population model of exercise effects in type 1 diabetes. We focus on the effect on the insulin pharmacokinetics in continuous subcutaneous insulin infusion (CSII) treated patients by modelling the absorption rate as a function of exercise. **Methods**: Three models are estimated from 17 data sequences. All of them are based on a linear three-compartment base model. The models are based on stochastic differential equations to allow noise to enter the dynamics. In the first model, the insulin absorption rate parameter is replaced by a random walk. In the second model, the relationship between the absorption rate and exercise is modelled as a linear dependency, while in the third model this linear relationship depends on the intensity. A Lamperti transformation is used to ensure non-negative state values. A special focus is put on the structural identifiability of the base model, while the posterior identifiability is checked for all models from the conditional likelihood profiles. **Results**: The first model is disregarded due to the small number of observations during the exercise bout. From likelihood-ratio tests and information criteria, the third model is appointed as the best model to model the relationship between exercise and the insulin absorption. The posterior identifiability check showed that it was not possible to identify the variance of the measurement variance. **Conclusion**: A model to predict the insulin appearance in plasma during exercise in CSII treated patients is identified. Further clinical studies are needed to confirm the increase in insulin plasma concentration during exercise in type 1 diabetes patients. These studies should include dense sampling to allow for a fully data driven identification of an appropriate model.

Keywords: Continuous subcutaneous insulin infusion, Stochastic differential equations, Population models, Exercise in type 1 diabetes, Lamperti transformation

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1 Introduction

The treatment of type 1 diabetes opposes a major challenge on the patients and their health care providers. Thus many initiatives are investigated to ease the burden and to simplify the daily management of the disease. A promising approach is the so-called *artificial pancreas* consisting of an insulin pump delivering insulin continuously, a continuous glucose monitor (CGM) and a control algorithm to regulate the insulin infusion automatically based on feedback from the CGM. The insulin pump and the CGM are commercially available today, but the patients are required to regulate the pump themselves several times daily. Hence, the connection of the pump and CGM via a control algorithm are believed to ease the management of type 1 diabetes for the patients substantially [1].

Currently, the research activities within the artificial pancreas area is rapidly developing due to an increasing number of researchers and technological advances. One of the main challenges for an artificial pancreas is the management of the plasma glucose level during and after exercise. The exercise effects on the blood glucose level are adverse and depends on intensity, duration, timing related to meals and insulin boluses, and type of activity [31].

Mathematical models resembling the dynamics of insulin-glucose system are important tools in the development of control algorithms for the artificial pancreas. *Virtual* type 1 diabetes patients enable the researchers to test various treatment scenarios and identify the most promising algorithms prior to expensive and time-consuming clinical studies.

Until now several models have been suggested to mimic the dynamic relation between exogenous insulin and blood glucose in type 1 diabetes. They include the transport of glucose from meals to the plasma [34, 7, 15]. Few models have dealt with the effect of exercise on the insulin sensitivity and blood glucose level [5, 6, 33, 18, 13, 8, 26].

Clinical studies investigating the effects of exercise in type 1 diabetes have mainly focused on the effects on changes in plasma glucose [31]. Several studies have however shown a significant increase in insulin absorption during physical activity in type 1 diabetes patients [11, 29, 30, 36, 3, 28, 27]. The cause of this increase is not clarified, but increasing blood flow or temperature in the peripheral area of the body could be the cause. In [2], they show that a hot bath and local massage at the injection site increase the speed of the insulin absorption after a subcutaneous injection. To our knowledge, the increase related to exercise has not been investigated from a pharmacokinetic modelling perspective. However, to understand the glucose dynamics during exercise it is necessary to determine whether the increase is caused by changes in insulin pharmacokinetic or pharmacodynamic parameters or if it is unrelated to the insulin concentration.

In this report, a model of the effects of exercise on the insulin pharmacokinetics is developed. We identify a proper population model for the effect of exercise on the subcutaneous absorption of insulin delivered continuously by an insulin pump. The model could potentially be implemented into a simulation model of the insulin-glucose dynamics.

We employ stochastic differential equations (SDEs) instead of the traditional ordinary differential equations (ODEs). In SDEs, the residual noise is split into a diffusion term and a normally distributed and uncorrelated measurement noise. This helps to ensure that the residuals are independent as required by standard statistical model validation tools. Furthermore, the noise is allowed to enter the system to account for the inherent uncertainties in all models of physiological systems. Finally, SDEs provide us with a method to pinpoint model deficiencies and to suggest how to extent the model to capture the relevant behavior [17, 32].

The structure of the paper is the following: In Section 2, the clinical data set is described. Then, in Section 3 the models and methods are described including a identifiability check. In Section 4, the results are presented. Section 5 presents a discussion of the study. Finally, in Section 6 the conclusions are stated.

2 Data

The insulin data for this study originates from a clinical study on 12 subjects with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII). The insulin pump was placed in the subcutaneous layer in either the abdominal or gluteal area. The purpose of the clinical study was to evaluate the effect of insulin boluses, meals and exercise on the plasma glucose level [27, 10]. Beside plasma glucose, insulin plasma levels were analysed. The insulin type was insulin aspart *Novorapid* - a fast acting insulin type.

Each patient went through two study days separated by at least three weeks. A study day consisted of a two hour stabilization period followed by three events separated by 150 min. The three event types were meals, insulin boluses and a 20 minutes-run on a treadmill at a predetermined heart rate (HR). Not two of the total 24 study days were identical as the order of events where different from study day to study day. The predetermined HR corresponded to either mild exercise with a HR equal to 50% of (maximum HR - resting HR) + resting HR or moderate exercise with a HR equal to 75% of (maximum HR - resting HR) + resting HR.

Insulin observations were sampled at a non-equidistantly sampling scheme with higher frequency just after each event and analysed with a LOCI technology. For each study day a data sequence was obtained. In some of the data sequences the plasma insulin concentration was not in steady-state during the stabilization period prior to the first event. Thus we removed data sequences with at min-max range $> 5mU/L$ during the stabilization period to ease the model estimation. Six of the study days included exercise on mild level, eight of them included exercise on moderate level, while three of them did not include exercise.

3 Methods

Our interest is to model population characteristics related to exercise. To identify a proper model taking into account the inter-individual variability we use a population modelling approach. This type of models is build as hierarchical models where the parameters are estimated in a two-stage manner. Individual parameters are modelled as a combination of fixed population effects and random individual effects as seen in (1):

$$\theta_i = h(\theta_{pop}, Z_i) \cdot exp(\eta_i) \tag{1}$$

Here θ_i is the parameter value for individual i, $h(\cdot)$ is a known function, θ_{pop} is the overall population parameter (fixed effect), Z_i are covariates (age, weight, gender etc.), and $\eta_i \sim N(0, \Omega)$ is the individual random effect. In the first stage, the random effects, η_i's, are estimated for each individual. The fixed effect parameters, θ_{pop}, are estimated in the second stage with the entire data set from an approximate population likelihood function [32].

In the single-subject modeling case, the R-package CTSM-R (Continuous Time Stochastic Modelling in R) can be used to identify SDE models [9]. However, currently CTSM cannot handle population models. Thus as a part of this study, a prototype of an population modelling extension to CTSM was developed.

The modelling procedure is the following. First, a base model is estimated without any exercise effects. A number of extensions to this model are then estimated to identify the most appropriate model of the exercise effects.

3.1 The Base Model

A linear three-compartment ODE model is used as basis to describe the pharmacokinetics of subcutaneous infused insulin in a single subject as suggested by Wilinska et al. [34]. The model is illustrated in Figure 1.

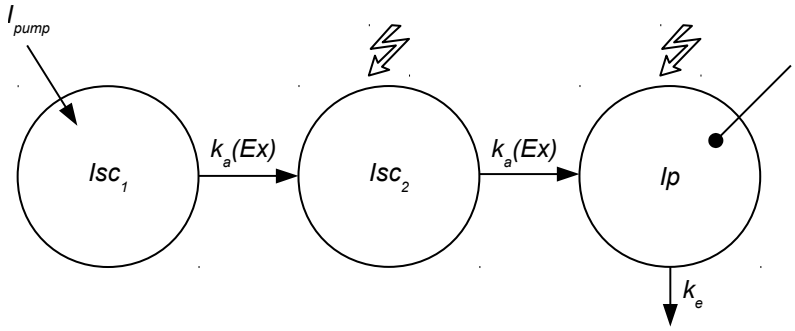

Figure 1: *Illustration of the three-compartment model describing the pharmacokinetics of insulin delivered continuously from an insulin pump. Lightnings indicate diffusion terms.*

The absorption is characterized by an identical rate parameter, k_a between all three compartments. Two compartments are affected by diffusion.

The total SDE model is presented on state-space form in (2) and (3):

$$d\begin{bmatrix} Isc_1 \\ Isc_2 \\ Ip \end{bmatrix} = \begin{bmatrix} (I_{pump} - k_a \cdot Isc_1)dt \\ (k_a \cdot Isc_1 - k_a \cdot Isc_2)dt + \sigma_{Isc} d\omega_{Isc} \\ (\frac{k_a}{V_I} \cdot Isc_2 - k_e \cdot I_p)dt + \sigma_{Ip} d\omega_{Ip} \end{bmatrix} \tag{2}$$

where Isc_1 [mU] and Isc_2 [mU] represent the subcutaneous layer and deeper tissues, respectively, and Ip [mU/L] represents plasma. I_{pump} is the input from the pump [mU/min]. k_a [min^{-1}] is the absorption rate and k_e [min^{-1}] is the clearance rate of insulin from plasma. V_I is the volume of distribution [L]. σ_{Isc} and σ_{Ip} are diffusion scaling parameters. ω_{Isc} and ω_{Ip} are Wiener processes with independent Gaussian increments [19]. They constitute the diffusion terms entering the system.

The observations are linked to the system with the observation equation:

$$log(y_k) = log(Ip_k) + e_k \tag{3}$$

where y_k are the discrete observations of plasma insulin concentration and $e_k \sim N(0, \xi)$ is the measurement noise.

To introduce the hierarchical structure of the model, the parameters are specified for each individual as in (1). The individual initial values and parameters are:

$$\theta_i = \begin{bmatrix} Isc_{1_0 i} \\ Isc_{2_0 i} \\ Ip_{0i} \\ k_{ai} \\ k_{ei} \\ V_{Ii} \\ \sigma_{Isci} \\ \sigma_{Ipi} \\ \xi_i \end{bmatrix} = \begin{bmatrix} Isc_{1_0} \cdot exp(\eta_{i1}) \\ Isc_{2_0} \cdot exp(\eta_{i1}) \\ Ip_{0i} \\ k_a \cdot exp(\eta_{i_2}) \\ k_e \cdot exp(\eta_{i3}) \\ V_I \cdot weight_i \\ \sigma_{Isc} \\ \sigma_{Ip} \\ \xi \end{bmatrix} \tag{4}$$

where $weight_i$ is the body weight [kg] of individual i. $\eta_{i1}, \eta_{i2}, \eta_{i3} \sim N(0, \Omega)$ where Ω is a diagonal matrix with three element: Ω_{Isc}, Ω_{ka}, and Ω_{ke}. The measurement noise is modelled as an exponential error

to approximate the assumption of a proportional measurement error. Furthermore, the variance of the measurement noise, ξ is parameterized as $\xi = S_{min} + S$, where S_{min} is fixed to the a reasonable minimum variance and S is estimated. The value of S_{min} is found from a mean value of estimated %CVs (coefficient of variation) for the relevant concentration range in [25].

As seen in (2), Ip is affected by additive diffusion and thus negative values can be obtained. This is problematic, first of all because it is non-physiological, but also due to the structure of the observation equation in (3) which cannot be computed when $Ip_k < 0$. Instead, we use a multiplicative state-dependent diffusion term for Ip to ensure that the state is strictly positive:

$$dIp_i = \left(\frac{k_{ai}}{V_{Ii}} \cdot Isc_{2i} - k_{ei} \cdot Ip_i \right) dt + \sigma_{Ip_i} Ip_i \, d\omega_{Ip} \tag{5}$$

3.2 Lamperti State Transformation

As CTSM cannot handle state-dependent multiplicative diffusion we transform the state, Ip_i into a space where this multiplicative noise becomes additive, z_{Ip_i}. This can be done by a *Lamperti* transformation. A description of the derivation of the Lamperti transformation is out of the scope of this report. However, details about the transformation can be found in [14, 24, 23, 4, 22]. We consider a general system equation:

$$dx_t = f(x_t, t, u_t)dt + \sigma_{x_t} x_t d\omega_{x_t} \tag{6}$$

where x_t represents the states and u_t represents the inputs to the system. We can then choose a transformed equation, z_t as:

$$z_t = \psi(x_t) = \int \frac{1}{s} ds \Big|_{s=x_t} = \log(x_t) \tag{7}$$

According to the theory behind the Lamperti transformation, z_t is governed by:

$$dz_t = \left(\frac{f(\exp(z_t), t)}{\exp(z_t)} - \frac{1}{2}\sigma_{x_t}^2 \right) dt + \sigma_{x_t} d\omega_{z_t} \tag{8}$$

As seen, the transformation eliminates the state-dependent diffusion term from x_t. Repeating this procedure for Ip_i, we get the transformed state, z_{Ip_i}:

$$dz_{Ip_i} = \left(\frac{\frac{k_{ai}}{V_{Ii}} \cdot Isc_{2i} - k_{ei} \cdot exp(z_{Ip_i})}{exp(z_{Ip_i})} + \frac{1}{2}\sigma_{Ip_i}^2 \right) dt + \sigma_{Ip_i} d\omega_{z_{Ip}} \tag{9}$$

The observation equation in (3) simply transforms into:

$$\log(y_{ki}) = z_{Ip_i k} + e_{ki} \tag{10}$$

For technical reasons, we used the following observation equation for the rest of the study:

$$y_{ki} = exp(z_{Ip_i k}) + e_{ki} \tag{11}$$

The Lamperti-transformation ensures that the diffusion term is additive while the parameters are the same as in the original model in (5) and (3).

3.3 Structural Identifiability

Prior to parameter estimation, the identifiability of the model is checked to make sure that we can find a reliable estimate of the model. Two types of identifiability exists: Structural identifiability and identifiability related to the experimental conditions. In the following, the structural identifiability of the base model for a single subject is investigated. For the sake of simplicity, the observation equation is considered to be continuous, but the result applies to the discrete observation equation as well. First, the state-space model in (2) is rewritten into the general form for linear state-space models:

$$\begin{aligned} dx_t &= (Ax_t + Bu_t)\,dt + \Sigma d\omega_t & (12)\\ y_t &= Cx_t + e_t & (13) \end{aligned}$$

For the base model, the matrices A, B, C and Σ are specified as:

$$\begin{aligned} A &= \begin{bmatrix} -k_a & 0 & 0 \\ k_a & -k_a & 0 \\ 0 & \frac{k_a}{V_I} & -k_e \end{bmatrix} \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \\ C &= \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \qquad\qquad \Sigma = \begin{bmatrix} 0 & 0 & 0 \\ 0 & \sigma_{Isc} & 0 \\ 0 & 0 & \sigma_{Ip} \end{bmatrix} \end{aligned} \tag{14}$$

To determine whether the model is structural identifiable, the transfer functions, G_p and H_p are used. G_p and H_p describe the relationship between the input and output, and the noise and output, respectively:

$$y_t = G_p \cdot u_t + H_p \epsilon_t \tag{15}$$

where ϵ_t is the part of the output that cannot be predicted exactly (the difference between the observed and estimated concentration). First, we consider the deterministic part of the model and hence G_p, which can be found from the following the relationship:

$$G_p = C\,(pI - A)^{-1}\,B \tag{16}$$

We are able to observe G_p from u_t and y_t in the following form:

$$G_p = \frac{b_j p^j + b_{j-1} p^{j-1} + ...b_0}{a_l p^l + a_{l-1} p^{l-1} + ...a_0} \tag{17}$$

where $a_l = 1$. In our case $j = 0$ and $l = 3$. From (16) and (14) we find:

$$G_p = \frac{\frac{k_a^2}{V_I}}{(p + k_a)^2 (p + k_e)} \tag{18}$$

If the model is structural identifiable we are able to identify k_a, k_e, and V_I from a_0, a_1, a_2, and b_0 in (17). We can obtain four equations from (17) to determine k_a, k_e, and V_I from (17) and (18):

$$\frac{b_0}{a_2 p^2 + a_1 p^1 + a_0} = \frac{\frac{k_a^2}{V_I}}{(p + k_a)^2 (p + k_e)} \Rightarrow \tag{19}$$

$$\begin{array}{rclrcl} b_0 & = & \frac{k_a^2}{V_I} & a_0 & = & k_a^2 k_e \\ a_1 & = & k_a (k_a + 2k_e) & a_2 & = & 2k_a + k_e \end{array} \tag{20}$$

Four equations and only three parameters is an overdetermined system. While there is no guarantee for all equations to be fulfilled there will be a solution in some appropriate norm (L2). Thus the system is structurally identifiable. Regarding the identifiability of the noise parameters, the analytical solution is cumbersome. However, the following holds for the number of identifiable noise parameters:

$$\#\, of\ ident.\ noise\ parameters\ \leq nm + m(m+1)/2 \tag{21}$$

where n is the order of the system, in our case $n = 3$ and m is the number of outputs; in our case $m = 1$. Thus we can identify at most four noise parameters. The model is specified with only three noise parameters as seen in (2) and (3). For more details about structural identifiability see [20]. Whether the base model is identifiable from the experimental conditions is checked in a posterior manner from the estimated conditional likelihood profiles for each parameter – see Section 4.

3.4 Exercise Effects

The aim of the study is to investigate the effect of exercise on the absorption rate parameter, k_a. To include this effect, three approaches are investigated. The first one exploits the ability of SDEs to track parameter variation. The parameter, k_a is modelled as a random walk to investigate if the absorption rate increases during exercise:

$$dk_a = 0\, dt + \sigma_{k_a} d\omega_3 \tag{22}$$

where σ_{k_a} is a scaling diffusion parameter. The model with this specification is named *Model A*

In the second approach, we specify k_a as:

$$k_a = \bar{k}_a + \alpha \cdot Ex \tag{23}$$

where $\bar{k}_a$ represents the basal rate and α determines the effect of exercise, Ex. Ex is specified as a vector with the value 0 when the patient is not exercising and the value 1 during exercise. This model is named *Model B*.

With the third approach we take into account the fact that the subjects exercised on two different intensity levels. Thus we extend (23) to:

$$k_a = \bar{k}_a + \alpha_{mild} \cdot Ex_{mild} + \alpha_{moderate} \cdot Ex_{moderate} \tag{24}$$

Here, α_{mild} and $\alpha_{moderate}$ determines the effect of mild and moderate exercise, respectively. Ex_{mild} and $Ex_{moderate}$ are specified as Ex just for each of the two levels. This model is named *Model C*.

In all cases the model becomes non-linear. Hence, the identifiability check presented earlier cannot be used for the extended models. However, the posterior check is performed for these models as well.

3.5 Parameter Estimation with CTSM

The parameters are estimated by minimising the likelihood function resulting in maximum likelihood estimates. Introducing random effects to the model changes the way the likelihood function is computed. Only the distribution of the random effects are really interesting, but technically the individual η_i must be estimated for a set of parameters. Thus the optimisation turns into a two step optimisation procedure: The overall model parameters (population or first stage) and the individual (or second stage) parameters.

For a given set of population parameters the second stage optimisation identifies the η_i's for each subject. The numerical noise for the individual log-likelihood function is sufficiently small such that the gradient based quasi-Newton optimisation can be used. Each subject is independent and depending on the computer the speed of this part of the estimation can be significantly increased when running in parallel.

For this report 17 data sequences are used. Some of these data sequences came from the same person being studied over two different days. For now all trials are considered independent. The numerical noise from each of the 17 log-likelihood functions accumulate making the resulting population log-likelihood function quite noisy and unsuitable for a deterministic gradient based optimisation. The genetic algorithm is a stochastic optimiser which attempts to mimic evolution. An initial population is randomly drawn. A selection of the parameters yielding the best log-likelihood values breeds a new population. This process is continued until the fitness function does not improve over a period or when the computational budget is spend. For each of the three models, 1000 iterations are computed with a population of 50 resulting in 50.000 evaluations of the population log-likelihood. Each of them requires the second stage optimisation of the individual log-likelihood. The 1000 iterations take about 35 hours using 17 cores at the DTU High-Performance- Computing servers.

Details on the population log-likelihood can be found in [16]. Details on the individual log-likelihood can be found in [17].

3.6 Model Comparison

As the base model is nested into all the extended models, the models in Section 3.4 are compared to the base model in (2) and (3) by a likelihood-ratio-test (LRT). The likelihood ratio, λ_y, between two likelihoods can be written as:

$$\lambda_y = \log(L_{Ext}\left(\theta; y\right)) - \log(L_{Base}\left(\theta; y\right)) \tag{25}$$

where $L_{Ext}(\theta; y)$ and $L_{Base}(\theta; y)$ are the maximum likelihood estimates for the parameters θ given the data y of one of the extended models including exercise and the base model, respectively.

Under the null-hypothesis (claiming that the base model and the extended model perform equally), the random variable $-2\lambda(y)$ follows a $\chi^2_{(p-q)}$ distribution, where p and q are the number of the parameters in the base model and the extended model, respectively [21].

As the different models with an exercise extension are not nested, their performance is compared with Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).

4 Results

Preliminary estimations showed that V_I was practically unidentifiable for the base model. Thus we fixed V_I for the rest of the study. The fixed parameters are seen in Table 1.

Table 1: *Value of fixed parameters*

Parameter	Value
S_{min}	0.438 [25]
V_I	0.19 [12]
Ip_{0i}	This value was fixed to the value of the first observation for each subject.

In the following, the three extended models will be evaluated.

4.1 Preliminary Model Evaluation

Initial estimations of *Model A* showed that the specification of k_a as an random walk was not appropriate. The variation in k_a was not significant. Thus this model was disregarded in the further evaluation.

4.2 Posterior Identifiability Check

The posterior identifiability is checked from the conditional likelihood profiles. They are computed for each estimated parameter by fixing all parameters except the parameter of interest and estimating the negative log-likelihood function. In Figure 2, the estimated profiles for the base model are seen. For all parameters except the variance of the measurement noise, S, the profile has a minimum. The same holds for *Model B* and *Model C* as seen in Figure 3 and 4.

The parameter estimates are within an acceptable range of the minimum for all parameters. The discrepancy between the estimate and the minimum of the curve for Ω_{Isc0} (the first element of the Ω matrix) in Figure 2 is caused by graphical issues. The curvature of the profiles around the minimum indicates the size of the uncertainty of the estimates. All three models seem to have a large uncertainty of $\hat{k}_e$ (ke.pop in the figures).

4.3 Model Comparison

The models are evaluated by comparing the maximum likelihood estimates with LRT, AIC and BIC. The estimates and the corresponding statistical measures can be seen in Table 2. As seen, *Model C* is assessed as the best model from all the criteria. Both *Model B* and *Model C* explain significantly more of the variability in the data than the base model.

Table 2: *Results of LRT, AIC and BIC*

Model	Number of estimated parameters	$-log(L)$	*p-value* from LRT	AIC	BIC
Base model	10	927	-	1878	1799
Model B	11	897	9.436896e-15	1817	1729
Model C	12	895	1.221245e-15	1815	1720

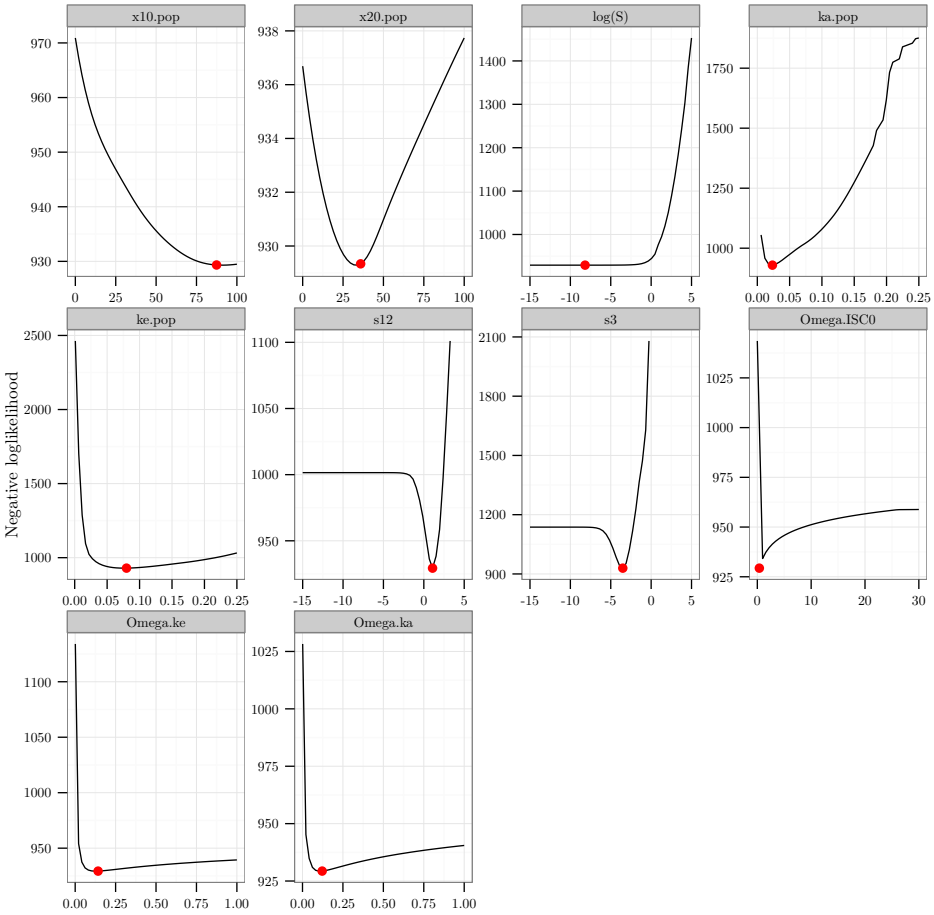

Figure 2: *Conditional loglikelihood profiles for the base model. The red points indicate the parameter estimates. x10.pop and x20.pop are the initial values of* Isc_1 *and* Isc_2*, respectively. S in the plot corresponds to* $\log(S)$ *in the model. ka.pop and ke.pop are* k_a *and* k_e*, respectively.* $s12 = \log(\sigma_{Isc})$ *and* $s3 = \log(\sigma_{Ip})$*. Omega.ISC0, Omega.ke, and Omega.ka are the diagonal elements of* Ω*.*

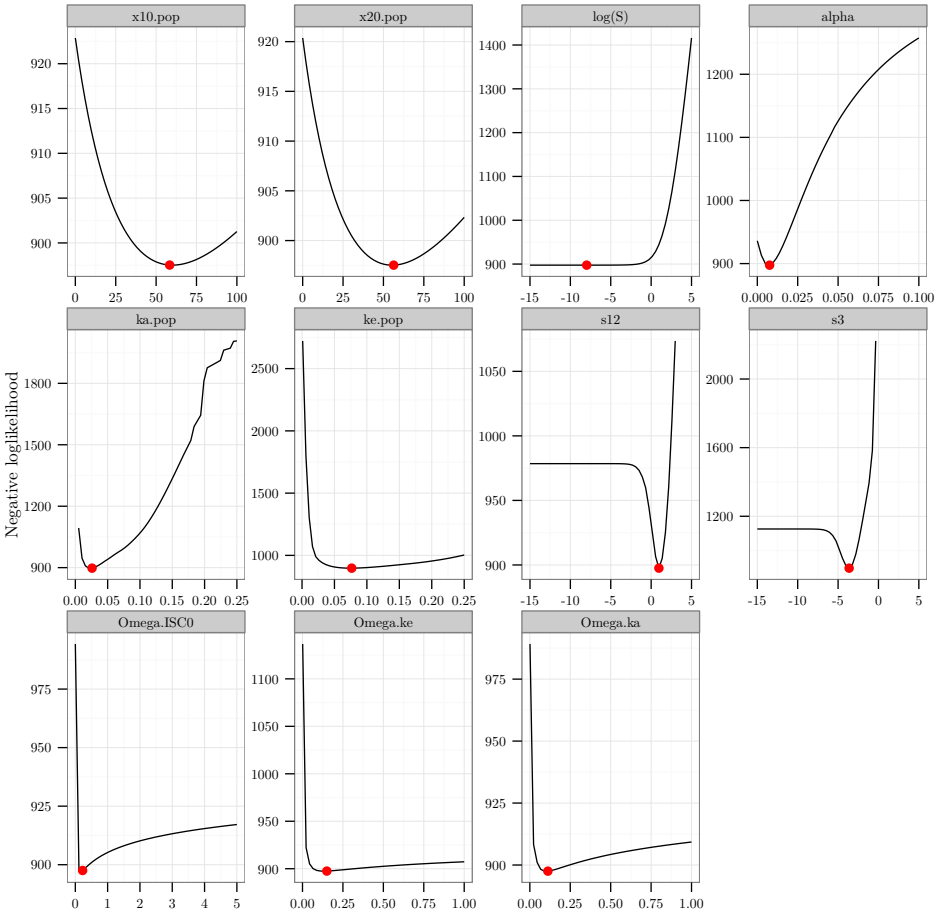

Figure 3: *Conditional loglikelihood profiles for Model B The red points indicate the parameter estimates. x10.pop and x20.pop are the initial values of* Isc_1 *and* Isc_2*, respectively. S in the plot corresponds to* $\log(S)$ *in the model .ka.pop and ke.pop are* $\bar{k}_a$ *and* k_e*, respectively.* $s12 = \log(\sigma_{Isc})$ *and* $s3 = \log(\sigma_{Ip})$*. Omega.ISC0, Omega.ke, and Omega.ka are the diagonal elements of* Ω*.*

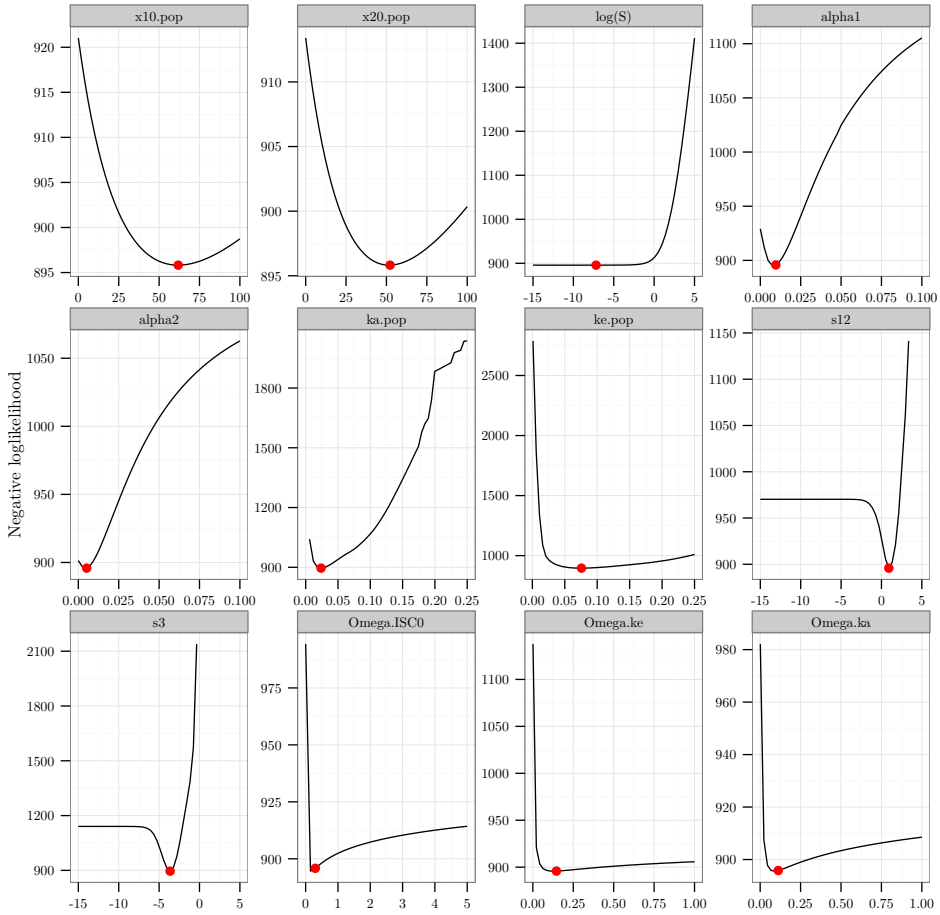

Figure 4: *Conditional loglikelihood profiles for Model C. The red points indicate the parameter estimates. x10.pop and x20.pop are the initial values of* Isc_1 *and* Isc_2*, respectively. S in the plot corresponds to* $\log(S)$ *in the model. ka.pop and ke.pop are* $\bar{k}_a$ *and* k_e*, respectively.* $s12 = \log(\sigma_{Isc})$ *and* $s3 = \log(\sigma_{Ip})$*. Omega.ISC0, Omega.ke, and Omega.ka are the diagonal elements of* Ω*.*

The parameter estimates for all three models are seen in Table 3. For *Model C*, the moderate intensity exercise results in a larger absorption rate than mild exercise.

Table 3: *Parameter estimates from the base model, Model B, and Model C*

	Base Model	*Model B*	*Model C*
Isc_{1_0}	87.4	58.3	61.8
Isc_{2_0}	35.9	56.3	52.2
k_a	0.023	0.026	0.024
k_e	0.079	0.077	0.076
σ_{Isc}	2.94	2.61	2.48
σ_{Ip}	0.030	0.027	0.026
S	0.000 28	0.000 34	0.000 75
Ω_{Isc}	0.379	0.226	0.299
Ω_{ka}	0.122	0.112	0.112
Ω_{ke}	0.142	0.150	0.146
α		0.007 62	
α_{mild}			0.009 61
$\alpha_{moderate}$			0.005 15

4.4 Model Predictions

From the above results, *Model C* with an intensity-dependent absorption rate is appointed as the best model to explain the dynamics. The one-step predictions from *Model C* for 3 representative data sequences are seen in Figure 5, 6 and 7. In general, the predictions are acceptable and the model does seem to capture the increase related to exercise. Especially, in Figure 7 the compliance between the predictions and the observations is good. The width of the prediction interval is however large in this case. The prediction in Figure 6 does not seem to follow the dynamics of the observations very well. The increase during exercise is underestimated and the increase due to the insulin bolus is overestimated. Finally, the prediction in Figure 6 underestimates the increase during exercise while the prediction of the bolus increase is acceptable.

4.5 Model Check

Diagnostic plots of the standardised residuals of *Model C* are depicted in Figure 8. Note that the initial value was fixed to the value of the first observations and thus the corresponding residual is equal to zero. The plots confirm that the model does not seriously violate the assumption of equally and normally distributed residuals.

5 Discussion

The purpose of this study is to evaluate three model extensions describing the relationship between exercise and the insulin absorption rate in CSII treated type 1 diabetes patients. From the model evaluations we appoint *Model C* as the best model extension. This model takes into account the intensity of the exercise bout. From a physiological point of view this is a reasonable hypothesis. The two separate terms for mild and moderate exercise could be replaced by the heart rate or percentage of maximum oxygen consumption.

During the estimation, seven of the 24 data sequences were disregarded due to non-steady initialization. The non-steady behavior could be caused by previously injected insulin in the early morning or changes in the basal delivery rate prior to study start. In future studies with these data, the observations from the initial stabilization period could be eliminated to avoid this problem. However, it is important to be

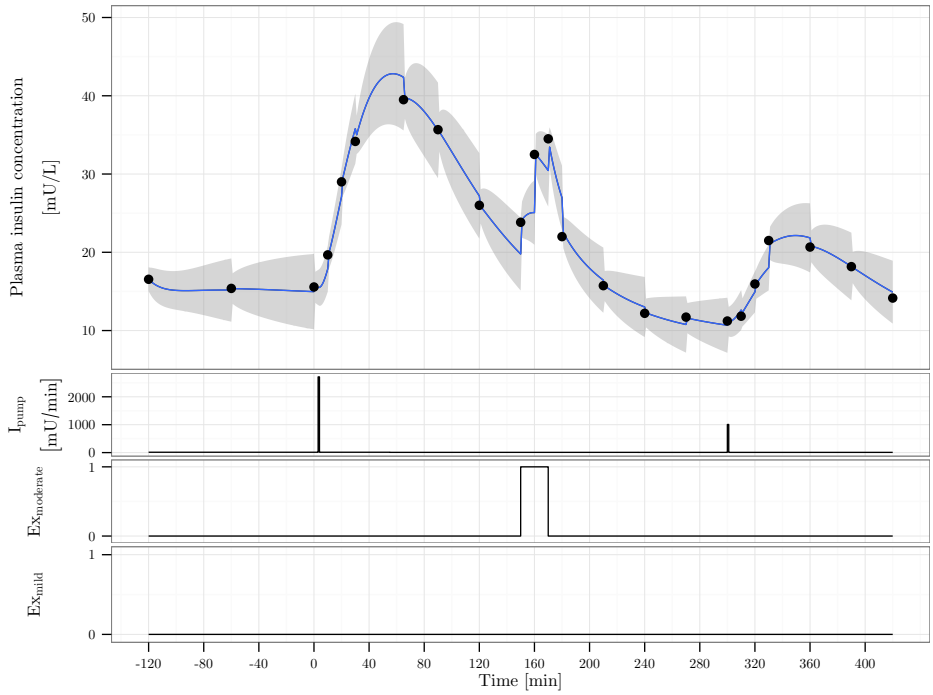

Figure 5: *Data sequence no. 8. Top: One-step predictions from Model C (Blue line). The observations are represented by dots. The grey area indicates 95% prediction interval. Middle and bottom: Insulin and exercise inputs.*

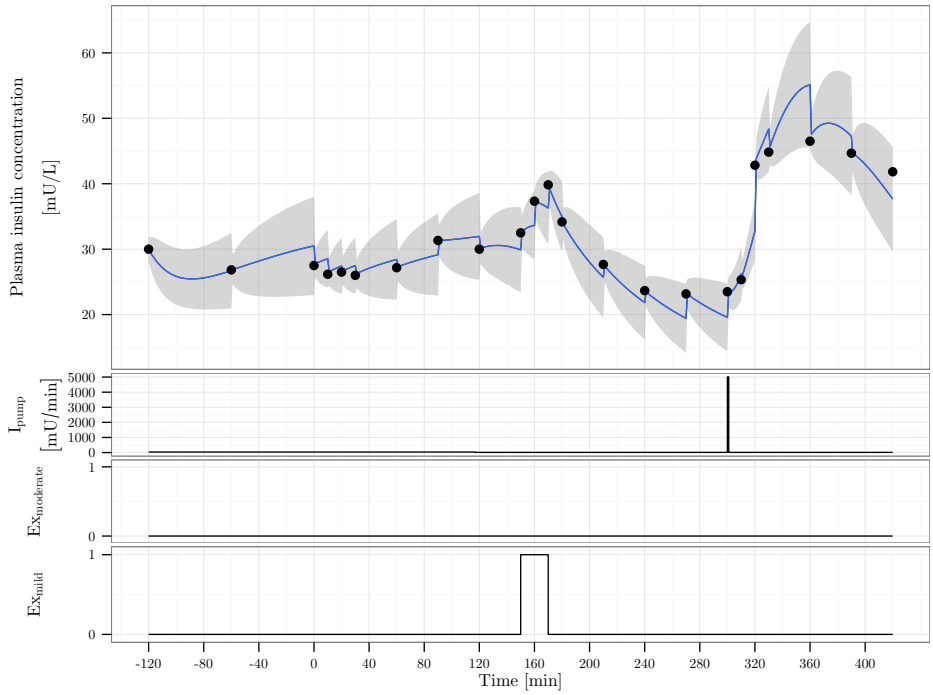

Figure 6: *Data sequence no. 9. Top: One-step predictions from Model C (Blue line). The observations are represented by dots. The grey area indicates 95% prediction interval. Middle and bottom: Insulin and exercise inputs.*

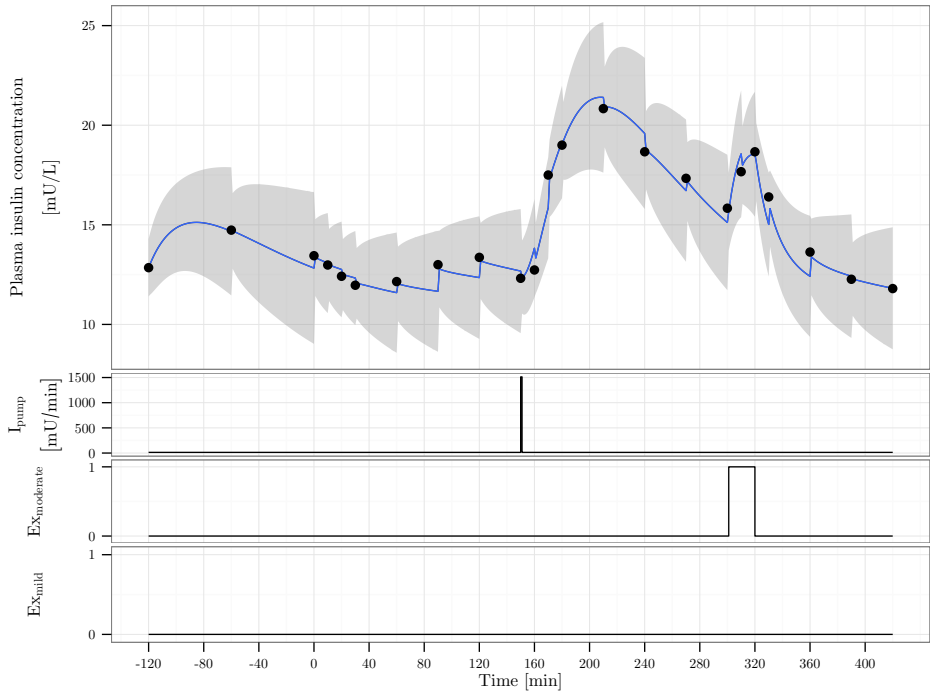

Figure 7: *Data sequence no. 10. Top: One-step predictions from Model C (Blue line). The observations are represented by dots. The grey area indicates 95% prediction interval. Middle and bottom: Insulin and exercise inputs.*

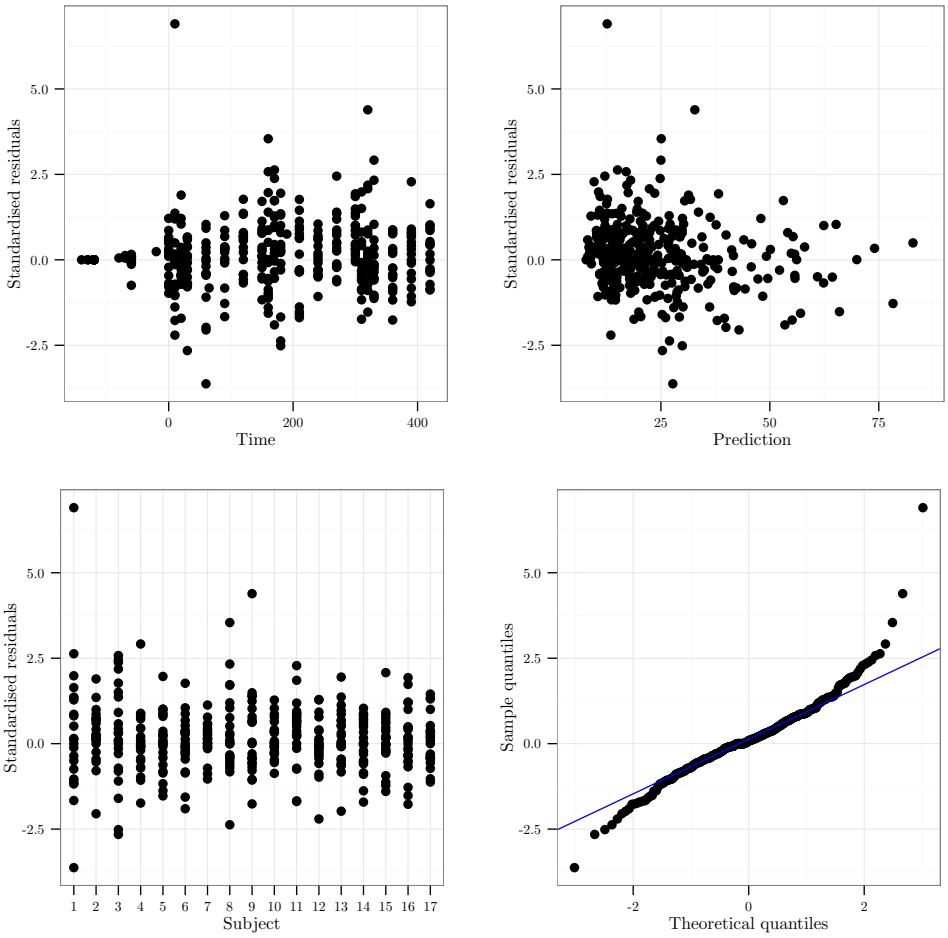

Figure 8: *Topleft: Standardised residuals versus time. Note that the initial value is fixed to the value of the first observations and thus the corresponding residual is equal to zero. Topright: Standardised residuals versus predictions. Bottomleft: Standardised residuals versus subjects (data sequences). Bottomright: QQ-plot of the standardised residuals versus a normal distribution.*

aware of any insulin boluses delivered during or in the hours prior to the stabilization period as some of the insulin would still be present in plasma at the time of the first event. Insulin is present in plasma upto 4-5 hours after the injection.

In the estimation, we have to assume that the data set was obtained from 17 individuals due to limitations in the software prototype. The original data set included 12 patients in total. Each patient went through two study days resulting in 24 data sequences. The 17 data sequences which were left after the initial data cleaning came from 10 patients. Thus we mix the inter-individual variability with the inter-occasion variability. In future versions of the software, the possibility to distinguish between these two variabilities is a necessity to ensure a correct handling of the variability.

The specification of the insulin absorption rate parameter k_a in *Model A* includes a random walk. This kind of parameter tracking is one of the main advantages of SDE models due to its ability to identify hidden relationships in the data. The random walk is predicted along with the other state predictions by a Kalman Filter. The data sequences included 23 observations each sampled non-equidistantly. The exercise bout lasted 20 minutes and plasma insulin was sampled at the start, after ten minutes, and at the end of the exercise bout. Thus, we had very few observations to drive the random walk. This could be the reason to the failure of *Model A*. Longer exercise bouts and very rich sampling are needed to use this method for model extension.

The clinical study investigated the effect of 20 minutes of exercise on a treadmill. Thus, the results cannot be extrapolated to other types of sport or other durations. Furthermore, the effect can be different for other types of insulin as well. To fully evaluate and model the effect of exercise on insulin kinetics in CSII treated type 1 diabetes patients, a clinical study designed to investigate this effect specifically is needed.

More complex models of the insulin pharmacokinetics have been proposed in the literature. In [35] 11 models were compared including the base model used here. The authors conclude that a more complex model is the most suitable model to explain the insulin dynamics. However, as the purpose of this study was to add complexity to the model, we prioritised to start with a simple model as base model.

The effect of exercise on the insulin absorption must be assumed to be exposed to inter-individual variability. Thus, the model fit would probably improve further by adding a random effect to α_{mild} and $\alpha_{moderate}$. This would likely improve the prediction of the increase in plasma insulin concentration during exercise, but as for the random walk in *Model A*, this extension would require longer time series to be identified.

As the software is a prototype, we cannot obtain the standard deviations of the parameters nor the covariances. Thus, the results are only tentative as we cannot fully validate the model. If we assume that the model is valid, the next step would be to perform covariate analysis to identify relationships between the individual η_i's and relevant covariates, e.g., age, level of fitness, weight, and gender.

The posterior identifiability check showed that for the base model, *Model B*, and *Model C* it is not possible to estimate a realistic variance of the measurement noise. This could indicate that the models are not able to fully capture the dynamics. Hence, the Kalman filter used in the estimation attempts to improve the fit by minimizing this variance.

The identified model has the potential to incorporated into a larger model of the insulin as well as glucose dynamics during exercise. The impact of the increased plasma insulin concentration on the plasma glucose concentration due to exercise still has to be investigated.

6 Conclusion

This study investigated the effect of exercise on the insulin absorption rate in CSII treated type 1 diabetes patients. Former models of exercise responses of the insulin-glucose system do not take this relationship into account. Three candidates for model extension of a population insulin pharmacokinetic model were evaluated. For all three models, the insulin absorption rate was assumed to be affected by exercise. In the first candidate, the absorption rate parameter was modelled as random walk. In this way, the model

structure was based completely on information from the data. However, as the data set did not include enough observations sampled during the exercise bout to drive the estimation, this model was disregarded. The two remaining models described a linear relationship between exercise and the absorption rate. One model included an absorption rate independent of intensity, and one included an intensity–dependent absorption rate. These two models were compared to a base model with a constant absorption rate with LRT, AIC and BIC. From these measures, the model with an intensity dependent absorption rate was evaluated as the best model to describe the data. A posterior identifiability check showed problems in estimating the variance of the measurement variance. The predictions from the best model showed that the model did capture behavior of the system and thus the model could be incorporated into an existing model of the insulin-glucose system in type 1 diabetes. Further clinical studies are needed to fully understand the increase in insulin plasma concentration during exercise. These studies should include dense sampling to allow for a fully data driven identification of an appropriate model.

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Appendix E

Paper C

Tuning of Controller for Type 1 Diabetes Treatment with Stochastic Differential Equations

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Tuning of Controller for Type 1 Diabetes Treatment with Stochastic Differential Equations ⋆

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Abstract: People with type 1 diabetes need several insulin injections every day to keep their blood glucose level in the normal range and thereby avoiding the acute and long term complications of diabetes. One of the recent treatments consists of a pump injecting insulin into the subcutaneous layer combined with a continuous glucose monitor (CGM) frequently observing the glucose level. Automatic control of the insulin pump based on CGM observations would ease the burden of constant diabetes treatment and management. We have developed a controller designed to keep the blood glucose level in the normal range by adjusting the size of insulin infusions from the pump based on model predictive control (MPC). A clinical pilot study to test the performance of the MPC controller overnight was performed. The conclusion was that the controller relied too much on the local trend of the blood glucose level which is a problem due to the noise corrupted observations from the CGM. In this paper we present a method to estimate the optimal Kalman gain in the controller based on stochastic differential equation modeling. With this model type we could estimate the process noise and observation noise separately based on data from the first clinical pilot study. In doing so we obtained a more robust control algorithm which is less sensitive to fluctuations in the CGM observations and rely more on the global physiological trend of the blood glucose level. Finally, we present the promising results from the second pilot study testing the improved controller.

Keywords: Stochastic differential equations, Model predictive control, Kalman filters, Artificial pancreas, Type 1 diabetes.

1. INTRODUCTION

Type 1 diabetes is a chronic disease characterized by destruction of the insulin producing beta cells of the pancreas. Insulin is crucial for the regulation of the blood glucose level and people with type 1 diabetes are therefore dependent on exogenous insulin supply. The size of the insulin dose must be determined carefully. Underdosing can result in a too high blood glucose level (hyperglycemia) which in the long term can lead to, e.g. kidney failure, blindness or nerve damage. Too much insulin (in case of overdosing) can lead to a too low blood glucose level (hypoglycemia) which can have serious acute effects such as coma or even death.

⋆ Funding for this research as a part of the DIACON project from the Danish Council of Strategic Research (NABIIT project 2106-07-0034) is gratefully acknowledged.

The insulin is most often delivered subcutaneously either via a pen needle or an insulin pump. The pump delivers a steady basal rate combined with meal boluses (dosages to cover meals) to resemble the normal insulin secretion from a healthy pancreas.

Patients are adviced to check their blood glucose level with finger prick measurements several times a day to obtain tight diabetes control [American Diabetes Association (2012)]. The goal is to keep their blood glucose level as close to normal range (4.00-8.00 mmol/L) as possible without compromising safety. Instead of finger prick measurements more and more patients rely on continuous glucose monitors (CGM) to keep track of the blood glucose level. The CGM uses minimally invasive sensors capable of reporting the glucose level every five minutes. The sensor is placed in the subcutaneous layer and thus the observations are delayed in relation to the discrete capillary blood glucose observations that normally are

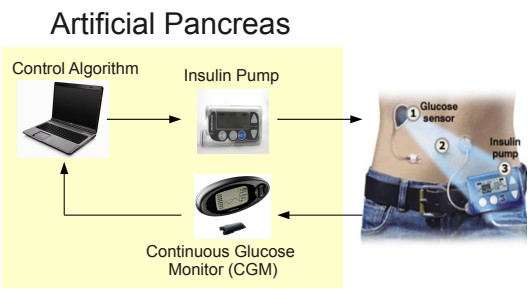

Fig. 1. An overview of the closed loop system consisting of a computer with the control algortihm, a CGM and an insulin pump.

measured from the finger tips. In addition, the sensors can experience problems with accuracy and precision due to physical, chemical and biological factors [Keenan et al. (2011); Hovorka (2006)].

Even though insulin pump therapy and CGMs can lead to better diabetes control, the treatment still requires constant attention and action from the patient. Furthermore, many patients with type 1 diabetes live in fear of getting severe hypoglycemia during sleep, while they are unable to react.

Several research groups are working on closing the loop with an automatic control algorithm regulating the insulin delivery based on feedback from the CGM [Cobelli et al. (2011); Hovorka (2011)]. The general principle behind this artificial pancreas is illustrated in Fig. 1.

We have developed a control algorithm based on model predictive control (MPC) that predicts future blood glucose values on the basis of the current level. If the control algorithm predicts hyperglycemia, insulin is delivered to bring the blood glucose level down to normal. If the control algorithm predicts hypoglycemia it decreases or shuts off the insulin supply until the blood glucose level increases again.

To test the performance of the controller we did a clinical pilot study on a type 1 diabetes subject. The challenge was to keep the blood glucose level in the normal range overnight. In Fig. 2 the blood glucose level is shown. At the time of starting the closed loop (22:00) the local trend was increasing but the global trend was decreasing after a meal with a corresponding insulin bolus. The MPC prediction of the blood glucose level at this time is also seen in Fig. 2. Due to the local increasing trend this prediction is unrealistically increasing and the controller suggests a too large bolus to compensate for this increase. This lead the subject into hypoglycemia and the clinician had to administrate I.V. glucose to bring the blood glucose level up again immediately.

The main conclusion from this pilot study was that the large amount of noise in the system was preventing the controller from predicting the blood glucose level and thus delivering the correct insulin bolus.

In this paper we address this problem by estimating the process and observation variances separately in the MPC

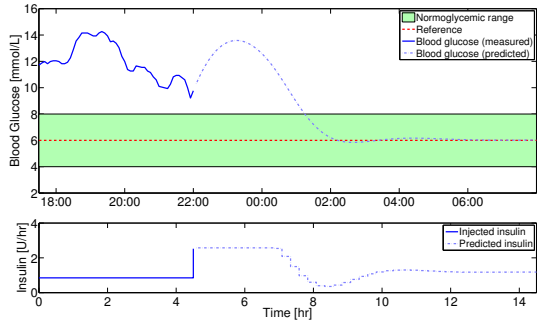

Fig. 2. Top: CGM observations (solid line) and blood glucose prediction at the time of closing the loop (dashed line) from the first pilot study. As seen, the controller relies too much on the local trend. Bottom: Insulin delivered by the pump (solid line) and predicted insulin supply (dashed line).

controller using *stochastic differential equations* with data from the pilot study. This paper describes this novel procedure and presents the promising results from the second pilot study testing the improved MPC controller.

2. THE PILOT STUDY SETUP

The data used for tuning the controller came from the first pilot study performed overnight on a type 1 diabetes subject. We chose to do the study overnight because the amount of disturbances to the system, e.g. meals and exercise are minimal at this time of day. In [Boiroux et al. (2012)] details about the setup is described. The subject wore an insulin pump (Medtronic Paradigm Veo, Minneapolis, USA) and two CGMs (Dexcom Seven Plus, San Diego, USA) measuring the glucose level every five minutes. From the two CGMs we had 162 and 158 observations, respectively and both were used for parameter estimation. The first 270 minutes of the pilot study were open loop where the patient was in control of the insulin supply and the last 540 minutes were closed loop.

3. CONTROLLER DESIGN

3.1 Control algorithm

The control algorithm is based on a single input-single output model in continuous time. It is a second order model with the following transfer function:

$$H_s(s) = \frac{M}{(\tau s + 1)^2} \tag{1}$$

(2)

The output is the blood glucose level in mmol/L and the input is the insulin supply from the pump in mU/min, the standard unit for insulin. τ is the insulin action time defined as the time in minutes it takes to reach the minimum blood glucose level after an insulin injection. M is defined as:

$$M = -\tau \exp(1) I_{SF} \tag{3}$$

I_{SF} is the *insulin sensitivity factor* defined as the maximum decrease in blood glucose level per unit of insulin. M and τ are patient specific and estimated from patient data. The insulin pump injects a bolus every 15 minutes based on the decision of the controller and the glucose level is observed every five minutes with the CGM. The bolus size is computed on the basis of the current glucose level and the blood glucose prediction. For more details on the MPC, see [Boiroux et al. (2012)].

Since the system is influenced by stochastic disturbances we modeled the system by an ARIMAX description:

$$A(q^{-1})y(t) = B(q^{-1})u(t) + \frac{C(q^{-1})}{1-q^{-1}}\varepsilon(t) \tag{4}$$

q^{-1} is the backward shift operator, $y(t)$ is the output, $u(t)$ is the input as previously defined. $\varepsilon(t)$ is $N_{iid}(0, \zeta^2)$. A and B are:

$$A(q^{-1}) = 1 + a_1 q^{-1} + a_2 q^{-2} \tag{5a}$$
$$B(q^{-1}) = b_1 q^{-1} + b_2 q^{-2} \tag{5b}$$

C is defined as:

$$C(q^{-1}) = 1 - \alpha q^{-1} \tag{6}$$

α is a tuning parameter. The model in (6) is obtained by considering the noise term, $\varepsilon(t)$ as a sum of white noise and a drift term. In this way the MPC control will ensure off set free tracking. In this paper we used $\alpha = 0.99$. For more details on the choice of α see [Huusom et al. (2010)].

We can realize (4) as a discrete state-space model on innovation form:

$$x_{k+1} = Ax_k + Bu_k + K\varepsilon_k \tag{7}$$
$$y_k = Cx_k + \varepsilon_k \tag{8}$$

where x_k is the blood glucose level [mmol/L] above basal level (6 mmol/L), u_k is the insulin input in [mU/min] above a basal rate of 14 mU/min , y_k is the observed blood glucose level above basal level, ε_k is the innovation noise:

$$\varepsilon_k = y_k - Cx_{k|k-1} \tag{9}$$

A, B, C, and K are matrices in canonical form. For the first pilot study they were defined as:

$$\begin{aligned} A &= \begin{bmatrix} -(a_1-1) & 1 & 0 \\ -(a_2-a_1) & 0 & 1 \\ a_2 & 0 & 0 \end{bmatrix} B = \begin{bmatrix} b_1 \\ b_2 - b_1 \\ -b_2 \end{bmatrix} \\ K &= \begin{bmatrix} \alpha - (a_1-1) \\ -(a_2-a_1) \\ a_2 \end{bmatrix} C = [1\ 0\ 0] \end{aligned} \tag{10}$$

As seen in Fig. 2 and stated in the section 1 this controller design was too sensitive to noise which resulted in a unrealistic prediction by the controller. For this reason we reformulated the model into a third order model in which

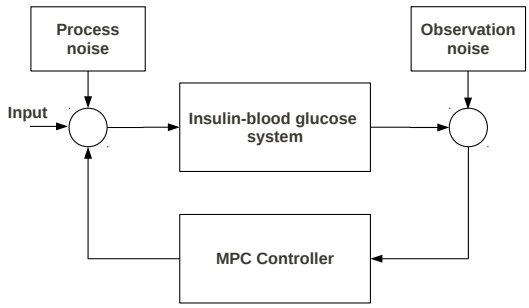

Fig. 3. An illustration of the closed loop system including process and observation noise.

the C polynomial in (6) was changed into a third order polynomial:

$$C(q^{-1}) = 1 + c_1 q^{-1} + c_2 q^{-2} + c_3 q^{-3} \tag{11}$$

This change resulted in the following Kalman gain, K, in (10):

$$K = \begin{bmatrix} c_1 - (a_1 - 1) \\ c_2 - (a_2 - a_1) \\ c_3 + a_2 \end{bmatrix} \tag{12}$$

(the matrices A, B, and C remained unchanged). The coefficients in (11) correspond to the coefficients in:

$$\chi(z) = z^3 + c_1 z^2 + c_2 z + c_3 \tag{13}$$

which is the characteristic polynomial of $(A - KC)$. By choosing the optimal eigenvalues of $(A-KC)$ i.e. optimal roots of (13) we obtain the best balance between a low sensitivity to noise and a fast decay of the estimation error. If the eigenvalues are close to 1 the controller is less sensitive to noise (and relying more on the global trend) but results in a slow decay of the estimation error. If the eigenvalues are close to 0 the decay of the estimation error is fast but on the other hand the controller is very sensitive to noise and thereby rely too much on the local trend as we saw in the first pilot study.

The optimal placement of the eigenvalues inside the unit circle depends on the amount of noise present in the system. Therefore we decided to use the data from the first pilot study to determine the optimal eigenvalues of $(A - KC)$. We kept $\alpha = 0.99$ as one of the eigenvalues and estimated the remaining two eigenvalues from an stochastic differential model as described in the following section.

3.2 Stochastic differential equations model

Earlier work with stochastic differential equations has mainly dealt with modeling of dynamical systems [Kristensen et al. (2005); Overgaard et al. (2007); Tornøe et al. (2004)]. In this paper we introduce a novel approach for parameter estimation in control algorithms based on stochastic differential equations.

Within the field of biomedical control, stochastic differential equations are highly relevant. Dealing with these often very complex systems, as in this case the insulin-blood glucose system, we have to take into account all the uncertainties not explained by the model in the controller. Especially, when we want to use a very simple model as the one in (1). Uncertainties can be present in the input to the system or occur due to other factors interfering with the system e.g. release of stress hormones or physical exercise.

In a stochastic differential model noise is entering the system in two separate entrances: a process noise and a observation noise as seen in Fig. 3. Using this method we could estimate the process and observation variances separately and thereby obtain a more realistic noise model. From here we could find the optimal roots of the characteristic polynomial in (13).

To estimate the process and observation variances we used CTSM (Continuous Time Stochastic Modelling), a freeware program available on the web. See [DTU Informatics, Technical University of Denmark (2012)] for more information. The control algorithm was first transformed from the continuous time transfer function in (1) into an ordinary differential equation by inverse Laplace:

$$y + 2\tau\frac{dy}{dt} + \tau^2\frac{d^2y}{dt^2} = Mu(t) \tag{14}$$

and from here to the stochastic state space model which in the general linear case can be written as:

$$dx_t = (A(\theta)x_t + B(\theta)u_t)dt + \sigma(\theta)d\omega_t \tag{15}$$

$$y_k = C(\theta)x_k + e_k \tag{16}$$

x_t is the state vector, x_k is the discrete state vector, u_t is the input vector, y_k is the output vector in discrete time, θ is a vector of parameters, $A(\cdot)$, $B(\cdot)$, $\sigma(\cdot)$, and $C(\cdot)$ are nonlinear functions, $\{\omega_t\}$ is a standard Wiener process representing the process noise and e_k is a white noise process representing the observation noise for which we assume that $e_k \in N(0, S)$.

In this case, (15) is:

$$\begin{bmatrix} dx_{1t} \\ dx_{2t} \end{bmatrix} = \left(\begin{bmatrix} 0 & 1 \\ \frac{-1}{\tau^2} & \frac{-2}{\tau} \end{bmatrix} \begin{bmatrix} x_{1t} \\ x_{2t} \end{bmatrix} + \begin{bmatrix} 0 & \frac{1}{\tau_G} \\ \frac{M}{\tau^2} & 0 \end{bmatrix} \begin{bmatrix} u_{1t} \\ u_{2t} \end{bmatrix} \right) dt + \begin{bmatrix} \sigma & 0 \\ 0 & \sigma \end{bmatrix} d\omega_t \tag{17}$$

and the discrete observation equation is:

$$y_k = [1\ 0] \begin{bmatrix} x_{1k} \\ x_{2k} \end{bmatrix} + e_k \tag{18}$$

x_{1t} is the glucose level [mmol/L] above basal level, x_{2t} is the derivative of the glucose level [mmol/L/min], u_{1t} is the insulin input from the pump above the basal rate, u_{2t} is the intravenously glucose input administered by the clinician in case of severe hypoglycemia [mmol/L]. The parameters are τ, M, τ_G, σ, and S. We decided to fix all parameters except from σ and S because all of them are subject specific and known by the subjects themselves or the clinician. The fixed parameter values used for variance estimation were $\tau = 300$ min, M = -4.077 min·mmol/L/U and $\tau_G = 1$ min. See [Boiroux et al. (2012)] for more details about the choice of these values.

3.3 Estimation of variance parameters

Parameter estimation was based on the Maximum likelihood criteria, see [Kristensen and Madsen (2003); Kristensen et al. (2004)]. Since the subject wore two CGMs we had two stochastically independent data sets. The likelihood function is the joint probability density of all the observations assuming that the parameters are known:

$$\mathcal{L}(\theta; Y) = p(Y|\theta) \tag{19}$$

where $Y = \left[\gamma^1_{N_1}, \gamma^2_{N_2}\right]$. θ is now the parameter vector only including the parameters we wish to estimate.

We assume that the densities are Gaussian and implicitly described by the mean and variance. Thus the likelihood function can be expressed as:

$$\mathcal{L}(\theta; Y) = \prod_{i=1}^{L} \left(\prod_{k=1}^{N_i} \frac{\exp\left(-\frac{1}{2}(\epsilon^i_k)^T (R^i_{k|k-1})^{-1} \epsilon^i_k\right)}{\sqrt{\det(R^i_{k|k-1})}(\sqrt{2\pi})} \right) \cdot p(y^i_0|\theta) \tag{20}$$

L is the number of datasets, in this case two, y_0 are initial values of Y and:

$$\hat{y}_{k|k-1} = \mathrm{E}\{y_k|\gamma_{k-1}, \theta\} \tag{21}$$

$$R_{k|k-1} = Var\{y_k|\gamma_{k-1}, \theta\} \tag{22}$$

are the one-step ahead prediction and variance, respectively. The one-step prediction error is:

$$\epsilon_k = y_k - \hat{y}_{k|k-1} \tag{23}$$

The exact solution is computationally infeasible so an approximative method is used. For a given set of parameters and initial states, x_0, the one-step ahead prediction error and variance are estimated from a continuous-discrete Kalman filter. The output prediction equations are computed as:

$$\hat{y}_{k|k-1} = C\hat{x}_{k|k-1} \tag{24}$$

$$R_{k|k-1} = CP_{k|k-1}C^T + S \tag{25}$$

$P_{k|k-1}$ is the predicted state covariance. The innovation equation is defined as the prediction error in (23). And the Kalman gain is determined by:

$$K_k = P_{k|k-1}C^T R^{-1}_{k|k-1} \tag{26}$$

From here we can update the state and state covariance equations:

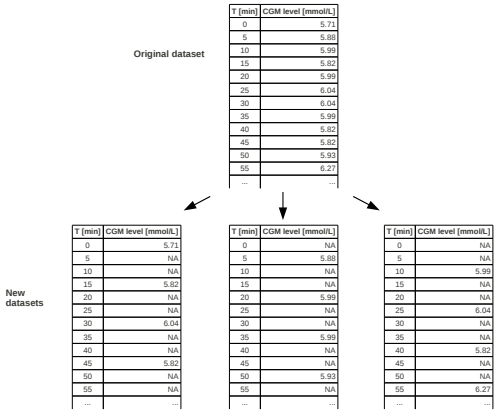

Fig. 4. The original data sets were separated into three different data sets with missing observations (NA) replacing those observations present in the other two new data sets.

$$\hat{x}_{k|k} = \hat{x}_{k|k-1} + K_k \epsilon_k \tag{27}$$

$$P_{k|k} = P_{k|k-1} - K_k R_{k|k-1} K_k^T \tag{28}$$

And finally, we can predict the state and covariance by solving the differential equations:

$$\frac{dx_{t|k}}{dt} = A\hat{x}_{t|k} + Bu_t, t \in [t_k, t_{k+1}[\tag{29}$$

$$\frac{dP_{t|k}}{dt} = AP_{t|k} + P_{t|k}A^T + \sigma\sigma^T, t \in [t_k, t_{k+1}[\tag{30}$$

Once the approximative likelihood function has been computed, the optimal parameter estimates are found by minimizing the log-likelihood function:

$$\hat{\theta} = \arg\min_{\theta \in \Theta} \{-ln(\mathcal{L}(\theta; Y|y_0))\} \tag{31}$$

This parameter estimation is per default based on the one-step ahead prediction as seen above. In our case the step size is 5 minutes corresponding to the time between two CGM observations. Since the controller regulates the insulin infusion every 15 minutes, we found it beneficial to base the parameter estimation on the three-step ahead prediction instead.

To handle this, we did a reconstruction of the original data file used for the parameter estimation in CTSM. From each original data set we constructed three new data sets starting in t_0, t_1, and t_2, respectively. As illustrated in Fig. 4, we replaced the two following observations with missing observations and repeated this pattern throughout the new data sets.

In the Kalman filter a missing observation is handled by setting the Kalman gain, K_k, to zero and thus the state predictions are computed from the state equations only until a new observation is available.

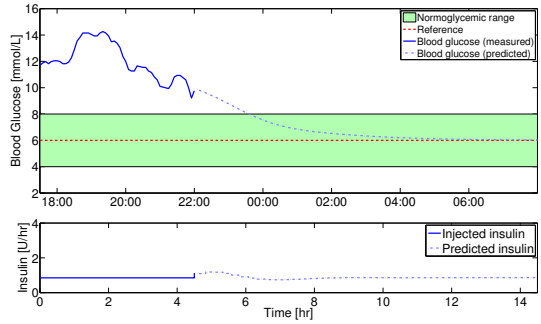

Fig. 5. Top: CGM observations (solid line) and blood glucose prediction (dashed line) from the first pilot study if the tuned Kalman gain had been used in the MPC controller. The normal range is indicated as the green area. Bottom: Insulin delivered by the pump (solid line) and suggested insulin supply (dashed line).

3.4 Tuning of control algorithm

The variance parameters, i.e. the process noise, σ, and the observation noise, S, were estimated to 0.0037 ± 0.00043 and 0.30 ± 0.030 respectively. We used the estimated process and observation variances to compute the Kalman gain, K, by a pole placement method as mentioned in section 3.1. First the continuous state space model in (15) was discretized and from here the two remaining eigenvalues could be computed by solving a Riccati equation. Together with α we computed the roots and thereby the coefficients in the characteristic polynomial in (13) and finally K in (12). The estimated values of the coefficients and K are:

$$c_1 = -2.61 \quad c_2 = 2.28 \quad c_3 = -0.67 \tag{32}$$

$$K = [0.36 \quad -0.66 \quad 0.30] \tag{33}$$

4. RESULTS

We simulated the first pilot study again, this time with the improved Kalman gain, K, in the MPC algorithm. As seen in Fig. 2 the controller originally overestimated the blood glucose prediction at the time of closing the loop. In Fig. 5 the same situation is shown, this time with the new K estimated on the basis of observed data. The controller now relies more on the global trend and the predictions are more realistic. The suggested bolus is likewise smaller and would not cause a hypoglycemic event as the bolus given in the first pilot study.

A second pilot study was performed on the same subject to validate the new algorithm before initiating a larger clinical study. This time the study was performed during day time but without any normal day time disturbances (e.g. meals and exercise) to mimic night time. The result is shown in Fig. 6. The subject had a very low blood glucose level from the beginning of the pilot study. Intravenously glucose was administrated at 10:00 and 12:00 to compensate.

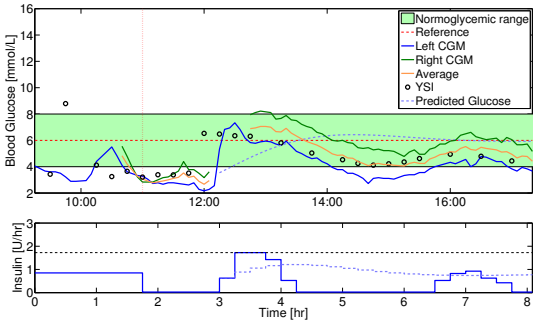

Fig. 6. Top: Results of the second pilot study after the controller had been tuned. The loop is closed at 11:00. The left CGM (solid blue curve) serves as input to the controller. The blood glucose prediction (dashed line) at 12:10 is also shown. YSI observations are blood glucose observations considered as gold standard. Bottom: Insulin delivered by the pump (solid line) and predicted insulin supply (dashed line).

Note that the insulin delivery is updated every 15 minutes as new CGM measurements are available. Thus the insulin delivery profile differs from the predicted profile.

The blood glucose prediction from the improved control algorithm at 12:10 is also seen in Fig. 6. At this point in time the CGM measurements are rapidly increasing due to the glucose administrated intravenously at 12:00. As seen, the controller predicts a slower and more realistic increase in blood glucose due to the improved performance. The rapid increase is an artificial situation and does not occur in daily life. The controller is thereby acting as expected and characterizes the local increase as noise.

Even though tuning has improved the prediction performance, the left CGM measurements decrease below the normal range after 14:00. This could indicate that despite the improvements, the intravenously glucose administration still causes the controller to overestimate the needed bolus size.

In general, the second pilot showed that the controller is able to keep the blood glucose level in the normal range after 12:00 despite the prior disturbances. However, since the second pilot study further improvements have been implemented to increase the robustness.

5. CONCLUSION

This work illustrates how MPC can benefit from stochastic differential equations modeling. By estimating the process and observation noise in two separate terms the Kalman gain was calibrated to the actual system with a rather simple and effective method using stochastic differential equations. Additionally, we based the parameter estimation on the three-step ahead prediction instead of the one-step ahead prediction which was in accordance with the time between controller inputs. It is important to note that this method is not only restricted to this specific application but can be used within many areas dealing with control of complex and stochastic systems.

Currently, a clinical study testing our artificial pancreas controller is ongoing including several subjects and different scenarios.

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Appendix F

Paper D

Predicting Plasma Glucose From Interstitial Glucose Observations Using Bayesian Methods

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Predicting plasma glucose from interstitial glucose observations using Bayesian methods

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Abbreviations: (CGM) continuous glucose monitor, (CSII) continuous subcutaneous insulin infusion, (IG) interstitial glucose, (MVP) Medtronic virtual patient, (PG) plasma glucose, (SDEs) stochastic differential equations, (SDE-GB) stochastic differential equation grey-box model, (T1DM) type 1 diabetes mellitus.

Keywords: Bayesian methods, Plasma glucose dynamics, PG-IG dynamics, stochastic differential equations, stochastic grey-box modeling, type 1 diabetes mellitus.

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Abstract: 249

Main text: 3090

2 tables

6 figures

Abstract

Background:

One way of constructing a control algorithm for an artificial pancreas is to identify a model capable of predicting plasma glucose (PG) from interstitial glucose (IG) observations. Stochastic differential equations (SDEs) make it possible to account both for the unknown influence of the continuous glucose monitor (CGM) and for unknown physiological influences. Combined with prior knowledge about the measurement devices, this approach can be used to obtain a robust predictive model.

Method

A stochastic-differential-equation-based grey-box (SDE-GB) model is formulated on the basis of an identifiable physiological model of the glucoregulatory system for type 1 diabetes mellitus (T1DM) patients. A Bayesian method is used to estimate robust parameters from clinical data. The models are then used to predict PG from IG observations from two separate study occasions on the same patient.

Results

First, all statistically significant diffusion terms of the model are identified using Likelihood ratio tests, yielding inclusion of $\sigma_{I_{sc}}$, σ_{G_p} and $\sigma_{G_{sc}}$. Secondly estimates using Maximum Likelihood are obtained, but prediction capability is poor. Finally a Bayesian method is implemented. Using this method the identified models are able to predict PG using only IG observations. These predictions are assessed visually. We are also able to validate these estimates on a separate data set from the same patient.

Conclusions

This study shows that SDE-GBs and a Bayesian method can be used to identify a reliable model for prediction of PG using IG observations obtained with a CGM. The model could eventually be used in an artificial pancreas

INTRODUCTION

The use of *continuous glucose monitors* (CGMs) on patients with type-1 diabetes mellitus (T1DM) has a positive effect on glycaemic control.[1–5] The advantages of continuous glucose monitoring are many, but there are also several well-documented problems.[6–8] These include: time-delay between *plasma glucose* (PG) and *interstitial glucose* (IG),[3–5] the drift of sensor sensitivity[9] and vulnerability to calibrations during rapidly increasing or decreasing glucose levels.[10,11] For optimal use of CGMs in the management of T1DM, e.g. for closed-loop control, it is necessary to know the relationship between PG and IG.[12] Due to the well-known issues with the sensor, the main challenge related to automatic control of the glucose is to predict PG from IG observations measured by a CGM. To do this, the dynamical relation between the PG and IG levels needs to be well described.

Modelling glucose dynamics using observations from CGMs is challenging. As described by Facchinetti et al. three of the major problems are:[13] a) PG observations have to be collected parallel with IG observations, b) a precise model for PG-IG dynamics is needed, c) sensor errors should be modelled as stochastic processes.

When using real-life data obtained with a CGM, the autocorrelation of data becomes an issue, requiring specific modelling techniques. This will be discussed in this paper. As the observations are closely sampled (e.g. 5 min. sample rate), interdependence between data points or autocorrelation is present.[14–16] Several approaches to overcome sensor issues, including

autocorrelation, have been investigated. Data-driven autoregressive models have been used by Reifman et al.[16] Chase et al. modelled sensor errors using Gaussian processes.[17] Breton and Kovatchev used a non-Gaussian Johnson distribution and autoregressive (AR(1)-processes).[18] One suggestion by Guerra et al. is to use deconvolution-based enhancement algorithms that, in real-time, improve CGM accuracy.[19]
In this study we use SDE-GBs and a Bayesian method to address all three issues described by Facchinetti et al.

When investigating the glucose-insulin dynamics (e.g. in closed-loop studies), patients receive inputs to excitate glucose values, such as meals, giving a positive excitation and insulin, giving a negative excitation. This article accommodates the need for an understanding of the dynamics with no external positive excitation. The negative excitation is provided by a continuous subcutaneous insulin infusion (CSII).

Glucose-insulin dynamics are a part of the complex, partly unknown, fuel metabolism.[20] Stochastic behaviour should therefore be considered in the modelling. One way of doing this is to apply *stochastic-differential-equation-based grey-box* (SDE-GB) models. Such models are established using a combination of physiological knowledge and statistical information from data. In general a SDE-GB model can be written as:

$$dx_t = f(x_t, u_t, t, \theta)dt + \sigma(x_t, u_t, t, \theta)d\omega \qquad (1)$$

$$y_j = h\big(x_j, u_k, t_j, \theta\big) + e_j \qquad (2)$$

where the states are described by the vector x_t, $f(\cdot)$ is the drift term and $\sigma(\cdot)d\omega$ is a diffusion term with ω as a Wiener process.[21] The states are unobserved, but the vector, y_j, of discrete time observations is linked to the states as described by the function $h(\cdot)$. The observations are contaminated by the measurement noise, e_j. The input is represented by u_t and θ represents the parameters.

The advantage of using SDE-GB models as compared to ordinary differential-equations-based models, is that noise is included in the state equations in terms of $\sigma(\cdot)d\omega$. As the noise affects the state equations, the overall system will have a stochastic influence, reflecting the fact that future values of the states can never be predicted exactly. The system noise enters through the dynamics of the system and will reveal e.g. model deficiencies, random fluctuations in the system or unknown inputs.[22] Residual information and analysis can be used in the validation process of the model building to ensure that uncorrelated residuals are obtained.[21] Uncorrelated residuals indicate that the model is adequate in the sense that all the systematic variation in the observations is described. Elaborations of these advantages exist in several articles.[22–27] Solutions to SDEs are stochastic processes. These stochastic processes are described by probability distributions.[28] This property enables the use of Maximum Likelihood techniques, thereby maintaining a data-driven model estimation.[29] In this paper the parameters of the Medtronic Virtual Patient (MVP)[30] model are estimated in an SDE-GB setting using the Maximum Likelihood principle. First, a method for identifying the need for diffusion terms, using forward selection, is presented. Secondly parameters are

estimated using Maximum Likelihood. Finally a Bayesian method is used to estimate the parameters related to the observation equations. These parameters are cross-validated on a different data set from the same patient.

METHODS

The data used in this study originates from an overnight closed-loop study, conducted as a part of the DIACON project.[31] Patient characteristics and study set-up are described by Schmidt et al.[32] Plasma glucose and plasma insulin were sampled every 30 min. Plasma glucose was analysed using YSI2300 STAT Plus (Yellow Springs Instruments, Yellow Springs, OH). Every 5 min. a subcutaneous glucose value was obtained using a DexCom SevenPLUS (DexCom, San Diego, CA) CGM. Insulin Aspart (Novorapid, Novo Nordisk, Bagsværd, Denmark) was administered using a Paradigm Veo (Medtronic, Northridge, CA) insulin pump. Patients were euglycemic (PG level 70-144 mg/dl) at study start. It is assumed that an evening meal given four hours before study start does not influence the glucose dynamics. For this study, data from one patient on two independent nights, at least two weeks apart was used for model identification. The first data set, $Data_1$, originates from a closed-loop study night, and the second data set, $Data_2$, originates from an open-loop study night.

The initial model

The MVP model was used as the basis for formulating the SDE-GB model. In essence, the model is based on the Bergman Minimal Model.[33,34] Fisher modified the model, replacing insulin secretion with insulin infusion.[35] In this study, we focus on the kinetics and dynamics when patients are at rest.

This reduces the model to the five equations below describing glucose-insulin dynamics with no meal input.

The insulin dynamics are described by:

$$dI_{sc} = \frac{1}{\tau_1}\left(\frac{ID}{C} - I_{sc}\right)dt + \sigma_{I_{sc}}d\omega_1 \quad (3)$$

$$dI_P = \frac{1}{\tau_2}(I_{sc} - I_P)dt + \sigma_{I_P}d\omega_2 \quad (4)$$

$$dI_{eff} = \left(p_2 \cdot S_I \cdot I_P - p_2 \cdot I_{eff}\right)dt + \sigma_{I_{eff}}d\omega_3 \quad (5)$$

where I_{sc}, I_P and I_{eff} are the subcutaneous insulin concentration $[\frac{IU}{L}]$, the plasma insulin concentration $[\frac{IU}{L}]$ and the effect of insulin $[\frac{1}{\text{min}}]$, respectively.

The glucose dynamics are described as:

$$dG_P = \left(-\left(GEZI + I_{eff}\right) \cdot G_P + EGP\right)dt + \sigma_{G_P}d\omega_4 \quad (6)$$

$$dG_{sc} = \frac{1}{\tau_3}(-G_{sc} + G_P)dt + \sigma_{G_{sc}}d\omega_5 \quad (7)$$

where G_P and G_{sc} are states representing the plasma glucose concentration $[\frac{\text{mg}}{\text{dl}}]$ and subcutaneous interstitial glucose concentration $[\frac{\text{mg}}{\text{dl}}]$, respectively.

The models contain a diffusion term $\sigma d\omega$ where σ is a scaling parameter and ω is assumed to be a Wiener process with normally distributed increments.[25] To accommodate available data, in our study $\tau_2 = \tau_1$, as insulin kinetics is very data-dependent.[36] The remaining parameters are defined in Table 1.

For our study the observation equations are:

$$YSI = G_P + \exp(e_{YSI}) \quad (8)$$

$$CGM = G_{sc} + \exp(e_{CGM}) \quad (9)$$

$$INS = I_{sc} + \exp(e_{INS}) \quad (10)$$

where $e_{YSI} \in N(0, S_{YSI})$, $e_{CGM} \in N(0, S_{CGM})$ and $e_{INS} \in N(0, S_{INS})$ are mutually independent white noise processes, and S is the variance of each measurement noise, respectively.

The Maximum Likelihood principle

The likelihood function captures all the information in the data about the parameters. For time-series data, the likelihood function is a product of one-step conditional densities. Due to the Gaussian increments of the Wiener processes, it is assumed that the conditional densities are Gaussian. In order to evaluate this, one-step conditional predictions are needed. These are calculated using an extended Kalman filter,[23,24] and the likelihood function has been identified as the key inferential quantity conveying all information in statistical modelling including uncertainty.[29,37]

Using the one-step prediction error, ϵ_k, and the associated variances, $R_{k|k-1}$, for the extended Kalman filter, it is possible to formulate a Bayesian method. Bayes Theorem can be applied to obtain an improved estimate by forming the posterior probability density function:[29]

$$p(\boldsymbol{\theta}|\Upsilon_N) = \frac{p(\Upsilon_N|\boldsymbol{\theta})p(\boldsymbol{\theta})}{p(\Upsilon_N)} \propto p(\Upsilon_N|\boldsymbol{\theta})p(\boldsymbol{\theta}) \qquad (11)$$

where Υ_N is the set of observations and $\boldsymbol{\theta}$ is a vector of parameters.

Assuming Gaussian distributions, the posterior probability density function becomes:

$$p(\boldsymbol{\theta}|\Upsilon_N) = \left(\prod_{k=1}^{N} \frac{\exp\left(\frac{1}{2}\epsilon_k^T R_{k|k-1}^{-1} \epsilon_k\right)}{\sqrt{\det(R_{k|k-1})}(\sqrt{2\pi})^{\dim(\Upsilon_N)}} \right) p(y_0|\theta) \qquad (12)$$

$$\times prior(\boldsymbol{\theta}_P, \Sigma_P)$$

where y_0 is the initial conditions and $\boldsymbol{\theta}_P$ and Σ_P are the mean and covariance of a prior distribution. The parameter estimates are found by minimising the negative log-posterior probability density function:

$$\widehat{\boldsymbol{\theta}} = \arg\min\left\{-ln\left(p(\boldsymbol{\theta}|Y_N, \boldsymbol{y}_0)\right)\right\} \quad (13)$$

where $\widehat{\boldsymbol{\theta}}$ is the Bayesian estimate. This estimate and the covariance matrix, can be used as new prior knowledge for further estimation.

In order to mimic potential future applications, three different setups for the prior knowledge have been considered:

i) A theoretical prior knowledge for the variance of the measuring devices: $prior(\boldsymbol{\theta}_{MD})$, shown in the appendix..

The prior knowledge of the YSI device is based on Khan et al.[38] For the DexCom SevenPLUS it is set as arbitrary but based on the user guide.[39] For the insulin measurement device it is set as arbitrary.

ii) A prior knowledge formed by the estimate and covariance $(\widehat{\boldsymbol{\theta}}_{11}, \Sigma_{\widehat{\boldsymbol{\theta}}_{11}})$ of Data$_1$: $prior(\boldsymbol{\theta_{11}})$

iii) A prior knowledge formed by the estimate and covariance $(\widehat{\boldsymbol{\theta}}_{22}, \Sigma_{\widehat{\boldsymbol{\theta}}_{22}})$ of Data$_2$: $prior(\boldsymbol{\theta_{22}})$

Modelling process

All computations are performed using the statistical software, R (version 2.15.1), and the "CTSM-R package".[40] The identified models are cross-validated by analysing the predictions from two study nights from the same patient. The following steps, are followed for both data sets – see Table 2:

Step 1 (Diffusion term identification and Maximum Likelihood):

In the initial model building process for diffusion step inclusion, forward selection and Likelihood ratio tests are used.[23,24] *a)* The parameters of the initial ordinary differential equation model, $\sigma = 0$, are estimated. *b)* The diffusion terms are included, one at a time, and the parameters are estimated again. *c)* Wilk's likelihood ratio test is applied to identify the most significant improvement.[29]

d) Steps *b-d* are repeated until addition of extra diffusion terms does not give a statistically significant improvement.

e) For $Data_1$ and $Data_2$ each respective Maximum Likelihood parameter set, $(\widehat{\boldsymbol{\theta}}_1, \Sigma_{\widehat{\boldsymbol{\theta}}_1})$ and $(\widehat{\boldsymbol{\theta}}_2, \Sigma_{\widehat{\boldsymbol{\theta}}_2})$ is estimated.

Step 2-6 (A Bayesian method):

Step 2:

For $Data_1$ and $Data_2$, each respective Bayesian estimate, $(\widehat{\boldsymbol{\theta}}_{11}, \Sigma_{\widehat{\boldsymbol{\theta}}_{11}})$ and $(\widehat{\boldsymbol{\theta}}_{22}, \Sigma_{\widehat{\boldsymbol{\theta}}_{22}})$, is obtained using the measurement device prior knowledge $prior(\boldsymbol{\theta}_{MD})$.

Step 3:

With the estimates obtained in Step 2, the predictions of PG for $Data_1$ and $Data_2$, are calculated using only the respective IG to verify the prediction capabilities.

Step 4:

The new prior knowledge $prior(\boldsymbol{\theta_{11}})$ and $prior(\boldsymbol{\theta_{22}})$ is formed from $(\widehat{\boldsymbol{\theta}}_{11}, \Sigma_{\widehat{\boldsymbol{\theta}}_{11}})$ and $(\widehat{\boldsymbol{\theta}}_{22}, \Sigma_{\widehat{\boldsymbol{\theta}}_{22}})$.

Step 5:

From $Data_1$, $prior(\boldsymbol{\theta_{11}})$, is used in a new Bayesian estimation using $Data_2$. Thereby a cross-validation estimation, giving a new Bayesian parameter estimation $\widehat{\boldsymbol{\theta}}_{12}$ (subscript is read as: prior knowledge from $Data_1$ used to estimate $Data_2$) is obtained. Likewise with $prior(\boldsymbol{\theta_{22}})$.

Step 6: With the obtained estimates $\widehat{\boldsymbol{\theta}}_{21}$ and $\widehat{\boldsymbol{\theta}}_{12}$, the predictions of PG for $Data_1$ and $Data_2$, are obtained using the respective IG observations only.

RESULTS

For all estimates presented, identifiability has been established by testing different starting points of the estimation. The forward selection method gave statistical reason for diffusion term inclusion, and resulted in the terms $\sigma_{I_{sc}}$, σ_{G_p} and $\sigma_{G_{sc}}$. For all results involving $Data_1$ an outlier was removed in the estimation and prediction. It is represented by a purple circle in the relevant figures.

Maximum Likelihood (Step 1)

For the Maximum Likelihood investigation only the results from $Data_1$ are presented. Results from $Data_2$ show identical modelling behaviour. Using CTSM-R, the one-step-ahead prediction of PG and IG is obtained with calibration at each data point. As seen in Figure 1 the Maximum Likelihood estimate, $\widehat{\boldsymbol{\theta}}_1$, will seek to explain all the variation in the data without reflecting

that the truth is better described by the PG observations. Thus the prediction of PG shows the unwanted IG dynamics.

It is evident that the overall prediction of PG follows the dynamic of the IG observations. Steep transitions in the prediction of PG are a direct result of a steep transition in IG observations. These transitions and the overall dynamic behaviour are attributed to the Maximum Likelihood estimate, visualising the challenge of the estimation technique. The parameter estimates are not presented, as the visual inspection shows suboptimal predictions. This is most easily seen by the persistent deviation between the predictions and the data over longer periods for the PG observations.

A Bayesian method (Step 2)

Figure 2 shows the predictions from a Bayesian estimation, $\widehat{\boldsymbol{\theta}}_{11}$, by implementation of prior knowledge, $prior(\boldsymbol{\theta}_{MD})$. It is evident that the prediction of PG follows the actual PG observations more precisely than Figure 1.

The prediction of IG is not as precise as before and the confidence interval is wider; a direct consequence of the Bayesian method. The Bayesian method makes the prediction band for IG statistically meaningless. As we are only interested in the PG prediction, this is a minor problem. The IG prediction band will not be shown in the remaining results.

The prediction of PG is improved and the 95% prediction band is narrower. From a visual inspection it is seen that S_{YSI} has decreased and S_{CGM} has

increased, as expected. The estimates, standard deviations and the correlation table are presented in the appendix for both $Data_1$ and $Data_2$, increasing the reproducibility.[41]

It is not meaningful to statistically compare Step 1 and Step 2, as information criteria are defined from the pure likelihood function; therefore a visual and physiological improvement are assessed.

Model validation

As it is desired to predict PG from IG observations, predictions without knowledge of the PG or insulin observations are computed.

Data 1

Prediction using $\widehat{\boldsymbol{\theta}}_{\mathbf{11}}$ (Step 3)

Figure 3 shows the one-step-ahead prediction using $\widehat{\boldsymbol{\theta}}_{\mathbf{11}}$ of PG using only IG observations. The prediction follows the true PG dynamic well. The 95%-prediction band contains all but one PG observation.

Prediction using $\widehat{\boldsymbol{\theta}}_{21}$ (Step 6)

Figure 4 shows the predictions using $\widehat{\boldsymbol{\theta}}_{21}$ and only IG observations. The dynamics of PG is captured well. The 95% prediction band contains all but one PG observation.

Data 2

Predicting using $\widehat{\boldsymbol{\theta}}_{22}$ (Step 3)

Figure 5 shows $Data_2$, with virtually no dynamic in the PG observations and the IG observations are very fluctuating and unphysiological. Despite this difference in observations, when predicting using $\widehat{\boldsymbol{\theta}}_{\boldsymbol{22}}$, it is seen that the one-step-ahead prediction of PG using only IG observations follows the PG dynamic well. The 95% prediction band contains all but one PG observation.

Predicting using $\widehat{\boldsymbol{\theta}}_{12}$ (Step 6)

Figure 6 shows the prediction using $\widehat{\boldsymbol{\theta}}_{12}$. It is still possible to predict the dynamics of PG using only IG observations. There is a tendency that the predictions are slightly elevated compared to PG observations, but the 95% prediction band, contains all PG observation.

DISCUSSION

This study shows that it is possible to predict PG from IG observations using a Bayesian method. This finding indicates that the final model can be used as a control algorithm that is implementable in a pump system.

Maximum likelihood (Step 1)

Using Maximum Likelihood estimation, the IG influence on the PG prediction is evident. The many closely spaced observations have a tremendous influence on the likelihood.[29] The optimisation minimises the one-step prediction, and as there are more IG observations, the optimiser will gain more from explaining the IG dynamics. To avoid this, a Bayesian method is suggested as a solution.

A Bayesian method (Steps 2, 5 and 6)

It is assumed that the global parameter set for a patient will vary between days. This variation is assumed to have a limited span. This assumption enables us to cross-validate within the same patient. We expect that the parameter estimates from a given night will be similar to parameter estimates from another night. This allows us to use prior knowledge from one study night to estimate a new parameter set.

The ideal solution for a Bayesian method implementation is estimation of the optimal prior knowledge. However, an estimation of the variance of the variance of the measurement device requires a large amount of data. Instead, the literature was used to approximate measurement-device prior knowledge. The 95% prediction band is wide on the IG prediction since a Bayesian method is used. But as the focus of the study is prediction of PG this is accepted. The 95% prediction bands for PG are narrow.

As discussed by Donnet and Samson, Bayesian methods have been proposed and implemented for population pharmacokinetics/pharmacodynamics SDE-GB.[42] Using CTSM-R it is possible to implement Bayesian estimation on a single subject, obtaining valid and interpretable models. Future studies should include several patients and preferably population modelling.

Physiological modelling

The SDE-GB models applied allow for a physiological, opposed to a purely statistical, interpretation of the models, since the model structure is based on physiology. From a visual inspection it is evident that the statistical best model is not the physiologically and technologically most correct model.

The use of CTSM-R allows optimal conditions for the modelling procedure: i.e. continuous-time dynamics with discrete time observations and a possibility of adopting a Bayesian modelling framework. This gives fewer parameters to estimate, which in turn gives a more robust estimation. Furthermore, previous knowledge is often given as differential equations, and therefore easily incorporated into existing models.[42] This maintains the physiological meaning of the model, and gives it interpretability for both the modellers and medical experts.

The examination of the covariance matrixes reveals that there is no severe parameter correlation. The covariance matrix has great potential in constructing a virtual patient database. Randomly selected parameter sets can be used to construct an infinite number of simulations for use as initial investigations, instead of costly human experiments.

Perspectives

A natural progression is to extend the Bayesian method to data where other factors, such as meals, have an influence. Building on Reifman et al.[16] a combination of data-driven AR models and Bayesian probability models should be investigated. The Bayesian probability ensures physiological interpretability and the AR processes capture sensor dynamics.

New optical-sensor techniques are currently under development as an alternative to the electrochemical transducer. Vaddiraju et al. provides an overview of advantages, disadvantages and perspectives.[7]

To obtain more knowledge about PG-IG dynamics, experiments with multiple glucose sensors, both electrochemical and optical, should be considered. Advantages of a multiple glucose sensor approach are not well investigated but reports describing the advantages exist.[43,44]

Conclusion

The aim of this article was to extend an existing model describing PG-IG dynamical behaviour to SDE-GB form. With the SDE-GB model, and clinical data from a closed-loop study, parameters were estimated. The initial investigation used a Maximum Likelihood approach. Afterwards a Bayesian method was investigated.

Using the Maximum Likelihood approach gave statistically reliable result, but there were deficiencies, as the ability to predict PG from IG observations was poor.

A Bayesian method was successfully implemented and it has been shown that parameters can be estimated using CTSM-R.

Using a Bayesian estimate we were able to predict PG using IG observations. Furthermore we were able to cross-validate parameter estimates using a different data set from the same patient. Using prior knowledge from a previous study night, we were able to estimate usable parameters, indicating a close relation in intrapatient parameters.

These findings indicate that the model can be incorporated in an artificial pancreas that can be used as a closed-loop controller.

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Name	Unit	Description
EGP	[mg/(dL×min)]	Endogenous glucose production rate, estimated at zero insulin
GEZI	[1/min]	Effect of glucose per se to increase glucose uptake into cells and lower endogenous glucose production at zero insulin
p_2	[1/min]	The delay in insulin action following an increase in plasma insulin
S_i	[L/(mU×min)]	Insulin sensitivity
$\sigma_{I_{SC}}$	-	Scaling of diffusion term for interstitial insulin
σ_{I_P}	-	Scaling of diffusion term for blood insulin*
$\sigma_{I_{eff}}$	-	Scaling of diffusion term for insulin effect*
σ_{G_P}	-	Scaling of diffusion term for PG observation
$\sigma_{G_{SC}}$	-	Scaling of diffusion term for IG observation
S_{YSI}	-	Variance of measurement noise of the PG observations
S_{CGM}	-	Variance of measurement noise of the IG observations
S_{INS}	-	Variance of measurement noise of the insulin observations
τ_1	[min]	Time constant related to the insulin movement between the subcutaneous tissue and plasma
τ_3	[min]	Time constant related to the glucose movement in the subcutaneous layer
ID	[IU/min]	INPUT. Insulin delivery to the subcutaneous layer
C	[L/min]	Clearance of insulin in the subcutaneous tissue (1.2**)
BA	-	Bioavailability of insulin (0.7***)

Table 1: Identifiable parameters in Medtronic Virtual Patient on SDE-GB form.
*** Found to be insignificant – see results**
****Clearance is fixed conservatively according to patient characteristic[32–34]**
***** Bioavailability is fixed conservatively according to Hori et al.[35]**
PG: plasma glucose, IG: interstitial glucose

	Step 1 ML estimation*	Step 2 Bayesian estimation* using $prior(\theta_{MD})$	Step 3 Prediction**	Step 4 Form prior	Step 5 Cross-validation Bayesian estimation*	Step 6 Prediction**
$Data_1$	$\widehat{\boldsymbol{\theta}}_1$	$\widehat{\boldsymbol{\theta}}_{11}$	$\hat{X}_1$	$prior(\boldsymbol{\theta}_{11})$	$\widehat{\boldsymbol{\theta}}_{21}$	$\hat{X}_{21}$
$Data_2$	$\widehat{\boldsymbol{\theta}}_2$	$\widehat{\boldsymbol{\theta}}_{22}$	$\hat{X}_2$	$prior(\boldsymbol{\theta}_{22})$	$\widehat{\boldsymbol{\theta}}_{12}$	$\hat{X}_{12}$

Table 2: Flow of the modelling process.
*** All observations in the data set are used for estimation.**
**** Only IG-observations are used in the prediction of PG in this step.**

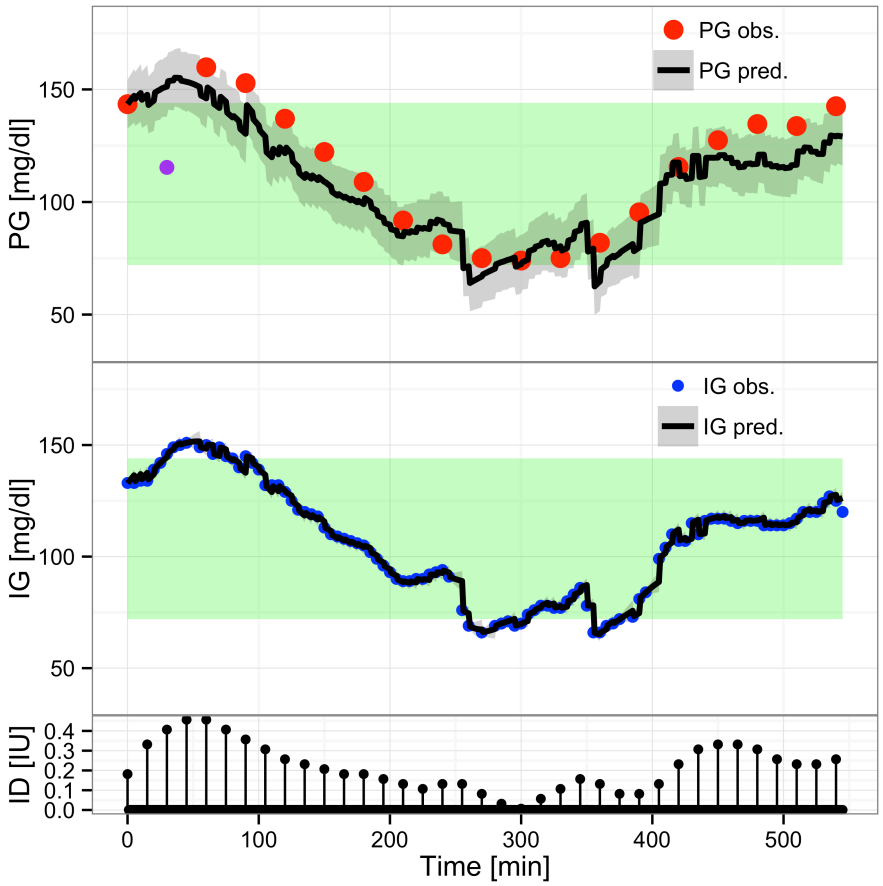

Figure 1: (Overall) Predicting with $\widehat{\theta}_1$ using both PG and IG observations. The green ribbon reflects the normoglycaemic range. The purple observation is an outlier not used in the Maximum Likelihood estimation nor prediction. (Top) One-step prediction and 95% prediction band of the PG observations. The prediction is not in agreement with the observations. Steep transitions are seen when there is a change in the IG observations. (Middle) One-step prediction of the IG observations and 95% prediction band. The prediction band is unrealistically narrow, reflecting the fact that the model seeks to explain the sensor error exactly, not reflecting that the PG observations are the truth. (Bottom) Insulin delivery as boluses.

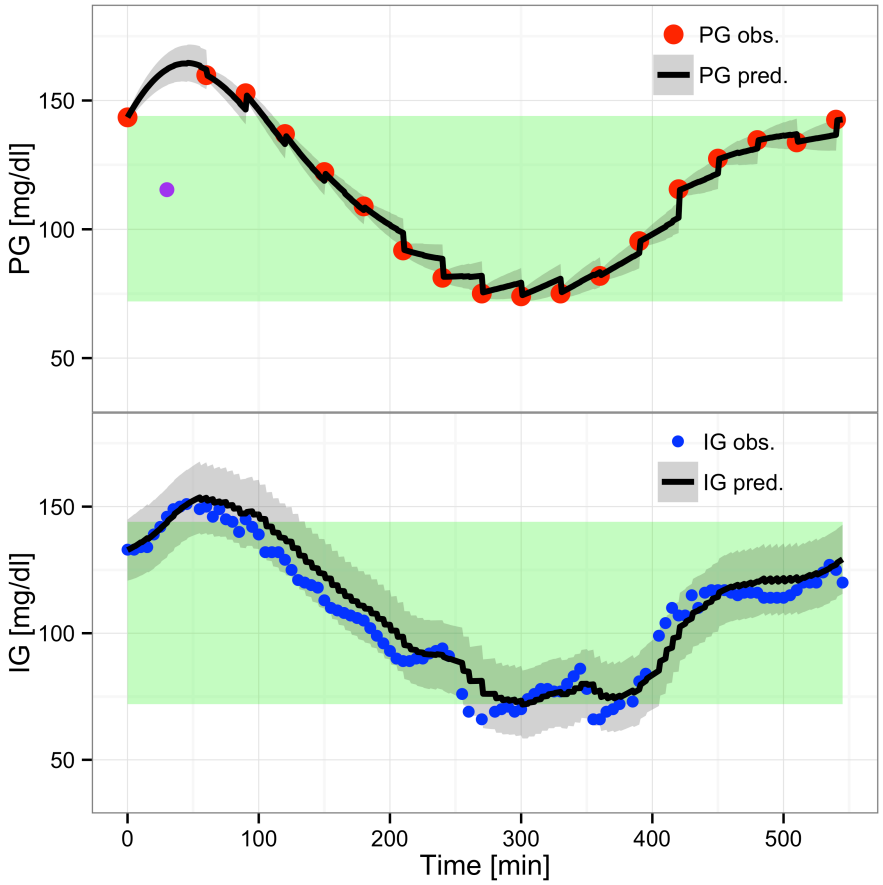

Figure 2: (Overall) Prediction with $\widehat{\theta}_{11}$ using both PG and IG observations. Green ribbon reflects the normoglycaemic range. The purple observation is an outlier not used in the Bayesian estimation nor prediction. (Top) One-step prediction and 95% prediction band of the PG observations. Small adjustments are seen when a new PG observation is obtained, but the prediction is in agreement with the observations. (Bottom) One-step prediction of IG observations and 95% prediction band.

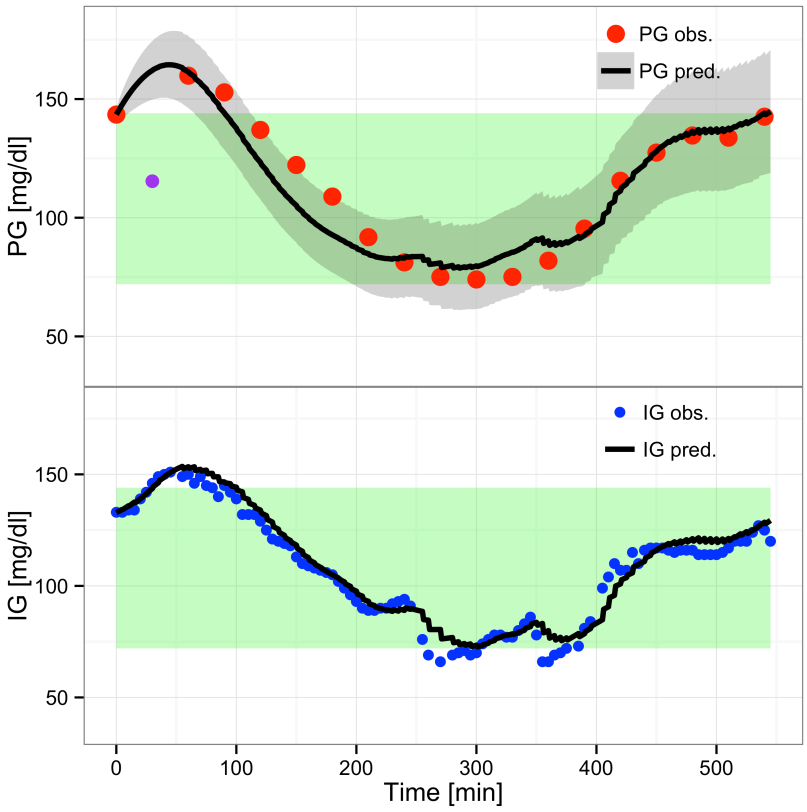

Figure 3: (Overall) Predicting with $\hat{\theta}_{11}$ using only IG observations. Green ribbon reflects the normoglycaemic range. The purple observation is an outlier not used in the Bayesian estimation nor prediction. (Top) One-step prediction of PG and 95% prediction band. The dynamics of PG are captured in the prediction and the prediction band covers all but one PG observation. (Bottom) One-step prediction of IG.

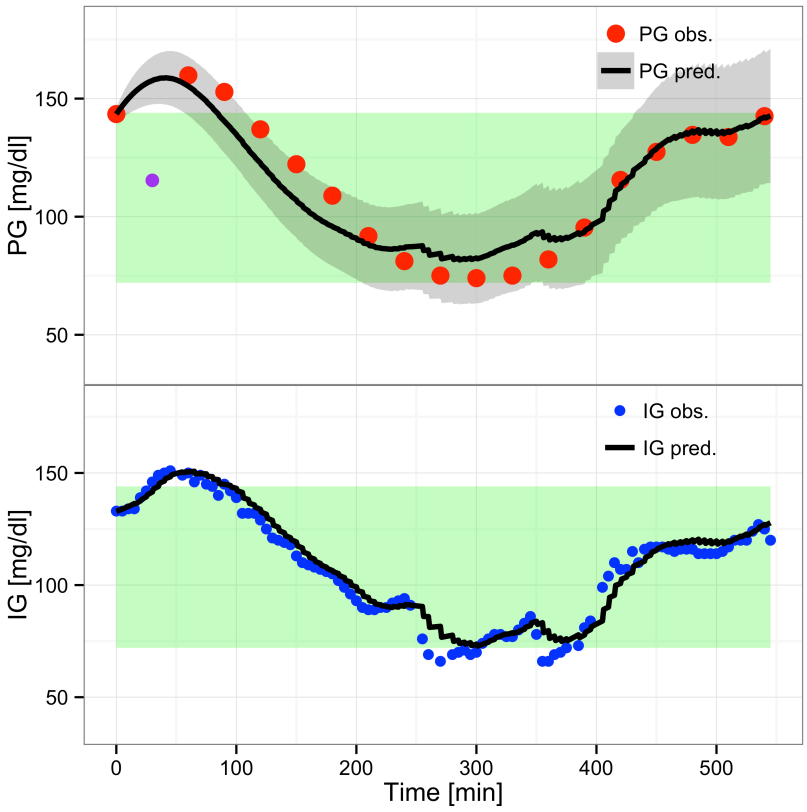

Figure 4: (Overall) Prediction with $\hat{\theta}_{21}$ using only IG observations. Green ribbon reflects the normoglycaemic range. The purple observation is an outlier not used in the Bayesian estimation nor prediction. (Top) One-step prediction of PG and 95% prediction band. The dynamics of PG are captured in the prediction and the prediction band covers all but two PG observations. (Bottom) One-step prediction of IG.

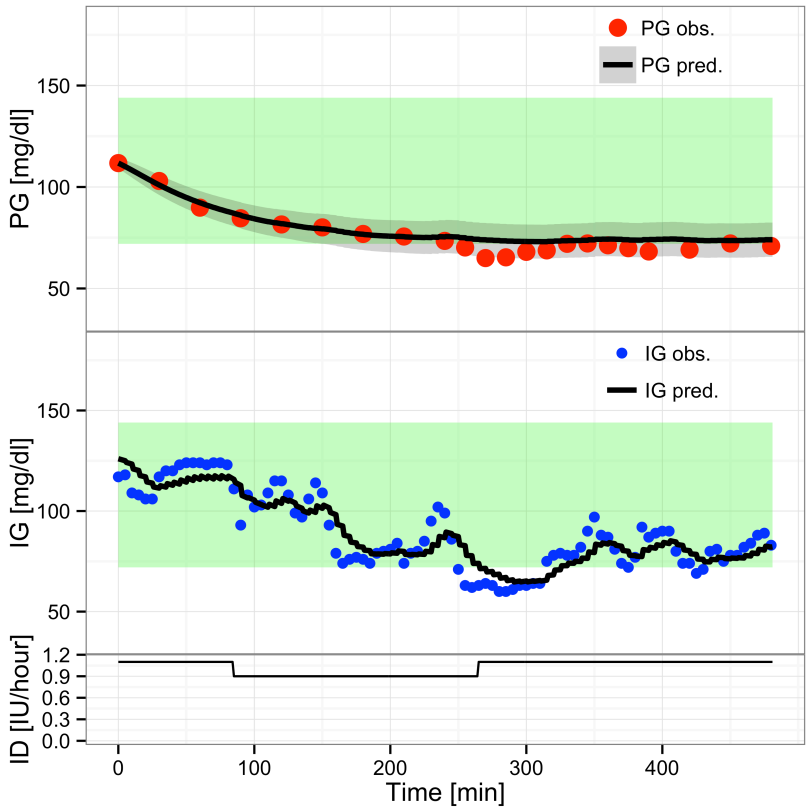

Figure 5: (Overall) Prediction with $\hat{\theta}_{22}$ (open-loop study) using only IG observations. Green ribbon reflects the normoglycaemic range. (Top) One-step prediction of PG and 95% prediction band. Despite the limited dynamics PG is predicted well with all but one PG observations within the 95% prediction band. (Middle) One-step prediction of IG. (Bottom) Insulin delivery per hour.

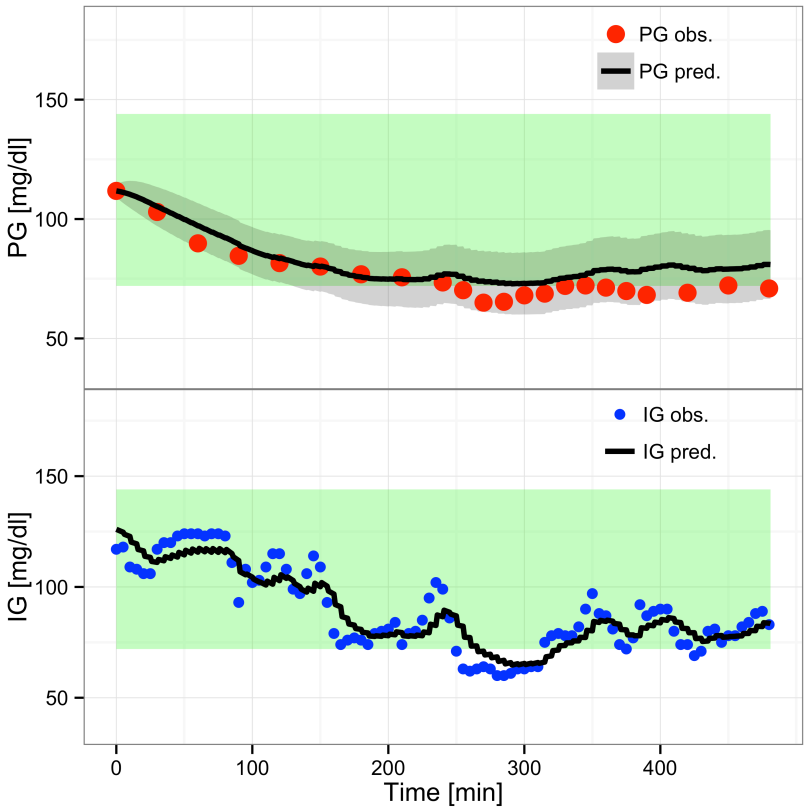

Figure 6: (Overall) Prediction with $\hat{\theta}_{12}$ (open-loop study) using only IG observations. Green ribbon reflects the normoglycaemic range. (Top) One-step prediction of PG and 95% prediction band. Despite the limited dynamics PG is predicted well with all PG observations within the 95% prediction band. (Bottom) One-step prediction of IG.

APPENDIX

$Data_1$	Prior $prior(\theta_{MD})$	Estimate	SD	Correlation table											
Parameters				EGP	GEZI	p2	e_{CGM}	Si	$\sigma_{I_{SC}}$	σ_{G_P}	$\sigma_{G_{SC}}$	e_{INS}	e_{YSI}	τ_1	τ_3
EGP		0.0504*	1.2274	1											
GEZI		0.0000001	exp(66.0415)	-0.0002	1										
p2		0.0098*	1.1878	-0.5797	0.017	1									
S_{CGM}	1.04971[v]	0.4481*	1.0493	0.0033	-0.005	0.000	1								
Si		0.3772*	1.2473	0.9509	-0.008	-0.709	0.003	1							
$\sigma_{I_{SC}}$		0.0012*	1.3123	0.0063	-0.004	0.028	-0.006	-0.004	1						
σ_{G_P}		0.0636*	1.1935	0.1266	-0.020	-0.064	-0.003	0.132	-0.008	1					
$\sigma_{G_{SC}}$		0.1040*	1.1969	-0.0231	0.022	-0.010	0.019	-0.021	0.046	0.006	1				
S_{INS}	20.0855[v]	0.0000*	1.7086	0.0076	-0.009	-0.040	-0.010	0.020	-0.054	-0.019	0.057	1			
S_{YSI}	1.12277[v]	0.0048*	1.1156	-0.0021	-0.033	0.016	-0.011	0.001	0.018	-0.005	0.018	-0.005	1		
τ_1		65.5687*	6.5622	-0.0182	0.026	0.025	-0.006	-0.009	-0.196	-0.005	0.039	0.262	0.032	1	
τ_3		42.6466*	16.6594	0.0500	-0.030	0.016	-0.042	0.047	-0.008	-0.035	-0.337	-0.007	-0.092	0.021	1

* Significant at $\alpha = 0.05$

v The major differences in prior knowledge comes from a transformation to log-scale in CTSM-R where the value of the prior is based on the initial value of the estimation.

Data 2	Prior $prior(\theta_{MD})$	Estimate	SD	Correlation table											
Parameters				EGP	GEZI	p2	e_{CGM}	Si	$\sigma_{I_{SC}}$	σ_{G_P}	$\sigma_{G_{SC}}$	e_{INS}	e_{YSI}	τ_1	τ_3
EGP		0.0392*	1.4112	1											
GEZI		0.0091*	1.6495	0.933	1										
p2		0.0573	5.5701	-0.735	-0.689	1									
S_{CGM}	1.04971[v]	0.0503*	5.9236	0.005	0.005	-0.003	1								
Si		0.4208	1.0458	-0.549	-0.809	0.377	-0.003	1							
$\sigma_{I_{SC}}$		0.0022*	1.2462	-0.003	-0.004	0.001	-0.015	0.005	1						
σ_{G_P}		0.0247*	1.2469	0.157	0.120	-0.121	0.016	-0.024	0.009	1					
$\sigma_{G_{SC}}$		0.0975*	1.2929	-0.005	-0.002	0.000	-0.059	-0.004	-0.027	0.0065	1				
S_{INS}	20.0855[v]	0.0000*	5.7784	0.022	0.021	-0.024	0.022	-0.012	-0.089	0.0231	-0.0149	1			
S_{YSI}	1.12277[v]	0.0047*	1.1186	0.011	0.021	-0.009	0.001	-0.032	-0.065	-0.0772	-0.0137	0.0171	1		
τ_1		54.0378*	13.1240	0.006	0.004	-0.011	-0.015	0.002	0.478	0.0126	-0.0018	0.1154	-0.0360	1	
τ_3		74.2980*	32.9908	-0.006	-0.010	0.018	0.018	0.015	0.011	-0.0330	-0.4300	-0.0319	0.0223	-0.0021	1

* Significant at $\alpha = 0.05$

v The major differences in prior knowledge comes from a transformation to log-scale in CTSM-R where the value of the prior is based on the initial value of the estimation.