Leveraging Artificial Pancreas Technology for Treatment Optimization in T2D

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Leveraging Artificial Pancreas Technology for Treatment Optimization in T2D

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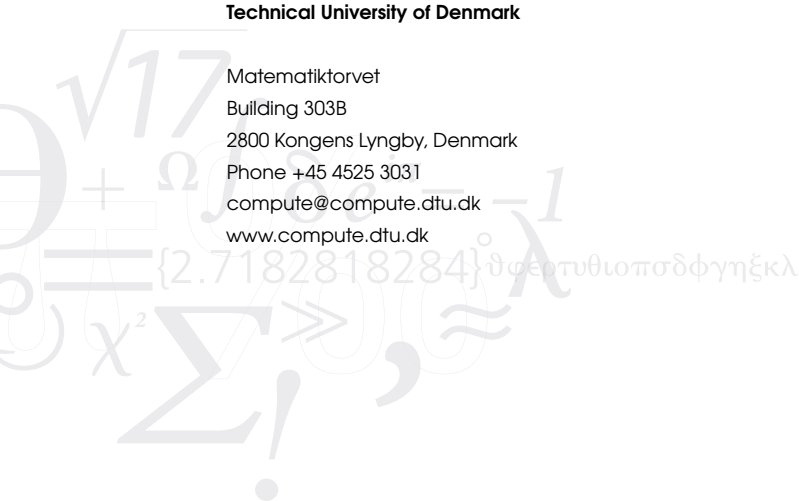

Summary

In type 2 diabetes (T2D), injections with long-acting insulin can become necessary to normalize blood glucose and avoid long-term complications. However, finding a safe and effective insulin dose, a process known as titration, is both challenging and time demanding. In this thesis, we propose a new titration method for swift and safe identification of a personalized insulin dose with long-acting insulin through short-term use of rapid-acting insulin in an artificial pancreas (AP).

We augment a published T2D model to simulate an AP driving the blood glucose into the clinical target range followed by a switch to injections with long-acting insulin. In simulation, the new titration method can reduce the titration period to a single week, compared to five weeks on standard-of-care titration. To explore how to best switch between rapid- and long-acting insulin, we use clinical trial data to assess the correlation between the insulin response to rapid- and long-acting insulin injections in the same individual. In an *in silico* cohort of a hundred people with T2D, we investigate how differences in bioavailability may influence the conversion from rapid-acting insulin delivered in a pump to an equivalent injection dose of long-acting insulin. The cohort simulation reveals that many individuals need more than one week of AP treatment to reach the clinical target range.

As an alternative to letting an AP drive the blood glucose into the target range, we explore how to predict a safe and effective long-acting insulin dose from 24 to 48 hours of AP data. With simulated AP data, we estimate parameters in dose-response models using maximum likelihood estimation (MLE). We apply the continuous-discrete extended Kalman filter (CDEKF) to approximate the likelihood function which is maximized in MLE. To improve the model-based dose predictions, we apply model-based design of experiment (MBDoE) and determine how to best run an AP system to collect data for parameter estimation. Finally, we obtain personalized dose-response models from the experimental data and evaluate their ability to predict a safe and effective insulin dose for each simulated individual.

In simulation, the proposed method is feasible. However, the efficacy and safety of the dose estimates heavily depend on the level of system excitation. The results indicate that MBDoE holds a potential to improve the performance of model-based dose-guidance solutions. Still, without clinical data, it is not possible to conclude on the clinical feasibility of a translating between pump- and pen-based treatment in T2D. In the future, commercial AP systems may enable clinical evaluation of the new titration method.

Summary (Danish)

Mange mennesker med type 2 diabetes (T2D) vil med tiden få behov for insulininjektioner for at normalisere deres blodsukker og undgå sendiabetiske komplikationer. Desværre kan det være en udfordring for den enkelte at finde en sikker og effektiv daglig dosis langtidsvirkende insulin, en proces kaldet titrering. I denne afhandling præsenterer vi en ny titringsmetode. Gennem kortvarig brug af hurtigvirkende insulin i en kunstig bugspytkirtel, vil vi idenficere den enkeltes insulinbehov og oversætte det til en daglig dosis langtidsvirkende insulin.

Vi udvider en publiceret T2D-model for at simulere behandling med en kunstig bugspytkirtel, samt injektioner med langtidsvirkende insulin. I simulation lader vi den kunstige bugspytkirtel styre blodsukkeret ned i det kliniske normalområde, hvorefter vi oversætter pumpens insulin infusion til en daglig dosis langtidsvikende insulin. Sammenlignet med standardbehandling, kan den nye titreringsmetode nedbringe titreringstiden fra fem uger til en enkelt uge. For at identificere den bedste omregning mellem pumpe- og penbehandling, bruger vi kliniske data til at vurdere korrelationen mellem insulinresponset på hurtigvirkende og langtidsvirkende insulin hos det samme individ. I en virtuel kohorte af hundrede mennesker med T2D undersøger vi, hvordan forskelle i insuliners biotilgængelighed kan påvirke oversættelsen fra hurtigvirkende insulininfusion til en tilsvarende injektionsdosis af langtidsvirkende insulin. Kohorte-simulationen viser at mange individer behøver mere end en uges kunstig bugspytkirtelbehandling for at nå det glykæmiske normalområde.

Som et alternativ til at lade den kunstige bugspytskirtel guide blodsukkeret helt ned i normalområdet, udforsker vi, hvordan vi kan forudsige en sikker og effektiv dosis af langtidsvirkende insulin ud fra 24 til 48 timers behandling. Vi estimerer parametre i dosisresponsmodeller ved hjælp af maximum likelihood-estimering (MLE). Vi anvender det kontinuerte-diskrete udvidede Kalman-filter (CDEKF) til at approksimere likelihood-funktionen, som maksimeres i MLE. For at forbedre dosisforudsigelserne anvender vi modelbaseret design af eksperimenter (MBDoE) til at bestemme, hvordan vi bedst doserer og skalerer insulin og måltider for at indsamle data til dosisforudsigelse. Til slut opnår vi personlige dosisresponsmodeller ud fra de eksperimentelle data. Vi evaluerer modellernes evne til at forudsige en sikker og effektiv insulindosis for hver simuleret person.

I simulation virker den foreslåede titreringsmetode, dog afhænger dosisestimaternes kvalitet og sikkerhed kraftigt af niveauet af systemeksitation. Re-

sultaterne indikerer at MBDoE har potentiale til at forbedre modelbaserede doserådgivningsløsninger. Desværre betyder manglen på kliniske data, at det ikke er muligt at konkludere om den simulerede løsning kan virke i praksis. I fremtiden, kan kommercielle kunstig bugspytkirtel systemer muliggøre kliniske tests af denne nye titreringsmetode.

Preface

This Ph.D. thesis was prepared at the Department of Applied Mathematics and Computer Science (DTU Compute) at the Technical University of Denmark in fulfillment of the requirements for acquiring a Ph.D. degree. The research covered in this thesis was performed between August 1st 2020 and October 31st 2023. The project was a collaboration between the Section for Scientific Computing at DTU Compute and the department for Devices and Delivery Solutions at Novo Nordisk A/S.

Professor John Bagterp Jørgensen was the principal supervisor at DTU Compute. At Novo Nordisk A/S, MBA Henrik Bengtsson was the main supervisor, supported by co-supervisors M.D., Ph.D. Amra Ciric Alibegovic and Ph.D. Jeppe Sturis. Part of the research was carried out during an external stay visiting Associate Professor Anders Lyngvi Fougner at the Norwegian University of Science and Technology (NTNU). The project was co-funded by Innovation Fund Denmark (grant no. 0153-00049B) and Novo Nordisk A/S as part of the Industrial Ph.D. program.

This thesis consists of five research papers, two conference abstracts and a short summary report describing the context and contributions of the work.

Kongens Lyngby, October 31, 2023

Sarah Ellinor Engell

List of Publications and Academic Dissemination

Scientific research publications in this thesis

A) **Engell, S. E.**, Aradóttir, T. B., Bengtsson, H., Ekelund, M. and Jørgensen, J. B., 2021, "Glucose response to fast- and long-acting insulin in people with type 2 diabetes" In: *IFAC-PapersOnline*, vol. 54, no. 15, pp. 496–501

B) **Engell, S. E.**, Aradóttir, T. B., Bengtsson, H. and Jørgensen, J. B., 2022, "Correlation in Dose-Response to Rapid- and Long-Acting Insulin for People with Type 1 Diabetes" In: *Proceedings of 44th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 2240–2243

C) **Engell, S. E.**, Aradóttir, T. B., Ritschel, T. K. S., Bengtsson, H. and Jørgensen, J. B., 2022, "Estimating a Personalized Basal Insulin Dose From Short-Term Closed-Loop Data in Type 2 Diabetes" In: *2022 IEEE 61st Conference on Decision and Control (CDC)*, pp. 2580–2585

D) **Engell, S. E.**, Bengtsson, H., Sturis, J., Boiroux, D., and Jørgensen, J. B., 2023, "From Optimal Design of Experiment to Safe System Identification in Type 2 Diabetes" In: *IFAC Proceedings Volumes (2023).* 22nd IFAC World Congress, pp. 10375–10379

E) **Engell, S. E.**, Bengtsson, H., Benam, K. D., Fougner, A. L. and Jørgensen, J. B., 2023, "Optimal Experimental Design to Estimate Insulin Response in Type 2 Diabetes" In: *Proceedings of the 7th IEEE Conference on Control Technology and Applications (CCTA)*, pp. 540–545

Conference abstracts in this thesis

F) Kronborg, T., Hangaard, S., **Engell, S. E.**, Aradóttir, T. B., Bengtsson, H., Hovorka, R., Vestergaard, P., Jensen, M.H. "Short-term usage of a closed-loop insulin delivery system for improving optimization of insulin doses: a trial protocol", In: ATTD 2021 Invited Speakers Abstracts, *Diabetes Technology & Therapeutics.* 23, Suppl. 2, pp. A-195-A-196, June 2021.

G) **Engell, S. E.**, Aradóttir, T. B., Bengtsson, H., Jørgensen, J. B. "Translation from pump to pen in type 2 diabetes: the effect of bioavailability", In: The Official Journal of ATTD Advanced Technologies & Treatments for Diabetes Conference, *Diabetes Technology & Therapeutics*. 24, Suppl. 1, pp. A-118-A-119, April 2022.

Scientific research publications not included in this thesis

I) Krishnamoorthy, D., Boiroux, D., Aradottir, T. B., **Engell, S. E.** and Jørgensen, J. B., 2021, "A Model-free Approach to Automatic Dose Guidance in Long Acting Insulin Treatment of Type 2 Diabetes" In: *IEEE Control Systems Letters*, vol. 5, no. 6, pp. 2030-2035

II) Sejersen, M., Boiroux, D., **Engell, S. E.**, Ritschel, T. K. S., Reenberg, A. T. and Jørgensen, J. B., 2021, "Initial titration for people with type 1 diabetes using an artificial pancreas" In: *IFAC-PapersOnline*, vol. 54, no. 15, pp. 484-489

Conference and workshop presentations

1. Engell, S. E., Aradóttir, T. B., Bengtsson, H., Ekelund, M. and Jørgensen, J. B. (2021, September). *Glucose response to fast- and long-acting insulin in people with type 2 diabetes*. Oral presentation at the 11th IFAC Symposium on Biological and Medical Systems, IFAC BMS 2021. Ghent, Belgium (online).

2. Engell, S. E., Aradóttir, T. B., Bengtsson, H. and Jørgensen, J. B. (2022, March). *Closed-Loop Treatment as a Diagnostic Tool in Type 2 Diabetes*. Oral presentation at the 23rd Nordic Process Control Workshop, NPCW 2022. Luleå, Sweden.

3. Engell, S. E., Aradóttir, T. B., Bengtsson, H., Jørgensen, J. B. (2022, April). *Translation from pump to pen in type 2 diabetes: the effect of bioavailability*. Poster presented at the 15th International Conference on Advanced Technologies & Treatments for Diabetes, ATTD 2022. Barcelona, Spain.

4. Engell, S. E., Aradóttir, T. B., Bengtsson, H. and Jørgensen, J. B. (2022, May). *Short-Term Artificial Pancreas Treatment as a Titration Tool*. Poster presented at the 2nd Nordic BioMathematics Days. Roskilde, Denmark.

5. Engell, S. E., Aradóttir, T. B., Bengtsson, H. and Jørgensen, J. B. (2022, July). *Correlation in Dose-Response to Rapid- and Long-Acting Insulin for People with Type 1 Diabetes*. Poster presented at the 44th International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2022. Glasgow, United Kingdom.

6. Engell, S. E., Aradóttir, T. B., Ritschel, T. K. S., Bengtsson, H. and Jørgensen, J. B. (2022, December). *Estimating a Personalized Basal Insulin Dose From Short-Term Closed-Loop Data in Type 2 Diabetes*. Oral presentation at the 2022 IEEE 61st Conference on Decision and Control, CDC 2022. Cancún, Mexico.

7. Engell, S. E. (2023, June). *From Optimal Experimental Design to Safe Dose Guidance in Type 2 Diabetes*. Oral presentation at the Model Based Design of Experiments Symposium 2023. London, United Kingdom.

8. Engell, S. E., Bengtsson, H., Sturis, J., Boiroux, D., and Jørgensen, J. B. (2023, July) *From Optimal Design of Experiment to Safe System Identification in Type 2 Diabetes*. Oral presentation at the 22nd World Congress of the International Federation of Automatic Control, IFAC WC 2023. Yokohamma, Japan.

9. Engell, S. E., Bengtsson, H. and Jørgensen, J. B. (2023, August). *Safe System Identification through Model-Based Design of Experiment: A Type 2 Diabetes Case Study*. Oral presentation at the 24th Nordic Process Control Workshop, NPCW 2023. Trondheim, Norway.

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Contents

CHAPTER 1

Introduction

1.1 Context and motivation

Type 2 diabetes (T2D) is a growing pandemic with severe consequences for the individual and society [1]. In the long run, poor treatment outcomes lead to complications and a significant socio-economic burden [1, 2]. Several treatment options, tablets, non-insulin injections and insulin exist, but still few people with T2D reach glycemic control [3, 4]. This project aims to help people with T2D reach recommended glycemic targets when using insulin.

1.1.1 Diabetes in numbers

In 2021, 537 million people were living with diabetes worldwide [1]. Of these cases, T2D accounts for approximately 90%. Over the next 25 years, the International Diabetes Foundation estimates that prevalence of diabetes will increase by almost 50% [1]. This adds a substantial cost to national healthcare budgets. Today, the direct cost of diagnosed diabetes accounts for 11.5% of the total global health expenditure [1]. This covers physician visits, hospitalizations, prescription of anti-diabetic drugs, devices, and diabetes supplies. However, the socioeconomic burden of diabetes is even larger [2, 5]. A significant amount of indirect costs stem from lost ability to work, reduced productivity at work and lost productivity due to premature mortality. To reduce the societal and personal costs, the growing numbers call for efficient treatment solutions for people with diabetes.

1.1.2 Glucose-Insulin dynamics

Glycemic control is a key goal in diabetes treatment. In healthy individuals, the body regulates the concentration of glucose in the bloodstream within a relatively narrow range. This regulation involves a complex interaction of various organs, hormones and processes [6].

When glucose levels in the blood increase, e.g. after carbohydrate intake, beta cells in the pancreas secrete insulin, a hormone that facilitates the uptake of glucose from the bloodstream into the cells. The absorbed glucose can supply various cells with energy or be stored in the liver as glycogen or in fat cells as triglycerides [6].

When glucose levels drop, alpha cells in the pancreas release the hormone glucagon, which signals the liver to convert stored glycogen into glucose, rais-

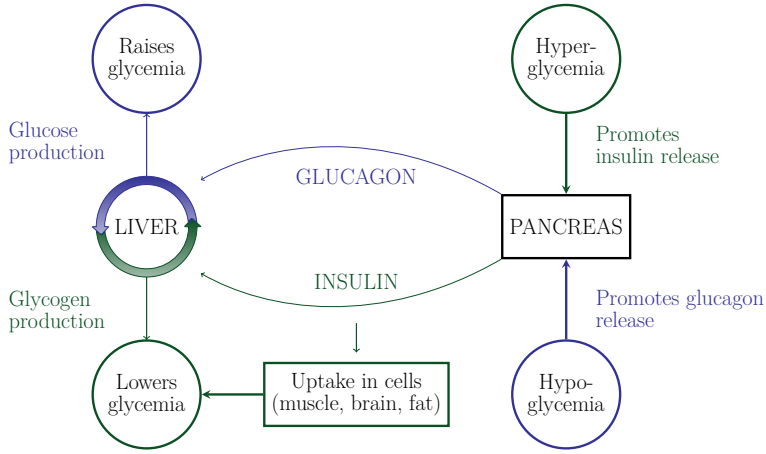


Figure 1.1: The glucoregulatory system in a healthy individual. Illustration adapted from [7].

ing the blood glucose levels [6]. When needed, the liver may produce glucose to cover the basic metabolic requirements, using non-carbohydrate sources. However, this process is not sustainable in the long run as it produces waste products that are toxic in large concentrations.

Managing glucose levels is crucial for overall health as glucose is the primary source of energy for cells, in particular in the brain. If glucose levels drop below 3.9 mmol/L, a condition known as hypoglycemia, it can lead to dizziness, confusion, and, in severe cases, loss of consciousness or even death [6]. Fear of hypoglycemia is common among people with diabetes using insulin, as an overdose induces low blood glucose [8].

High blood glucose levels, known as hyperglycemia, can also cause complications in the long run. Hyperglycemia is characterized as a fasting blood glucose above 7.0 mmol/L, or a glucose level greater than 10.0 mmol/L two hours after the latest food intake [3]. Over time, uncontrolled hyperglycemia can lead to complications such as cardiovascular disease, nerve and kidney damage, blindness and amputations [6, 8]. Long-term complications significantly reduce the quality of life for people living with diabetes, and are a burden on national healthcare budgets [1, 8].

Despite the risk of persistent hyperglycemia, a quick transition into normoglycemia can also cause complications. From a state of chronic hyperglycemia, starting an aggressive treatment regimen may lower glucose levels faster than the body can adapt. In some cases, the treatment itself induces nerve and eye damage [9].

As all forms of diabetes are characterized by elevated plasma glucose concentrations, the treatment goal is to reach and maintain normoglycemia whilst avoiding hypoglycemia. The clinical guidelines recommend to stay within the 3.9 mmol/L to 10.0 mmol/L target range [3, 10].

1.1.3 Diabetes treatment

Different types of diabetes exist and the treatment requirements depend on the underlying pathophysiology. In type 1 diabetes (T1D), an autoimmune response eliminates the beta cells in the pancreas, leaving the body unable to produce insulin and control glycemic levels. To survive, people with T1D need life-long insulin therapy [3].

In T2D, elevated glucose levels occur, initially, when the body's cells fail to respond adequately to insulin [1]. This condition is referred to as insulin resistance or reduced insulin sensitivity. Over time, insulin resistance prompts an increase in insulin production. However, the insulin production is insufficient to meet metabolic requirements. At the onset of T2D, life-style changes, oral treatment, and non-insulin injections can improve insulin sensitivity and lower glycemic levels into the clinical target range [3]. In late-stage T2D, insulin production may drop as the excessive demand on the pancreatic beta cells leads to cell failure. Gradually, insulin injections can become necessary to sufficiently lower glycemic levels if non-insulin medications fail to achieve glycemic control [3, 8].

Typically, a daily dose of long-acting insulin is the first step when initiating insulin treatment [3]. Long-acting insulin, also known as basal insulin, lowers the fasting glucose level. If necessary, injections of rapid-acting insulin can be added later to cover glucose excursions after meals [3]. The initiation of basal insulin treatment, a process known as titration, is complex and time-consuming. As insulin is a potent drug and the insulin dose-response varies greatly between individuals, the initial dose is often conservative. When initiating basal insulin treatment, the American Diabetes Association (ADA) recommends 10 units per day or 0.1-0.2 units/kg per day [3]. After treatment initiation, the individual with T2D monitors their fasting blood glucose (FBG) values through pre-breakfast finger-prick measurements. Based on the FBG measurements, simple paper-based algorithms guide the insulin dose adjustments until the clinically recommended fasting blood glucose target is met. Table 1.1 shows an example of a titration algorithm.

Insulin titration primarily takes place at home without monitoring from a health care provider (HCP). Short clinic visits occur every few months, but the time available for dosage consulting is usually only a fraction of the

Table 1.1: The 2-0-2 titration algorithm for long-acting insulin. Dose adjustments happen once- or twice-weekly. Adjustments are based on the lowest FBG value below target, or an average of the FBG values from the past three days.

FBG [mmol/L]	Dose Adjustment [U]
> 7.2	$+2$
$4.4 - 7.2$	No change
< 4.4	-2

visit time. This setup places a significant responsibility and burden on the individual with diabetes. Lack of confidence in the treatment, a demanding titration task, and the fear of hypoglycemia may lead to omitted injections and limited dose escalations [4]. Consequently, less than 40% of people with T2D on insulin treatment reach glycemic targets [4, 11]. Failure to meet glycemic targets within the first three months of titration is linked to an increased risk of failed insulin titration two years after treatment initiation [4]. For this reason, dose guidance support in the initial phases of titration holds a potential to improve treatment outcomes in the long run. Research indicates that people with T2D prefer simple and easy-to-use titration solutions and fewer in-person visits [12]. Thus, adoptable solutions must cater to these needs, whilst supporting the titration process.

1.1.4 Diabetes technology and digital health

Technology is playing a growing part in the management of diabetes [13, 14, 15]. In the past two decades, sensors, wearables, connected devices, apps, dose guidance algorithms and artificial pancreases have become commercially available, enabling a more personalized care. Given the many options, the use of technology can be individualized based on a person's needs, desires, skill level, and availability of devices.

The use of continuous glucose monitors (CGMs) is increasing in the T2D population [16]. CGMs measure the interstitial glucose levels continuously through a small sensor inserted into the tissue just below the skin [14]. The measurements are transmitted every five minutes to a receiver or a smartphone, where the user can see a graphical representation of their data. Sensor use leads to improved glucose control as it enables real-time diabetes management decisions. In addition, the data stream facilitates more detailed discussions with the HCP compared to self-logged FBG values. In recent years, the CGM-based metric Time in Range (TIR) has become part of the glycemic control assessment [3, 10]. TIR quantifies the proportion of time spent within the clinical target glucose range, usually 3.9-10 mmol/L, and studies show a correlation between increased TIR and a reduction in long-term complications [17, 18]. If a consensus on CGM and long-term cost-effectiveness is reached, it may lead to a more widespread CGM-use despite the high sensor cost compared to traditional finger-pricking [13].

Similar to CGM data, the introduction of connected insulin pens can create a detailed overview of diabetes management. Inadequate record-keeping of insulin doses represents a significant obstacle to optimizing glycemic control for individuals using insulin pens [13]. Connected insulin pens log the dose size and timing of insulin injections. The data can be displayed together with CGM curves to better understand how dosing decisions affect glycemic control.

The artificial pancreas (AP) offers another way of administering insulin. An AP is a closed-loop system that consists of 1) a CGM to measure the

glucose concentration every five minutes, 2) a control algorithm that based on the CGM measurements computes a dose of rapid-acting insulin to reach glycemic targets, and 3) an insulin pump that infuses the computed insulin dose. In recent years, automated insulin delivery with an AP system has become commercially available to people with T1D [19], and clinical studies indicate the potential of extending AP treatment to people with late stage T2D [20, 21]. Today, a notable minority of people with T2D are using patch pumps as they are simple and easy to use [22]. In coming years, patch pumps with a closed-loop algorithm may offer an automated alternative to daily insulin injections in T2D. Insulet is running trials in a T2D population with a system of this type [20]. Once on the market, the adoption and distribution of such systems will depend heavily on their long-term cost-effectiveness and ease of use [21].

The technology development in recent years has fueled a strong interest in integrating new data sources into health apps designed for diabetes care [15]. A meta-analysis on mobile apps for diabetes found a statistically significant improvement in glycemic control among participants using mobile apps compared to those in the control group [23]. Some of these apps offer dose guidance. For insulin titration, dose-guidance algorithms have been tested in simulation [24, 25], in clinical trials [26, 27], and under free-living conditions [28]. To provide decision support, these algorithms incorporate FBG measurements or CGM data in combination with manual or automatic dose logs of insulin injections. Inspired by this approach, we explore how to leverage new data sources, i.e. data from AP systems, to provide titration guidance to people with T2D and their caregivers.

1.2 Thesis objective

Today, AP systems are an expensive treatment option, and distributing these devices to a growing T2D population may not be economically viable. Compared to AP systems, injection pen-based treatment is a cheaper solution. However, the emergence of AP technology may enable new titration concepts for pen-based insulin treatment. To leverage AP technology at a limited cost increase, we propose short-term use of an AP system to automate insulin titration, improving injection-based treatment outcomes.

In this work, we assess the feasibility of the Dose Finder titration concept, a dose guidance tool for insulin titration in T2D. The Dose Finder consists of an AP system and a conversion algorithm to translate rapid-acting insulin infused by an insulin pump to a daily injection of long-acting insulin. Figure 1.2 visualizes the Dose Finder concept. In a limited period, the insulin pump infuses rapid-acting insulin based on measurements from a CGM. Over time, the control algorithm drives the fasting blood glucose into the clinical target range. Once in target, we convert the infusion rate of rapid-acting insulin to a daily injection of long-acting insulin.

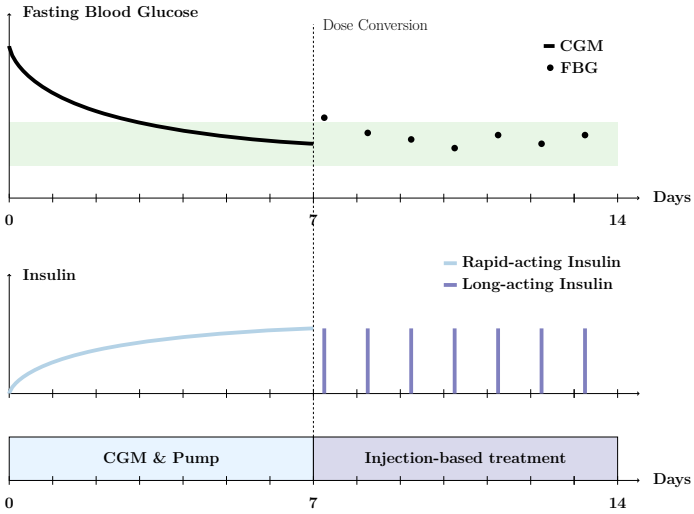


Figure 1.2: The Dose Finder titration concept.

1.2.1 Research questions

To assess the technical feasibility of the Dose Finder, we aim to answer the following research questions:

Research Question 1: To what extent can we use dose-response models to predict outcomes of changed drug and/or regimen?

We test the Dose Finder concept in a mathematical simulation. We augment a published T2D model to enable the simulation of virtual people with T2D who undergo artificial pancreas treatment and subsequently receive injections of long-acting insulin. A clinical trial was planned to assess the validity of the simulation results.

Research Question 2: What is the correlation between a profile of rapid-acting insulin delivered in closed-loop treatment, and the amount of long-acting insulin needed with an injection pen?

As closed-loop data is not readily available for a T2D population, we investigate different factors that may influence the translation from rapid- to long-acting insulin injections. We use clinical data from a dose-response study in 25 people with T1D to assess the correlation between the dose-response to rapid- and long-acting insulin. Additionally, in a simulation study, we explore how differences in drug bioavailability can influence the conversion from rapid- to long-acting insulin.

Research Question 3: Can we predict a suitable dose for injection-based therapy from fully closed-loop data?

Based on 24 to 48 hours of simulated closed-loop data, we examine whether we can predict an individualized, safe and effective dose of long-acting insulin. To improve dose-estimates, we apply model-based experimental design (MBDoE) to determine the optimal meal intake and the insulin infusion profile during closed-loop treatment. Finally, we explore how to improve experimental safety within the MBDoE-framework.

1.3 Thesis structure

In the following chapters, we aim to answer the three research questions through a summary of the publications in Appendix A to G:

Chapter 2:

We explore how mathematical models can guide new ways of dosing insulin and present a simulation model from **Appendix A**. We address **Research Question 1** and show how the Dose Finder concept works in the simulation model. From **Appendix F**, we present a clinical trial protocol to outline the data which could have facilitated a clinical feasibility assessment.

Chapter 3:

To address **Research Question 2**, we investigate whether a correlation exists between rapid- and long-acting insulin injections in a T1D data set (**Appendix B**). To further assess how a change in insulin analogue may affect the dose-response, we simulate how differences in bioavailability can influence the treatment efficacy after a pump-to-pen switch (**Appendix G**). Finally, to address **Research Question 3**, we look into how fully-closed loop data may be used to predict a safe and effective dose of long-acting insulin for people with T2D (**Appendix C**).

Chapter 4:

We address **Research Question 3** and investigate how experimental design can improve dose predictions for injection-based insulin therapy. We use a Model-Based Design of Experiment (MBDoE) framework to design experimental protocols and collect informative data during short-term closed-loop treatment (**Appendix E**). As safety is critical in clinical applications, we explore how to improve the safety of the MBDoE approach (**Appendix D**).

Chapter 5:

We summarize the results of the project and present future perspectives of the findings in this work.

CHAPTER 2

Insulin Dose Response

In this chapter, we include work from Appendix A and F. We explore how mathematical models can guide new ways of dosing insulin. In a review of physiological models of people with T2D, we select a simulation model and extend it to simulate titration with an AP. We address the first research question and present how a Dose Finder solution could work in simulation. Finally, we present a clinical trial protocol to outline the clinical data which could have facilitated an assessment of the simulated results.

2.1 Physiological models

Physiological models are powerful tools for advancing diabetes treatment. Simulation studies, known as *in silico* or virtual trials, can help drive drug development and support treatment optimization in a time- and cost-effective manner [29]. A virtual trial population consists of a mathematical model with which we express a cohort of *in silico* subjects spanning the variability of a population. Simulation studies can test a large variety of scenarios which may be difficult, unsafe or unethical to conduct in a real trial population. Such virtual trials can for specific insulin treatments, including closed-loop algorithms, serve as a substitute for pre-clinical trials. In 2008, the U.S. Food and Drug Administration (FDA) accepted a T1D simulator for this purpose [30].

Physiological models are more than just simulation tools. Part of the diabetes modeling efforts aims to create and parameterize prediction models for model-based control algorithms in AP systems [31, 32]. As the AP community in particular has catered to people with T1D, many simulation and prediction models describe this population. However, as T2D accounts for 90% of the global population with diabetes, published models have over the years been extended to cover T2D populations as well [33, 34].

2.1.1 T2D model overview

In this work, we test insulin dose guidance algorithms for people with T2D in simulation studies. To select a suitable T2D simulator and a dose-response model for predictions, we review published models and their T2D adaptations and extensions.

Since the 1960s, mathematical models have described the glucose–insulin dynamics in man [35]. One of the early models, Bergman's minimal model, is the foundation of many physiological models in use today. In three compartments, Bergman et al. describe the metabolic effects of insulin on glucose in healthy and obese individuals [36]. The model provides a framework to quantify insulin sensitivity, a physiological parameter which cannot be assessed directly, from data. The original model compartments describe the glucose concentration in plasma, the insulin effect, and the insulin secretion. T1D adaptations of the model exclude the insulin secretion. Bergman's minimal model is highly simplified to enable parameter identification. However, the excessive minimalism has also led to criticism. One major point of concern is that negative (or zero) estimates of the insulin sensitivity index are not uncommon when fitting data to the model [29]. The model has been used to assess insulin sensitivity in clinics, but is not an ideal simulator due to its simplicity.

The glucose-insulin kinetics of the minimal model serve as the core of the Medtronic Virtual Patient (MVP) model [31]. Originally, the MVP model was designed for individuals with T1D using rapid-acting insulin in pump therapy. Its structure includes meal and insulin absorption compartments. The model has undergone augmentation by Aradóttir et al. to incorporate endogenous insulin secretion and long-acting insulin, thereby enabling simulations of T2D populations undergoing basal insulin therapy [33, 37]. Aradóttir et al. validate their model on fasting glucose measurements. As a result, the model is not fit for simulations involving meals, but may still be well-suited as a dose-response model for prediction of basal insulin need.

In 1985, Sørensen presented a simulation model to describe the glucose-insulin dynamics in healthy individuals [38]. Vahidi et al. adapted the Sørensen model to reflect a T2D population by including a relative deficiency in insulin production, an impaired hepatic regulation of glucose, and a low peripheral glucose uptake [34]. Later, the model came to include the incretin effect in connection with meals [39]. Subsequently, the model extensions by Eftekhari et al. [40] and Al Ahdab et al. [41] added several anti-diabetic drug-responses, as well as the gluco-regulatory response to physical activity and stress. Although the T2D extensions of the Sørensen model offer a framework for many different treatment simulations, only the mean set of model parameters is available. This limits the use of the model as a simulator as the distributions to span a full trial cohort are not published.

In diabetes research, the UVA-Padova simulator offers a test-bed for insulin dosing algorithms [30]. The foundation of the FDA-approved T1D simulator derives from a T2D model structure developed by Dalla Man et al.[42]. In its latest model extension, the T2D model consists of 15 differential equations and 39 parameters, complete with their associated distributions, to reproduce the main glucose fluxes in a T2D population [43]. The model is limited to simulate single-meal scenarios as it does not include intrapatient variations over time.

Another model that offers parameter distributions is the integrated glucose-insulin (IGI) model [44]. In all extensions, population parameter estimation methods quantify inter-individual variability in the model parameters. The IGI model therefore offers a potential basis for realistic simulations of clinical studies. The original glucose homeostasis model by Jauslin et al. describes people with T2D and healthy individuals. The model has multiple extensions to cover circadian rhythms [45], glucagon kinetics [46], the effect of various anti-diabetic drugs [47, 48], and gastric emptying [49].

A model's level of complexity should align with its application. The simpler models enable the identification of parameters for personalized dose predictions, whilst more extensive models can support simulations of virtual clinical trials in a cohort. In this work, we utilize Bergman's Minimal Model for estimating insulin sensitivity, Aradóttir's MVP model for predicting dose-response, and the IGI model for simulating a T2D population.

2.1.2 Integrated Glucose-Insulin model

We use the Integrated Glucose-Insulin (IGI) model for simulation as it covers different elements of T2D pathophysiology. In addition to compartments to represent glucose-insulin kinetics and oral glucose absorption, the model includes delays in glucose and insulin signals to affect the glucose clearance and

Table 2.1: Type 2 Diabetes models

Base Model	**Type**	**T2D Extensions**
Sørensen (1985) [38]	Healthy	Relative deficiency in insulin production, impaired hepatic gluco-regulatory effect, and low peripheral glucose uptake [34]
		Meal absorption and incretin effect [39]
		Metformin and vildagliptin drug response [40]
		Multiple meal model, insulin injections, multiple metformin doses, and the effect of physical activity and stress [41]
Dalla Man (2007) [42]	T2D & healthy	Full population parameter set [43]
Jauslin (2007) [44]	T2D & healthy	Circadian rhythms [45]
		Glucagon-insulin-glucose kinetics [46]
		Biphasic insulin injections [47]
		GLP-1 agonist dose-response [50]
		Gastric emptying and glucose absorption [49]
Kanderian (2009) [31]	T1D	Endogenous insulin production from Ruan (2015), and basal insulin injections [33]
		Model reduction to improve identifiability [37]

production. Simple mechanisms describe insulin secretion and its increase after meal intake, known as the incretin effect. To simulate AP treatment and injections with long-acting insulin, we augment the model with insulin absorption models for rapid- and long-acting insulin and a compartment for subcutaneous glucose concentration. Figure 2.1 shows the updated model structure.

2.1.2.1 Extensions to the IGI model

An extension from Røge et al. includes the dose-response to biphasic insulin injections, an insulin analogue combining the dynamics of rapid- and long-acting insulin [47]. However, we wish to simulate the response to both rapid-acting insulin infusion and long-acting insulin injections. To enable this, we augment the IGI model structure with an insulin absorption model from Hovorka et al. [32]. For each of the insulin analogues, we include two absorption compartments to describe how insulin moves from the subcutaneous tissue to plasma,

$$\dot{S}_{1,ia}(t) = u_{ia}(t) - \frac{1}{\tau_{ia}} S_{1,ia}(t), \tag{2.1a}$$

$$\dot{S}_{2,ia}(t) = \frac{1}{\tau_{ia}} S_{1,ia}(t) - \frac{1}{\tau_{ia}} S_{2,ia}(t), \tag{2.1b}$$

where a time constant, τ_{ia}, determines the speed with which each insulin analogue, $u_{ia}(t)$, enters the body. To describe the distribution of exogenous insulin in the body after absorption, we include a compartment with first-order elimination from Hovorka et al.,

$$\dot{I}_{exo}(t) = \left(\frac{1}{\tau_R} S_{2,R}(t) + \frac{1}{\tau_L} S_{2,L}(t) \right) - k_{exo} I_{exo}(t), \tag{2.2}$$

where k_{exo} is the clearance of the exogenous insulin. We add the exogenous insulin to the the insulin effect equation in the IGI model,

$$\dot{I}_E(t) = \frac{k_{IE}}{V_I} \left(I(t) + c_f \cdot I_{exo}(t) \right) - k_{IE} I_E(t), \tag{2.3}$$

where c_f is a conversion factor to change the units of insulin amount from unit to pmol [52]. To simulate CGM measurements, we include a subcutaneous glucose compartment from [53],

$$\dot{G}_{sc}(t) = \frac{1}{\tau_{sc}} \left(\frac{G_c(t)}{V_G} - G_{sc}(t) \right). \tag{2.4}$$

The time constant τ_{sc} is the time it takes before a rise in the plasma glucose can be detected in the interstitial fluid. The IGI definition of the plasma glucose concentration is the amount of glucose in the central compartment divided by the glucose distribution volume V_G.

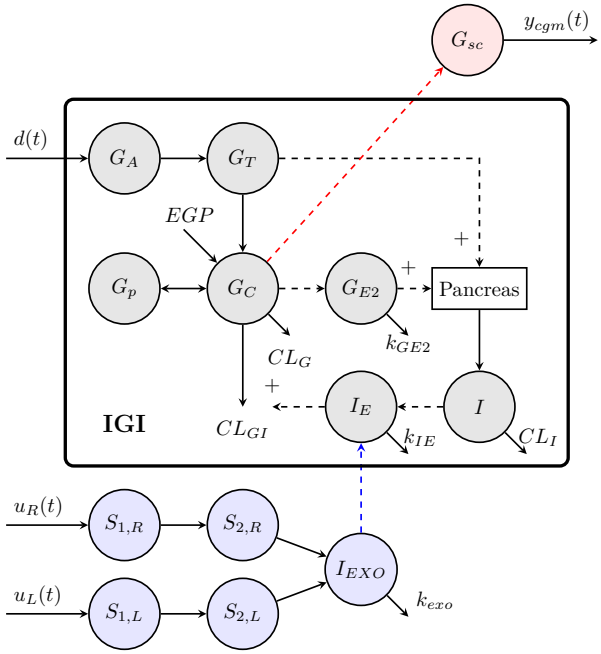


Figure 2.1: Model structure for the augmented IGI model adapted from [51]. The original model compartments have been augmented with absorption models for rapid- and long-acting insulin (blue) and a compartment for subcutaneous glucose concentration (red).

With the augmentations, we obtain a 13-compartment simulation model with the following compartments,

$$
\mathrm{x} = \begin{bmatrix} G_A \\ G_T \\ G_c \\ G_p \\ G_{E2} \\ I \\ I_E \\ S_{1,R} \\ S_{2,R} \\ S_{1,L} \\ S_{2,L} \\ I_{exo} \\ G_{sc} \end{bmatrix}
\begin{array}{ll} \text{mg} & \text{Meal intake - Glucose absorption} \\ \text{mg} & \text{Meal intake - Glucose transport} \\ \text{mmol} & \text{Glucose in plasma} \\ \text{mmol} & \text{Glucose in peripheral compartment} \\ \text{mmol/L} & \text{Glucose effect on insulin secretion} \\ \text{pmol} & \text{Insulin in plasma} \\ \text{pmol/L} & \text{Insulin effect} \\ \text{U} & \text{Rapid-acting insulin absorption} \\ \text{U} & \text{Rapid-acting insulin absorption} \\ \text{U} & \text{Long-acting insulin absorption} \\ \text{U} & \text{Long-acting insulin absorption} \\ \text{U} & \text{Exogenous insulin} \\ \text{mmol/L} & \text{Subcutaneous glucose concentration} \end{array}
$$

The model inputs are the infusion of rapid-acting insulin, $u_R(t)$ [U/min],

the injection of long-acting insulin, $u_L(t)$ [U/min], and the carbohydrate uptake through meals, $d(t)$ [mg/min].

2.2 The Dose Finder in simulation

With the augmented IGI model, we simulate an individual with T2D using a Dose Finder titration concept to identify a safe and effective daily dose of long-acting insulin [51]. To compare the new titration method to standard of care titration, we simulate the outcomes when the same individual titrates long-acting insulin with a simple 2-0-2 algorithm.

2.2.1 Simulation setup and controller

To simulate an individual with T2D, we apply the parameters from Table 2.2. We simulate three daily meals. Details regarding the simulation setup are listed in [51]. The purpose of the simulation study is not to showcase an advanced control algorithm, but rather to demonstrate how an AP may replace traditional titration. Therefore, we employ a simple integrator to determine the rapid-acting insulin infusion, u_R, in the fasting state based on CGM measurements, y_{cgm},

$$v(k) = v(k-1) + K_i \cdot (y_{ref} - y_{cgm}(k)) \cdot T_s, \tag{2.5a}$$

$$u_R(k) = \max(v(k), 0), \tag{2.5b}$$

where $y_{ref} = 5.8$ mmol/L is the desired glucose concentration. K_i is the controller gain, k is the sample number, and T_s is the sample time. We initialize the integrator with $v(0) = 0$. To ensure physiologically feasible insulin amounts, we constrain u_R to non-negative values. The controller receives meal announcements to avoid changes in the insulin infusion rate after meals. When a meal is announced at sample k_m, the controller switches off for 5.5 hours and the infusion rate is fixed to the value $u_R(k_m)$.

2.2.2 Dose conversion

To get a daily dose, we calculate the total insulin delivered over 24 hours,

$$u_L[\text{U/day}] = \frac{24[\text{h/day}] \cdot 60[\text{min/h}] \cdot u_R[\text{U/sample}]}{T_s[\text{min/sample}]}. \tag{2.6}$$

2.2.3 The Dose Finder vs. standard of care

The virtual individual spends one week on AP treatment, where a control algorithm slowly increases the insulin infusion rate and drives the glucose into the target range. After one week, we convert the insulin infusion rate of

Table 2.2: Model parameters for the augmented IGI model.

M_{wG}	180.1559	[g/mol]	Molar weight of glucose
c_f	6000	[pmol/U]	Insulin unit conversion factor
A_G	0.8	unitless	CHO bioavailability
k_a	0.0214	[1/min]	CHO absorption constant
V_G	9.33	[L]	Distribution volume for central glucose compartment
V_p	8.56	[L]	Distribution volume for peripheral glucose
Q	0.442	[L/min]	Intercompartmental clearance of glucose
CL_G	0.0287	[L/min]	Insulin-independent glucose clearance
CL_{GI}	0.000355	[L/min/(pmol/L)]	Insulin-dependent glucose clearance
G_{ss}	5.93	[mmol/L]	Baseline glucose concentration
$IPRG$	1.42	unitless	Control parameter for glucose effect on insulin secretion
E_{max}	0.590	unitless	Maximal effect of G_T on the insulin secretion
ED_{50}	38.2	[mg]	Glucose amount in G_T resulting in half of E_{max}
I_{ss}	24.2	[pmol/L]	Insulin concentration at steady state
CL_I	1.22	[L/min]	Endogenous insulin clearance
V_I	6.09	[L]	Distribution volume for insulin
k_{GE2}	0.0289	[1/min]	Rate constant of glucose effect compartment
k_{IE}	0.0213	[1/min]	Rate constant of insulin effect compartment
EGP	$8.2 \cdot 10^{-3}$·BW	[mmol/min]	Endogenous glucose production
BW	70	[kg]	Body weight
τ_{sc}	10	[min]	Time delay to subcutaneous glucose
$k_{I,R}$	55	[min]	Rate constant for rapid-acting insulin absorption
$k_{I,L}$	720	[min]	Rate constant for long-acting insulin absorption
k_{exo}	0.138	[1/min]	Exogenous insulin clearance

the pump, unit-to-unit, to a daily injection of long-acting insulin. To limit a rise in glycemia in the transition phase, we keep the AP running for two hours after the first injection of long-acting insulin. Figure 2.2 shows the results.

During AP treatment, the fasting blood glucose drops safely from 12 mmol/L to 6 mmol/L. In this period, all measured glucose concentrations are above or within the target range. In the transition from pump- to pen-based treatment, the fasting blood glucose rises above 7.2 mmol/L but later settles back into the target range after three days of pen-based treatment. The results show how a AP system may simplify titration. However, the transition-phase between pump and pen-based treatment can be optimized to reduce the loss of glycemic control on the first day of injection-based treatment.

In Figure 2.3, we compare the outcomes for the Dose Finder (DF) method to standard of care titration with the 2-0-2 algorithm, and to continued AP treatment. With the 2-0-2 algorithm, the dose converges after five weeks. Using a Dose Finder solution reduces the titration period to a single week. Continued AP treatment drives the fasting blood glucose to a lower value within the target range. This simulation represents an ideal scenario where the individual with T2D is adherent and the measurements are not corrupted by noise. In the real world, titration periods may extend significantly due to physiological variation, missed injections and misunderstood guidelines. Hence, the potential to improve titration speed may be even greater than shown in the simulation. In this simple AP system, unannounced meals and

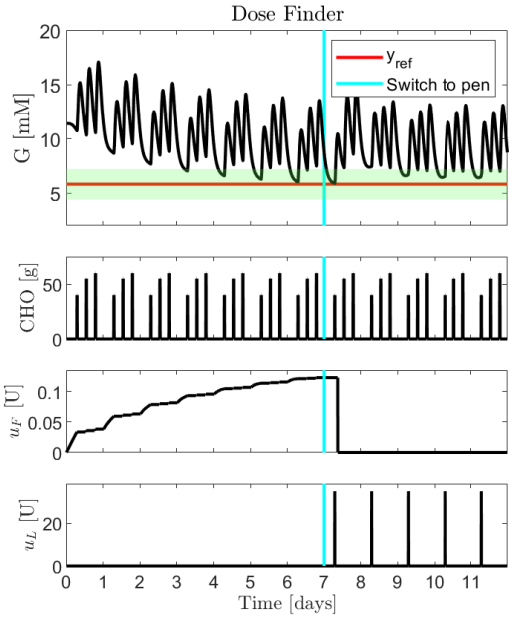


Figure 2.2: The top-to-bottom panels display the glucose concentration, meal intake, infusion rapid-acting insulin, and injections of long-acting insulin. Throughout the initial week, the artificial pancreas dynamically adjusts the insulin infusion rate during fasting periods to reach $y_{ref} = 5.8$ mmol/L. At the start of the second week, we convert the infusion rate, unit-to-unit, into a daily, long-acting insulin dose administered before breakfast. To smooth the transition from pump to pen-based treatment, insulin infusion persists for two hours after the initial pen-injection. The green area marks the clinical target range of 4.4-7.2 mmol/L. Figure adapted from [51].

sensor noise may affect safety. However, the simulation is purely meant to serve as a conceptual visualization. In the following chapters, we shed light on different aspects and challenges to consider in the development of a Dose Finder solution.

2.3 The clinical trial

A clinical trial was part of the original project scope to support the Dose Finder feasibility assessment with clinical data [54]. We present the preliminary trial protocol to outline the data set meant to facilitate a clinical feasibility assessment.

The aim of the study was to investigate whether short-term usage of

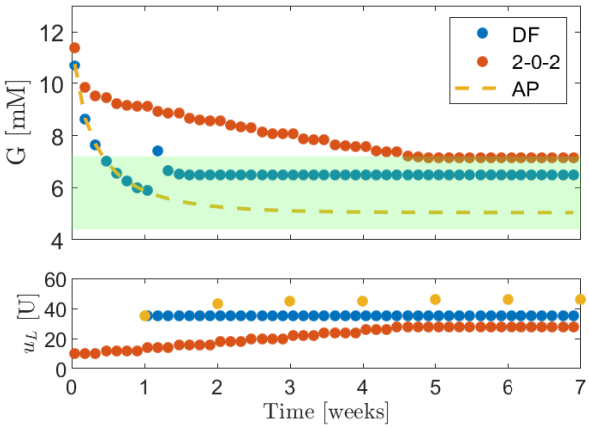


Figure 2.3: Titration with the Dose Finder (DF), the 2-0-2 algorithm and the implemented artificial pancreas (AP). The top panel depicts daily FBG values for the DF and the 2-0-2 titration. For the AP, the plot displays a pre-breakfast CGM measurement. The lower panel shows the daily dose of long-acting insulin for the DF and the 2-0-2 titratation. For the AP, the plot shows a weekly unit-to-unit conversion of the rapid-acting insulin delivered by the AP. Figure adapted from [51].

an AP system could improve optimization of insulin doses under free living conditions. The proposed design was a randomized, parallel-arm study with 32 basal-only or multiple-daily-injections-treated patients with T2D. Figure 2.4 illustrates the preliminary trial design. To have a measurement

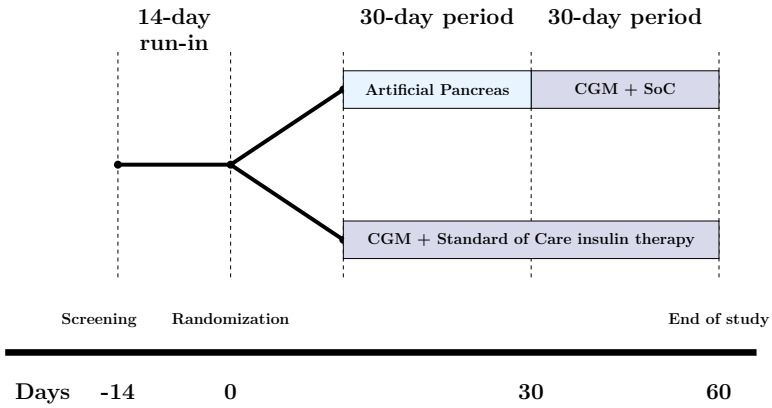


Figure 2.4: Schematic diagram depicting the Dose Finder trial design. Illustration adapted from [54].

for time-in-range at baseline, the participants would have a 2-week run-in period continuing their current insulin therapy whilst wearing a CGM. After two weeks, the participants would then be randomized 1:1 into an AP or a standard insulin therapy arm. In the AP arm, participants would use an AP system for 30 days. Afterwards, the participants would transition to standard insulin therapy for 30 days whilst wearing a CGM. In this period, insulin doses would be optimized every 5–7 days. In the standard insulin therapy arm, participants would continue their current therapy while wearing a CGM for 60 days. Here as well, insulin doses would be optimized every 5–7 days. The primary outcome of the study was to assess the efficacy of an AP system in maintaining CGM glucose levels within the target range from 3.9 to 10.0 mmol/L compared to standard insulin therapy. The secondary outcome was to develop a translation algorithm between rapid-acting insulin delivered in an insulin pump and long-acting insulin injections.

Through this study, we aimed to determine whether a closed-loop system could lead to improved glycemic control and provide insights for tailoring insulin dose selection for individuals. In T2D, the use of closed-loop systems is still novel and at the initiation of this project, no systems were available on the market for this population. As a result, it was a challenge to run the study under free living conditions. No other existing data sets could directly support the assessment of a Dose Finder solution. In the future, data sets with both pen-based treatment, CGM and closed-loop data may appear when AP systems become commercially available to people with T2D.

2.4 Summary

Mathematical models are valuable tools when assessing physiological responses in diabetes. To simulate the Dose Finder, a novel way of titrating long-acting insulin with an AP, we extend an existing simulation model with compartments for exogenous insulin absorption and subcutaneous glucose concentration. In simulation, one week of AP treatment can drive the fasting glucose concentration into the glycemic target range with continuous infusion of rapid-acting insulin. After one week, unit-to-unit conversion of the AP's insulin infusion rate results in a safe and effective daily injection of long-acting insulin. In simulation, the Dose Finder solution can reduce the time-to-target to a single week, compared to five titration weeks with the current standard of care. The extent to which these simulations represent clinical reality remains unknown. A clinical feasibility assessment is currently not possible with existing data sources. In the future, access to commercial AP systems may enable testing the titration solution in clinics.

CHAPTER 3

Correlation and Dose Prediction

In this chapter, we present work from Appendix B, C and G, addressing the second and third research question. To assess the feasibility of a switch between AP- and pen-based insulin therapy, we investigate whether a correlation exists between rapid- and long-acting insulin. To further explore the feasibility of a unit-to-unit dose conversion, we simulate how differences in bioavailability can influence the treatment efficacy after a pump-to-pen switch. Finally, we look into how fully-closed loop data from an AP may be used to predict a safe and effective dose of long-acting insulin for people with T2D.

3.1 Parameter estimation

In this work, we use estimates of model parameters to assess correlation in dose-response [55] and predict personalized insulin doses [56, 57, 58]. We apply maximum likelihood estimation (MLE) to estimate parameters in physiological models. In the following section, we briefly present how we apply continuous-discrete system models and the continuous-discrete extended Kalman filter (CDEKF) to express and maximize the likelihood function.

3.1.1 Continuous-discrete models

We describe the glucoregulatory system as a continuous, stochastic process with noise-corrupted discrete sensor measurements,

$$dx(t) = f(t, x(t), u(t), d(t), \theta)dt + \sigma d\omega(t), \tag{3.1a}$$

$$y_k = h(t_k, x(t_k)) + v_k, \tag{3.1b}$$

where $f(\cdot)$ is a drift function and $h(\cdot)$ is a discrete measurement function. $x(t)$ represents the state vector, $u(t)$ is the input vector for insulin, $d(t)$ is the meal input, and θ denotes the model parameters.The process noise, $\{\omega(t), t \geq 0\}$, is a standard Wiener process and its increment has covariance Idt. $\omega(t)$ is scaled using a time-invariant diagonal matrix, σ, which introduces noise to the system. We assume that the measurement noise associated with y_k follows a normal distribution, represented as $v_k \sim N_{iid}(0, R_k)$.

3.1.2 Maximum Likelihood Estimation

From a discrete series of measurements,

$$\mathcal{Y}_N = \{y_0, y_1, ..., y_N\}, \tag{3.2}$$

we estimate the parameter set, θ, that maximizes the conditional probability,

$$p(\mathcal{Y}_N|\theta) = p(y_N, y_{N-1}, ..., y_0|\theta), \tag{3.3}$$

i.e. the probability that the measurements arise from a model parameterized by θ. This is equivalent to minimizing the negative log-likelihood as a function of the parameter set, i.e.

$$\hat{\theta} = \arg\min_{\theta} V(\theta), \tag{3.4}$$

where

$$\begin{aligned} V(\theta) &= -\ln(p(\mathcal{Y}_N|\theta)), \\ &= \frac{1}{2}(N+1)n_y \ln(2\pi) \\ &\quad + \frac{1}{2}\sum_{k=0}^{N} \ln[\det(R_{e,k})] + e_k^T R_{e,k}^{-1} e_k. \end{aligned} \tag{3.5}$$

Here, n_y denotes the number of measurement sources. e_k and $R_{e,k}$ are CDEKF outputs for the parameter set θ.

3.1.3 Continuous-Discrete Extended Kalman Filter

For the N measurements, we compute e_k and $R_{e,k}$ in the iterative framework of the CDEKF. At every incoming measurement, y_k, we update the estimate of the system states, $\hat{x}_{k|k-1}$, and the state covariance matrix, $P_{k|k-1}$. For this update, we compute the innovation,

$$e_k = y_k - \hat{y}_{k|k-1}, \tag{3.6}$$

as the difference between the measured value, y_k, and the model predicted output, $\hat{y}_{k|k-1} = C_k \hat{x}_{k|k-1}$. The matrix C_k is a linearization of the measurement equation, $h(t_k, \hat{x}_{k|k-1})$, at the current state estimate, $\hat{x}_{k|k-1}$,

$$C_k = \frac{\partial h}{\partial x}(t_k, \hat{x}_{k|k-1}). \tag{3.7}$$

Using the variance of the measurement noise, R_k, we can obtain the covariance of the innovation signal, $R_{e,k}$, and compute the Kalman gain, K_k,

$$R_{e,k} = C_k P_{k|k-1} C_k^T + R_k, \tag{3.8a}$$

$$K_k = P_{k|k-1} C_k^T R_{e,k}^{-1}. \tag{3.8b}$$

Finally, we update the estimate of the states and their covariance using the Joseph stabilized form,

$$\begin{aligned}\hat{x}_{k|k} &= \hat{x}_{k|k-1} + K_k e_k, \\ P_{k|k} &= (I - K_k C_k) P_{k|k-1} (I - K_k C_k)^T \\ &\quad + K_k R_k K_k^T.\end{aligned} \tag{3.9a}$$

To obtain the one-step prediction of the states and their covariance, we solve a system of differential equations between times t_k and t_{k+1},

$$\frac{d\hat{x}_k(t)}{dt} = f(t, \hat{x}_k(t), u_k, d_k, \theta), \tag{3.10a}$$

$$\frac{dP_k(t)}{dt} = A_k(t)P_k(t) + P_k(t)A_k(t)^T + \sigma\sigma^T, \tag{3.10b}$$

with the initial conditions

$$\hat{x}_k(t_k) = \hat{x}_{k|k}, \tag{3.11a}$$

$$P_k(t_k) = P_{k|k}, \tag{3.11b}$$

and where

$$\begin{aligned}A_k(t) &= A(t, \hat{x}_k(t), u_k, d_k, \theta) \\ &= \frac{\partial f}{\partial x}(t, \hat{x}_k(t), u_k, d_k, \theta),\end{aligned} \tag{3.12}$$

is a linearization of the drift function f evaluated at $\hat{x}_k(t)$ with input u_k, disturbance d_k, and parameters θ.

3.2 Correlation between rapid- and long-acting insulin

In order to standardize the switch between AP treatment and injection-based therapy, it is key that a correlation exists between the glucose-lowering efficacy of rapid- and long-acting insulin, and in particular, that this correlation does not differ significantly between individuals. In a T1D data set, we estimate and compare the glucose-lowering effect when equal doses of two insulin analogues are administered to the same individual on separate dosing days.

3.2.1 The clinical data set

We use data from the clinical Phase I trial NCT01173926 [59]. In this dose-response trial, subjects with T1D receive single-dose, subcutaneous injections of rapid-acting insulin (insulin Aspart, iAsp) and long-acting insulin (insulin

Degludec, iDeg) over two separate dosing visits. Following an insulin injection, the dose-response is evaluated over a 24-hour euglycemic clamp.

For the analysis, we select data subsets where the glucose infusion rate (GIR) is actively compensating for the effect of insulin, and where observations are available for plasma glucose and insulin concentration. Figure 3.1 shows a conceptual example of the selected data for the insulin analogues. Out of 27 subjects in the trial, we include 25 subjects that meet the selection criteria. For more details on the data set and pre-procssing, we refer to [59] and [55].

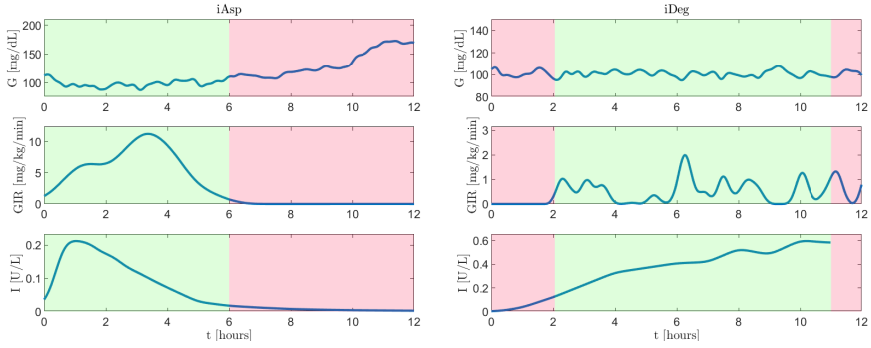
3.2.2 Estimating insulin sensitivity

To quantify the insulin effect, we estimate the insulin sensitivity in a T1D adaption of Bergman's minimal model [36, 60],

$$\dot{G}(t) = -S_G G(t) - \frac{X(t)G(t)}{c_{sf}} + S_G G_b + \frac{1}{V_G} R_a(t), \tag{3.13a}$$

$$\dot{X}(t) = -p_2 X(t) + c_{sf}(p_2 S_I (I(t) - I_b)). \tag{3.13b}$$

G [mg/dL] is the plasma glucose concentration and X [min^{-1}] is the insulin effect. $R_a(t)$ [mg/kg/min] is the rate of appearance of glucose input, and $I(t)$ [U/L] is the insulin input. To reduce the risk of numerical errors in the Kalman filter, we employ a constant scaling factor, c_{sf}, to align the orders of magnitude of the two states. We apply the parameter values from Table 3.1. We use MLE and apply the CDEKF to approximate the likelihood function which is maximized. For details on the tuning of the Kalman filter, we refer to Appendix B. From the data set, we use the glucose infusion rate (GIR)



(a) Insulin Aspart **(b)** Insulin Degludec

Figure 3.1: Data example from the clinical Phase I trial NCT01173926. For analysis, we apply the data subset marked in green, where G is the plasma glucose concentration, I is the plasma insulin concentration and GIR is the intravenous glucose infusion rate. Figure adapted from [55].

as the model input $R_a(t)$, insulin concentration in plasma as the input $I(t)$, and plasma glucose concentration, $G(t)$, as the output.

We constrain the parameter estimates for the insulin sensitivity to non-negative values and initialize the estimation with $S_I = 0.15$ L/(U·min). For the estimated insulin sensitivities in Figure 3.2, the Kalman filtered insulin effects may be negative. Although not physiologically feasible, we contribute this feature to the Bergman minimal model, which has been criticized for causing non-physiological estimates. We choose to see the model as a purely mathematical fitting function and apply it in the analysis.

3.2.3 Correlation

Figure 3.2 shows the fit along with the corresponding 95% confidence interval for the estimated rapid- and long-acting insulin sensitivities. The Pearson correlation coefficient is $r = 0.5077$ with the p-value $p = 0.0096$. Although the correlation is statistically significant, it may be hard to translate into an in-clinic insulin analogue conversion algorithm.

The insulin sensitivity estimates for iDeg are significantly lower than for iAsp. This difference aligns with the drug dynamics of iDeg. In the clinical trial, both iAsp and iDeg's total insulin concentrations are measured in plasma. However, a large fraction of iDeg in plasma is bound to albumin leaving it unavailable to interact with the insulin receptor, in contrast to the measured concentration of iAsp. Consequently, the insulin sensitivity of iDeg will appear significantly lower.

Interday variations in insulin sensitivity may influence the analysis. Even in a carefully controlled experimental setup, the PK/PD response of two identical injections of insulin preparations can differ in the same individual [62]. Standard-of-care translation algorithms typically employ a unit-to-unit conversion from pump- to pen-based treatment, and vice versa [63, 64, 65]. From this, we expect to see a clear correlation across individuals in the dose-response to rapid- and long-acting insulin. Nonetheless, the results on this limited data set do not strongly support the assumption that insulin dose conversion between analogues can be standardized for all individuals.

Table 3.1: Model parameters for the Minimal Model

S_G	$1.4 \cdot 10^{-2}$	[min$^-$]	Glucose effectiveness	[61]
V_g	1.7	[dL/kg]	Distribution volume of glucose	[61]
p_2	$3.0 \cdot 10^{-2}$	[min$^-$]	Rate constant of insulin action	[61]
G_b	36	[mg/dL]	Basal glucose concentration	[60]
I_b	0	[pmol/L]	Basal insulin concentration	[60]
c_{sf}	1000	no unit	Constant scaling factor	

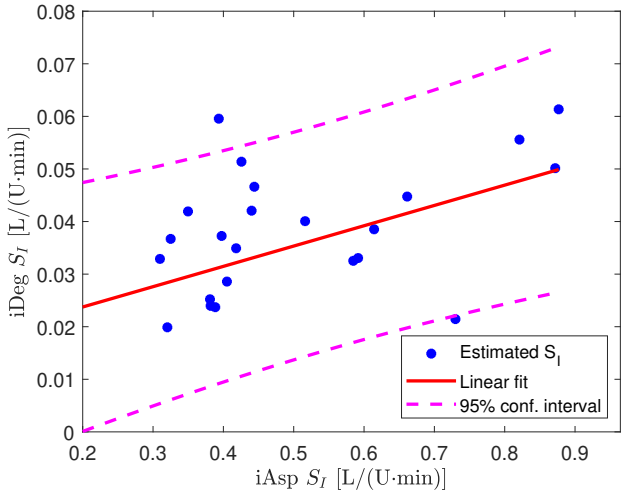


Figure 3.2: Correlation in insulin sensitivity (S_I) between rapid-acting insulin (iAsp) and long-acting insulin (iDeg). Figure adapted from [55].

3.3 The role of bioavailability

In section 2.2, we show how short-term AP treatment can safely identify an efficient daily dose of long-acting insulin for injection-based treatment. Here, we revisit the initial simulations and assess the treatment efficacy of the new titration method in a cohort of people with T2D. We investigate how differences in bioavailability may affect the translation from pump to pen, as pump studies in T2D populations have shown a 20% reduction in insulin need compared to injection-based treatment [66]. In the simulator, we incorporate differences in the bioavailability between rapid- and long-acting insulin and simulate a cohort using a Dose Finder solution [67].

3.3.1 Incorporating bioavailability in the IGI model

We augment the IGI model from section 2.1.2 to include differences in insulin analogue bioavailability. To have independent clearance rates for the two insulin analogues, we split the exogenous insulin compartment, I_{exo}, into two analogue-specific compartments, $I_{exo,R}$ and $I_{exo,L}$ with the clearance rates $k_{exo,R}$ and $k_{exo,L}$. Figure 3.5 shows the new model structure.

3.3.2 Simulating a cohort of people with T2D

We vary a subset of the model parameters to simulate a cohort of a hundred virtual patients. T2D is a heterogeneous disease and in particular the insulin resistance and insulin production differ between individuals. To reflect

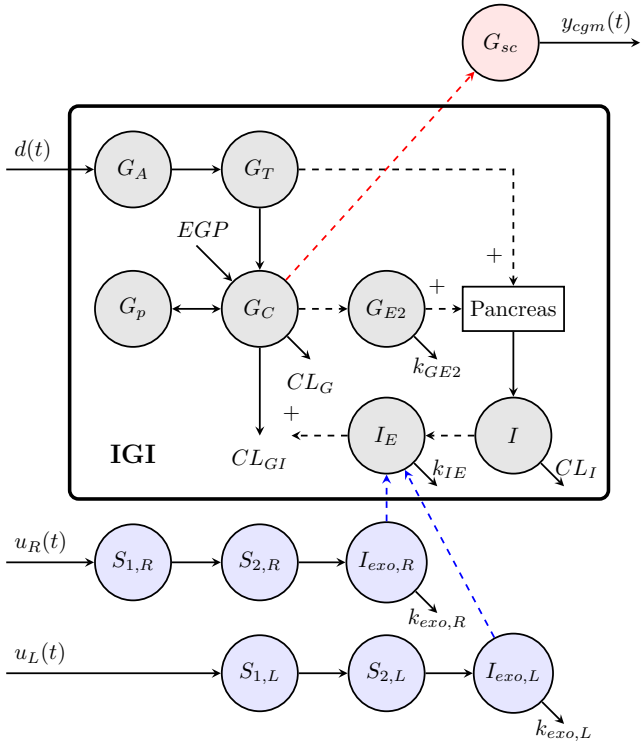


Figure 3.3: Model structure for the augmented IGI model. The original model compartments have been augmented with absorption models for rapid- and long-acting insulin (blue) and a compartment for subcutaneous glucose concentration (red). Different clearance rates, $k_{exo,R}$ and $k_{exo,L}$, determine the bioavailability of rapid- and long-acting insulin, respectively.

this, we sample individual values for the insulin-dependent glucose clearance, CL_{GI}, and insulin concentration at steady state, I_{ss}. Table 3.2 lists the published parameter distributions. In the cohort simulation, we limit the standard deviation of I_{ss} and CL_{GI} to 50%. To ensure non-negative values, we apply a lognormal transformation of the I_{ss} and CL_{GI} parameter distributions. We sample body weights from the normal distribution in [68] and scale the weight-dependent parameters (EGP, V_G, and V_I). Table 3.3 lists the weight-dependent parameters.

Table 3.2: Parameter distributions

$BW \sim \mathcal{N}(89.4, 17.7^2)$	[kg]	Body weight	[68]
$CL_{GI} \sim \mathcal{N}(0.000355, (0.000355 \cdot 77\%)^2)$	[L/min/(pmol/L)]	Insulin-dependent glucose clearance	[47]
$I_{ss} \sim \mathcal{N}(24.2, (24.2 \cdot 96\%)^2)$	[pmol/L]	Steady state endogenous insulin concentration	[47]

Table 3.3: Parameters scaled by sampled body weight

V_I	0.087	[L/kg]	Endogenous insulin distribution volume	[47]
V_G	0.133	[L/kg]	Distribution volume for central glucose compartment	[47]
EGP	$8.2 \cdot 10^{-3}$	[mmol/min/kg]	Endogenous glucose production	[47]

After parameter sampling, we screen the cohort to ensure that all the insulin responses are feasible for a T2D population. Before insulin treatment, 95% of the individuals in a titration study by Zinman et al. have a fasting blood glucose level below 15 mmol/L [68]. As the cohort in the clinical study represents only a segment of the insulin-requiring T2D population in real-world settings, we permit higher fasting blood glucose values within the simulated cohort. We define the following constraints:

- When no insulin is administered, the fasting blood glucose must lie within a 7.5-20 mmol/L range.
- The insulin dose required to reach a glucose level of 5.8 mmol/L must not surpass 150 U.

If the constraints are violated, we re-sample the model parameters until the constraints are met.

3.3.3 The effect of bioavailability

With the new model structure, we simulate a virtual clinic of insulin-naïve people with T2D on AP treatment. For the control algorithm, we apply (2.5). After three weeks of AP treatment, we translate the insulin infusion rate, unit-to-unit, into a daily injection of long-acting insulin. Figure 3.4 is a conceptual illustration of the simulation setup.

In three scenarios, we assess how differences in the insulin analogue clearance rate affects the translation between pump and pen-based treatment. We fix $k_{exo,R}$ to the nominal insulin clearance rate from [32] and scale the nominal rate by a factor of 0.8, 1 or 1.2 for $k_{exo,L}$. Figure 3.5 and Table 3.4 show the simulation results.

Before the switch to injection-based treatment, the average pre-breakfast glucose level is 7.7 ± 1.3 mmol/L. Despite the extended AP period, only a fragment of the cohort has reached the target glucose range after three weeks.

Table 3.4: Average pre-breakfast glucose concentration (standard deviation) for the 100 simulated patients.

Baseline [mmol/L]	**Before Switch** [mmol/L]	**After Switch** [mmol/L]		
		1:0.8	**1:1**	**1:1.2**
12.8 (2.7)	7.7 (1.3)	7.3 (1.2)	8.0 (1.3)	8.6 (1.4)

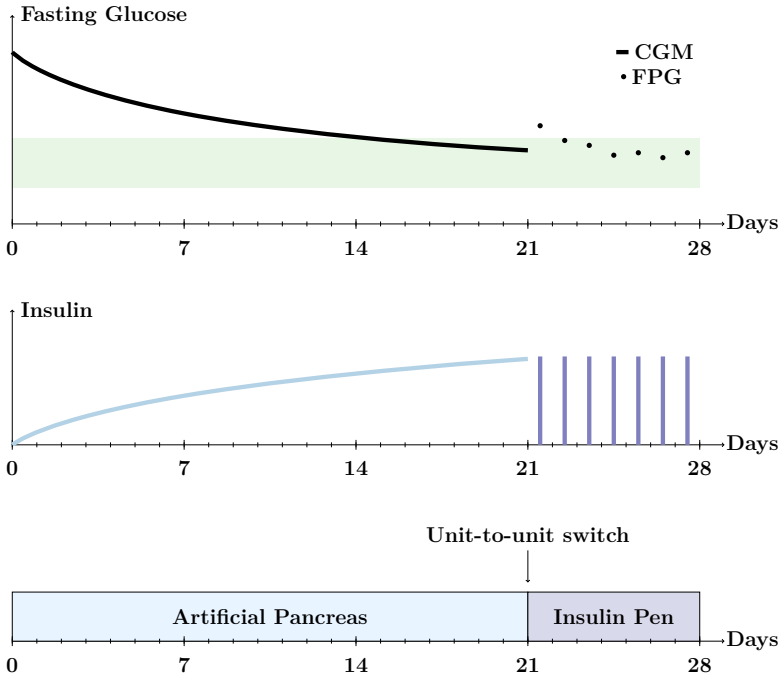


Figure 3.4: In the first three weeks, the AP drives the fasting glucose levels towards the green target range through a continuous and increasing infusion of rapid-acting insulin. In week four, we convert the infusion rate, unit-to-unit, to a daily injection of long-acting insulin. FPG denotes the fasting plasma glucose measured via finger-pricking.

For the 100 individuals, we translate the personalized insulin infusion rate, unit-to-unit, to a daily injection dose of long-acting insulin. After stabilizing on the injection-based treatment, the $k_{exo,R} : k_{exo,L}$ ratios of 1:0.8, 1:1, and 1:1.2 result in an average pre-breakfast glucose level of 7.3 ± 1.2 mmol/L, 8.0 ± 1.3 mmol/L, and 8.6 ± 1.4 mmol/L, respectively.

In simulation, a higher clearance rate of the long-acting insulin could mimic a reduction in insulin need compared to injection-based treatment. For the investigated bioavailability ratios, the results indicate no hypoglycemia risk associated with a unit-to-unit translation from pump to pen. However, to achieve comparable glycemic control, the bioavailability ratio is key to successful dose conversion from pump to pen.

3.3.4 A need for dose predictions?

Figure 3.5 reveals that the majority of the simulated cohort does not reach the target range within a few weeks of AP treatment. A direct conver-

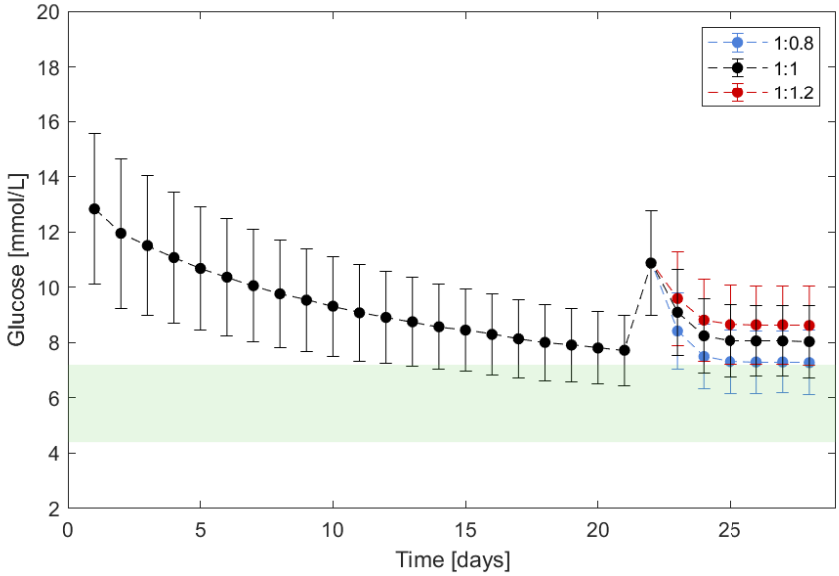


Figure 3.5: The average pre-breakfast glucose levels (± standard deviation) for the rapid- to long-acting insulin clearance ratios ($k_{exo,R} : k_{exo,L}$) of 1:0.8, 1:1, and 1:1.2. The 4.4-7.2 mmol/L target range is marked in green.

sion from pump to pen may therefore not be possible after short-term AP treatment. Nevertheless, a longer duration of the AP treatment would significantly increase the price of the treatment solution. As an alternative, we revisit the Dose Finder titration concept to see if short-term AP data can support prediction of a safe and effective insulin dose for pen-based treatment. Figure 3.6 visualizes the new concept. In the following section, we investigate the technical feasibility of using short-term AP treatment to predict a suitable dose of long-acting insulin.

3.4 Estimating pen-based insulin treatment from closed-loop data

In the cohort of virtual people with T2D from Section 3.3.2, we simulate 24 to 48 hours of AP treatment. During the short closed-loop period, the cohort is fasting. In pump-based treatment for people with diabetes, it is not unseen to use fasting periods of up to 24 hours to identify a suitable insulin infusion rate [69]. With the 24 to 48 hours of AP data, we estimate three parameters in a four-compartment insulin dose-response model by Aradóttir et al. [37].

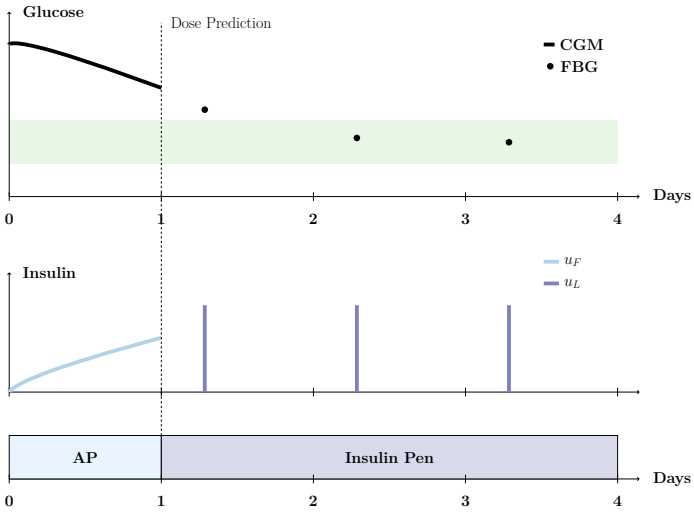


Figure 3.6: The Dose Finder concept revisited. An AP drives the glucose levels towards the green target range through a continuous and increasing infusion of rapid-acting insulin, u_R. After one day, we use the AP data to identify parameters in a dose-response model. The model is used to predict an insulin dose to reach target glucose concentrations. After dose-prediction, a daily dose of long-acting insulin (u_L) is injected before breakfast and fasting blood glucose (FBG) measurements are used for daily monitoring. The illustration has been adapted from [57].

3.4.1 Prediction model

To personalize the dose prediction for each individual in the cohort, we estimate the parameter set $\theta = [p_4, p_6, p_7]$ in the dose-response model,

$$\dot{x}_1(t) = \frac{1}{p_1}u(t) - \frac{1}{p_1}x_1(t), \tag{3.14a}$$

$$\dot{x}_2(t) = \frac{1}{p_1}x_1(t) - \frac{1}{p_1}x_2(t), \tag{3.14b}$$

$$\dot{x}_3(t) = p_3(x_2(t) + p_7x_4(t)) - p_3x_3(t), \tag{3.14c}$$

$$\dot{x}_4(t) = -(p_5 + p_4x_3(t)) \cdot x_4(t) + p_6. \tag{3.14d}$$

The compartments x_1 and x_2 describe the absorption of the insulin input, $u(t)$, from subcutaneous tissue to plasma. x_3 is the insulin effect, and x_4 is the glucose concentration. Table 3.5 lists the parameter descriptions and values. To estimate θ, we apply MLE and approximate the likelihood function using the CDEKF as described in Section 3.1.

Table 3.5: Population parameters for the prediction model

p_1	60 [min]	Time constant for rapid-acting insulin absorption	[31]
p_3	0.011 [1/min]	Delay in insulin action	[37]
p_4	0.44 [1/U]	Insulin sensitivity	[37]
p_5	0.0023 [1/min]	Insulin-independent glucose clearance	[37]
p_6	0.0672 [mmol/L·min]	Endogenous glucose production	[37]
p_7	0.0018 [U·L/mmol·min]	Endogenous insulin production	[37]

3.4.2 Dose predictions

For each individual in the cohort, we estimate a personalized set of parameters to describe the dose-response. We apply the parameter values to compute an insulin infusion rate, u_{target}, to reach target glucose concentration, y_{ref},

$$u_{target} = \frac{p_6 - y_{ref} \cdot p_5}{y_{ref} \cdot p_4} - p_7 \cdot y_{ref}. \tag{3.15}$$

For the parameter p_5, we use the population parameter value and we fix the target glucose value to $y_{ref} = 5.8$ mmol/L. We convert the individual insulin infusion rate to a daily injection dose of long-acting insulin,

$$u_L[U/day] = u_{target}\ [\text{U/min}] \cdot 60\ [\text{min/h}] \cdot 24\ [\text{h/day}]. \tag{3.16}$$

3.4.3 Outcomes of the dose predictions

Figure 3.7 shows the new Dose Finder solution. When we predict the daily insulin dose from 48 hours of closed-loop data, the majority of the simulated individuals reach glucose levels within the 4.4-7.2 mmol/L target range following the transition to injection-based treatment. However, for three virtual people, we overestimate the insulin dose and the glucose levels drop below 3.9 mmol/L. This can be dangerous and is considered unsuitable for clinical implementation. Note that the dose estimates for the three individuals do not coincide with the outliers in the boxplot of long-acting insulin doses. The three virtual individuals with suboptimal insulin dose estimates display only a marginal reduction in glucose values during the closed-loop period. We anticipate that introducing higher system excitation, such as a more aggressive controller, may enhance dose estimates for these individuals.

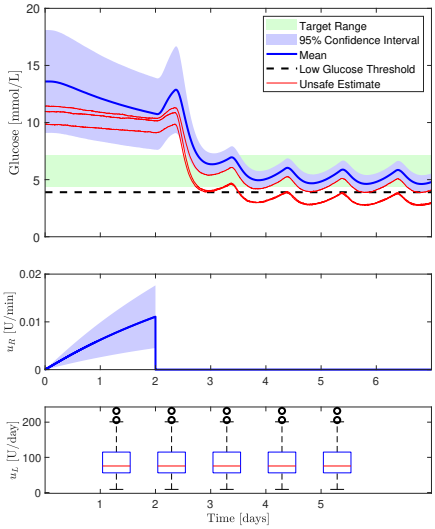
Across the simulated cohort, overall performance is good when using 48 hours of data to estimate a personalized daily insulin dose in a fasting scenario. We wish to determine whether we can achieve comparable performance with less data. Figure 3.7b shows the outcomes when we only collect 24 hours of closed-loop data. Unfortunately, we overestimate 78% of the daily insulin doses when less data is available. For the majority of the

cohort, the glucose levels drop far below the 3.9 mmol/L threshold. The limited system excitation does not appear to be sufficient to capture essential system dynamics. In Figure 3.7c, we triple the controller gain in an attempt to increase system excitation and improve performance. Compared to the nominal gain, a tripled controller gain improves the prediction quality after 24 hours of closed-loop data. Only seven individuals in the cohort experience hypoglycemia. The remaining people achieve target glucose levels with the predicted insulin doses. As in Figure 3.7a, the red curves, representing the unfortunate individuals, have a smaller gradient in the closed-loop period compared to the population mean. The small gradient can indicate a lower degree of system excitation in these individuals.

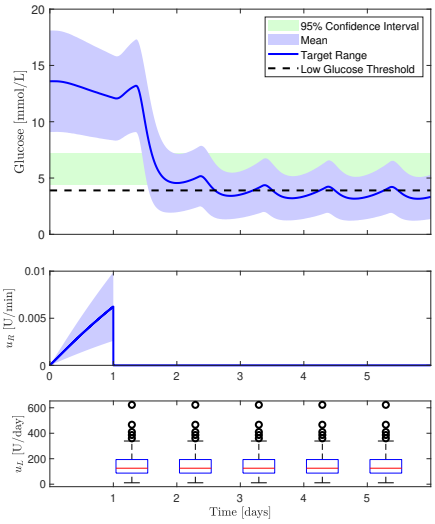
In conclusion, we reach the best performance when the AP collects data over 48 hours, suggesting that sufficient system excitation is crucial if this method is to be applicable in clinical practice.

3.5 Summary

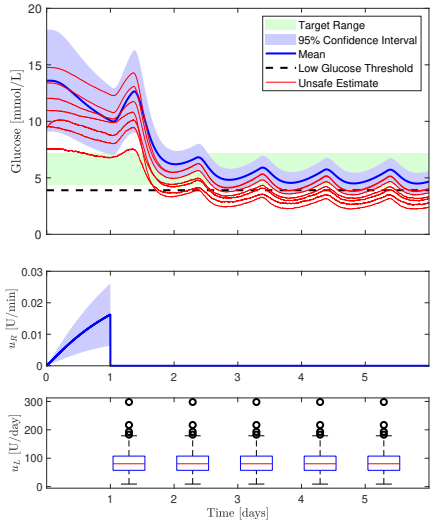
In this chapter, we explore factors that may influence the translation from rapid-acting insulin delivered in a pump to long-acting insulin injected with a pen. In the analysis, we estimate parameters in physiological models using MLE and express the likelihood function with the CDEKF. In a T1D data set, we estimate insulin sensitivity and show a statistically significant correlation between the sensitivity to rapid- and long-acting insulin injections in the same individual. Although significant, the correlation offers limited value as a translation factor between insulin analogues. To describe how insulin need may change when transitioning between pump and pen-based treatment, we augment the physiological model from Section 2.1.2. With the new model, we can simulate differences in bioavailability. We generate a hundred virtual people with T2D and simulate three weeks of AP treatment followed by a unit-to-unit switch to pen-based treatment. The results show that the bioavailability ratio between insulin analogues is key to achieve a successful dose conversion from pump to pen. The cohort simulation shows many individuals who do not reach the clinical target range within a few weeks of AP treatment. As a result, we redefine the Dose Finder titration concept and test whether 24 to 48 hours of AP data can facilitate prediction of a safe and effective dose of long-acting insulin. From short-term AP data, we estimate three individual parameters in a dose-response model and predict a personalized dose for each individual in the cohort. We see the best performance when we use 48 hours of AP data, indicating that sufficient system excitation is essential for this method to succeed.



(a) 48 hours of AP treatment.



(b) 24 hours of AP treatment.



(c) 24 hours with tripled gain.

Figure 3.7: During the 24- or 48-hour closed-loop period, glucose levels in the cohort are driven towards the target range (4.4-7.2 mmol/L) by rapid-acting insulin infusion, u_R. Based on the closed-loop data, we predict a target insulin dose and administer it as a daily injection of long-acting insulin, u_L, in the five last simulation days. With 48 hours of AP data, dose predictions lead to three individuals with glucose levels below 3.9 mmol/L. With only 24 hours of data, 78 people experience hypoglycemia. With a tripled controller gain and 24 hours of data, seven individuals experience blood glucose concentrations below 3.9 mmol/L. Figure adapted from [56].

CHAPTER 4

Experimental Design

In this chapter, we present work from Appendix A and E. We address the third research question and investigate how experimental design of the AP period can improve dose predictions for injection-based insulin therapy. We use a Model-Based Design of Experiment (MBDoE) approach to collect informative data during short-term closed-loop treatment. As safety is critical in clinical applications, we explore how to improve the safety of the MBDoE approach.

4.1 Model-Based Design of Experiments

The aim of MBDoE is to determine an optimal set of experimental preconditions, e.g. system inputs or sampling times, that enhance parameter estimation under a number of fixed input and output constraints [70]. The optimization is based on a preliminary system model known as the design model.

4.1.1 Design model

To characterize the system, we use a model of ordinary differential equations given by

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), u(t), d(t), \theta), \\ \hat{y}_k &= h(t_k, x(t_k)) + v_k, \end{aligned}$$

where $x \in \mathbb{R}^{n_x}$ is the state vector, $u \in \mathbb{R}^{n_u}$ is a vector of controlled inputs to the system, and $d \in \mathbb{R}^{n_d}$ is a vector of known system disturbances. $\theta \in \mathbb{R}^{n_p}$ is the vector of parameters we wish to estimate from the experimental data. The vector $\hat{y} \in \mathbb{R}^{n_y}$ contains the model-predicted discrete system outputs contaminated by measurement noise $v_k \sim N_{iid}(0, C_y)$.

4.1.2 Experimental design as an optimization problem

Based on the design model, we define an optimization problem to identify an experimental design variable, ϕ, that enhances the estimation of the pa-

rameter set θ,

$$\min_{\phi} \quad \psi(\phi, \theta), \tag{4.1a}$$

$$s.t. \quad x(0) = x_0, \tag{4.1b}$$

$$\dot{x}(t) = f(t, x(t), u(t), d(t), \theta), \tag{4.1c}$$

$$\hat{y}_k = h(t_k, x(t_k)) + v_k, \tag{4.1d}$$

$$0 \geq c(t, x(t), u(t), d(t), \theta). \tag{4.1e}$$

$x(0)$ are the initial states and c denotes the constraints. The cost function of the optimization problem is the design criterion, ψ, an assigned measurement function of the parameter variance-covariance matrix C_θ. As C_θ quantifies the parametric uncertainty, minimizing its value is equivalent to improving the parameter estimates. As an approximation of C_θ, we apply the inverse of Fisher's information matrix, $I(\theta, \phi)$. Hence, we wish to determine

$$\phi = \arg\min\{\psi[C_\theta(\theta, \phi)]\} \approx \arg\min\{\psi[I(\theta, \phi)^{-1}]\}. \tag{4.2}$$

4.1.3 Computing Fisher's information matrix

We compute Fisher's Information matrix, I,

$$I(\theta, \phi) = \sum_{k=1}^{n_t} S_y(t_k)^T C_y^{-1} S_y(t_k), \tag{4.3}$$

where C_y is the covariance of the measurements $\hat{y}$, and S_y is the output sensitivity to changes in the parameter set $\hat{\theta}$,

$$S_y(t_k) = \begin{bmatrix} \frac{\partial \hat{y}_1(t_k)}{\partial \hat{\theta}_1} & \cdots & \frac{\partial \hat{y}_1(t_k)}{\partial \hat{\theta}_{n_\theta}} \\ \vdots & \ddots & \vdots \\ \frac{\partial \hat{y}_{n_y}(t_k)}{\partial \hat{\theta}_1} & \cdots & \frac{\partial \hat{y}_{n_y}(t_k)}{\partial \hat{\theta}_{n_\theta}} \end{bmatrix}. \tag{4.4}$$

Given that the measurement noise is independent and normally distributed, the covariance of Fisher's information matrix is lower bounded by the Cramér-Rao bound,

$$C_\theta \geq I^{-1}(\theta, \phi). \tag{4.5}$$

As the Cramér-Rao bound asymptotically (i.e. $n_t \to \infty$) becomes equality, we can apply the inverse of Fisher's Information matrix as an approximation of the parameter variance-covariance matrix [70]. In this work, we apply central differentiation to numerically approximate $S_y(k)$, and we assume that C_y is known.

4.1.4 Design criteria

Based on Fisher's information matrix, a series of scalar criteria may assess the optimality of the experimental design. A-, D- and E-optimality are common measures from literature [70].

A-optimality. The A-criterion minimizes the trace of the inverse of Fisher's information matrix. Geometrically, this minimizes the hyper box that bounds the variance ellipsoid and is equivalent to minimizing the arithmetic mean of all the parameters' errors.

$$\psi_A(\phi, \theta) = \text{tr}\left(I(\theta, \phi)^{-1}\right) \tag{4.6}$$

D-optimality. The D-criterion minimizes the determinant of Fisher's information matrix which corresponds to minimizing the volume of the joint confidence interval for the parameters.

$$\psi_D(\phi, \theta) = -\det\left(I(\theta, \phi)\right) \tag{4.7}$$

E-optimality. The E-criterion minimizes the largest axis of the variance ellipsoid which is expressed through the smallest eigenvalue of Fisher's information matrix. This is equivalent to minimizing the largest parameter correlation or error.

$$\psi_E(\phi, \theta) = \lambda_{min}(I(\theta, \phi)) \tag{4.8}$$

Figure 4.1 illustrates the geometrical interpretation of the three criteria.

4.1.5 MBDoE in diabetes research

In diabetes research, MBDoE publications focus on the identification of physiological models and improving control algorithms for artificial pancreas systems [71, 72, 73, 74, 75, 76, 77]. Most work in this field dates ten years back, where the aim was to determine the timing of blood samples to obtain the most information about an individual's physiological response to insulin and meals. Today, advancements in sensor technology have excluded the need for identifying blood sampling times, as CGMs provide reliable measurements every five minutes. Still, only a few studies on optimal experimental design have exploited this technological development [76, 74]. We believe there is a potential to improve model-based insulin dosing algorithms in T2D using MBDoE and CGM signals.

4.2 Improving dose estimation through optimized meals and insulin infusion

Compared to Chapter 3, we aim to improve the individual dose predictions through an optimization of the data collection protocol. We define a set of

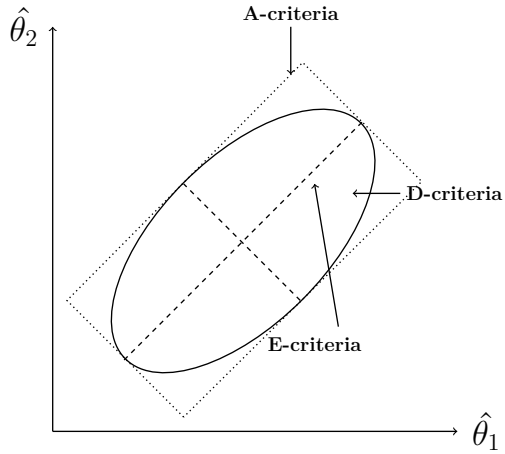


Figure 4.1: Illustration of three common design criteria for optimal experimental design. We can minimize the variance ellipsoid based on the hyper box bounding the ellipsoid (A-optimality), the volume of the ellipsoid (D-optimality), or the largest axis of the ellipsoid (E-optimality). Illustration adapted from [70].

input and output constraints and compute a decision variable to maximize the information in the experimental data set [58].

4.2.1 Decision variable

As we wish to compare to the experimental design in Section 3.4, we fix the length of the experiment to 24 hours. We describe the inputs of the design vector, ϕ, in the following way,

$$\phi = [u(t), d(t)] = [u_1, u_2, \ldots, u_{24}, d_B, d_L, d_D]. \tag{4.9}$$

To make the optimization problem tractable, we apply a zero-order hold parametrization on $u(t)$, and fix the start time and duration of the meal input, $d(t)$. The three meals are consumed over five minute intervals starting at 07:00, 12:30 and 18:00. We determine the optimal size of each meal. For the insulin input, we determine the optimal insulin infusion over 24 one-hour blocks of piece-wise constant input.

4.2.2 Design constraints

To improve safety and ensure physiologically feasible inputs, we compute the optimal experiment under a number of input and output constraints.

Output constraints

Before initiating insulin treatment, people with T2D have often experienced elevated glucose levels over a significant length of time. Although the hyperglycemic condition is unhealthy to remain in, a swift drop towards normoglycemia can cause nerve and eye damage as the body requires time to adapt to new glycemic levels. To design a protocol that graduates the drop in glycemia, we introduce output constraints. In simulation, we determine the maximal glucose drop rate. We simulate a cohort of 100 insulin-naïve people with T2D who receive rapid-acting insulin at the rate 0.07 mU/kg/min for 24 hours. Over 24 hours, the total insulin delivered is equivalent to the lowest initial dose recommended in standard of care guidelines, i.e. 0.1U/kg/day [3]. Figure 4.2 shows the simulation results.

We note that the fasting glucose on average decreases by 1.8 mmol/L after a 0.1U/kg/day insulin infusion and we define a glucose drop rate, r_d, based on the results. We allow the glucose to fluctuate within the constraints

$$\begin{aligned} y_k &\geq y_0 - r_d \cdot t_k - \delta, \\ y_k &\leq y_0 - r_d \cdot t_k + \delta + M_k, \end{aligned} \tag{4.10}$$

where y_0 [mmol/L] is the initial fasting glucose, $r_d = 0.001$ [mmol/L/min] is the drop rate, t_k [min] is the time, y_k [mmol/L] is the output at time t_k, and δ [mmol/L] is half of the width of the target range. M_k is the meal buffer at time t_k. The buffer raises the upper constraint in the postprandial period,

$$M = \begin{cases} b_G & \text{if } t_k \geq t_m \text{ and } t_k \leq t_m + b_t, \\ 0 & \text{otherwise,} \end{cases} \tag{4.11}$$

where t_m is the meal start time, b_t is the duration of the buffer after the beginning of the meal, and b_G is the magnitude of the added buffer.

Input constraints

We include three daily meals in the experimental design. To guarantee that the optimal protocol includes all three meals, we select a minimal meal size of 20 g of carbohydrates (CHO) for each meal. The maximal meal size is 100 g of CHO.

To be physically feasible, the insulin input must be non-negative. We include an upper bound on the insulin input to add an additional safety measure against overdosing. If the preliminary design model underestimates the insulin response in the subject, the output constraints alone cannot ensure safety. We select the maximal insulin infusion rate to be 15 mU/min. If the person receives insulin at this rate for the full duration of the experiment, the total insulin dosage is 21.6 U/day. For many individuals, this dose exceeds the highest initial dose recommended in standard of care guidelines, 0.2 U/kg/day. However, if the protocol does not have maximal insulin

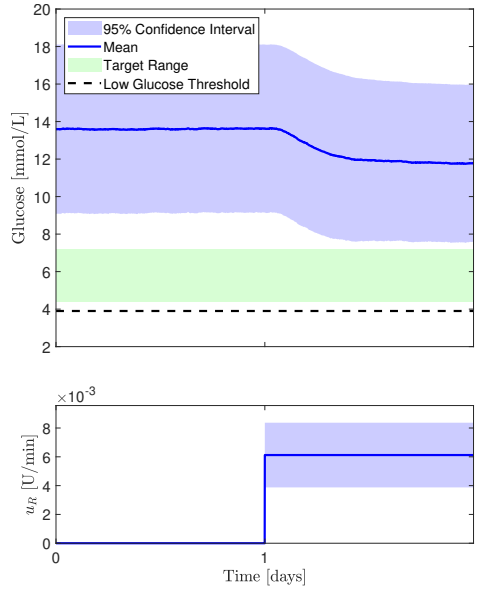


Figure 4.2: To determine a safe drop rate in glucose levels, we simulate how much the fasting blood glucose decreases in an insulin-naïve T2D cohort after an insulin infusion of 0.1U/kg/day. Over 24 hours, the mean glucose concentration drops from 13.6 mmol/L to 11.8 mmol/L, approximately -0.001 mmol/L/min.

infusion for the full duration of the experiment, the daily input can comply with clinical guidelines. Prior to implementation of the computed protocol, we assess the compliance of the total insulin dose.

4.2.3 Design model

To include meal input in the experimental design, we add meal absorption compartments from Aradóttir et al. [33] to the prediction model in (3.14),

$$\dot{D}_1(t) = d(t)\frac{1000 \cdot A_G}{MwG} - \frac{1}{\tau_m}D_1(t), \tag{4.12a}$$

$$\dot{D}_2(t) = \frac{1}{\tau_m}D_1(t) - \frac{1}{\tau_m}D_2(t), \tag{4.12b}$$

$$\dot{x_1}(t) = \frac{1}{p_1}u(t) - \frac{1}{p_1}x_1(t), \tag{4.12c}$$

$$\dot{x_2}(t) = \frac{1}{p_1}x_1(t) - \frac{1}{p_1}x_2(t), \tag{4.12d}$$

$$\dot{x_3}(t) = p_3(x_2(t) + p_7x_4(t)) - p_3x_3(t), \tag{4.12e}$$

$$\dot{x_4}(t) = -(p_5 + p_4x_3(t)) \cdot x_4(t) + p_6 + R_A(t). \tag{4.12f}$$

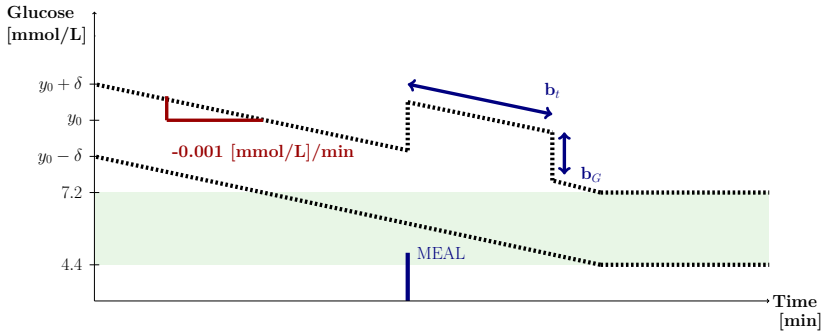


Figure 4.3: Output constraints for the optimal experimental design. Over the course of the experiment, the glucose concentration must drop slowly towards the target range. Once the target range is reached, it defines the output constraints. After meals, the output constraint is raised by $b_G = 5.0$ mmol/L for the next $b_t = 5.5$ hours. Adapted from [58].

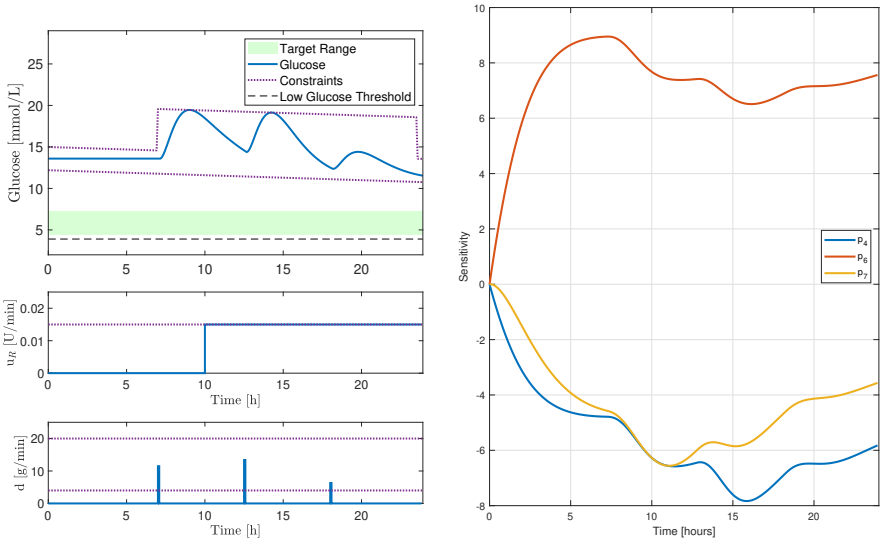
D_1 [mmol/min] and D_2 [mmol/min] are meal compartments representing absorption of carbohydrate intake, $d(t)$ [g/min]. The time constant τ_m describes the meal absorption speed, A_G is the bioavailability of the carbohydrates, and MwG is the molecular weight of glucose to convert the input into mmol. $R_A(t) = \frac{D_2(t)}{V_G \tau_m}$ [mmol/L/min] is the rate of appearance of glucose from consumed meals, where V_G [L] is the glucose distribution volume. Appendix E lists the parameter values. For the measurement function, $h(\cdot)$, we apply,

$$y_k = x_4(t_k) + v_k. \tag{4.13}$$

We assume the measurement noise is normally distributed, $v_k \sim N_{iid}(0, R)$, and apply $R = 0.1872$ mmol^2/L^2 [78].

4.2.4 Dose estimates from a new experimental design

Given the design model and the design constraints, we solve (4.1) with the A-optimality criteria to determine the meal and insulin input during the experiment. Figure 4.4a presents the optimized experimental design and Figure 4.4b shows the output sensitivities of the three estimated parameters during the experiment. In the experimental design, breakfast and lunch drive the glucose level to the upper bound, maximizing the effect of p_7. The dinner has fewer grams of carbohydrate and allows the insulin input to push the glucose level towards the lower bound, emphasizing the influence of p_4. The insulin infusion resembles a step function, where the input increases from 0 mU/min to 15 mU/min at 10AM and remains at maximal infusion until the end of the experiment. The sensitivities appear to be somewhat correlated and all three sensitivities are of similar absolute magnitude. We



(a) MBDoE **(b)** Output sensitivities

Figure 4.4: The optimal meal and insulin intake for parameter estimation given the design assumptions. The three meal sizes are 57g, 67g, and 31g of carbohydrates. Three hours after the first meal, insulin infusion starts and remains at the maximal infusion rate, 15mU/min, throughout the rest of the experiment. The output sensitivities show that the input strategy separates different model dynamics to the extent the correlation between the parameters allows. Figure adapted from [58].

run the experiment on the cohort of 100 people with T2D to test if the new design improves the dose predictions. Figure 4.5 shows the results.

The response of cohort differs from the design in Figure 4.4a. For the majority of the experiment, the mean glucose curve does not violate the output constraints. However, the breakfast and dinner lead to glucose levels slightly above the constraints. In the last few hours of the experiment, the insulin input pushes the glucose levels lower than the design model prediction. Compared to the performance in Figure 3.7, the new experimental protocol improves the quality and safety of the dose predictions. With the MBDoE protocol, the whole cohort safely reaches the 4.4-7.2 mmol/L target range on injection-based treatment.

Due to the tight constraints in the optimization problem, the over and undershoot is minimal. Still, serious constraint violations may happen due to a mismatch between the design model and the physical system. It is essential to consider this limitation of the MBDoE framework when designing clinical protocols.

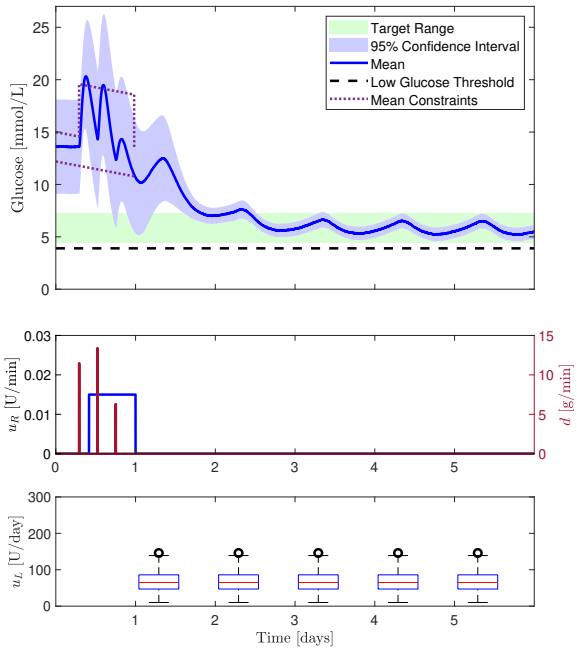


Figure 4.5: Test of the MBDoE on 100 virtual people with T2D. In the first 24 hours, the MBDoE protocol dictates the meal input, $d(t)$, and rapid-acting insulin infusion, $u_R(t)$. During the experiment, the mean glucose curve marginally surpasses the output constraints after the first and second meal. After the experiment, we estimate parameters in a dose-response model for each individual and predict a daily insulin dose, $u_L(t)$, to reach the glucose target range. In the following days, all subjects receive a daily injection with the estimated daily insulin dose at 7AM. To test if the predicted insulin dose can control the fasting glucose levels, the last five days of the simulation study are without meals and oscillations in glucose are the result of insulin dynamics. All insulin dose estimates are safe and effective. Figure adapted from [58].

4.3 MBDoE and safety

The MBDoE framework can incorporate safety constraints. However, we cannot guarantee a safe response in the real system as the experimental design is based on a model that approximates the underlying system. The mismatch between design model and system can have undesired consequences [79]. In the less severe case, a presumed optimal design leads to uninformative experiments. In the worst case, the inputs cause violations of the safety constraints. Different approaches can reduce the risk of violating constraints. With back-off strategies, tightened design constraints on the output increase the likelihood to remain within the system's safety constraints [79,

80]. However, restricting the output space makes the experimental design conservative and can lead to limited system excitation and uninformative data sets [79].

An alternative is online re-design, where the design model is continuously re-parameterized to identify a new optimal experimental protocol to replace the previous one [79, 81]. In this way, the optimal design is always based on the newest information about the system and can reduce the parametric mismatch between the design model and the system. Still, the mismatch is rarely only parametric and discrepancies in model structure can still lead to unexpected outcomes. Although a back-off strategy and online re-design can improve safety, both methods cannot remove the risk completely.

In controller design, optimal control methods can offer insights into how to best regulate system outputs. An advanced control strategy, e.g. model predictive control, may be mimicked in a simpler design, e.g. a PID controller, once the patterns of optimal behaviour are known [82]. We propose a similar approach to experimental design. To improve safety, we mimick the optimal experimental design in a closed-loop setup [57].

4.4 Learning from optimal excitation behaviors

In this section, we present an alternative method to enhance system identification by mimicking model-based optimal experimental design. To avoid the risk of open-loop implementation, we approximate the output curve from a MBDoE and apply it as a reference for the physical system. With a reference-tracking controller, we follow the output trace to collect experimental data in a closed-loop setup.

4.4.1 Decision variable and design model

As in the previous experimental design, we fix the length of the experiment to 24 hours. To determine the dynamic input profile, $u(t)$, we define the design vector, ϕ, with a piece-wise constant insulin infusion rate per hour of the experiment,

$$\phi = u(t) = [u_1, u_2, \ldots, u_{24}]. \tag{4.14}$$

To achieve a simpler design, we disregard meals in this case-study. We apply the prediction model from (3.14) as the design model.

4.4.2 Design constraints

To ensure physiologically feasible inputs, we constrain the insulin infusion to non-negative values. As in Section 4.2.2, we confine the glucose levels to

$$\begin{aligned} y_k &\geq y_0 - r_d \cdot t_k - \delta, \\ y_k &\leq y_0 - r_d \cdot t_k + \delta, \end{aligned} \tag{4.15}$$

where y_0 [mmol/L] is initial fasting glucose level, $r_d = 0.001$ [mmol/L/min] is the drop rate, t_k [min] is the time, y_k [mmol/L] is the glucose measurement at time t_k, and δ [mmol/L] is half of the width of the target range. Figure 4.6 illustrates the constraints.

4.4.3 The *optimal* design

Using the design model and the constraints, we solve (4.1) with the A-optimality criteria and identify the optimal insulin infusion throughout the experiment. Figure 4.7 depicts the new design. Throughout the experiment, the insulin infusion fluctuates and moves the glucose concentration between the upper and lower output constraint. We test the design in the cohort of 100 people with T2D. Figure 4.8 shows the outcomes. For all in the simulated cohort, the experimental data enables effective and safe dose predictions. However, for three individuals, the new protocol results in hypoglycemia. Furthermore, the mean glucose curve for the cohort violates the output constraints. Although the open-loop implementation of the design is unsafe, the solution to (4.1) offers some insights into how to best excite the system to identify θ.

4.4.4 A mimicked experiment

From visual inspection of the glucose curve in Figure 4.7, we hypothesize that system identification improves when the glucose concentration oscillates between the upper and lower constraint. To avoid open-loop implementation, we define an oscillating reference for the system and use a reference-tracking controller to follow it in closed-loop. To mimick the glucose trace from the MBDoE, we select a phase-shifted cosine curve as the reference. We

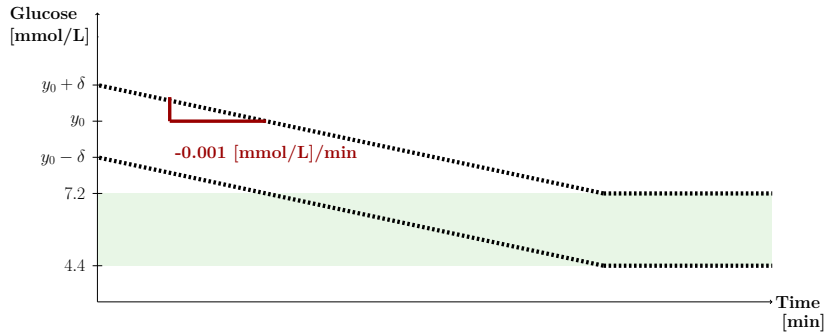


Figure 4.6: Output constraints for the optimal experimental design. To avoid treatment-induced complications, the glucose concentration must drop slowly towards the target range. Once the target range is reached, it defines the output constraints. Figure adapted from [57].

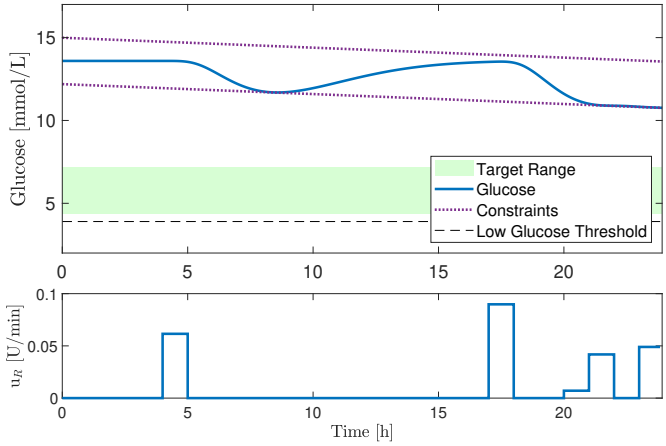


Figure 4.7: Optimized experimental design. The insulin input drives the glucose concentration between the upper and lower constraint in a sinusoidal manner. Figure adapted from [57].

individualize the reference, y_{ref}, by starting the cosine curve at the initial fasting glucose measurement, y_0 [mmol/L], for each simulated individual,

$$y_{ref}(t) = \delta \cos\left(\frac{3\pi \cdot t}{60 \cdot 24} + \frac{\pi}{2}\right) + y_0 - 0.001t. \tag{4.16}$$

t is time in minutes and $60 \cdot 24$ is the number of minutes per 24 hours. As in the constraint definition, δ [mmol/L] is half of the width of the 4.4-7.2 mmol/L target range. We let the glucose concentration drop gradually over time by 0.001 (mmol/L)/min.

To track the glucose reference y_{ref}, we manually tune a proportional controller. We mimick the MBDoE from Figure 4.7 and collect closed-loop data for 24 hours using the controller and y_{ref}. With the closed-loop data, we estimate parameters in (3.14) and predict a daily dose of long-acting insulin for each individual in the cohort. To test the predicted doses, all individuals in the cohort receive a daily, personalized injection of long-acting insulin at 7AM in the following days. Figure 4.9 depicts the closed-loop experiment and the outcomes of the individual dose predictions. Based on the mimicked MBDoE protocol, all members of the cohort receive a safe and effective long-acting insulin dose prediction. Compared to the baseline in Figure 3.7, the closed-loop data set improves system identification, whilst minimizing the risks of implementing a MBDoE in open-loop.

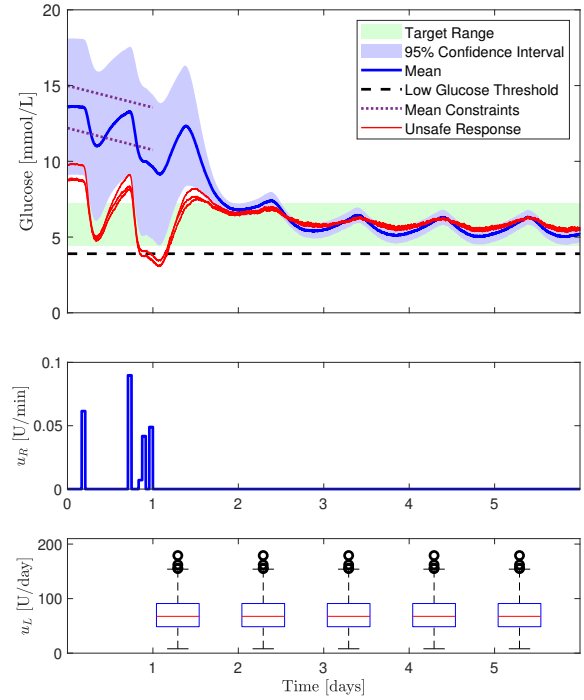


Figure 4.8: Open-loop implementation of the MBDoE from Figure 4.7. Three participants experience hypoglycemia due to the experimental design. On average, the output exceeds the constraints, marking the design as potentially unsafe. Disregarding the risk, the data from the experiment can support effective and safe dose predictions for the entire cohort. Figure adapted from [57].

4.5 Summary

Model-Based Design of Experiment (MBDoE) has a potential to improve the performance of model-based dose-guidance solutions. With MBDoE protocols, we collect data during short-term pump-based treatment in a simulated cohort of 100 people with T2D. We optimize meal and insulin inputs in a 24-hour data-collection period to parameterize a dose-response model. In simulation, we test the safety and efficacy of the model-based dose predictions. Compared to the results in Section 3.4, we can run a safer and more informative experiment by exploiting MBDoE to optimize the experimental protocol. With the new experimental design, all of the dose predictions are safe and effective in the simulation. Still, mismatches between the design model and the simulated cohort lead to potentially unsafe constraint violations during the experiment. As safety is critical in clinical applications, we explore how to improve the safety of the MBDoE approach. To avoid the

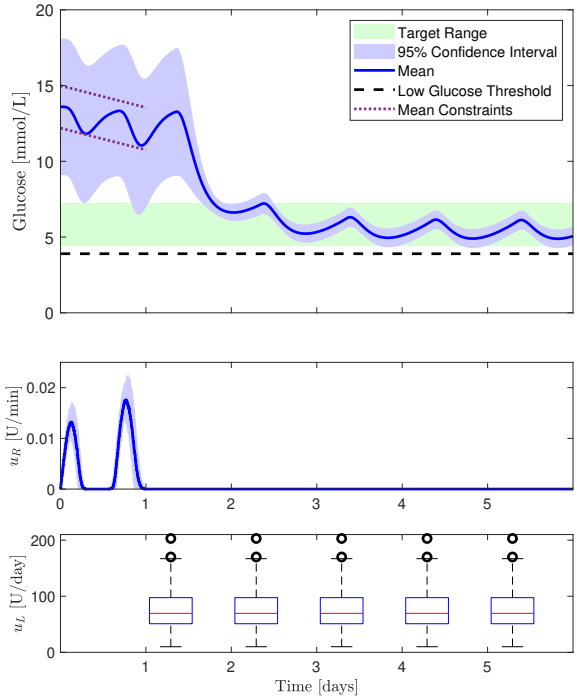


Figure 4.9: A mimicked MBDoE experiment where a reference-tracking controller follows a cosine-shaped glucose reference. Throughout the experiment, the average glucose curve remains within the output constraints. Following the transition to pen-based treatment with long-acting insulin, u_L, all dose estimations are safe and effective. Figure adapted from [57].

risk associated with an open-loop experiment, we approximate the output curve from the MBDoE and use it as a reference for the glucose concentration. With a reference-tracking controller, we follow the output trace to collect experimental data in closed-loop. The proposed design method provides informative experimental data to predict safe and effective doses for all individuals in the cohort.

Despite promising results in simulation, implementation of an untested experimental design may have limited uptake in clinics. Instead, a qualitative assessment of the MBDoE design, rather than a direct implementation, can act as a guidance tool in the design of clinical trial protocols. In a real-world implementation, HCPs may adjust the design to match existing treatment guidelines, e.g. by selecting a maximal insulin infusion rate for each individual. Closed-loop control could provide an additional safety measure.

CHAPTER 5

Conclusion

In this work, we explore the technical feasibility of a new dose-guidance solution for people with T2D initiating pen-based insulin therapy. To identify a personalized, daily injection-dose of long-acting insulin, we leverage data from short-term AP treatment.

To simulate the switch from AP- to pen-based treatment in people with T2D, we present a physiological model including rapid- and long-acting insulin treatment and CGM measurements. In the simulation model, we demonstrate how the insulin infusion rate from an AP can be converted into a personalized dose of long-acting insulin delivered with an injection pen. For a virtual individual initiating insulin treatment, we show that one initial week of AP treatment can reduce the titration period from five weeks to a single week compared to the standard of care 2-0-2 algorithm.

The use of APs in T2D treatment is still novel. As a result, no AP data paired with logged insulin injections was available to assess the clinical validity of the simulated dose-guidance solution. Instead, we investigate if a correlation in dose-response exists between different insulin analogues. In a T1D data set, we identify a statistically significant correlation between the sensitivity to rapid- and long-acting insulin injections in the same individual. Although significant, the correlation offers limited value as a translation factor.

The insulin need may change when transitioning between pump and pen-based treatment. We adjust the simulation model to show how differences in bioavailability may affect a switch from rapid- to long-acting insulin. In the new model, we simulate a cohort of a hundred people with T2D. After three weeks of AP treatment, the bioavailability ratio proves important to achieve a successful dose conversion from pump to pen in the cohort. However, many individuals do not reach the clinical target range within a few weeks of AP treatment, indicating that the results from the first simulated individual cannot be generalized.

Instead of letting the AP drive the fasting glucose level all the way into the target range, we explore the technical feasibility of predicting a safe and effective insulin dose from short-term AP data. From 24 to 48 hours of AP data, we estimate three individual parameters in a dose-response model and predict a personalized dose for each individual in the cohort. We achieve the best performance with 48 hours of AP data, indicating that sufficient system excitation is essential for this method to succeed.

To improve dose predictions, we investigate how model-based experimental design can guide the AP data collection period. In a 24-hour experiment,

we use MBDoE to select the meal and insulin input and maximize the output sensitivity to the three parameters in the dose-response model. With the new experimental protocol, all dose predictions in the cohort are safe and effective. However, when running the experiment, the cohort experiences minor constraint violations. The safety limitations of implementing a MBDoE protocol in open-loop are important to consider in clinical applications.

In a closed-loop setup, we let the MBDoE framework provide insights on how to sufficiently excite a system. We approximate the output curve from an insulin-only MBDoE and adjust it to each individual in the cohort to achieve a personalized glucose reference. With a reference-tracking controller, we follow the personalized glucose trace to collect experimental data in closed-loop. The proposed design method does not violate output constraints and provides informative experimental data to predict safe and effective doses for all individuals in the cohort.

In this work, we have explored the technical feasibility of using short-term artificial pancreas treatment as an insulin titration tool for people with T2D. In simple simulations, the proposed solution holds potential. Larger simulation cohorts, tests in different simulation models and more stochasticity in the simulated scenarios can help further cement the technical feasibility. However, without clinical data, it is a challenge to conclude on the feasibility of successfully translating infusion of rapid-acting insulin in a pump to injections of long-acting insulin with a pen. In the future, access to commercial AP systems may enable clinical feasibility assessments.

5.1 Future perspectives and opportunities

In the pharmaceutical industry, experts predict that package solutions, which combine drugs, sensors, apps, and services, will be a major driving force in the future [83]. Given the growing prevalence of T2D, it is critical that new treatment solutions ease the workload for HCPs rather than adding more tasks. With a Dose Finder titration concept, the initiation of insulin treatment may be simplified to the journey presented in Figure 5.1.

Today, common limitations of dose guidance apps include their complexity, poor user engagement, and limited documentation of clinical effect. For a Dose Finder titration concept to gain traction in diabetes clinics, it must easily integrate with existing workflows and be intuitive to use for people with diabetes and their health care professionals. Over time, the Dose Finder concept could provide data for a long-term cost-effectiveness analysis, revealing whether the solution enables better titration outcomes and improved long-term health.

In this work, we disregard postprandial glucose excursions and only consider the titration of long-acting insulin to control fasting glucose levels. Compared to current finger-prick measurements, the combined data streams from CGMs and insulin pumps provide detailed insights on the meal re-

(a) **(b)** **(c)** **(d)**

Figure 5.1: A Dose Finder titration journey. a) Clinical visit: The individual with T2D is not reaching desired outcomes on the current treatment. b) Collect closed-loop data: The individual is sent home with a kit for collecting CL data. c) Selecting the optimal treatment from CL data: The algorithm supports the HCP in selection of an optimal drug and dose. d) Initiate treatment: The individual with T2D initiates the selected treatment.

sponse. In future work, an analysis of CGM alone or in combination with insulin infusion changes around meals could help identify individuals with T2D who may benefit from adding mealtime insulin.

Although AP systems will soon be available to a T2D population, the impending launch of once-weekly insulins is predicted to reduce the need for AP systems in a T2D population [21]. This new generation of drugs will require titration. For drugs where the dose escalation can only happen weekly, the potential to increase titration speed with a Dose Finder solution may be even greater than shown in this work, given that a translation from rapid-acting to weekly insulin is clinically feasible.

In general, translation algorithms between different insulin analogues and treatment forms can benefit many people, not only in the T2D population. With the growing distribution of AP systems and the launch of new generation insulins, the need for safe and effective dose conversion will grow. Personalized translation algorithms, leveraging new data streams, hold a potential to improve glycemic control in the transition phase and to ease the life of people using insulin.

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APPENDIX A

Conference Paper

Glucose Response to Fast- and Long-Acting Insulin in People with Type 2 Diabetes

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Glucose Response to Fast- and Long-Acting Insulin in People with Type 2 Diabetes

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Abstract: In type 2 diabetes (T2D), injections with long-acting insulin can become necessary to regulate blood glucose and avoid long-term complications. However, finding a safe and effective insulin dose, a process known as titration, is both challenging and time demanding. In this paper, we propose a new method for safe and rapid identification of a personalized insulin dose with long-acting insulin through short-term use of fast-acting insulin in an artificial pancreas (AP). To illustrate this novel concept, we simulate our method by modelling the glucose response to fast- and long-acting insulin in people with T2D. We apply a simple control-algorithm for the AP to adjust the insulin infusion rate during fasting periods. In this case-study, we simulate an insulin naïve T2D patient on AP treatment for one week, gradually adjusting the insulin infusion rate. After one week, we convert the insulin infusion rate, unit-to-unit, to a daily injection of long-acting insulin. We compare our method to titration with the standard of care 2-0-2 algorithm. Our simulations indicate that we can reduce the titration period from five weeks to a single week, whilst easing the burden on the patient.

Keywords: Mathematical Modeling, Physiological Model, Simulation, Type 2 Diabetes, Insulin

1. INTRODUCTION

Diabetes is a chronic disease where the body is unable to lower blood glucose levels sufficiently with the secretion of insulin. In type 2 diabetes (T2D), this regulatory deficiency is caused by an imbalance between insulin secretion and insulin sensitivity in the body. Left untreated, elevated glucose levels can lead to blindness, kidney failure and amputations, resulting in a high cost for both the individual and society. In late-stage T2D, insulin injections may become necessary to successfully regulate glucose levels. When initiating insulin treatment in T2D, daily injections of long-acting insulin can be used to lower glucose levels. If needed, fast-acting insulin can be added at meal times. The insulin dose must be selected carefully as too much insulin can result in life-threatening low blood glucose concentrations. To avoid overdoses, a lengthy iterative process called *titration* is used to gradually increase the amount of injected long-acting insulin such that the fasting glucose concentration reaches the normal range. Based on fasting self-measured blood glucose (SMBG) values, the patient adjusts the daily insulin dose until the desired glucose concentration is reached. This can take several months. Unfortunately, many patients never reach treatment goals as the burdensome titration task and a lack of confidence in the treatment can lead to adherence problems (Arnolds et al., 2013; Khunti et al., 2020).

The burden on the patient may be eased through automated insulin delivery. In recent years, several studies have shown promising results with automated insulin delivery, also known as an artificial pancreas (AP), for people with T2D (Bally et al., 2018; Taleb et al., 2019). An AP consists of three components; (i) a continuous glucose monitor (CGM), (ii) a control algorithm, and (iii) an insulin pump with fast-acting insulin. The components automatically measure glucose, adjust the insulin dose accordingly and deliver the dose to the user at a frequent interval, typically every five minutes. Multiple AP systems are available on the market for people with type 1 diabetes, however commercial AP systems for T2D have not yet been launched. Even though APs may become available as a treatment solution for T2D in the near future, AP-usage will require high levels of self-engagement and a specific skill-set from the user, such as learning to change the infusion set and learning to carb-count (Tanenbaum et al., 2017). Widespread usage of APs in the T2D population, may be hampered by high cost, the burden of device wear, and the individual's wish to conceal their condition to avoid being labelled as *sick*. In the light of this, the greater patient population's treatment needs may be met with simpler, less visible and cheaper treatment forms, such as injection-based insulin treatment. For successful injection-based treatment, a swift, safe and simple identification of the individual's insulin-need is critical.

Methods for quickly achieving target glucose levels have been used for decades in critical care (Rohrbach et al., 2017). Here, a gradual increase in intravenous insulin in-

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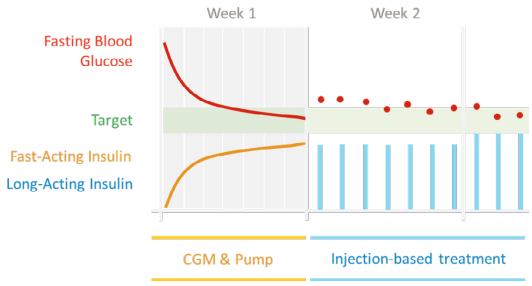

Fig. 1. The Dose Finder Concept. Short-term use of an artificial pancreas regulates the fasting blood glucose into the target range. The identified infusion rate is converted to a pen-based injection with long-acting insulin. Final dose-adjustments are made based on SMBG measurements and a standard of care algorithm.

fusion over two to three days is used to steer very high glucose concentrations into the target range. Upon reaching the target range, the infusion rate may be converted to an injection-based insulin dose (Kelly, 2014). The method is efficient, however, it is invasive and would not be considered applicable outside of critical care, where patients do not already have a intravenous catheter inserted. Similar to insulin delivered intravenously, literature suggests that a correlation exists between fast-acting insulin delivered in a pump and long-acting insulin injected from a pen (Aronson et al., 2016; Meneghini and Sparrow-Bodenmiller, 2010). We hypothesize, that the methods used in critical care can be mimicked through short-term usage of an AP. In this way, the AP system may enable a less burdensome initiation of injection-based insulin treatment.

In this paper, Section 2 presents The Dose Finder, a new method for rapid insulin titration using an artificial pancreas. To demonstrate The Dose Finder, we in Section 3 introduce a physiological model for simulating the glucose response to fast- and long-acting insulin in people with T2D. Section 4 describes a simple control algorithm for the AP. Section 5 presents the method we use to switch from AP to pen-based treatment. Our simulation setup is documented in Section 6. We present and discuss our results in Section 7 and 8, respectively, before concluding the paper in Section 9.

2. THE DOSE FINDER CONCEPT

We propose a new method, The Dose Finder, where we use an AP as a tool to find the insulin-need with fast-acting insulin. Figure 1 shows the Dose Finder concept.

The AP is used for a short time period, e.g. a week, and lowers fasting glucose levels into the target range by adjusting the insulin infusion rate. A short wear-time will allow the doctor to set up the AP for the patient, and the patient may *connect and forget* until the next doctor appointment. We only adjust insulin infusion rates during fasting periods, as the goal of the insulin treatment is to regulate fasting glucose rather than post-prandial glucose. After the AP period, we translate the identified insulin infusion rate from the pump into an injection-based treatment with long-acting insulin. In the case where the optimal dose of long-acting insulin has not been identified after the AP period, we follow the dose translation with dose adjustments based on SMBG values and a standard of care (SoC) algorithm, such as the 2-0-2 titration algorithm shown in Table 1.

Table 1. The 2-0-2 Titration Algorithm for Long-Acting Insulin. Dose adjustments are based on the lowest SMBG value below target, or an average of the SMBG values from the past three days. (American Diabetes Association, 2021)

SMBG [mmol/L]	Dose Adjustment [U]
> 7.2	$+2$
$4.4 - 7.2$	No change
< 4.4	-2
Initial dose is 10 U	

3. MATHEMATICAL MODELS

To simulate subjects with T2D treated with both fast- and long-acting insulin, we augment the integrated glucose-insulin (IGI) model (Jauslin et al., 2011; Røge et al., 2014) with an extended version of the exogenous insulin model from Hovorka et al. (2004). We include a subcutaneous glucose concentration compartment from Biagi et al. (2017) for simulating sensor measurements as input to the artificial pancreas. The resulting model consists of a submodel for carbohydrate (CHO) absorption, a pharmacodynamic (PD) model describing the interaction between glucose and insulin concentration, and two pharmacokinetic (PK) models to simulate the absorption dynamics of fast- and long-acting insulin. Figure 2 shows the model structure. We present the model equations in the following subsections and Table 2 lists selected parameter values.

3.1 Glucose Sub-Model

In the IGI model, glucose is split between the central $G_c(t)$ [mmol] and the peripheral compartment $G_p(t)$ [mmol],

$$\dot{G}_c(t) = EGP + R_A(t) + \frac{Q}{V_p}G_p(t) - \frac{1}{V_G}(CL_G + CL_{GI}I_E(t) + Q)G_c(t) \quad (1a)$$

$$\dot{G}_p(t) = \frac{Q}{V_G}G_c(t) - \frac{Q}{V_p}G_p(t) \quad (1b)$$

where the plasma concentration is the glucose in the central compartment divided by the distribution volume, V_G [L]. Glucose enters the central compartment through the endogenous glucose production, EGP [mmol/min], the absorbed meals, $R_A(t)$ [mmol/min], and from the peripheral glucose compartment via the inter-compartmental clearance, Q [L/min]. V_p [L] is the distribution volume in the peripheral compartment. Both glucose-dependent clearance, CL_G [L/min], and insulin-dependent clearance, CL_{GI} [L/min/(pmol/L)], remove glucose from the central compartment. I_E [pmol/L] is the insulin effect compartment.

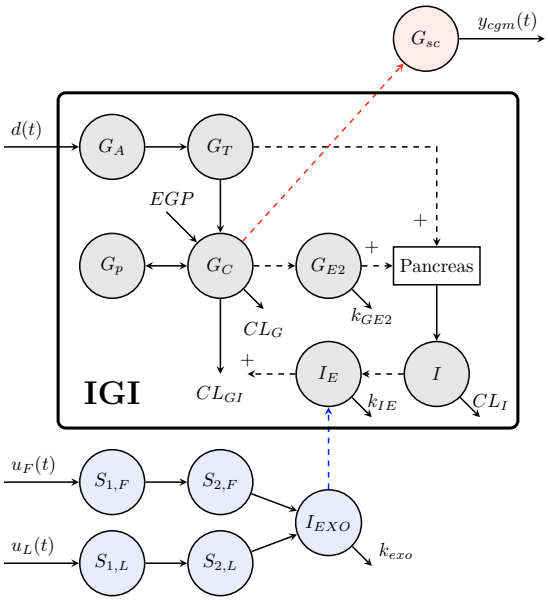

Fig. 2. Model structure for the augmented IGI model. The original model compartments have been augmented with absorption models for fast- and long-acting insulin (blue) and a compartment for subcutaneous glucose concentration (red).

3.2 Carbohydrate Absorption Model

The IGI model describes oral meal ingestion with a two-compartment model,

$$\dot{G}_A(t) = d(t)A_G - k_a G_A(t) \tag{2a}$$
$$\dot{G}_T(t) = k_a G_A(t) - k_a G_T(t) \tag{2b}$$
$$R_A = \frac{k_a}{M_{wG}} G_T(t) \tag{2c}$$

where $d(t)$ [mg/min] is the amount of ingested carbohydrates (CHO). G_A [mg] and G_T [mg] represent the amounts of CHO in the absorption and the transit phase, respectively. A_G [unitless] describes the bio-availability of the CHO. k_a [1/min] is a rate constant for the absorption of CHO. The absorbed meals, R_A [mmol/min] enter the central glucose compartment. To match units of R_A and G_c, we convert G_T to [mmol/min] by dividing with the molecular weight of glucose $M_{wG} = 180.1559$ mg/mmol.

3.3 Endogenous Insulin Sub-Model

Endogenous insulin is described through the compartment, I [pmol], with the secretion and elimination of insulin produced in the pancreas,

$$\dot{I}(t) = I_{sec}(t) - \frac{CL_I}{V_I} I(t) \tag{3a}$$
$$I_{sec}(t) = I_{sec,0} \cdot G_{CM2} \cdot INC(t) \tag{3b}$$
$$I_{sec,0} = CL_I \cdot I_{ss} \tag{3c}$$

where the insulin secretion, I_{sec} [pmol/min], is regulated by the ability of glucose to stimulate secretion, G_{CM2} [unitless], and the incretin effect, INC [unitless]. The basal insulin secretion, $I_{sec,0}$ [pmol/min], is given by the product of the endogenous insulin clearance, CL_I [L/min], and the insulin concentration at steady state, I_{ss} [pmol/L].

3.4 Glucose Effect on Insulin Secretion

The effect compartment, G_{E2} [mmol/L], links the plasma glucose concentration to insulin secretion,

$$\dot{G}_{E2}(t) = k_{GE2} \frac{G_c(t)}{V_G} - k_{GE2} G_{E2}(t) \tag{4a}$$
$$G_{CM2}(t) = \left(\frac{G_{E2}(t)}{G_{ss}} \right)^{IPRG} \tag{4b}$$

where k_{GE2} [1/min] is a rate constant. The glucose effect on insulin secretion, G_{CM2}, is determined through the baseline glucose concentration, G_{ss} [mmol/L], and the control parameter $IPRG$ [unitless].

3.5 Incretin Effect

Ingested meals can boost the insulin secretion through the incretin effect. In the IGI model, the effect is described as a saturable function,

$$INC(t) = 1 + \frac{E_{max} \cdot G_T(t)}{ED_{50} + G_T(t)} \tag{5}$$

where E_{max} [unitless] is the maximal effect with which glucose in the transit compartment can affect insulin secretion, and ED_{50} [mg] is the amount of glucose needed to obtain half of the E_{max}-effect.

3.6 PK model

We augment the IGI model with the exogenous insulin model from Hovorka et al. (2004) to describe the absorption dynamics of fast- and long-acting insulin analogues. The absorption of exogenous insulin is described as a third-order system,

$$\dot{S}_{1,ia}(t) = u_{ia}(t) - \frac{1}{\tau_{ia}} S_{1,ia}(t) \tag{6a}$$
$$\dot{S}_{2,ia}(t) = \frac{1}{\tau_{ia}} S_{1,ia}(t) - \frac{1}{\tau_i a} S_{2,ia}(t) \tag{6b}$$
$$U_{I,ia}(t) = \frac{1}{\tau_{ia}} S_{2,ia}(t) \tag{6c}$$

where $u_{ia}(t)$ [U/min] is the amount of subcutaneously injected insulin analogue. The time constant, τ_{ia} [min], is the time to maximum insulin absorption for the specific analogue. $S_{1,ia}$ [U] and $S_{2,ia}$ [U] are absorption compartments and $U_{I,ia}$ [U/min] is the absorption rate. The absorption rates of fast- and long-acting insulin, $U_{I,F}$ and $U_{I,L}$, enter the exogenous insulin concentration compartment I_{exo} [U/L],

$$\dot{I}_{exo}(t) = \frac{U_{I,F}(t) + U_{I,L}(t)}{V_{I,exo}} - k_{exo} I_{exo}(t) \tag{7}$$

$V_{I,exo}$ is the distribution volume for exogenous insulin and k_{exo} [1/min] is the clearance rate.

3.7 Insulin Effect

The insulin effect compartment describes the delay in glucose utilization caused by both endogenous and exogenous insulin,

$$\dot{I}_E(t) = \frac{k_{IE}}{V_I} \left(I(t) + c_f \cdot I_{exo}(t) \right) - k_{IE} I_E(t) \tag{8}$$

where k_{IE} [1/min] is the rate constant describing the effect delay, and V_I [L] is the insulin distribution volume. To align units, we multiply I_{exo} [U/L] by the conversion factor c_f [pmol/U] from Knopp et al. (2019).

3.8 Continuous Glucose Monitor Model

CGMs measure glucose levels in the interstitial tissue. We use a model relating plasma glucose and interstitial glucose from Biagi et al. (2017),

$$\dot{G}_{sc}(t) = \frac{\frac{G_c(t)}{V_G} - G_{sc}(t)}{\tau_{sc}} \tag{9}$$

where the time constant τ_{sc} [min] describes the lag between glucose concentrations in plasma, $G_c(t)/V_G$, and the glucose concentration in the interstitial tissue, G_{sc} [mmol/L].

3.9 Parameters

We use parameter values from Røge et al. (2014) and Hovorka et al. (2004) for the IGI model and the exogenous insulin dynamics, respectively. To simulate long-acting insulin, we introduce $\tau_L = 12$ h as in Aradóttir et al. (2017). The endogenous glucose production (EGP) is taken from Røge et al. (2014) and is normalized to a body weight of 70 kg in order to match the distribution volumes (V_G, V_p, V_I) that are stated to be proportional body weight and are normalized to 70 kg. For the lag to the subcutaneous glucose compartment, we select a time constant from the distribution in Biagi et al. (2017). To convert from pmol to U, we use the conversion from Knopp et al. (2019).

Table 2. Model Parameters

	Parameter	Value	Source
τ_{sc}	[min]	10	Biagi et al. (2017)
τ_F	[min]	55	Hovorka et al. (2004)
τ_L	[min]	720	Aradóttir et al. (2017)
k_{exo}	[1/min]	0.138	Hovorka et al. (2004)
EGP	[mmol/min]	0.574	Røge et al. (2014)
c_f	[pmol/U]	6000	Knopp et al. (2019)

4. AP CONTROL ALGORITHM

We implement a simple control algorithm to simulate closed-loop control with the AP. Inspired by the integral component in PID-controllers, we adjust the insulin infusion rate u_F at every sample based on the integrated error,

$$v(k) = v(k-1) + K_i \cdot (y_{ref} - y_{cgm}(k)) \cdot T_s \tag{10a}$$
$$u_F(k) = \max(v(k), 0) \tag{10b}$$

where k is the sample number, K_i $\left[\frac{U \cdot L}{min^2 \cdot mmol}\right]$ is the integral gain, and T_s [min] is the sample time. The error term is the difference between the reference value, $y_{ref} = 5.8$ mmol/L, and the glucose concentration measured by the CGM sensor, $y_{cgm}(k)$. We set $v(0) = 0$. As negative insulin infusion rates are not physiologically possible, we constrain the infusion rate to $u_F(k) \leq 0$ U/min.

Sudden drops in blood glucose values can be uncomfortable for patients. We select $K_i = -3 \cdot 10^{-6} \frac{U \cdot L}{min^2 \cdot mmol}$ to ensure a balance between rapid convergence towards the reference value and a smooth transition for patient comfort. We wish to regulate the the insulin infusion rate such that the fasting glucose is lowered into the target range. To avoid adjusting u_F during post-prandial peaks, meals are announced to the controller. Following a meal announcement, the controller is switched off for 5.5 hours and the insulin infusion rate is fixed to the latest u_F value.

5. SWITCH FROM PUMP TO PEN

For this simplified case simulation, we assume that the bio-availability of fast-acting insulin delivered in a pump is identical to that of long-acting insulin injected in a pen. We calculate the long-acting insulin dose as the total amount of insulin delivered with the pump during 24 hours using the identified insulin infusion rate,

$$u_L[\text{U/day}] = \frac{24[\text{h/day}] \cdot 60[\text{min/h}] \cdot u_F[\text{U/sample}]}{T_s[\text{min/sample}]} \tag{11}$$

The calculated dose, u_L, is injected daily prior to breakfast. As fast-acting and long-acting insulin have different dynamics, a direct switch from pump to pen will result in a rise in blood glucose. This happens because the effect of the fast-acting insulin disappears before the long-acting insulin becomes effective. In critical care, the transition from intravenous to subcutaneous insulin treatment is often overlapped to avoid a rise in blood glucose (Kelly, 2014). Likewise, we compensate for the difference in dynamics by continued infusion of fast-acting insulin for 2 hours after the first injection with long-acting insulin. Starting one week after the transition from pump to pen, we apply a standard of care titration algorithm for final dose adjustments until dose convergence.

6. SIMULATION SETUP

We simulate three different ways to initiate insulin for the same virtual patient with; (i) The 2-0-2 Titration Algorithm twice-weekly with titration on day 1 and 4, (ii) AP treatment until the translated insulin infusion rate

Table 3. Titration Results

Titration Method	Dose at end of Week 1	Week 2	Week 4	Final Dose	Titration Length
2-0-2	12 U	16 U	24 U	28 U	5 weeks
AP	35 U	43 U	45 U	46 U	5 weeks
DF	35 U	35 U	35 U	35 U	1 week

converges to a fixed pen-dose, and (iii) The Dose Finder: One week of AP followed by dose-conversion to long-acting insulin, and weekly dose-adjustments with the 2-0-2 algorithm, if needed. In all simulations, we assume full adherence. We start the study at midnight. We simulate three daily meals of 40 g, 55 g, and 60 g of carbohydrates with meal times at 7:00 AM, 1:00 PM and 7:00 PM, respectively. The duration of each meal is 15 minutes. SMBG values are recorded at 7:00 AM, and the three latest SMBG values are used as input to the 2-0-2 algorithm. We use a sample time of $T_s = 5$ min, and simulate insulin injections as a fixed rate over a five minute sample.

7. SIMULATION RESULTS

With our extension to the IGI model, we are able to simulate treatment with both fast- and long-acting insulin. Figure 3 illustrates the first 12 days of the Dose Finder scenario, where an AP is used for 7 days before switching to pen-based treatment. We see that the fasting glucose levels are reduced as the insulin infusion rate is gradually increased. The controller is mainly active overnight where the patient is fasting. After one week of AP treatment, the fasting blood glucose has been lowered from 12 mmol/L to 6 mmol/L and is within the target range. During AP treatment, all measured glucose concentrations are above or within the target range, and the treatment is considered safe. When transitioning from AP to injection-pen, a small rise is seen in the glucose values until they stabilize after 3-4 days of pen-treatment. After 3 days, all the fasting blood glucose values are within the target range, and no adjustments are needed with the 2-0-2 algorithm.

We compare the outcomes for the Dose Finder (DF) method to two other titration approaches in Table 3 and Figure 4. With the 2-0-2 algorithm, the dose converges after five weeks. We see that our method can reduce the titration period to a single week. If the AP period is extended, we can complete the titration period after five weeks and reach a lower fasting blood glucose value within the target range.

8. DISCUSSION

With one week of AP treatment, we can identify a dose of long-acting insulin that can bring the patient's blood glucose into the target range. We identify a dose of 35 U, however, our simulations show that several dose sizes will allow the patient to reach target. Some patients may desire a tighter target range, e.g. $4.0 - 6.0$ mmol/L. In this case, the patient will need additional dose-adjustments to reach target after the switch from AP to pen-based treatment. As another option, we can extend the AP period to reach a lower fasting blood-glucose before switching to pen-based treatment. When we run the AP, the dose converges to 46 U after five weeks. Due to integrator wind-up, the AP stabilizes the fasting blood glucose at 5 mmol/L. Although

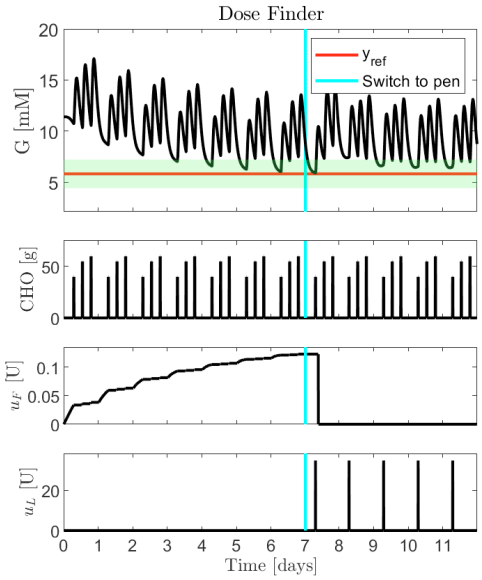

Fig. 3. Simulation of the Dose Finder. The panels from top to bottom show the glucose concentration, the consumed carbohydrates, the infused fast-acting insulin and the injected long-acting insulin, respectively. Over the first week, the AP adjusts the insulin infusion rate during fasting periods. At the start of week 2, the infusion rate is converted, unit-to-unit, to a daily, long-acting insulin dose administered pre-breakfast. Insulin infusion is continued for 2 hours after the first pen-injection to reduce the rise in glucose levels during transition. The green area shows the target range of $4.4 - 7.2$ mmol/L

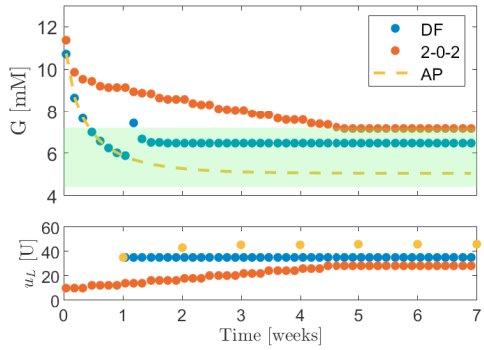

Fig. 4. Titration with The Dose Finder (DF), the 2-0-2 algorithm and the implemented artificial pancreas (AP). The upper panel shows the daily SMBG values for DF and 2-0-2, and the pre-breakfast CGM measurement for the AP. The lower panel shows the daily dose of long-acting insulin for DF and 2-0-2, and the unit-to-unit conversion of the fast-acting insulin delivered by the AP on the last day of each week.

the prolonged AP wear-time can quickly steer the blood glucose to a lower target, it comes at a cost. The patient would need frequent clinic visits to change the cartridge, infusion set, and sensor. Alternatively, the patient would have to learn to manage the AP themselves. Both scenarios complicate the procedure and may reduce the benefits compared to regular titration.

We simulate an ideal scenario where the patient is adherent and the measurements are without noise. In practice, titration periods may be extended greatly due to physiological variation, forgotten injections and misunderstood guidelines. Additionally, the safety of the control algorithm for the AP may be affected by unannounced meals and sensor noise. The control algorithm in this paper serves the purpose of visualizing the the Dose Finder concept and would need additional safety measures and extensive testing to be applicable in a clinical setup.

In our exogenous insulin compartment, the clearance of fast-acting insulin delivered in a pump and long-acting insulin delivered in a pen are identical. Aronson et al. (2016) showed that on average subjects with T2D who switch from pen-based treatment to insulin pumps will need 20% less insulin. If less insulin is needed in pumps, the unit-to-unit conversion we use to transition from AP to pen-based treatment can be considered safe as it systematically underestimates the insulin-need. As a result, the subject may need additional dose-adjustments in order to reach the final titration target after the switch to pen-based treatment. In future work, the difference between insulin delivery methods may be included in our model as an analogue-dependent clearance by implementing an I_{exo}-compartment for each analogue.

9. CONCLUSION

This work presents a model to simulate fast- and long-acting insulin in people with type 2 diabetes. With our model, we simulate how the insulin infusion rate from an artificial pancreas can be converted into a personalized dose of long-acting insulin delivered with an insulin pen. For a virtual patient initiating insulin treatment, we show that one initial week of AP treatment can reduce the titration period from five weeks to a single week compared to the standard of care 2-0-2 algorithm.

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APPENDIX B

Conference Paper

Correlation in Dose-Response to Rapid- and Long-Acting Insulin for People with Type 1 Diabetes

Correlation in Dose-Response to Rapid- and Long-Acting Insulin for People with Type 1 Diabetes

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***Abstract*— In diabetes, it can become necessary to switch between pump- and pen-based insulin treatment. This switch involves a translation between rapid- and long-acting insulin analogues. In standard-of-care translation algorithms, a unit-to-unit conversion is applied. However, this simplification may not fit all individuals. In this paper, we investigate the correlation between dose-response to rapid- and long-acting insulin in the same individual, and compare the correlation across individuals. As a measure of dose-response, we estimate the insulin sensitivity in clinical data from 25 subjects with type 1 diabetes. For parameter estimation, we use maximum likelihood with a continuous-discrete extended Kalman filter and Bergman's minimal model. The results show a weak correlation between insulin sensitivity to rapid- and long-acting insulin across individuals. On this sparse data set, the analysis suggests that the standardized unit-to-unit translation between insulin analogues may not benefit all subjects.**

I. Introduction

In recent years, insulin treatment with artificial pancreas (AP) systems has become a viable solution for people living with diabetes [1]. However, pump malfunctions, infusion set complications or allergic reactions to adhesives may force AP-users to switch to injection pen-based treatment for shorter or longer periods [2], [3]. In this switch, continuous rapid-acting insulin infusion from the pump is replaced by multiple daily injections of rapid- and long-acting insulin analogues to cover the post-prandial glucose excursions and the basal insulin need, respectively. Several methods exist for the conversion between pump and pen [4]–[6]. Generally, these conversion algorithms build upon the assumption that one unit of insulin lowers the blood glucose equally, no matter the analogue or delivery form. Nonetheless, several studies on the switch from pen- to pump-based treatment report that a reduced total daily dose of insulin is required for the same individual to stay in glycemic control on pump-based treatment [5], [7]. In order to standardize the switch between pump and pen, it is key that a correlation exists between the glucose-lowering efficacy of rapid- and long-acting insulin, and in particular, that this correlation does not differ significantly between individuals.

A common way to quantify the insulin effect is by estimating the insulin sensitivity. In personalized dose-guidance algorithms, insulin sensitivity is estimated with a Kalman filter and an estimator model of insulin-glucose dynamics [8], [9]. We apply this approach to examine the glucose-lowering efficacy of rapid- and long-acting insulin. The purpose of this work is to determine the correlation between dose-response to single-dose injections of rapid- and long-acting insulin in the same individual. We compare the glucose-lowering efficacy when an equal dose of two insulin analogues are administered on separate dosing days.

This paper is organized as follows. In Section II, we present a simple physiological model in which the insulin sensitivity parameter can be estimated from clinical data, and we briefly describe the parameter estimation technique. In Section III, we describe the applied clinical data set, and in Section IV, we document how we select and pre-process data. Section V presents the results of the analysis. In Section VI, we present the conclusions.

II. Methods

In this paper, we estimate the insulin sensitivity in a non-linear model of the insulin-glucose dynamics in people with diabetes. We use maximum likelihood with a continuous-discrete extended Kalman filter (CDEKF).

A. Bergman's Minimal Model

As our estimator model, we employ a scaled version of the non-linear model from Bergman et al. [10]:

$$\frac{dG}{dt} = -S_G G(t) - \frac{X(t)G(t)}{c_{sf}} + S_G G_b + \frac{1}{V_G} R_a(t), \tag{1a}$$

$$\frac{dX}{dt} = -p_2 X(t) + c_{sf}(p_2 S_I (I(t) - I_b)). \tag{1b}$$

The two states describe the glucose concentration in plasma, G [mg/dL], and the insulin action, X [min^{-1}]. Inputs to the system are the rate of appearance of glucose in plasma, $R_a(t)$ [mg/kg/min], and the insulin concentration in plasma, $I(t)$ [U/L]. The glucose concentration, $G(t)$, is measured, i.e. $y(t) = G(t)$. To reduce the risk of numerical errors in our Kalman filter, we apply a constant scale factor, c_{sf}, to get similar orders of magnitude for the two states. We estimate the parameter S_I [L/U/min], which describes the insulin sensitivity. For the remaining model parameters, we use the published population parameters. Table I lists the parameters applied.

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B. Parameter Estimation with Maximum Likelihood

Given a set of measurements

$$\mathscr{Y}_N = \{y_0, y_1, ..., y_N\}, \tag{2}$$

we want to maximize the joint probability density

$$p(\mathscr{Y}_N|\theta) = p(y_N, y_{N-1}, ..., y_0|\theta) \tag{3}$$

i.e. the maximum likelihood function. By maximizing (3), or equivalently minimizing the negative log-likelihood function (4), we can obtain an estimate of unknown parameters, $\hat{\theta}$, in our model.

$$\begin{aligned} V(\theta) &= -\ln(p(\mathscr{Y}_N|\theta)) \\ &= \frac{1}{2}(N+1)n_y \ln(2\pi) \\ &\quad + \frac{1}{2}\sum_{k=0}^{N} \ln[\det(R_{e,k})] + e_k^T R_{e,k}^{-1} e_k, \end{aligned} \tag{4}$$

where N is the number of measurements, n_y is the number of system outputs, e_k is the innovation from the CDEKF, and $R_{e,k}$ is the corresponding covariance. From this, we estimate the unknown parameters, $\hat{\theta}$ (the insulin sensitivity, S_I).

$$\hat{\theta} = \arg\min_{\theta} V(\theta) \tag{5}$$

C. The Continuous-Discrete Extended Kalman Filter

To obtain the innovation, e_k, and its covariance, $R_{e,k}$, we must estimate the states of the system. The CDEKF estimates the states based on a stochastic continuous-time model and discrete-time measurements from the underlying system, i.e.

$$dx(t) = f(t, x(t), u(t), \theta)dt + \sigma d\omega(t) \tag{6a}$$

$$y_k = h(t_k, x(t_k)) + v_k \tag{6b}$$

where $x(t)$ is the state vector, $u(t)$ is the input vector, and θ represents the model parameters. For $u(t)$, we assume a zero-order hold parametrization, i.e. $u(t) = u_k$ for $t_k \leq t < t_{k+1}$. The process noise, $\{\omega(t), t \geq 0\}$, is a standard Wiener process with covariance Idt. $\omega(t)$ is scaled by a time-invariant diagonal matrix, σ. The measurement noise is assumed normally distributed, $v_k \sim N_{iid}(0, R_k)$.

The CDEKF consists of a measurement update and a time update. In the measurement update, we use a new measurement, y_k, to correct the current state estimate, $\hat{x}_{k|k-1}$, and its covariance, $P_{k|k-1}$. To obtain the updated state estimate, $\hat{x}_{k|k}$, and covariance, $P_{k|k}$, we compute the innovation as the difference between the incoming measurement, y_k, and the one-step prediction of the output, $\hat{y}_{k|k-1} = C_k \hat{x}_{k|k-1}$,

$$e_k = y_k - C_k \hat{x}_{k|k-1}, \tag{7}$$

where

$$C_k = \frac{\partial h}{\partial x}(t_k, \hat{x}_{k|k-1}) \tag{8}$$

is a linearization of the output function h evaluated at $\hat{x}_{k|k-1}$. Through the covariance of the innovation, $R_{e,k}$, we compute the Kalman gain, K_k,

$$R_{e,k} = C_k P_{k|k-1} C_k^T + R_k, \tag{9a}$$

$$K_k = P_{k|k-1} C_k^T R_{e,k}^{-1}. \tag{9b}$$

We conclude the measurement update with an update of the state and its covariance

$$\hat{x}_{k|k} = \hat{x}_{k|k-1} + K_k e_k, \tag{10a}$$

$$P_{k|k} = (I - K_k C_k) P_{k|k-1} (I - K_k C_k)^T + K_k R_k K_k^T. \tag{10b}$$

The measurement update is followed by a time update, where we compute the mean and variance of the one-step predictions. The one-step predictions, $\hat{x}_{k+1|k} = \hat{x}_k(t_{k+1})$ and $P_{k+1|k} = P_k(t_{k+1})$, are the solutions to the system of differential equations,

$$\frac{d\hat{x}_k(t)}{dt} = f(t, \hat{x}_k(t), u_k), \tag{11a}$$

$$\frac{dP_k(t)}{dt} = A_k(t)P_k(t) + P_k(t)A_k(t)^T + \sigma\sigma^T, \tag{11b}$$

given the initial conditions

$$\hat{x}_k(t_k) = \hat{x}_{k|k}, \tag{12a}$$

$$P_k(t_k) = P_{k|k}. \tag{12b}$$

and where

$$A_k(t) = A(t, \hat{x}_k(t), u_k) = \frac{\partial f}{\partial x}(t, \hat{x}_k(t), u_k), \tag{13}$$

is a linearization of the drift function f evaluated at $\hat{x}_k(t)$ with input u_k.

D. Tuning of the Kalman Filter

We use a sampling time of 1 minute as this aligns with the measurement frequency. In our CDEKF time-update, we use 10 sub-samples and the Euler method to compute the one-step predictions. The initial state is defined as $\hat{x}_{1|0} = [G, X]^T = [y_0, 2]^T$ with an initial covariance $P_0 = I$, where I here denotes the identity matrix. We select the measurement covariance as $R_k = 100$ and use $\sigma = \text{diag}(10, 10)$ to scale the process noise.

TABLE I: Parameter Values used in the estimator model.

Parameter			Description
S_G	$1.4 \cdot 10^{-2}$ min^{-1}	[11]	Glucose effectiveness
p_2	$3.0 \cdot 10^{-2}$ min^{-1}	[11]	Rate constant of insulin action
V_G	1.7 dL/kg	[11]	Distribution volume of glucose
G_b	36 mg/dL	[12]	Basal glucose concentration
I_b	0 U/L	[12]	Basal insulin concentration
c_{sf}	1000		Scale factor

III. Clinical Data

We use data from the clinical Phase I trial NCT01173926 [13]. In this dose-response trial, 27 subjects with type 1 diabetes receive single-dose, subcutaneous injections of three different insulin analogues over three separate dosing visits. The trial compares pharmacokinetics and pharmacodynamics (PK/PD) of insulin aspart (iAsp), insulin degludec (iDeg) and insulin degludec/insulin aspart (iDegAsp). Following an

insulin injection, the PD response is evaluated over a 24-hour euglycemic clamp. The PK profile is evaluated over 120 hours for iDeg and 12 hours for iAsp.

IV. Data Selection and Pre-processing

In the analysis, we include the available subset of PK/PD data from the first 12 hours following iAsp and iDeg injection. Although the action of iDeg stretches over more hours, the data subset includes its peak action. From the data set, we use the glucose infusion rate (GIR) as the model input $R_a(t)$, insulin concentration in plasma as the input $I(t)$, and plasma glucose concentration, $G(t)$, as the output. We select subsets where the GIR is actively compensating for the effect of insulin, and where observations are available for plasma glucose and insulin concentration. Fig. 1 shows a conceptual example of the selected data for iAsp and iDeg. The subset marked in green is used for analysis. Out of 27 subjects in the trial, we included 25 subjects that fulfilled our criteria of a complete data set for the analysis. For pre-processing, we cap the plasma glucose measurements at 250 mg/dL to remove outliers that can disturb our filter. In the plasma glucose measurements, we fill in missing values with the latest observation. The GIR and plasma glucose concentration are measured every minute, however the plasma insulin concentration is only measured every 10-60 minutes with reduced frequency over the course of the trial. To obtain a value for insulin concentration every minute, we extrapolate linearly between the measurements.

V. Results

We estimate the rapid- and long-acting insulin sensitivities for each of the 25 subjects. We present insulin sensitivity estimates for the cases when the insulin effect, $X(t)$, is unconstrained and constrained to be positive. We correlate the insulin sensitivity estimates for the rapid- and long-acting insulin. We do a steady state model analysis to explain negative insulin effects.

A. Unconstrained CDEKF

Fig. 2 shows the fit along with the corresponding 95% confidence interval for the estimated rapid- and long-acting insulin sensitivities. The Pearson correlation coefficient is $r = 0.5077$ with the p-value $p = 0.0096$. Linear regression and the plotted estimates show that the S_I for iDeg is significantly lower that for iAsp. This difference mirrors the drug dynamics of iDeg. In the clinical trial, the total insulin concentration in plasma is measured for both iAsp and iDeg. However, a large proportion of iDeg in plasma is bound to albumin and not free to interact with the insulin receptor unlike the measured concentration of iAsp. As a result, the insulin sensitivity of iDeg will appear significantly lower.

B. Constrained CDEKF

For the estimated insulin sensitivities in Fig. 2, the filtered insulin effects may be negative. To ensure positive filtered insulin effects, we scale the filter gain, K_k, by the factor α in an iterative back-tracking procedure until $\hat{x}_{k|k}$ is non-negative. Consequently, while $x_{k|k} < 0$, $K_k = \alpha K_k$ and $\hat{x}_{k|k} =$

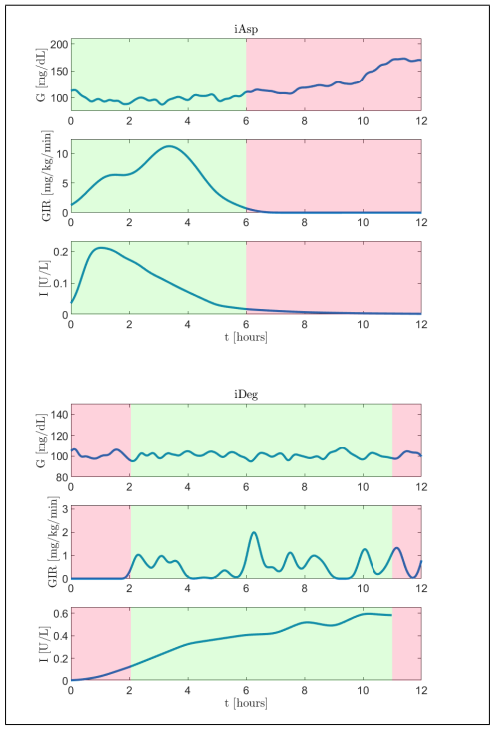

Fig. 1: A conceptual example of a data subsets for iAsp and iDeg. The sets include glucose concentration in plasma, G [mg/dL], glucose infusion rate, GIR [mg/kg/min], and insulin concentration in plasma, I [U/L]. In our analysis, we use the subsets highlighted in green.

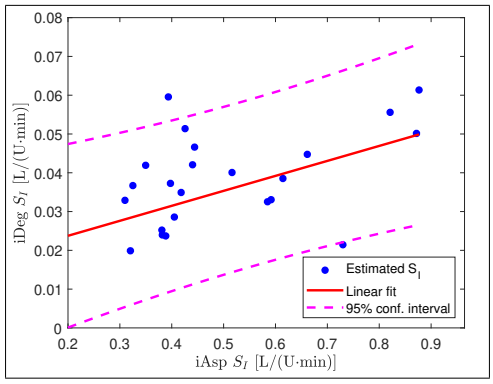

Fig. 2: Unconstrained CDEKF insulin sensitivity estimation. The estimated insulin sensitivity, S_I [L/(U·min)], when $\hat{x}_{k|k}$ obtains negative states. S_I of iDeg is shown as a function of iAsp for the 25 subjects. The linear fit between the estimated values is displayed together with the 95% confidence interval. $S_{I,iDeg} = 0.0314 \cdot S_{I,iAsp} + 0.0223$.

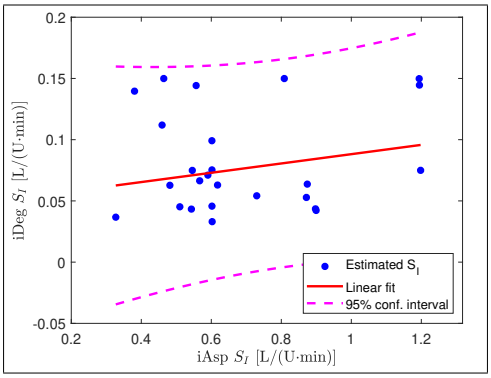

Fig. 3: Constrained CDEKF insulin sensitivity estimation. The estimated insulin sensitivity, S_I [L/(U·min)] of iDeg shown as a function of iAsp for the 25 subjects. The linear fit between the estimated values is displayed together with the 95% confidence interval. $S_{I,iDeg} = 0.0276 \cdot S_{I,iAsp} + 0.0626$.

$\hat{x}_{k|k-1} + K_k e_k$. We use $\alpha = 0.8$ and maximally iterate 30 times. The filter equations (10) use this scaled gain, K_k. Fig. 3 shows the estimated insulin sensitivities (S_I) in each of the 25 subjects for iDeg as a function of iAsp when the filtered states are constrained to be positive. The correlation coefficient between S_I-estimates, $r = 0.1650$, is weaker than when estimated using an unconstrained CDEKF (Fig. 2) as can also be seen from the high p-value, $p = 0.4306$.

C. Model-Based Steady State Target Values

Consider (1) in a fasting situation, i.e. $R_a = 0$. Given a steady state target value for the insulin concentration, $\bar{I}$, the corresponding target values for the insulin effect, $\bar{X}$, and the glucose concentration, $\bar{G}$, are

$$\bar{X} = c_{sf} S_I (\bar{I} - I_b), \tag{14a}$$

$$\bar{G} = \frac{S_G}{S_G + \bar{X}/c_{sf}} G_b = \frac{S_G}{S_G + S_I(\bar{I} - I_b)} G_b. \tag{14b}$$

Reversely, given a steady state target fasting glucose concentration, $\bar{G}$, the corresponding target values for the insulin effect, $\bar{X}$, and the insulin concentration, $\bar{I}$, are

$$\bar{X} = c_{sf} S_G \left(\frac{G_b}{\bar{G}} - 1 \right), \tag{15a}$$

$$\bar{I} = \frac{1}{c_{sf} S_I} \bar{X} + I_b = \frac{S_G}{S_I} \left(\frac{G_b}{\bar{G}} - 1 \right) + I_b. \tag{15b}$$

This analysis reveals that the target insulin effect may be positive or negative depending on the parameters and in particular the pair (G_b, I_b). Accordingly, as fitting functions, negative insulin effects can be accepted.

VI. Conclusions

In standard-of-care translation algorithms, a unit-to-unit switch is applied when switching from pump- to pen-based treatment, and vice versa. From this, we expect to see a clear correlation across individuals in the dose-response to rapid- and long-acting insulin. Nonetheless, our results do not strongly support the assumption that insulin dose-conversion between analogues can be standardized for all individuals.

Using the Bergman model (1) and a CDEKF for the stochastic extension (6), we estimated the insulin sensitivity for rapid- and long-acting insulin, i.e. aspart and degludec. In the unconstrained estimation, a correlation between these insulin sensitivities exists. However, the uncertainties in the insulin sensitivities (PD) as well as the insulin absorption uncertainties (PK) may make clinical utilization of the correlation for dosing in the switch from pump to pen difficult.

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APPENDIX C

Conference Paper

Estimating a Personalized Basal Insulin Dose From Short-Term Closed-Loop Data in Type 2 Diabetes

Estimating a Personalized Basal Insulin Dose from Short-Term Closed-Loop Data in Type 2 Diabetes

Sarah Ellinor Engell[1,2], Tinna Björk Aradóttir[1], Tobias K. S. Ritschel[2], Henrik [1], John Bagterp Jørgensen[2]

***Abstract*— In type 2 diabetes (T2D) treatment, finding a safe and effective basal insulin dose is a challenge. The dose-response is highly individual and to ensure safety, people with T2D "titrate" by slowly increasing the daily insulin dose to meet treatment targets. This titration can take months. To ease and accelerate the process, we use short-term artificial pancreas (AP) treatment tailored for initial titration and apply it as a diagnostic tool. Specifically, we present a method to automatically estimate a personalized daily dose of basal insulin from closed-loop data collected with an AP. Based on AP-data from a stochastic simulation model, we employ the continuous-discrete extended Kalman filter and a maximum likelihood approach to estimate parameters in a simple dose-response model for 100 virtual people. With the identified model, we compute a daily dose of basal insulin to meet treatment targets for each individual. We test the personalized dose and evaluate the treatment outcomes against clinical reference values. In the tested simulation setup, the proposed method is feasible. However, more extensive tests will reveal whether it can be deemed safe for clinical implementation.**

I. Introduction

Worldwide, one in eleven people live with diabetes, whereof approximately 90% have type 2 diabetes (T2D). Left untreated, people with T2D suffer from persistent high blood glucose levels that eventually lead to complications in many parts of the body. Fortunately, numerous treatment options exist. As T2D progresses, daily injections of basal insulin become necessary to lower the elevated blood glucose levels [1]. However, basal insulin initiation, a process known as titration, is challenging as the insulin response in the body varies greatly between individuals. It is crucial to avoid over-dosing as too much insulin can quickly cause life-threatening low glucose levels. To obtain a safe and effective dose, the amount of injected insulin is gradually increased in size, until the desired fasting blood glucose level is reached. The insulin dose is adjusted manually based on pre-breakfast finger-prick blood glucose measurements. Typically, this titration is performed at home and can take several months. For more than half of the individuals initiating insulin treatment, the task is so demanding that it leads to non-adherence and failed insulin titration [2]. In the future, the burden of self-titration may be overcome with automated titration solutions.

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Several automated solutions have been proposed in the literature, ranging from model-free extremum seeking control [3], to model predictive control [4], and iterative learning [5]. In simulation, these methods have shown to speed up the titration process, improve safety and reduce the workload compared to standard-of-care methods. A few methods have been tested in clinical trials with promising results [6]–[8]. Still, simple self-titration remains the standard-of-care solution in clinics today [1].

Another way to automate insulin treatment is through closed-loop control with an artificial pancreas (AP) system. In recent years, this has become a viable treatment option for people with type 1 diabetes [9]. In the coming years, commercial AP systems are expected to become available to people with T2D as well [10]. An AP system consists of a control algorithm that, based on frequent sensor measurements from a continuous glucose monitor (CGM), automatically adjusts and infuses fast-acting insulin via an insulin pump to achieve target glucose values. Although these systems automate insulin dose selection and delivery, their technical complexity may limit the uptake in an older T2D population [11]. In light of this, the greater population's treatment needs may be met with simpler injection-based solutions. However, the emergence of closed-loop treatment for T2D can enable new forms of automated titration through short-term AP-use [12]. We propose that pump-induced system excitation can determine what basal insulin dose will bring each individual to treatment targets on once-daily injection-based treatment.

In this work, we present a method to estimate a personalized basal insulin dose from short-term closed-loop data. Based on data from a stochastic simulation model, we use maximum likelihood estimation (MLE) to identify parameters in a simpler prediction model for 100 virtual people. For a given set of parameters, we use the continuous-discrete extended Kalman filter (CDEKF) to approximate the likelihood function which is maximized in MLE. With the identified model, we compute a personalized insulin dose to meet treatment targets. Finally, we test the computed daily dose of insulin in our simulation model and evaluate the treatment outcomes.

This paper is organized as follows. In Section II, we present the two physiological models for data generation and parameter estimation. We briefly describe the parameter estimation technique. Section III presents the results with the proposed method for three different data-collection scenarios. In Section IV, we evaluate and discuss the performance of

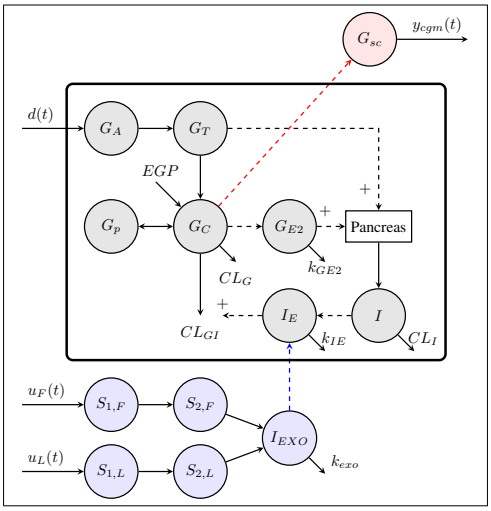

Fig. 1. Model Structure for the Simulation Model. Meals, $d(t)$, fast-acting insulin, $u_F(t)$, and long-acting insulin, $u_L(t)$, are the inputs. The continuous glucose monitor (CGM) outputs the subcutaneous glucose concentration, $y_{cgm}(t)$. The compartments denote the glucose absorption, G_A, glucose transport, G_T, peripheral glucose, G_p, central glucose, G_C, subcutaneous glucose, G_{sc}, glucose effect on insulin secretion, G_{E2}, plasma insulin, I, insulin effect, I_E, and the exogenous insulin, I_{EXO}. Exogenous fast-acting insulin is absorbed via the compartments $S_{1,F}$ and $S_{2,F}$, and exogenous long-acting insulin is absorbed through $S_{1,L}$ and $S_{2,L}$. The shown inputs and outputs from compartments are endogenous glucose production, EGP, glucose-dependent clearance, CL_G, insulin-dependent clearance, CL_{GI}, endogenous insulin clearance, CL_I, exogenous insulin clearance rate, k_{exo}, and the rate constants for effect delay, k_{IE} and k_{GE2}.

the tested control strategy. Section V concludes the paper and presents ideas for future work.

II. Methods

In this section, we introduce the simulation model used to generate data for 100 virtual people on closed-loop treatment. We use the data for parameter estimation in a simpler prediction model, presented in Section II-B. We use the CDEKF and MLE to identify model parameters. Section II-D and II-E briefly describe the estimation technique. To conclude, we present how an optimal basal insulin dose is calculated from the estimated parameters.

A. Simulation Model

To simulate a cohort of 100 virtual people with T2D, we employ a stochastic version of the integrated glucose-insulin (IGI) model [12], [13]. The model consists of 14 differential equations that together describe how glucose and insulin interact in the human body. We apply an extended version where exogenous fast- and long-acting insulin can be added as inputs and the subcutaneous blood glucose can be measured. Fig. 1 shows the model structure and the model equations are listed in [12].

The glucose-insulin dynamics are a continuous process observed through discrete measurements,

$$dx(t) = f(t, x(t), u(t), d(t), \theta)dt + \sigma d\omega(t) \tag{1a}$$
$$y_k = h(t_k, x(t_k)) + v_k \tag{1b}$$

where $x(t)$ is the state vector, $u(t)$ is the input vector containing both u_F and u_L, $d(t)$ is the meal disturbance, and θ constitutes the model parameters. The drift function, f, is given by the IGI model. For the input, we assume a zero-order hold parametrization, i.e. $u(t) = u_k$ for $t_k \leq t < t_{k+1}$. The process noise, $\{\omega(t), t \geq 0\}$, is a standard Wiener process and its increment has covariance Idt. $\omega(t)$ is scaled by a time-invariant diagonal matrix, σ, adding noise to the central glucose compartment, G_c. The measurement noise on y_{cgm} is assumed normally distributed, $v_k \sim N_{iid}(0, R_k)$.

B. Prediction Model

We use the fasting blood glucose model by Aradóttir et al. [14] to obtain a personalized dose-response model for each virtual person. The authors designed the model such that it allows for identification of glucose-insulin dynamics with one input (insulin) and one output (fasting glucose) [14]. The model consists of four differential equations,

$$\frac{dx_1(t)}{dt} = \frac{1}{p_1}u(t) - \frac{1}{p_1}x_1(t) \tag{2a}$$
$$\frac{dx_2(t)}{dt} = \frac{1}{p_1}x_1(t) - \frac{1}{p_1}x_2(t) \tag{2b}$$
$$\frac{dx_3(t)}{dt} = p_3(x_2(t) + p_7x_4(t)) - p_3x_3(t) \tag{2c}$$
$$\frac{dx_4(t)}{dt} = -(p_5 + p_4x_3(t)) \cdot x_4(t) + p_6, \tag{2d}$$

that represent the glucose-insulin dynamics in a human body. The states x_1 [U/min] and x_2 [U/min] describe the body's absorption of insulin input, u [U/min]. The effect of the insulin is represented by x_3 [U/min] and the blood glucose concentration is x_4 [mmol/L]. The system outputs discrete sensor measurements,

$$y_k = x_4(t_k) + v_k. \tag{3}$$

As in the simulation model, the measurement noise is assumed normally distributed, $v_k \sim N_{iid}(0, R_k)$.

We estimate the parameters, $\theta = [p_4; p_6; p_7]$, as these are known to be identifiable from sparse data [14] and therefore may also be identified from our intense data capture. We apply published population parameters for p_1, p_3 and p_5. We use the published population parameters as the initial guess for p_4, p_6, and p_7 in the parameter estimation. Parameter descriptions and published values are found in Table I.

C. Data Generation

To simulate a cohort of a hundred virtual patients, we draw parameters from the published distribution for the insulin sensitivity and insulin production [13]. We select body weights from the distribution in [16] and scale the weight-dependent parameters accordingly. After parameter selection, we screen the virtual people to ensure that their insulin response is feasible for a T2D population. Before

TABLE I
POPULATION PARAMETERS FOR THE PREDICTION MODEL

Parameter	Value	Unit	Description	Reference
p_1	60	[min]	Time constant for fast-acting insulin absorption	[15]
p_3	0.011	[1/min]	Delay in insulin action	[14]
p_4	0.44	[1/U]	Insulin sensitivity	[14]
p_5	0.0023	[1/min]	Insulin-independent glucose clearance	[14]
p_6	0.0672	[mmol/L·min]	Endogenous glucose production	[14]
p_7	0.0018	[U·L/mmol·min]	Endogenous insulin production	[14]

insulin treatment, 95% of the individuals in [16] have a fasting blood glucose level below 15 mmol/L. As the cohort in [16] is a subset of the insulin-requiring T2D population in the real world, we allow for higher fasting blood glucose values in our simulated cohort. When no insulin is given, the fasting blood glucose must lie within a 7.5-20 mmol/L range. Additionally, the insulin dose required to reach a glucose level of 5.8 mmol/L must not surpass 150 U. If the constraints are violated, we re-sample the model parameters until the constraints are met.

As a simplified AP system, we employ an integrator-based control algorithm [12] that drives the blood glucose towards the 5.8 mmol/L reference value. We simulate closed-loop treatment in a fasting state with no meals, $d(t) = 0$, for 24 and 48 hours. The selected scenario does not represent a realistic setup to apply in clinic. However, it facilitates an undisturbed assessment of how the controller gain and the duration of excitation influences the quality of a target dose estimate for basal insulin.

To mimic the continuous-discrete nature of sensor measurements from a physiological system, we simulate the IGI model using an Euler-Maruyama scheme with a time step size of one minute. Every five minutes, the CGM outputs a noise-corrupted measurement, y_k, of the subcutaneous glucose concentration. When estimating parameters in the prediction model, we use the CGM measurements from this simulation as input to the CDEKF.

The simulation and parameter estimation was implemented in `Matlab R2020b`.

D. Continuous-Discrete Extended Kalman Filter

We use the iterative framework of the CDEKF for parameter estimation. At every sample point, k, we update the estimate of our system states, $\hat{x}_{k|k-1}$, and the state covariance matrix, $P_{k|k-1}$, using the incoming measurement, y_k. For this update, we compute the innovation,

$$e_k = y_k - \hat{y}_{k|k-1} \tag{4}$$

as the difference between the measured value, y_k, and the model predicted output, $\hat{y}_{k|k-1} = C_k\hat{x}_{k|k-1}$. The matrix C_k is a linearization of the measurement equation, $h(t_k, \hat{x}_{k|k-1})$, at the current state estimate, $\hat{x}_{k|k-1}$,

$$C_k = \frac{\partial h}{\partial x}(t_k, \hat{x}_{k|k-1}). \tag{5}$$

Using the variance of the measurement noise, R_k, we can obtain the covariance of the innovation signal, $R_{e,k}$, and compute the Kalman gain, K_k,

$$R_{e,k} = C_k P_{k|k-1} C_k^T + R_k, \tag{6a}$$
$$K_k = P_{k|k-1} C_k^T R_{e,k}^{-1}. \tag{6b}$$

Finally, we update the estimate of the states and their covariance,

$$\begin{aligned} \hat{x}_{k|k} &= \hat{x}_{k|k-1} + K_k e_k, \\ P_{k|k} &= (I - K_k C_k) P_{k|k-1} (I - K_k C_k)^T \\ &\quad + K_k R_k K_k^T. \end{aligned} \tag{7a}$$

To obtain the one-step prediction of the states and their covariance, we solve a system of differential equations,

$$\frac{d\hat{x}_k(t)}{dt} = f(t, \hat{x}_k(t), u_k, d_k, \theta), \tag{8a}$$
$$\frac{dP_k(t)}{dt} = A_k(t)P_k(t) + P_k(t)A_k(t)^T + \sigma\sigma^T, \tag{8b}$$

with the initial conditions

$$\hat{x}_k(t_k) = \hat{x}_{k|k}, \tag{9a}$$
$$P_k(t_k) = P_{k|k}, \tag{9b}$$

and where

$$\begin{aligned} A_k(t) &= A(t, \hat{x}_k(t), u_k, d_k, \theta) \\ &= \frac{\partial f}{\partial x}(t, \hat{x}_k(t), u_k, d_k, \theta) \end{aligned} \tag{10}$$

is a linearization of the drift function f evaluated at $\hat{x}_k(t)$ with input u_k, disturbance d_k, and parameters θ.

E. Maximum Likelihood Estimation

From a discrete series of measurements,

$$\mathcal{Y}_N = \{y_0, y_1, ..., y_N\}, \tag{11}$$

obtained from the simulation model, we estimate the parameter set, θ, that maximizes the conditional probability,

$$p(\mathcal{Y}_N|\theta) = p(y_N, y_{N-1}, ..., y_0|\theta). \tag{12}$$

This is equivalent to minimizing the negative log-likelihood as a function of θ, i.e.

$$\hat{\theta} = \arg\min_{\theta} V(\theta) \tag{13}$$

where

$$V(\theta) = -\ln(p(\mathcal{Y}_N|\theta)) \\ = \frac{1}{2}(N+1)n_y \ln(2\pi) \\ + \frac{1}{2}\sum_{k=0}^{N} \ln[\det(R_{e,k})] + e_k^T R_{e,k}^{-1} e_k. \quad (14)$$

Here, e_k and $R_{e,k}$ are CDEKF outputs for a selected parameter set θ. n_y denotes the number of system outputs.

F. Computing the Target Insulin Dose

Once we identify a set of parameters for a personalized dose-response model, we calculate a daily insulin dose. With the estimated parameter set, we solve for the insulin infusion rate in (2),

$$u_{target} = \frac{p_6 - y_{ref} \cdot p_5}{y_{ref} \cdot p_4} - p_7 \cdot y_{ref} \quad (15)$$

that will bring the blood glucose concentration to the desired reference value, $y_{ref} = 5.8$ mmol/L. The infusion rate, u_{target}, is given in U/min. To get a daily dose, we calculate the total insulin delivered over 24 hours,

$$u_{basal} = u_{target} \text{ [U/min]} \cdot 60 \text{ [min/h]} \cdot 24 \text{ [h/day]} \quad (16)$$

In our simulation model, we inject the daily dose of basal insulin, u_{basal}, at 7:00 AM on the five consecutive days after closed-loop treatment.

III. Results

In the first simulation scenario, we collect closed-loop data for 48 hours as shown in Fig. 2. Throughout the closed-loop period, the controller gradually increases the infused insulin and the glucose levels are steered towards the green target area for the 100 virtual people. Based on the collected data, we compute a basal insulin dose at the end of day 2 and implement it on day 3. After the switch to injection-based treatment on day 3, the majority of the simulated people have glucose levels within the 4.4-7.2 mmol/L target area. For three virtual people, the calculated insulin dose is too high and the glucose levels drop below 3.9 mmol/L. This is dangerously low, and would not be accepted in a clinical implementation. Note that the poor dose estimates do not coincide with the outliers in the boxplot of basal insulin doses. The three virtual people with poor insulin dose estimates show a minimal reduction in glucose values during the closed-loop period. We expect that a higher system excitation for these individuals, e.g. a more aggressive controller, can improve dose estimates.

Across the simulated cohort, the general performance is good when 48 hours of data is used to estimate a personalized basal insulin dose in a fasting scenario. We wish to determine whether an equivalent performance can be reached with less data. In Fig. 3, we see the outcomes for only 24 hours of closed-loop data collection.

With 24 hours of data, 78% of the basal insulin doses are overestimated, driving blood glucose concentrations far below the 3.9 mmol/L threshold. In conclusion, the system

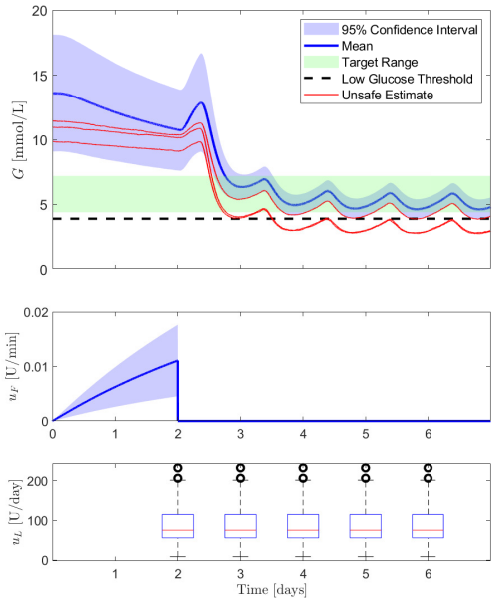

Fig. 2. 48 Hours of Closed-Loop Data for 100 Virtual People. In the closed-loop period, glucose levels, G, are driven towards the $4.4 - 7.2$ mmol/L target range by fast-acting insulin infusion, u_F. Based on the recorded closed-loop data, a target insulin dose is computed and administered as a daily injection of long-acting insulin, u_L, in the five last simulation days. In red, we plot the individual curves where the glucose level drops below 3.9 mmol/L.

excitation does not appear to be sufficient to capture essential system dynamics. In an attempt to increase system excitation and improve performance, we increase the controller gain by a factor of three. The result is shown in Fig. 4.

With a tripled controller gain over a 24-hour period, we see an improved performance compared to the nominal gain. Of the 100 virtual people, only seven have overestimated doses. As in the 48 hour simulation, the people with poor dose estimates have a smaller gradient compared to the population mean. This could indicate a lower degree of system excitation with the chosen controller gain. The majority of simulated people achieve target glucose values when treated with the computed basal insulin dose. Still, the best performance is seen in the scenario where closed-loop data is collected over 48 hours, suggesting that both data quantity and system excitation are crucial if this method is to be applicable in clinical practice.

IV. Discussion

In this work, we investigate the feasibility of an automated titration solution for people with T2D. We show how a closed-loop system may be used for system excitation and enable target dose estimation. Both the the magnitude of the controller gain and the length of the closed-loop treatment affect the efficacy and safety of the proposed method.

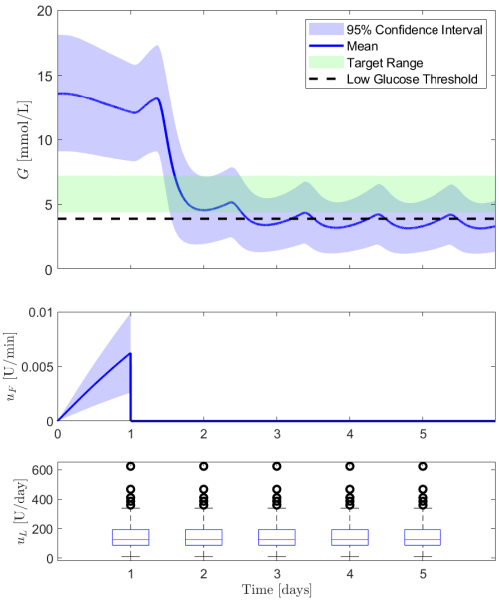

Fig. 3. 24 Hours of Closed-Loop Data for 100 Virtual People. For 24 hours, the control algorithm gradually increases fast-acting insulin, u_F, to steer the blood glucose, G, into the $4.4-7.2$ mmol/L target range. After the closed-loop data collection, we estimate a personalized, daily insulin dose. We simulate the outcomes when the dose is administered as a daily injection of long-acting insulin, u_L. With the short data-collection period, we overestimate the required daily dose of insulin for 78 people.

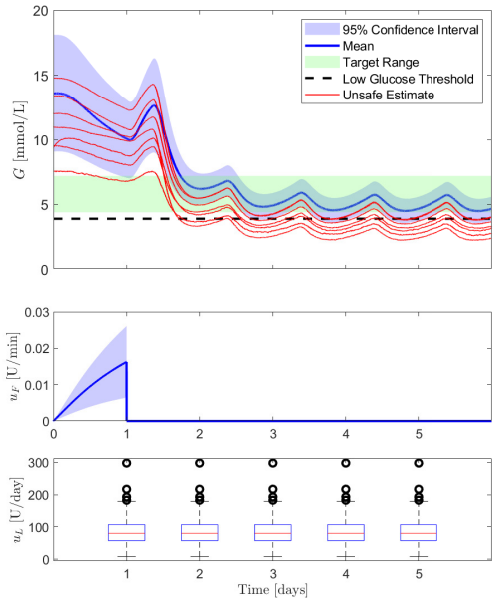

Fig. 4. Tripled Controller Gain and 24 Hours of Closed-Loop Data. To improve the system excitation, we triple the controller gain compared to Fig. 3. As a result, the blood glucose, G, drops quicker towards the $4.4-7.2$ mmol/L target range, and the pump infuses more fast-acting insulin, u_F. We see that the daily dose estimate of long-acting insulin, u_L, is safer. Only seven people experience blood glucose concentrations below 3.9 mmol/L. In red, we show the seven individual curves with poor dose estimates.

The controller gain applied in Fig. 2 and 3, results in a total daily dose of less than 0.2 U/kg body weight after 24 hours. This is in accordance with standard-of-care titration guidelines for basal insulin that recommend an initial daily dose of 0.1-0.2 U/kg body weight. We have seen in Fig. 4 that an increased controller gain excites the underlying system to a greater extent, and consequently, the parameter estimates improve. In a real-world setting, an increased controller gain may not cause a direct risk of low blood glucose levels, however, a sudden drop in glucose concentration driven by the AP can be highly uncomfortable for the user. Additionally, people with sustained high blood glucose levels over long periods are at risk of nerve and eye damage when blood glucose decreases rapidly [17].

Ideally, the AP system should be worn for several days with a moderate gain to estimate a safe and effective basal insulin dose. Modern patch pumps, i.e. tubeless insulin pumps that are fixed to the skin with adhesives, have a wear-time of 72 hours. These pumps could provide a user with a convenient way to collect multiple days of data for system identification. However, if the user is expected to refrain from eating in the whole closed-loop period, the parameter estimation must be made feasible within a shorter time frame, e.g. 12 hours. This may not be possible. In simulation, we can choose to disregard multiple disturbances from meals and interday variations in insulin response. In reality, the identification is more complicated. In an uncontrolled real-world setting, the complexity of the model identification process will increase as glucose excursions after, e.g. un-documented meals interfere with the administered insulin infusion rate. A way to circumvent this could be to introduce controlled meal tests, i.e. known quantities of carbohydrates consumed at fixed hours. The meal tests can be used for additional system excitation and will additionally make the identification process more comfortable for the user. To improve system identification, the controller input and meal tests could be tuned in an optimal design of experiment.

In a real-world setting, we may experience the unfortunate situation that the model parameters cannot be estimated from the collected data. If no more closed-loop data collection is possible, we propose a unit-to-unit conversion from the pump infusion rate to an injection-based dose of basal insulin, followed by manual titration. In this way, the titration already performed by the AP would not be lost.

In the case where dose estimates are found, clinicians can be hesitant to deem them safe. To increase the safety margin in a clinical implementation, a fraction of the predicted dose may be used instead of the full dose, e.g. 75% of the predicted dose. Alternatively, the daily injection size can be increased in controlled steps until the predicted target dose is

reached. Compared to standard-of-care titration, these steps would be larger and would allow us to reach treatment targets faster. A step-wise increase in dose size may be safer and less unpleasant for the user, as it will result in a more controlled decrease in blood glucose. Another way to test the predicted dose would be to continue the pump treatment and increase the infusion rate. In this way, it remains possible to quickly shut off insulin infusion if the predicted dose brings the blood glucose into dangerously low values.

In this paper, we test the proposed method on a simple simulated scenario. As a result, the implementation is, in the current state, not ready for clinical use. However, this work presents a new approach to insulin titration in T2D that may hold clinical potential. For future work, a higher complexity in the simulation scenario will allow evaluation in a setup that closer resembles real-world cases.

V. Conclusion

In this work, we employ closed-loop data for system identification in people with T2D. Based on 24-48 hours of glucose-insulin data, we identify a personalized basal insulin dose using the CDEKF and maximum likelihood estimation. The proposed method is feasible in the chosen simulation setup, however, the efficacy and safety of the dose estimates heavily depend on the system excitation. We can affect the system excitation by increasing the controller gain and extending the data collection period. In future work, we aim to instigate how meal tests can be included in using optimal experiment design to make the implementation viable in a real-world setting allowing people to eat.

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APPENDIX D

Conference Paper

From Optimal Design of Experiment to Safe System Identification in Type 2 Diabetes

From Optimal Design of Experiment to Safe System Identification in Type 2 Diabetes

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Abstract: Model-based design of experiment (MBDoE) provides a framework to collect informative data for system identification. However, a parametric and structural mismatch between the design model and the underlying physical system can lead to hazardous experiments in safety critical systems. In this work, we present a method to safely improve system identification based on insights from a model-based optimal experimental design. From a visual inspection of a MBDoE, we select an approximated output curve fulfilling system constraints as a reference for the physical system. To avoid open-loop implementation of the MBDoE, we use our approximated reference together with a reference-tracking controller to collect experimental data in closed-loop. In this type 2 diabetes (T2D) case study, the proposed design method is safe and provides informative experimental data for system identification.

Keywords: Diabetes, Optimal Experimental Design, Insulin, System Identification, Artificial Pancreas, Simulation

1. INTRODUCTION

At the time of formulation, most models contain unknown parameters to identify. However, experimental data for parameter estimation can be tedious and costly to obtain. In many systems, it is a challenge to collect sufficiently informative data as the modelled system must operate within fixed safety constraints. Hence, it is of economic interest to optimize the experimental design to collect informative data in a safe way. Model-based design of experiment (MBDoE) offers a systematic approach to improve experimental design (Galvanin and Bezzo, 2018). Based on a preliminary system model, the aim of MBDoE is to determine the experimental preconditions, e.g. control inputs or sampling times, that provide the optimal data for parameter estimation under input and output constraints. As the experimental design is based on the preliminary model, the initial assumptions influence the quality and safety of the optimal solution. When the physical system and its model have significant parametric and structural mismatches, the computed *optimal* experiment is far from optimal. At best, the model assumptions lead to scarcely informative experiments. Under the least favorable conditions, the optimized design is unsafe for the physical system.

Parametric and structural mismatch is a known issue that various MBDoE approaches address (Galvanin and Bezzo, 2018; Petsagkourakis and Galvanin, 2020; Pankajakshan et al., 2021). One approach is online model-based redesign of experiments (OMBRE). This method exploits incoming information to improve the design whilst the experiment is running. Prior to redesign, the preliminary model parameters are updated and the new model is used for design optimization. In this way, the uncertainty on the initial parameter values may be reduced such that the new optimization model corresponds closer to the underlying physical system. Another approach is to use a back-off strategy. Here, the model uncertainty is incorporated into the design constraints resulting in a more conservative, and commonly less informative, experimental design. By design, a back-off strategy improves the likelihood that the executed experiment will remain within the constraints. However, neither a back-off strategy nor an online redesign approach can guarantee safety.

Due to the safety risks, direct implementation of MBDoE may not be feasible in all systems. Still, we hypothesize that it is possible to safely improve an experimental design by incorporating the knowledge gained through MBDoE. In controller design, optimal control methods can be used to learn how to best regulate system outputs. An advanced control strategy, e.g. model predictive control, may be mimicked in a simpler design, e.g. a PID controller, once the patterns in optimal behaviour are known (Stoustrup, 2013). We propose a similar approach to experimental design. We compute an optimal system output with MBDoE and use its characteristics, e.g. sinusoidal behaviour, to design a reference for our system output. To mimic the optimal experiment, we employ a reference-tracking controller to steer the system along the selected output trace. We hypothesize that the resulting set of inputs and outputs will improve parameter estimation compared to the baseline experiment, whilst avoiding the risks of a

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direct MBDoE implementation. In this work, we present our method with an example from type 2 diabetes (T2D) treatment.

This paper is structured as follows. In Section 2, we introduce the challenges in insulin treatment for people with T2D and how these challenges may be met with a model-based dose-guidance algorithm. To refine this algorithm, Section 3 presents how to apply learnings from MBDoE to improve system identification. In Section 4, we show results from a baseline case, a direct implementation of a MBDoE and an implementation of the proposed method. We discuss and evaluate the performance of the three approaches in Section 5. Section 6 summarizes the key contributions of this paper.

2. INSULIN TREATMENT IN T2D

In T2D, an imbalance between insulin secretion and insulin sensitivity leads to elevated blood glucose concentrations. Daily insulin injections may be used to lower the blood glucose into a healthy range (American Diabetes Association Professional Practice Committee et al., 2022). However, the response to insulin therapy varies greatly between individuals and overdosing is dangerous. To reach target glycemia safely, people with T2D gradually increase the daily injected insulin dose through an iterative process known as titration. Titration is performed at home with minimal guidance from health care professionals. This places a significant workload on the individual. Based on daily measurements of fasting blood glucose, people with T2D adjust the insulin dose in small increments until the desired glucose concentration is reached. This process can take several months. Unfortunately, less than half of the people initiating treatment reach glycemic targets. The high workload is one of the main reasons for failed titration (Khunti et al., 2020).

To reduce the burden of titration, the process may be automated. In previous work, we propose a model-based dose-guidance algorithm to automate insulin titration (Engell et al., 2022). To predict a safe and effective dose, we use a closed-loop system to collect data for 24-48 hours. With this data, we identify parameters in a personalized dose-response model and predict a daily dose of injected insulin to reach glucose targets. We test the predicted target dose in our simulation model and evaluate the clinical outcomes. Figure 1 illustrates the dose-guidance solution. In this paper, we apply optimal design of experiment to improve parameter estimates in the personalized dose-response models. Compared to the base case in Engell et al. (2022), we evaluate whether a MBDoE-based method leads to safer and more efficient dose predictions.

3. METHOD

In this section, we briefly introduce the two models used in design and simulation. We describe the MBDoE optimization problem. For the optimization problem, we define the decision variable and the system constraints. From the MBDoE solution, we learn optimal behaviours of the output and run a new 24-hour experiment with reference tracking of the glucose trace.

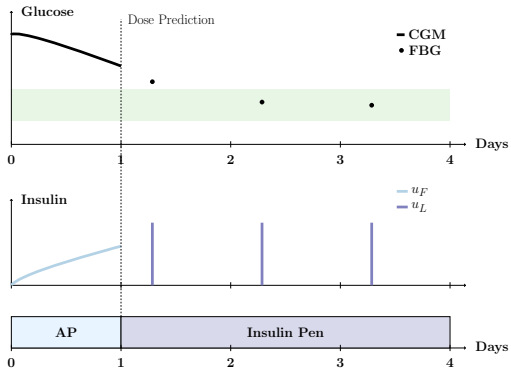

Fig. 1. A visualization of the dose-guidance solution from Engell et al. (2022). An artificial pancreas (AP) may be used to predict a safe and effective insulin dose for injection-based therapy with long-acting insulin. In the AP period, fast-acting insulin (u_F) is infused based on glucose measurements from a continuous glucose monitor (CGM). We use the AP data to identify parameters in a dose-response model. The model is used to predict an insulin dose to reach target glucose concentrations. After dose-prediction, a daily dose of long-acting insulin (u_L) is injected before breakfast and fasting blood glucose (FBG) measurements are used for daily monitoring.

3.1 Models for Experimental Design and Simulation

We employ a simple model for MBDoE and test the design on a model with higher complexity. For our design model, we use a fasting glucose model from Aradóttir et al. (2018). The model consists of four differential equations,

$$\frac{dx_1(t)}{dt} = \frac{1}{p_1}u(t) - \frac{1}{p_1}x_1(t) \tag{1a}$$

$$\frac{dx_2(t)}{dt} = \frac{1}{p_1}x_1(t) - \frac{1}{p_1}x_2(t) \tag{1b}$$

$$\frac{dx_3(t)}{dt} = p_3(x_2(t) + p_7x_4(t)) - p_3x_3(t) \tag{1c}$$

$$\frac{dx_4(t)}{dt} = -(p_5 + p_4x_3(t)) \cdot x_4(t) + p_6, \tag{1d}$$

to represent the glucose-insulin dynamics in a person with T2D. The states x_1 [U/min] and x_2 [U/min] describe the absorption of insulin input, u [U/min]. x_3 [U/min] is the effect of insulin and x_4 [mmol/L] is the blood glucose concentration. A sensor outputs discrete measurements from the system,

$$y_k = x_4(t_k) + v_k. \tag{2}$$

We assume the measurement noise is normally distributed, $v_k \sim N_{iid}(0, R)$. We apply $R = 0.1872$ mmol^2/L^2 (Mahmoudi et al., 2018). For the design model, we use the published population parameters listed in Table 1.

To simulate a virtual cohort with diabetes, we use an augmented version of the integrated glucose-insulin (IGI) model from Engell et al. (2021). The model has 14 compartments and incorporates more physiological mechanisms than the simpler model by Aradóttir et al. To generate 100 virtual people, we apply the simulation setup from Engell et al. (2022).

Table 1. Design Model Parameters

θ	Value	Unit	Reference
p_1	60	[min]	Kanderian et al. (2009)
p_3	0.011	[1/min]	Aradóttir et al. (2018)
p_4	0.44	[1/U]	Aradóttir et al. (2018)
p_5	0.0023	[1/min]	Aradóttir et al. (2018)
p_6	0.0672	[mmol/L·min]	Aradóttir et al. (2018)
p_7	0.0018	[U·L/mmol·min]	Aradóttir et al. (2018)

3.2 Optimal Experimental Design

MBDoE aims to design an experiment that increases the accuracy of parameter estimates by reducing the value of the parameter variance-covariance matrix. To do this, we determine the decision variable, ϕ, which can dictate one or more of the experimental preconditions, e.g. the inputs, the sampling times, or the initial states. In this work, we determine the dynamic input profile, $u(t, \phi)$. To ensure the MBDoE is tractable, we assume a zero-order hold parametrization on $u(t, \phi)$. The input to the system is piece-wise constant. We wish to optimise the selection of ϕ to gain maximal information through the statistical criterion $V(\phi, \theta)$,

$$\min_{\phi} \quad V(\phi, \theta) \tag{3a}$$
$$s.t. \quad x(0) = x_0 \tag{3b}$$
$$\dot{x}(t) = f(t, x(t), u(t, \phi), \theta) \tag{3c}$$
$$y_k = h(t_k, x(t_k)) + v_k \tag{3d}$$
$$0 \geq c(t, x(t), u(t, \phi), \theta) \tag{3e}$$

where $f(\cdot)$ is the design model with the assumed parameter values, θ, states, $x(t)$, and inputs, $u(t, \phi)$. The model predicts discrete system outputs, y_k, through the measurement function, $h(\cdot)$. The output is corrupted by measurement noise, $v_k \sim N_{iid}(0, R)$. Constraints on the states and inputs are given by 3e.

Different statistical criteria, $V(\phi, \theta)$, for MBDoE exist (Bhonsale et al., 2022). To minimize the arithmetic mean of all the parameters' errors, we apply A-optimality, i.e. minimizing the trace of the inverse Fisher Information matrix, F,

$$V(\phi, \theta) = \text{tr}\left(F^{-1}\right), \tag{4}$$

where

$$F = \sum_{k=1}^{N} S_y(k)^T R^{-1} S_y(k). \tag{5}$$

R is the covariance matrix of the measurements, and S_y is the output sensitivity matrix. We compute the sensitivity matrix at each time step, k,

$$S_y(k) = \frac{\partial y}{\partial \hat{\theta}}(t_k) \tag{6}$$

where $S_y(k)$ is a measure of the change in the output for each of the m estimated parameters. We apply central differentiation to numerically approximate $S_y(k)$, and we assume that R is known.

3.3 Decision Variable

We fix the length of the experiment to 24 hours. In diabetes treatment, it is not unseen to use fasting periods of up to 24 hours to identify the right insulin dose (Nauck et al., 2021). In this work, we let the decision variable, ϕ, consist of 24 one-hour blocks of piece-wise constant insulin input.

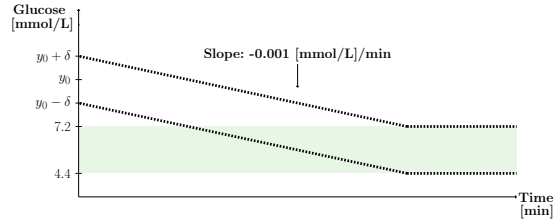

Fig. 2. Output constraints for the experimental design. Over the course of the experiment, the glucose concentration must drop slowly towards the target range. We allow the glucose to fluctuate within the constraints $y_0 - 0.001 \cdot t_k - \delta \leq y_k \leq y_0 - 0.001 \cdot t_k + \delta$. Where y_0 is initial fasting glucose, t_k is the time in minutes, y_k is the output at time t_k, and δ is half of the width of the target range. Once the target range is reached, it defines the output constraints.

We optimize how much fast-acting insulin [mU/min] must be infused through an insulin pump at every time point in order to best identify three parameters in the design model. The parameters $\theta = [p_4,\ p_6,\ p_7]$ describe insulin sensitivity, endogenous glucose production, and endogenous insulin production, respectively. They are identical to the parameters estimated in Engell et al. (2022).

3.4 Design Constraints

We select input and output constraints for our design. The input, infused insulin, must be non-negative to be physiologically feasible. To ensure safety, we incorporate output constraints on the glucose concentration. We apply the 4.4-7.2 mmol/L target glucose range from clinical guidelines (American Diabetes Association Professional Practice Committee et al., 2022). Despite the desire to quickly reach the target range, we aim to avoid rapid decreases in blood glucose concentration as this can cause nerve- and eye-damage (Gibbons, 2020). We simulate how low the fasting glucose drops when an insulin naive cohort is given a standardized first dose of 0.1U/kg insulin (American Diabetes Association Professional Practice Committee et al., 2022). From the simulation, we select a rate of change of -0.001 (mmol/L)/min for the output constraints.

Given the initial fasting blood glucose measurement, y_0, and the 4.4-7.2 mmol/L target range, we define constraints that describe how much the fasting glucose concentration may drop over time. Figure 2 shows the output constraints.

3.5 Reference-Tracking based on MBDoE Output

We cannot be sure that the physical system aligns with the design model assumptions. However, the solution to (3) offers some insights into what kind of data is optimal for identification of θ. We solve the optimization problem in (3) with the selected constraints and design model assumptions. Figure 3 shows the optimal experimental design.

In Figure 3, the insulin infusion causes the glucose concentration to fluctuate between the upper and lower constraint in a sinusoidal manner. Based on this observation, we hypothesize that system identification will improve if

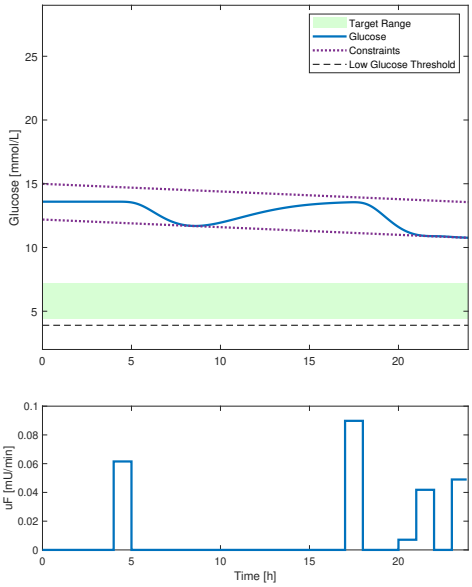

Fig. 3. The MBDoE for the given constraints and preliminary model assumptions. The optimized input profile of fast-acting insulin, u_F, causes fluctuations of the glucose concentration over the course of the experiment.

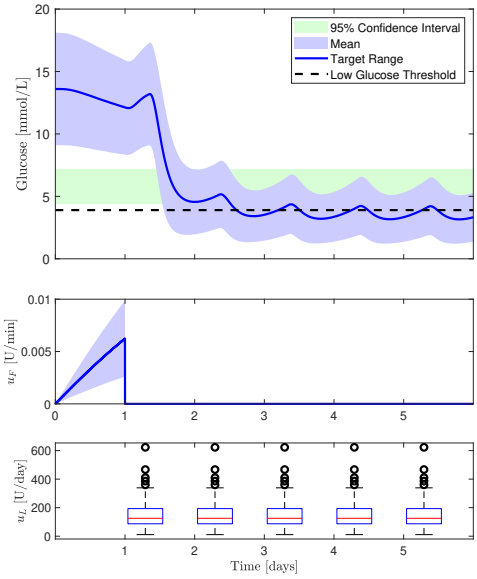

Fig. 4. The baseline scenario for 100 virtual people, where a simple controller is used to gradually increase the infusion of fast-acting insulin, u_F, over the first 24 hours. The resulting system excitation leads to only 22 safe dose estimates of long-acting insulin, u_L.

we apply a phase-shifted cosine curve as a reference for the system output in the first 24 hours.

To individualize the reference, we let the cosine curve start at the initial fasting glucose measurement, y_0 [mmol/L], for each person. We define the reference by

$$y_{ref}(t) = \delta \cos\left(\frac{3\pi \cdot t}{60 \cdot 24} + \frac{\pi}{2}\right) + y_0 - 0.001t \qquad (7)$$

where t is time in minutes and $60 \cdot 24$ is the number of minutes per 24 hours. As in the constraint definition, δ [mmol/L] is half of the width of the 4.4-7.2 mmol/L target range. We let the glucose concentration drop gradually over time by 0.001 (mmol/L)/min.

We manually tune a proportional controller to track the glucose reference, y_{ref}. We collect closed-loop data for 24 hours and use the data to estimate parameters in (1). We apply maximum likelihood estimation (MLE) and use the continuous-discrete extended Kalman filter (CDEKF) to approximate the likelihood function. For a more detailed description of the parameter estimation, we refer to Engell et al. (2022).

The simulation, MBDoE and parameter estimation was implemented in `Matlab R2020b`.

4. RESULTS

In this work, we use optimal experimental design to improve parameter estimation in a dose-guidance algorithm for T2D treatment. In Figure 4, we show the baseline case from Engell et al. (2022). Here, limited system excitation leads to poor system identification and unsafe dose estimates. A simple controller runs for the first 24 hours gradually increasing the insulin infusion and steering the fasting glucose towards the target range. After 24 hours, Engell et al. (2022) estimate a personalized model and predict a target insulin dose for daily injection therapy. In only 22 cases, the predicted dose is safe for the individual, i.e. the glucose concentration stays above the low glucose threshold, 3.9 mmol/L.

We test the MBDoE from Figure 3 with the same 100 virtual people. During the first 24 hours, we use the computed *optimal* insulin infusion as input to the simulator. Figure 5 shows the outcomes. The optimized insulin input leads to improved system identification. The dose-guidance algorithm suggests safe injection-based treatment for all the simulated people. However, in 24-hour open-loop period, three individuals experience dangerously low glucose values. Moreover, in the first 24 hours, the mean curve shows a faster drop towards the target range than the set constraints allow. This occurs because of a mismatch between the design model and the simulation model.

Instead, we use a MBDoE-inspired approach. In Figure 6, we mimic the optimal experiment by following a sinusoidal glucose trace with a simple, reference-tracking controller. The resulting set of inputs and outputs lead to an improved system identification compared to the baseline (Figure 4), whilst minimizing the risks of open-loop implementation of a MBDoE (Figure 5). All of the 100 people have safe dose predictions after 24 hours of closed-loop data collection.

5. DISCUSSION

In diabetes treatment, it is highly unlikely that an untested experimental design will be implemented in open-loop as

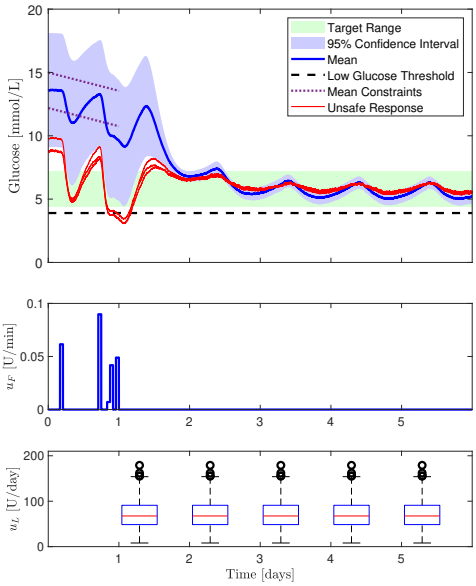

Fig. 5. Outcomes for 100 virtual people when the optimal insulin input from MBDoE is applied in open-loop for the first 24 hours. For three individuals, the experimental design drives their glucose levels dangerously low. In the mean case, the output constraints are violated and the design can also be considered unsafe. Although unsafe, the experimental data from the first 24 hours enables effective and safe dose predictions for all in the simulated cohort.

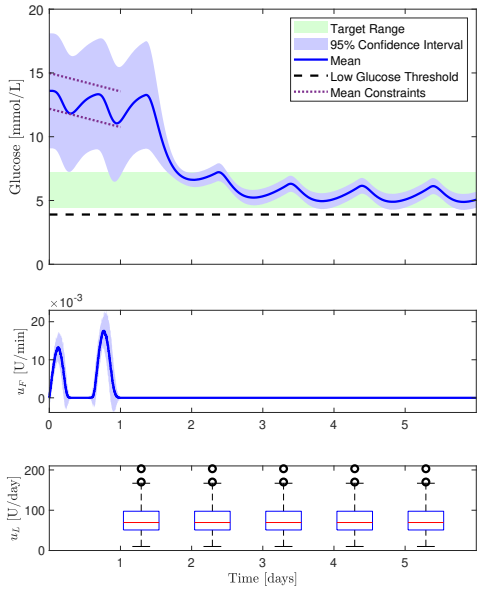

Fig. 6. Outcomes for 100 people when using cosine-shaped glucose reference for the closed-loop system during the first 24 hours. During the experiment, the mean glucose curve stays within the set output constraints. After the switch to pen-based treatment with long-acting insulin, u_L, all the dose estimates are safe.

demonstrated in Figure 5. Safety is crucial and in open-loop there are no guarantees that the input does not cause dangerously low glucose concentrations. Still, insights from MBDOE can enhance clinical trial protocols. In this work, we present a method to safely improve system identification in closed-loop with an approximation of a MBDoE. Figure 3, indicates that the MBDoE output resembles a phase-shifted cosine curve and we define a glucose trace with these characteristics. With a proportional controller, we track the cosine-shaped glucose reference in closed-loop for 24 hours and collect experimental data. In Figure 6, the excitation of the glucose-insulin system over 24 hours leads to effective dose predictions. Despite being an approximation of the MBDoE system excitation, the dose predictions in Figure 6 are comparable to the predictions in the *optimal* experimental design in Figure 5. This indicates that learnings from a MBDoE can be used to obtain good results in a safer setup than implementing the MBDoE in open-loop.

An alternative to approximating the MBDoE output with a sinusoidal curve is to use the output from the MBDoE directly as a reference to the system. In this case, the initial fasting glucose measurement of each person dictates the starting point for the reference curve from the MBDoE. In a system with input-output delay, as this one, the output trace may prove hard to follow with simpler control strategies. The MBDoE output in Figure 3 has swift changes in glucose concentrations and to reference-track the output trace requires more advanced control strategies, e.g. model predictive control (MPC). As the name suggests, the MPC methodology relies on a predictive model of the physical system, which is exactly the model we try to estimate with MBDoE. Hence, the predictions of the controller may not be safer than the designed experiment.

Another approach is to look at the computed optimal insulin infusion. Instead of implementing the optimal insulin infusion in open-loop, a controller could re-evaluate the dose every five minutes and adjust the insulin infusion. In this way, the controller may alter the insulin input every time the output constraints are violated. An implementation like this is only applicable in cases where the insulin doses are slightly off as no insulin-dosing controller is able to ensure safety after a large overdose. An insulin overdose can be corrected with the hormone glucagon in a dual hormone artificial pancreas. However, this work indicates that safe system identification can be reached with simpler means.

The quality of system identification depends greatly on the level of system excitation. Table 2 shows the insulin input given to the cohort of people with T2D in the baseline case, the direct implementation of the MBDoE and the MBDoE approximation. The insulin input in the MBDoE approximation is the lowest. Still, the input ensures that all the dose predictions in Figure 6 are safe. Compared to the direct MBDoE implementation, the MBDoE approximation has a reduced input over 24 hours. In spite of this, the system identification leads to the same number of safe and effective dose predictions. This hints that an approximation of the MBDoE can provide sufficient system excitation.

Table 2. Insulin input

Excitation Type	Input [U/24h]
Baseline (mean)	4.6670
MBDoE	2.9904
MBDoE approx. (mean)	1.4797

In a clinical implementation, the predicted target dose cannot not be injected on the first day after ended closed-loop treatment. In Figure 4, 5 and 6, the sudden drops in glucose concentration on day two can cause irreversible damage in the body. All three figures serve to show whether the predicted insulin doses bring the cohort into the target range. They are not suggestions for a clinical implementation. Instead, the person with T2D may gradually increase the daily dose over a number of weeks, similar to traditional insulin titration. Compared to standard of care, this titration could have greater step-wise increases and reduce the length of the titration period. The predicted target dose can provide people with T2D and their health care professionals with insights that enable a meaningful titration communication. The predicted target dose can be used to set goals, balance expectations and evaluate progress of the insulin titration process. Additionally, knowing the target dose size may reduce the individual's fear of overdosing, when increasing the dose size gradually to reach target. However, to be ready for in clinic tests, the method we present in this paper must undergo stress-tests in a more complex simulation scenario to account real-world system disturbances and variations.

6. CONCLUSION

In this work, we present a method to improve system identification by mimicking model-based optimal experimental design. To avoid the risk of an open-loop experiment, we approximate the output curve from the MBDoE and use it as a reference for the physical system. With a reference-tracking controller, we follow the output trace to collect experimental data in closed-loop. In this T2D case study, the proposed design method provides informative experimental data for system identification. In other safety critical systems, the method may offer a safer alternative to implementing a MBDoE in open-loop.

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APPENDIX E

Conference Paper

Optimal Experimental Design to Estimate Insulin Response in Type 2 Diabetes

Optimal Experimental Design to Estimate Insulin Response in Type 2 Diabetes

Sarah Ellinor Engell[1,2], Henrik Bengtsson[1], Karim Davari Benam[3], Anders Lyngvi Fougner[3], John Bagterp Jørgensen[2]

***Abstract*— In late-stage type 2 diabetes, automated titration algorithms provide a promising alternative to the current standard-of-care. Many published methods rely on personalized dose-response models to predict a safe and effective insulin dose. In this case study, we address the challenge of how to collect an informative data set to ensure practical identifiability of such models. We apply optimal experimental design to enhance the performance of a published titration algorithm. For a 24-hour experiment, we solve an optimization problem to select the size of three meals and the hourly fast-acting insulin infusion rate. In simulation, we demonstrate how the optimized protocol improves the safety of the algorithm's dose-predictions. The results indicate that optimal experimental design has the potential to improve model-based algorithms and may be used as a qualitative tool when planning clinical experiments.**

I. Introduction

Worldwide, one in eleven people lives with diabetes and the prevalence continues to rise. Of all diabetes cases, type 2 diabetes (T2D) accounts for 90%. In T2D, persistent high blood glucose levels occur due to an imbalance between the secretion of the regulatory hormone insulin and the insulin sensitivity in the body. Left untreated, elevated glucose levels can have serious consequences, e.g., vision loss or amputations. Numerous medications exist to enhance insulin secretion or improve the insulin sensitivity. However, as T2D progresses over time, daily basal insulin injections can become necessary to sufficiently lower the glucose levels [1].

Initiating basal insulin treatment is a challenge. The response to insulin is highly individual and overdoses can be both uncomfortable and dangerous. To safely reach the target glucose range, people with T2D *titrate* to find a personalized daily injection dose. Based on daily pre-breakfast finger-prick measurements, the individual adjusts the insulin dose in small steps to reach clinical targets. This process can take several months, and for some even years. Despite a high drug efficacy in clinical trials, up to 60% of the people initiating basal insulin treatment never reach clinical targets. The daily workload is one of many reasons for failed insulin titration [2].

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To improve clinical outcomes, the titration burden can be reduced through automation. Published algorithms for automated titration use combinations of data from insulin injection pens, finger-prick measurements, continuous glucose monitors (CGM) and/or insulin pumps to identify a personalized target insulin dose [3]–[7]. Many of these methods rely on identifying a dose-response model for the individual [5]–[7]. The quality of the dose prediction therefore critically depends on successful model identification.

Model-based design of experiments (MBDoE) has been applied in diabetes research to enhance the identification of physiological models and improve control algorithms for artificial pancreas (AP) systems [8]–[13]. Most work in this field dates ten years back, where the aim was to identify when to draw blood samples to obtain the most information about an individual's physiological response to insulin and meals. Today, improvements in sensor technology have excluded the need for selecting blood sampling times, as CGMs present reliable measurements every five minutes. Still, only a few studies on optimal experimental design have exploited this technological development [12]–[14]. To the best of our knowledge, no studies have used MBDoE to guide insulin and meal inputs for identification of dose-response models in T2D. We believe there is a potential to improve model-based insulin dosing algorithms in T2D using MBDoE to select these inputs.

In this case study, we apply optimal experimental design to improve model identification in a personalized dose-guidance algorithm from [7]. We design a 24-hour experiment with three meals and insulin infusion to estimate parameters in a dose-response model. To evaluate the safety of the new design, we test the protocol in 100 virtual subjects. From the experimental data, we identify parameters in a personalized dose-response model for each subject. With the identified models, we predict a daily insulin dose to reach clinical targets. In simulation, we evaluate the safety and efficacy of the dose prediction and compare the results to [7].

This paper is organized as follows. In Section II, we introduce the model-based dose-guidance algorithm that we aim to improve through optimal experimental design. Section III describes the optimization problem and briefly presents the two models employed for experimental design and simulation. In Section IV, we present the new experimental design and show the performance of the dose-guidance algorithm with the optimal data collection protocol. Section V discusses the design and results in comparison to [7]. In Section VI, we conclude on the main findings from this case study.

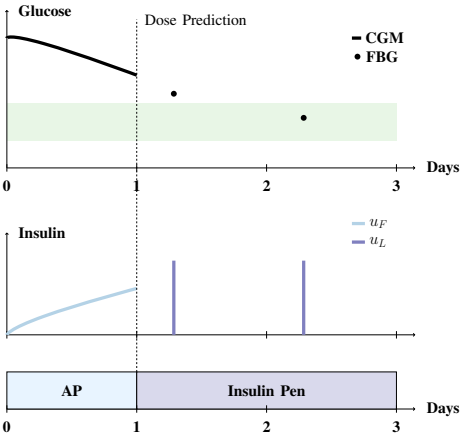

Fig. 1. A visualization of the titration solution from [7]. Data from an artificial pancreas (AP) enables the prediction of an insulin dose for injection-based therapy with long-acting insulin. In the AP period, fast-acting insulin (u_F) infusion is based on glucose measurements from a continuous glucose monitor (CGM). We use the AP data to identify parameters in a dose-response model. The model predicts an insulin dose to reach target glucose concentrations. After dose-prediction, a daily dose of long-acting insulin (u_L) is injected before breakfast and fasting blood glucose (FBG) measurements are used for daily monitoring.

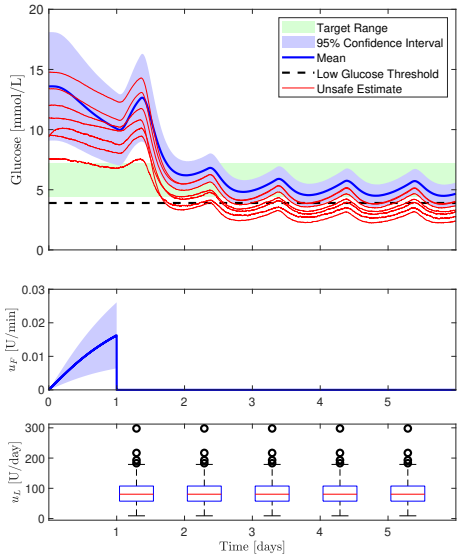

Fig. 2. Simulation results for 100 virtual people using the titration solution in [7]. During the first 24 hours, a closed-loop system gradually increases fast-acting insulin infusion and the plasma glucose drops. After 24 hours, the collected data enables parametrization of a dose-response model. The model predicts a daily insulin dose to reach glucose targets. For the remaining days, the predicted dose is injected prior to breakfast. Seven people have unsafe dose-estimates.

II. The Test Case

In previous work, we present a model-based titration algorithm to predict a personalized daily insulin dose [7]. With 24 hours of data from an AP, we identify a dose-response model. For parameter estimation, we use a one step prediction error method (PEM) using maximum likelihood estimation (MLE). We apply the continuous-discrete extended Kalman filter (CDEKF) to approximate the likelihood function. We refer to [7] for technical details on the titration algorithm. Fig. 1 shows the conceptual setup of the original titration solution. In this paper, we revisit this algorithm and apply optimal experimental design to maximize the information collected with the AP. The former design does not include meals and requires fasting for the 24 hour long AP period. In this work, we solve an optimization problem to find a protocol for both meal and insulin inputs. Fig. 2 (adapted from [7]) shows that several dose predictions are unsafe when we use the original data collection protocol. We aim to decrease the amount of unsafe dose estimates, whilst meeting clinical safety requirements during experimental data collection.

III. Methods

In this section, we introduce the two models we use for experimental design, prediction, and simulation. We define the optimization problem, the decision variable and the constraints.

A. Design model

To optimize the experimental design, we employ a physiological T2D model from [15]. We include the adaptations from [5] to ensure structural identifiability. The design model describes the impact of meals and insulin on plasma glucose levels and consists of six differential equations,

$$\dot{D}_1(t) = d(t)\frac{1000 \cdot A_G}{MwG} - \frac{1}{\tau_m}D_1(t) \tag{1a}$$

$$\dot{D}_2(t) = \frac{1}{\tau_m}D_1(t) - \frac{1}{\tau_m}D_2(t) \tag{1b}$$

$$\dot{I}_{sc}(t) = \frac{1}{\tau_I}u(t) - \frac{1}{\tau_I}I_{sc}(t) \tag{1c}$$

$$\dot{I}_p(t) = \frac{1}{\tau_I}I_{sc}(t) - \frac{1}{\tau_I}I_p(t) \tag{1d}$$

$$\dot{I}_{eff}(t) = p_3[I_p(t) + \beta G(t)] - p_3 I_{eff}(t) \tag{1e}$$

$$\dot{G}(t) = -[p_{GEZI} + S_I I_{eff}(t)] \cdot G(t) + p_{EGP} + R_A(t). \tag{1f}$$

D_1 [mmol/min] and D_2 [mmol/min] are meal compartments representing absorption of carbohydrate intake, $d(t)$ [g/min]. The exogenous insulin input, $u(t)$ [U/min], is absorbed subcutaneously in I_{sc} [U/min] before reaching plasma, I_p [U/min]. $I_{eff}[U/min]$ describes the combined insulin effect of exogenous insulin input and the endogenous insulin production, β [U·L/mmol·min]. G [mmol/L] is the plasma glucose level. $R_A(t) = \frac{D_2(t)}{V_G \tau_m}$ [mmol/L/min] is the rate of appearance of glucose from consumed meals. Table I lists parameter descriptions and provides a reference for each parameter value.

The system outputs discrete sensor measurements,

$$y_k = G(t_k) + v_k. \tag{2}$$

affected by independent and identically distributed noise, $v_k \sim N_{iid}(0, R)$. Through these measurements, we aim to determine the parameter set $\theta = [S_I, p_{EGP}, \beta]$. The selected parameters are known to be identifiable from sparse data [16] and therefore may also be identified from this experimental data set. To provide dose-guidance, we utilize a personalized version of the model (1) with the individual estimates of θ, and for the rest of the model parameters we adopt the published values listed in Table I.

B. Optimal Experimental Design

The aim of optimal experimental design is to maximize the information collected in an experimental data set [19]. To enhance the estimation of the parameter set, θ, we solve an optimization problem to find an experimental design vector, ϕ, that best excites the system,

$$\begin{aligned}
\min_{\phi} \quad & \psi(\phi, \theta) && && \text{(3a)}\\
s.t. \quad & \phi && = [u(t), d(t)] && \text{(3b)}\\
& x(0) && = x_0 && \text{(3c)}\\
& \dot{x}(t) && = f(t, x(t), u(t), d(t), \theta) && \text{(3d)}\\
& \hat{y}_k && = h(t_k, x(t_k)) + v_k && \text{(3e)}\\
& 0 && \geq c(t, x(t), u(t), d(t), \theta). && \text{(3f)}
\end{aligned}$$

The dynamics of the system we wish to identify are approximated by the model, $f(\cdot)$, a discrete measurement function, $h(\cdot)$, and measurement noise, $v_k \sim N_{iid}(0, R)$. The system states, $x(t)$, are a N_x-dimensional vector and x_0 contains the initial state values. The exogenous insulin, $u(t)$, and the meals, $d(t)$, are the system inputs. $\hat{y}$ denotes a vector of discrete measurements estimated by the model. The constraints on the inputs and output are given by (3f).

The cost function of the optimization problem acts on the parameter variance-covariance matrix, C_θ, which quantifies the parametric uncertainty. Reducing the value of C_θ is equivalent to improving the parameter estimates. Hence, we wish to determine,

$$\phi = \arg\min\{\psi[C_\theta(\theta, \phi)]\} \approx \arg\min\{\psi[I(\theta, \phi)^{-1}]\} \quad (4)$$

where ψ is the design criterion, an assigned measurement function of C_θ. As an approximation of C_θ, we apply the inverse of Fisher's information matrix, $I(\theta, \phi)$.

Several design criteria exist [19]. To minimize the volume of the hyper box which bounds the variance ellipsoid, we apply A-optimality, i.e. minimizing the trace of the inverse Fisher Information matrix,

$$\psi_A(\phi, \theta) = \text{tr}\left(I(\theta, \phi)^{-1}\right), \quad (5)$$

where Fisher's Information matrix is defined as

$$I(\theta, \phi) = \sum_{k=1}^{N} S_y(t_k)^T R^{-1} S_y(t_k). \quad (6)$$

R is the covariance matrix of the measurements, N is the total number of measurements over the length of the experiment, and S_y is the output sensitivity matrix. $S_y(t_k)$ is a measure of the change in the output, y, for each of the n_θ estimated parameters at sampling point k,

$$S_y(t_k) = \begin{bmatrix} \frac{\partial y(t_k)}{\partial \hat{\theta}_1} & \cdots & \frac{\partial y(t_k)}{\partial \hat{\theta}_{n_\theta}} \end{bmatrix} \quad (7)$$

We compute S_y using central differentiation. To avoid numerical issues during the optimization, we normalize the parameters with respect to the (supposed) true values for the subject shown in Table I. We adjust the value for insulin sensitivity, S_I, to ensure that the design and simulation models reach the same fasting glucose, y_0, at zero insulin infusion,

$$S_I = \frac{\frac{p_{EGP}}{y_0} - p_{GEZI}}{\beta \cdot y_0}. \quad (8)$$

To reduce the risk of numerical errors, we scale the state I_{eff} by a factor $c_f = 1000$ and obtain similar orders of magnitude for all states. The equations (1e) and (1f) become,

$$\dot{I}_{eff}(t) = c_f \cdot p_3[I_p(t) + \beta G(t)] - p_3 I_{eff}(t) \quad (9a)$$

$$\dot{G}(t) = -[p_{GEZI} + S_I I_{eff}(t)/c_f] \cdot G(t) + p_{EGP} + R_A(t). \quad (9b)$$

C. Decision Variable

We fix the length of the experiment to 24 hours. To ensure that the optimization problem is tractable, we describe the inputs of the design vector, ϕ, in the following way.

$$\phi = [u(t), d(t)] = [u_1, u_2, \ldots, u_{24}, d_B, d_L, d_D] \quad (10)$$

We apply a zero-order hold parametrization on $u(t)$, and fix the duration and mealtimes for the meal input, $d(t)$. For the insulin input, we determine the optimal insulin infusion over 24 one-hour blocks of piece-wise constant input. The three meals are consumed over five minute intervals at 07:00, 12:30 and 18:00. We determine the optimal size of each meal.

D. Design Constraints

To design a physically feasible and safe experiment, we select a set of input and output constraints. The insulin input must be non-negative and may not exceed an infusion rate of 15 mU/min. All three meals must be within a minimum 20 g and maximum 100 g of carbohydrates. We select a minimal meal size to ensure that the optimal solution contains all three meals.

In current clinical guidelines, the target range for fasting glucose levels is 4.4-7.2 mmol/L [1]. We strive to achieve glucose levels within the range, however a swift drop in glucose concentration can lead to complications, e.g., vision-loss and nerve-damage [20]. To avoid complications, we enforce a maximal drop rate for the glucose concentration. We simulate how much the fasting glucose decreases in an insulin naive cohort after a standardized first dose of 0.1U/kg insulin [1]. Based on the simulation results, we fix the drop rate to -0.001 (mmol/L)/min.

From the initial fasting blood glucose measurement, y_0, and the 4.4-7.2 mmol/L target glucose range, we select

TABLE I

POPULATION PARAMETERS FOR THE DESIGN MODEL

Parameter	Value	Unit	Description	Reference
τ_I	60	[min]	Time constant for fast-acting insulin absorption	[17]
τ_m	40	[min]	Time constant for meal absorption	[18]
V_G	25	[L]	Glucose distribution volume	[17]
A_G	0.8	[unitless]	Bioavailability of consumed carbohydrates	[18]
M_wG	180.1559	[g/mol]	Molecular weight of glucose	[15]
p_3	0.011	[1/min]	Delay in insulin action	[16]
S_I	0.44	[L/U·min]	Insulin sensitivity	[16]
p_{GEZI}	0.0023	[1/min]	Insulin-independent glucose clearance	[16]
p_{EGP}	0.0672	[mmol/L·min]	Endogenous glucose production	[16]
β	0.0018	[U/mmol]	Endogenous insulin production	[16]

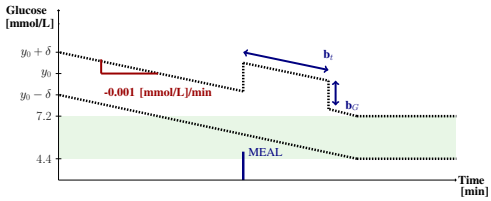

Fig. 3. Output constraints for the optimal experimental design. Over the course of the experiment, the glucose concentration must drop slowly towards the target range. We allow the glucose to fluctuate within the constraints $y_0 - 0.001 \cdot t_k - \delta \leq y_k \leq y_0 - 0.001 \cdot t_k + \delta$. Where y_0 is initial fasting glucose, t_k is the time in minutes, y_k is the output at time t_k, and δ is half of the width of the target range. Once the target range is reached, it defines the output constraints. After meals, the output constraint is raised by $b_G = 5.0$ mmol/L for the next $b_t = 5.5$ hours.

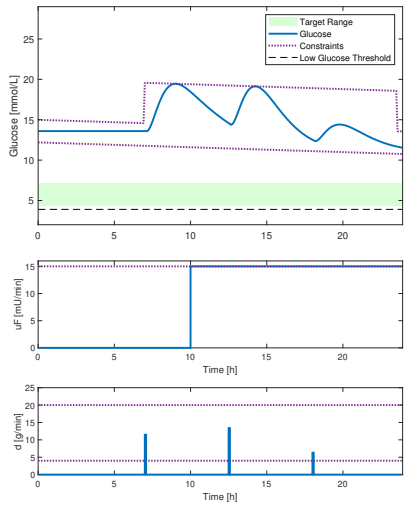

Fig. 4. The optimal experimental design for parameter estimation given the input and output constraints. Meal consumption happens over a five minute interval, hence the three meal sizes are 57g, 67g, and 31g of carbohydrates. The insulin infusion starts three hours after the first meal and remains on the maximal infusion rate, 15mU/min, throughout the rest of the experiment.

constraints that define how quick the fasting glucose concentration may drop. Following meals, we increase the upper glucose constraint by 5 mmol/L for 5.5 hours to ensure that the optimized insulin input is selected to excite the system, rather than compensating for postprandial peaks. Fig. 3 shows the output constraints.

E. Simulation model and implementation

We test the MBDoE protocol in simulation on a model with higher complexity. In [7], Engell et al. employ an augmented version of the integrated glucose-insulin (IGI) model from [21]. We use the same model together with the simulation setup from [7] to generate a virtual cohort of 100 people with T2D. We implement the simulation, MBDoE and parameter estimation in `Matlab R2020b`, and solve the optimization problem using `sqp`.

IV. RESULTS

In this work, we investigate how optimal experimental design may improve the performance of an insulin titration algorithm for people with T2D. We solve the optimization problem in (3) to design a 24 hour long experiment to capture data for parameter identification. Fig. 4 shows the resulting experimental protocol where all design constraints are met. The first two meals (57g and 67g of carbohydrate, respectively) drive the glucose concentration to the upper bound and maximize the effect of β. The last meal is smaller, 31g of carbohydrate, and lets the insulin input drive the glucose concentration closer to the lower bound emphasizing the influence of S_I. The insulin infusion resembles a step function. At 10AM, the infusion increases from 0 mU/min to 15 mU/min and remains at maximal infusion until the end of the experiment. The optimal input strategy separates different model dynamics as the insulin input increases three hours after the first meal. Fig. 5 presents the output sensitivity of each of the three estimated parameters during the experiment. The sensitivities appear to be somewhat correlated and all three are of similar absolute magnitude.

We test the design protocol in a simulation model which has a higher complexity than the design model. Fig. 6 shows how the structural mismatch leads to a different glucose response. Over the majority of the experiment, the mean glucose curve remains within the output constraints. However, the first two meals cause a slightly higher rise in glucose than the design model prediction in Fig. 4. Towards

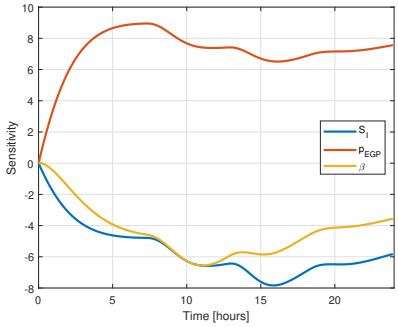

Fig. 5. The output sensitivities for the three estimated parameters over the course of the experiment. The parameters show some correlation.

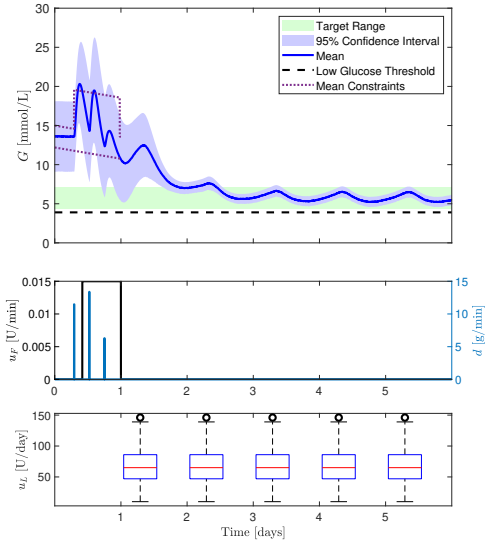

Fig. 6. Test of the experimental design on 100 virtual patients. Over the first 24 hours, we administer the optimized meal, $d(t)$, and fast-acting insulin, $u_F(t)$, inputs. Meals are consumed over 5 minute intervals. In the experiment, the mean glucose curve mildly exceeds the output constraints after the first and second meal. After 24 hours of data collection, we parameterize a dose-response model for each individual and predict a basal insulin dose, $u_L(t)$, to reach the glucose target range. Each subject receives a daily injection with the estimated basal insulin dose at 7AM. To test if the basal insulin dose can control the fasting glucose levels we do not administer meals during the last five days of the simulation. All basal dose estimates are safe and effective.

the end of the experiment, the insulin infusion drives the glucose concentration lower than the design model predicts. Still, due to the tight constraints in the optimization problem, the over and undershoot is minimal and the experiment appears to be safe for all the people in the simulated cohort. Compared to the original algorithm performance in Fig. 2, the new protocol improves the quality and safety of the dose predictions. In Fig. 6, all 100 dose predictions for injection-based treatment drive the glucose concentration into the 4.4-7.2 mmol/L target range.

V. Discussion

Safety is critical in diabetes treatment. An open-loop implementation of an untested experimental design poses a significant risk and may have limited uptake in clinics. Instead, a qualitative assessment of the new design, rather than a direct implementation, may still improve dose predictions. Fig. 6 shows that the system identification improves when insulin infusion starts three hours after the first meal. This split between insulin and meal response could be incorporated when collecting data for parameter estimation. In a real-world implementation, health care professionals may select the maximal insulin infusion rate for each individual or adjust it to match existing treatment guidelines. Closed-loop control could provide an additional safety measure as an AP would reduce the insulin infusion in case of too low glucose values.

Compared to the original design, the new protocol has an equivalent amount of insulin input. The mean fast-acting insulin infusion in Fig. 2 is 13 U/day. In the new experimental protocol, each individual receives 12.6 U/day. The combined excitation from meals and insulin appears to benefit system identification. However, fixed meal sizes and times can be hard to enforce in a real-world setting. Based on the optimal design, the evening meal needs to have a low carbohydrate content, but the exact number of carbs in each meal may be less important. Still, the timing of and carbohydrate content of meals must be recorded accurately to provide data for system identification. Compared to the original design, meal logging will place a larger work load on the individual. Still, one day of logging carbs may pose an appealing alternative to 24 hours of fasting or several months of manual titration.

In manual titration, the slow iterative journey to the clinical target minimizes the risk of nerve- and eye-damage caused by swift drops in glucose concentration. Although the simulation results in this work show that it is possible to find a personalized insulin dose in 24 hours, it can be unsafe to deliver the full dose in an injection of long-acting insulin on the next day. In Fig. 2 and 6, the glucose levels drop drastically on the second simulation day when the first long-acting insulin injection is administered. The figures are not meant as implementation proposals to use in clinics. The plots serve to evaluate whether the predicted dose is safe and effective, i.e. that it does not cause low glucose levels and can drive the fasting glucose levels into the target range. To only evaluate the control of fasting blood glucose, we do not consider meals in the last four days. Here, the oscillations in glucose stem from the dynamics of the long-acting insulin. In a real-world implementation, the individuals would eat as usual during these days of injection-based treatment.

For a clinical implementation, the person with T2D may step-wise increase the daily dose over a number of weeks, similar to standard-of-care insulin titration. Knowing the target insulin dose, would allow greater step-wise increases and reduce the length of the titration period. The predicted target dose can help people with T2D and their health care professionals to set goals, balance expectations and evaluate

progress of the insulin titration process. Additionally, knowing the target dose size may reduce the fear of overdosing.

In this case study, 24 hours of experimental data is enough to parameterize a dose-response model. In a real-world setting, inter and intraday variations in insulin response may call for longer data collection periods and a different approach to computing the output sensitivities. Due to interday variations, a model identified today may not be representative tomorrow. Hence, data collection over several days, and potentially even weeks, could very well be required to fully understand the dose-response. Additionally, intraday parameter variations can lead to sub-optimal experimental designs, since we base the optimization on output sensitivities we compute from a fixed parameter value.

In this work, we evaluate the output sensitivities locally based on the published population parameters. The local sensitivities provide information about the relevance of θ in the proximity of the reference point. Ideally, the reference point should be the true parameter set for the population as a wrong assumption can lead to sub-optimal design protocols. We test our design in a simulation model with structural and parametric differences. Despite model mismatch, the new experimental protocol improves dose predictions hinting that the parameter assumptions are sufficiently representative to design an informative experiment. For future work, testing alternative computation methods for global sensitivities could be a relevant step before clinical implementation of an experimental design in a nonlinear physiological system.

VI. Conclusion

In this case study, we use MBDoE to improve the performance of a model-based insulin titration algorithm. In the framework of a published algorithm, we optimize meal and insulin inputs in a 24-hour data collection period to parameterize a dose-response model. In simulation, we test the safety and efficacy of the model-based dose predictions. The previously published algorithm provides 93% safe and effective insulin doses. By exploiting MBDoE to optimize the titration experiment, the safety and effectiveness is improved and all of the dose predictions are safe in the simulations. We conclude that MBDoE has a potential to improve the performance of model-based dose-guidance solutions. However, it is essential to consider the variations in real-world data before implementing an *optimal* protocol in clinics.

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APPENDIX F

Conference Abstract

Short-term usage of a closed-loop insulin delivery system for improving optimization of insulin doses: a trial protocol

score. 140 patients who met eligibility criteria were selected in study using probability sampling-technique. Data analysing SPSS.

Results: Among patients (52 males and 88 females) who have mean age around 58.6 years-old, mostly married, from various education level, have EQ-5D-3L scores with no problem: Mobility (77.1 %), self-care (97.1 %), usual activities (90.7 %), pain/discomfort (45.0 %) and anxiety/depression (46.4 %). VAS Score in male is much better than female, 66.3 vs. 62.4 respectively with significant p-value 0.044. Otherwise duration of diabetes and type of medication significantly decrease quality of life showed by VAS score.

Conclusions: Quality-of-Life for patients with T2DM is affected by numerous factors such as sex, BMI, occupation, duration of diabetes and type of treatment.

P309 / #67

Topic: ***AS15-Trials is progress***

TRANSITION FROM INSULIN PUMP TO MULTIPLE DAILY INJECTIONS USING INSULIN DEGLUDEC: INTERIM RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

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Background and Aims: We evaluated the efficacy and safety of an 'overlap' strategy (OLS) compared to standard of care (SOC) for insulin pump (CSII) to multiple daily injections (MDI) transition using an ultralong acting insulin degludec (IDeg) in adults with type 1 diabetes (T1D).

Methods: In this single center randomized clinical trial, adults with T1D > 1 year, using CSII for >3 months, and A1c between 6.5% and 8.5% were randomized to OLS or SOC after 1 week of run-in-phase. Participants wore blinded Dexcom G6 and insulin dose was not changed during the trial. Participants stopped CSII and started IDeg in 1:1 dose (same as total basal insulin) at randomization in SOC. In OLS, IDeg in 1:1 dose and CSII basal insulin were overlapped (50% basal reduction for 24 hours and 75% basal reduction between 24–48 hours) for first 48 hours from randomization. CGM time-in-range (TIR- 70–180 mg/dL) and time below range (TBR, <70 mg/dL) were compared after randomization.

Results: Nine adults with T1D (age 33.8 ± 7.9 years, A1c 7.5 ± 0.3%, diabetes duration 21.8 ± 3.8 years, 62% females) were randomized to SOC, and seven adults with T1D (age 36.7 ± 10.2, A1c 7.2 ± 6.5%, diabetes duration 23.0 ± 15.1, 57% females) were randomized to OLS. Percent differences for TIR was significantly higher and no differences in TBR in OLS compared to SOC (Figure).

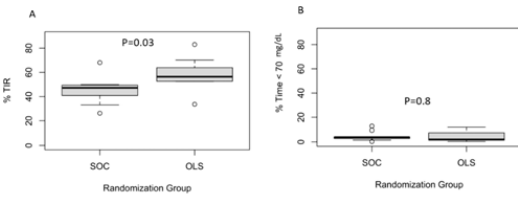

Figure 1: Difference in time-in-range (TIR) [Figure 1A] and time spent below 70 mg/dL [Figure 1B] between standard of care (SOC) and overlap (OLS) group during first week after transition from insulin pump to multiple daily injections using long-acting insulin degludec U-100.

Conclusions: Overlap of IDeg and insulin pump for first 48 hours results in better glycemic control without increasing hypoglycemia during transition to MDI using IDeg in adults with T1D.

P310 / #244

Topic: ***AS15-Trials is progress***

CAN AN ADVANCED LANCING DEVICE ALLEVIATE PAIN AND IMPROVE HBA1C?

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Background and Aims: Pain has been perceived as a major impediment to SMBG. We assessed benefits of using Genteel, vacuum based lancing device in improving HbA1c and pain of pricking.***NCT04214704***

Methods: This is the interim result of an ongoing, open-label, 24-week cross over trial where diabetes patients were matched using propensity score and allocated to GC or CG arm (G-Genteel; C- Conventional). GC arm exclusively used Genteel for 12 weeks, and then switched to conventional method of SMBG for additional 12 weeks, and vice versa for CG arm. A total of 110 patients were recruited with 55 in each arm. Both arms were provided with same glucometer. CG arm used the lancet and lancing device which they were using prior to randomization and GC used BT Lancets during first 3 months. Primary outcomes were reduction in HbA1c and %SMBG adherence over 24-weeks. Subjective assessment of pain in both arms was assessed.

Results: Data from 22 patients(13 TIDM, age: 25 ± 8.29, duration of diabetes 10 ± 7.12y and 9 T2DM, age: 43 ± 13.40, duration of diabetes: 11 ± 6.75y) showed a significant reduction in A1c in both arms while using Genteel(9.05 ± 0.93% at baseline to 7.76 ± 0.84% at week 12 in GC arm and 7.52 ± 1.22% at 12 to 7.21 ± 0.90% in CG arm at 24 weeks; $p < 0.001$*).This was reinforced by increased SMBG adherence to genteel due to alternate testing sites and contact tips.

Conclusions: This study demonstrates Genteel superior in terms of A1c reduction and pain of pricking.

P311 / #265

Topic: ***AS15-Trials is progress***

SHORT-TERM USAGE OF A CLOSED-LOOP INSULIN DELIVERY SYSTEM FOR IMPROVING OPTIMIZATION OF INSULIN DOSES: A TRIAL PROTOCOL

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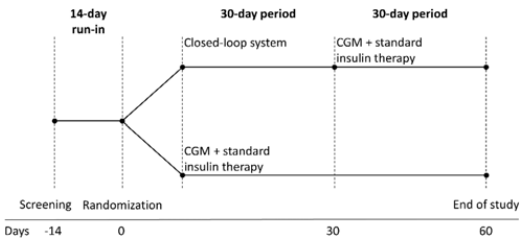

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Background and Aims: Closed-loop insulin delivery systems may be viable for treating type 2 diabetes. However, this is not always feasible, and the price is a barrier for long-term usage in a large proportion of patients. The novel objective of the present study is to investigate whether short-term usage of a closed-loop system can improve optimization of insulin doses under free living conditions.

Methods: The design is a randomized, parallel-arm study with 32 basal-only or MDI treated patients with type 2 diabetes. Participants will have a 2-week run-in period continuing their current insulin therapy while wearing a CGM. Participants will then be randomized 1:1 into a closed-loop arm or a standard insulin therapy arm. In the closed-loop arm, participants will use a closed-loop system for 30 days. Afterwards, participants will transition to standard insulin therapy for 30 days wearing a CGM, where insulin doses are optimized every 5–7 days. In the standard insulin therapy arm, participants will continue standard insulin therapy wearing a CGM for 60 days, where insulin doses are optimized every 5–7 days. The primary outcome of the study is to assess the efficacy of a closed-loop system in maintaining CGM glucose levels within the target range from 3.9 to 10.0 mmol/L compared to standard insulin therapy.

Results: The study is expected to begin in the summer of 2021, and the results published from the spring of 2022.

Conclusions: The study will reveal whether a closed-loop system can lead to better glycemic control and provide insights on patient-tailored optimization of insulin doses.

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Topic: ***AS15-Trials is progress***

ASSOCIATION OF DIABETIC NEPHROPATHY WITH INSTRUMENTS FOR PREDICTION OF CARDIOVASCULAR RISK IN PATIENTS WITH TYPE 1 DIABETES

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Background and Aims: Cardiovascular diseases (CVD) were the cause of death in 31.9% patients with type 1 diabetes (T1D). Patients with diabetic nephropathy (DN) have higher rates of CVD and mortality than patients without DN. Prevention and treatment of CVD have been extrapolated from type 2 diabetes experience. There are two T1D specific scales for predicting CVD risk. To evaluate association of DN with T1D specific scales predicting CVD risk.

Methods: Screening of 176 T1D patients was performed: age 32 years [25.5–42.5]; T1D duration 15 years [9–20]; HbA1c 8.2% [7.2–9.6]. 68.2% had normal albuminuria, 27% microalbuminuria, 4.5% macroalbuminuria, median 25.5 mg/day [15.0–36.5]. Mean eGFR (CKD-EPI) 80.55 ± 18.13 ml/min/1.73m^2: C1 30.1%, C2 58.5%, C3a 8.5% and C3b 2.9%. Steno T1 Risk Engine scale 5-year risk 3.7% [2.1-8.0], 10-year risk 7.1% [4.2-8.15]. Swedish T1D risk score 5-year risk 0.93% [0.50-1.79]. The median CVD risk was rated as low for both scales.

Results: There were significant direct correlation of albuminuria stage and inverse correlation of eGFR with 5-year risk ($r = 0.388$ and $r = -0.506$; $p < 0,0001$), 10-year risk ($r = 0.393$ and $r = -0.500$; $p < 0.0001$) in Steno scale and risk in Swedish scale ($r = 0.189$; $p = 0.012$ and $r = -0.497$; $p < 0.0001$). There is high density positive correlation between Steno and Swedish risk score ($r = 0.893$; $p < 0.0001$).

Conclusions: Steno and Swedish T1D risk scales correlate with DN stage and are equivalent to each other for assessing cardiovascular risk in T1D patients. Swedish T1D risk score doesn't require quantitative albumin loss assessment and more convenient in real clinical practice.

P313 / #325

Topic: ***AS15-Trials is progress***

INDUCING BETA CELL REST WITH INSULIN – A PART OF THE AZITHROMYCIN INSULIN DIET INTERVENTION IN TYPE 1 DIABETES (AIDIT) STUDY

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Background and Aims: Repeated induction of beta-cell rest, by episodes of intensified insulin treatment, is part of the ongoing, RCT AIDIT study protocol aiming at preservation of beta-cell function in children recently diagnosed with type 1 diabetes. All children are treated with SAP from diagnosis and normally aiming for a blood glucose value 4.0-8.0 mmol/l. In this report, beta-cell rest induced by insulin given intravenously and subcutaneously is evaluated.

Methods: Insulin lispro is given as an intravenous (iv) infusion (1U/ml) for 72 hours within one week after diagnosis and by sc subcutaneous (sc), intensified infusion with a Tandem T:slim insulin pump (100 U/ml) 6–8 hours during one day in study week 5, 9, 13, 17, 25, 34, 43. The treatments target a glucose level of 4.0 ± 0.5 mmol/l . Dexcom G6 and p-glucose (Stat-Strip) are used for glucose monitoring. Extra insulin diluted to 10 U/ml can be given iv when needed during sc treatment. The

APPENDIX G

Conference Abstract

Translation from pump to pen in type 2 diabetes: the effect of bioavailability

Conclusions: Hypoglycemia risk reduction depends on patient education and self-empowerment. If the patient's hypoglycemic episode is not severe, utilizing simple glucose intake orally is often done without any need to use the emergency kit. Thus, the emergency kit may expire in shelf life, get lost, or not be properly utilized when needed due to lack of experience of the patient or care-givers in using it.

EP090 / #472

Topic: ***AS04-Clinical Decision Support Systems/Advisors***

THE MY FRIEND DIABETES CARBOHYDRATE BOLUS CALCULATOR: USER EXPERIENCES

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Background and Aims: Meal management in T1D has barriers such as not knowing the carbohydrate values of foods, miscalculated doses, not fully understanding the mathematics of T1D. ''My Friend Diabetes Carbohydrate Bolus Calculator'' mobile app was developed as a hybrid version of nutrition apps and insulin titration apps to calculate meal's carbohydrates and the matching bolus dose(figure1). A nutrition database was created based on weights and equivalent carbohydrate ingredients of foods, which served with practical units such as a tablespoon, pieces, glasses. The app calculates the bolus dose according to glucose value, carbohydrates(grams), insulin sensitivity, and Carbs/insulin ratio.We investigated the possible benefits of the app through an online survey.

Methods: In an online survey, the effects of the app on carbohydrate counting, diabetes management, and the usability of the app were examined with a 5-point Likert scale of 17 questions.

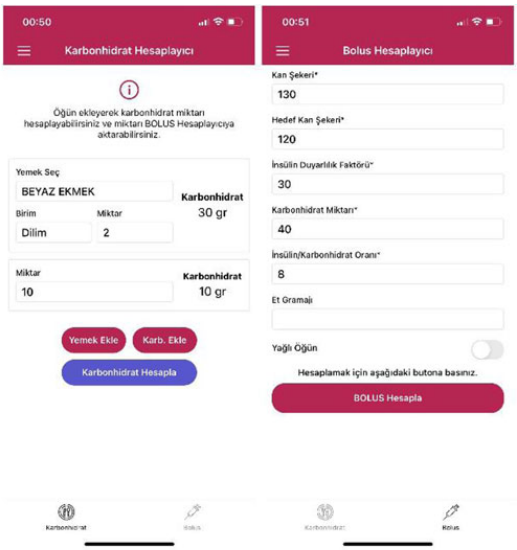

Figure1: My Friend Diabetes Carbohydrate-Bolus Calculator: Carbohydrate calculator(on left) and Bolus Calculator(on right).

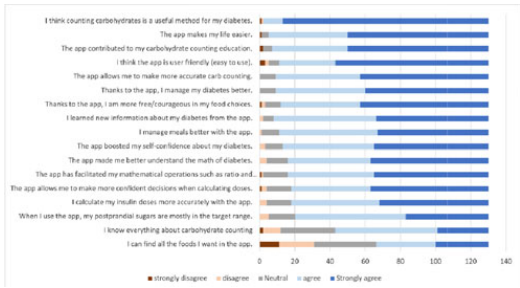

Figure2: 5-point Likert questions about the app.

Results: Of 165 people who fully participated in the survey, 58 had T1D (35.2%), 107 had relatives with T1D (64.8%), 87 participants (52.7%) were female, and the mean duration of diabetes was 4.72 years. 130 participants used the app. Participants showed agreement that the app improved the users' meal management, diabetes management, carbohydrate and dose calculations(N = 130,Mean = 4.38,SD = 0.57). They are more confident in the dose calculation, freer in the food choices, and more confident in diabetes care because of the app(N = 130,Mean 4.46, SD = 0.57)(figure2).

Conclusions: People with T1D benefit from the ''My Friend Diabetes Carbohydrate-Bolus Calculator'' mobile app. Diabetes teams can reach more people through mobile apps and improve their clinical outcomes.

EP091 / #541

Topic: ***AS04-Clinical Decision Support Systems/Advisors***

TRANSLATION FROM PUMP TO PEN IN TYPE 2 DIABETES: THE EFFECT OF BIOAVAILABILITY

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Background and Aims: Artificial pancreas (AP) systems may offer an alternative to standard of care titration in type 2 diabetes (T2D). Preliminary simulations show that short-term AP treatment can safely identify an efficient daily dose of long-acting insulin for pen-based treatment. However, these initial simulations do not incorporate the difference in bioavailability between rapid- and long-acting insulin. Pump studies in T2D populations have shown a 20% reduction in insulin need compared to pen-based treatment. In simulation, we investigate how the bioavailability of insulin analogues affect the translation from pump to pen.

Methods: We simulate a virtual clinic of 100 insulin-naïve people with T2D using an extended, stochastic version of the integrated glucose insulin (IGI) model. After three weeks of AP treatment, we translate the insulin infusion rate, unit-to-unit, into a daily injection of long-acting insulin. In a series of simulations, we scale the bioavailability of long-acting insulin with a factor between 0.8 and 1.2 compared to rapid-acting insulin.

Results: Before the switch to pen-based treatment, the average pre-breakfast glucose level is 7.7 ± 1.3 mmol/L. After stabilizing on pen-based treatment, the rapid- to fast-acting insulin

bioavailability ratios of 1:1.2, 1:1, and 1:0.8 result in an average pre-breakfast glucose level of 7.3 ± 1.2 mmol/L, 8.0 ± 1.3 mmol/L, and 8.6 ± 1.4 mmol/L, respectively.

Conclusions: For the investigated bioavailability ratios, our results indicate no hypoglycemia risk associated with a unit-to-unit translation from pump to pen. However, to achieve comparable treatment outcomes after the pump to pen switch, the bioavailability ratio is key to successful dose conversion.

EP092 / #561

Topic: ***AS04-Clinical Decision Support Systems/Advisors***

DEAPP (DIABETESEDUCATIONAPPLICATION) CHILDREN'S TYPE 1 DIABETES STRUCTURED EDUCATION PROGRAM POST PILOT OUTCOME DATA 2018-20

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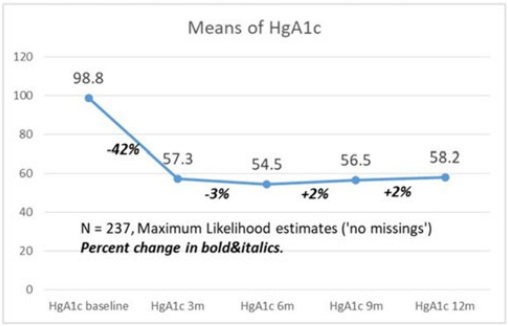
Background and Aims: Diagnosis of type 1 diabetes is the critical period to embed knowledge and understanding of diabetes. Deapp overcomes this, Triangulating: quality assured structured education, interactive education and learning resources using flipped learning. We tested the Deapp program promoted self-learning , engagement and management of diabetes.

Methods: 5 units and subgroup analysis deapp vs control, were compared.Hypoglycaemia awareness (Clarke) ; fear of hypoglycaemia; problems associated in diabetes 20 (PAID-20) & kaufmann competency. HbA1c trajectory,user surveys and length of inpatient stay

Results: N = 237 (55 excluded (no baseline Hba1c) analysed N = 193 (77%) showing reduced HbA1c baseline to 3 months: 98.9 - 57.3 mmol/l (M difference = 46.02, p < .001) and no significant change from 3-12 months. Qualitative questionnaires (n = 59 (24.9%) low scores (all 4 questionnaires and survey.

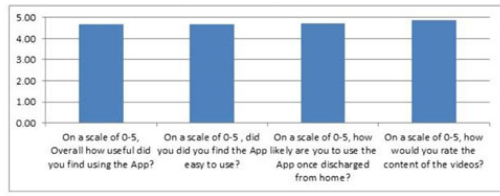
Table 1: mean Hba1c and % change of the mean (0-12 months).



Subgroup-deapp vs control: n = 32 (n = 17 control, n = 15 deapp) control mean hba1c : 52% (109mmol/l -53mmol)fall in hbA1c (18 months) control vs 48% deapp(101mmol/l- 52mmol/l). Clarke scores 0.3 (control) -1.4 (deapp). Fear of hypoglycaemia 8 (control)- 10 (deapp). PAID-20 16 (control) -22 (deapp). Kaufmann 35 (control) -39 (67% post-deapp). Bed stay = 3 days(control)vs 2 days (Deapp):

Conclusions: Deapp is able deliver structured education using flipped learning Deapp achieved at least parity of glycaemic control to existing education programs HbA1c trajectory acheived target hba1c of <58 mmol/l by 3 months and remained unchanged up-to 12 months. Subgroup showed similar hba1c

Table 2. The opinions about the app from a subsample of parents (n=59).



Question	M	SD
Overall how useful did you find using the App?	4.68	1.08
Did you did you find the App easy to use?	4.71	.99
How likely are you to use the App once discharged home?	4.25	1.22
How would you rate the content of the videos?	4.75	.77

Note: The parents used a scale from 0 (not at all) to 5 (very much) to indicate their response

Standardise diabetes scores (n=59 (60% of the pilot)

Measure	Site	Average	Range
Kauffman competency (scoring 0-8) as a measure of self-competency of management	Other 4 pilot sites	4.1	range 2-6
	Nottingham	4	range 3-5
Paid "problem areas in diabetes"	Other 4 pilot sites	10.29	range 5-14
	Nottingham	10	range 7-13
Clarke hypo scores	Other 4 pilot sites	<4	range 0-3
	Nottingham	<4	range 0-2

Interpretation: although numbers are small at this stage deapp demonstrated at least parity with traditional education and low qualitative scoring. (By default: centre Nottingham didn't obtain qualitative outcomes so has worked as a de-facto control group)

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